# The Role of Mismatch Repair and Recombination in Cellular Responses to the DNA Damaging Anticancer Drug Cisplatin

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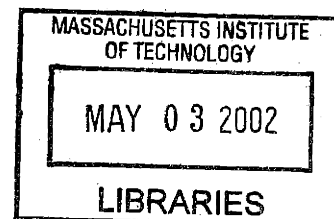


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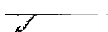
Professor Steven R. Tannenbaum 

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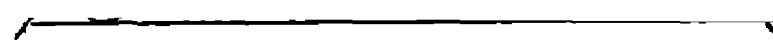
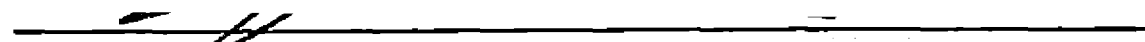
Dr. Gerald Wogan 

Professor Bevin P. Engelward 

Professor Martin G. Marinus

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## Abstract

Cisplatin (*cis*-diamminedichloroplatinum(II)) is a successful DNA-damaging anticancer drug used in the treatment of testicular, ovarian and other tumors. In the past decade, several mutually non-exclusive hypotheses have been presented to explain the cytotoxic and organotropic effects of this compound. In this work we have focused on the opposing effects of mismatch repair and recombination in mediating cisplatin cytotoxicity. Recombination mutants showed strikingly high sensitivity to cisplatin, while mismatch repair mutants showed low sensitivity and resistance to the drug. These results further illustrated that while recombination promotes cellular survival following cisplatin damage, mismatch repair, in contrast, promotes cisplatin toxicity.

The mismatch repair protein MutS recognized cisplatin-DNA adducts with 2-fold higher affinity than adducts of oxaliplatin, a cisplatin analog that does not elicit resistance in mismatch repair mutants. MutS recognized the major cisplatin DNA-adduct, the 1,2-d(GpG) intrastrand crosslink, with equal affinity as a G/T mismatch in the same sequence context. Furthermore, MutS inhibited RecA catalyzed strand exchange reaction at the level of joint molecule formation when the substrate was platinated DNA. In the cell, mismatch repair could potentiate cisplatin toxicity by inhibiting the high levels of recombination that are required for cisplatin survival.

Microarray analysis of gene expression following cisplatin damage showed that in contrast to wild type and methylation *dam* mutant, the methylation-mismatch repair double mutant did not show induction of any significant SOS DNA damage response. Yet, this strain showed abrogated sensitivity in comparison to the *dam* mutant and high survival rate. The low damage response in the *dam mutS* mutants might allow for adduct tolerance and survival. Finally, genetic studies with yeast deficient in the meiosis specific mismatch repair proteins MSH4 and MSH5 showed both mutants to be resistant to cisplatin indicating that these proteins are involved in potentiating cisplatin toxicity. Taken together, these results further elucidate the role of recombination and mismatch repair in modulation of the cellular responses to cisplatin. Furthermore, because of the specific roles of these DNA metabolic pathways in meiotic cells, these results provide the framework in which the organotropic effects of cisplatin can be viewed from a molecular perspective.

Thesis Supervisor: Dr. John M. Essigmann
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## Acknowledgements

It is the dream of every talented student in Skopje to walk down the Infinite corridor one day, and I always felt humbled to have been given the opportunity. I hold this institution as a place where idealism in the pursuit of the ultimate scientific truth stripped from politics, religion or nationalism is still possible and there have been many moments in the last five years when that has meant everything to me.

Personally, I had some trepidation to embrace science following art school. I feared that science would be less creative and spiritually lass fulfilling endeavor. I must say now that I have found the process of making art intellectually to be very similar to the process of doing scientific experimentation. Ultimately, I found the pursuit of scientific truth to be creative and exciting. As an artist I have created "beautiful" things, paintings and sculptures, but the intricate and infinite beauty of nature goes far beyond anything that I could ever imagine. For me the few moments at the end of an experiment when slivers of that infinite beauty are revealed have been the ultimate reward during these five years. And to be able to traverse nature from a complete perspective of both, art and science, has brought greater spiritual satisfaction to me than either alone. This accomplishment would not be possible without the help, love and support of many people that I would like to acknowledge in the following pages.

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I dedicate this thesis to Jill A. Mello.

*Vouz touchez tout.*

Paris and Cambridge
Summer of 2001

*To my Melete, Aoide, Mnemne*

*Jill Ann Mello*

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## List of Abbreviations

| | |
|---|---|
| A | adenine |
| β-gal | β-galactosidase |
| Cisplatin | cis-diamminedichloroplatinum(II) |
| C | cytosine |
| DDP | diamminedichloroplatinum(II) |
| DNA | deoxyribonucleic acid |
| DNA-PK | DNA dependent phosphorkinase |
| DSB | double strand break |
| *E. coli* | *Escherichia coli* |
| ERCC | excision repair cross-complementing factor |
| FDA | Food and Drug Administration |
| G | guanine |
| h | hour |
| IV | intra venous |
| LTR | long terminal repeat |
| NER | nucleotide excision repair |
| NMR | nuclear magnetic resonance |
| PCNA | proliferating cell nuclear antigen |
| RNA | ribonucleic acid |
| RPA | single strand binding protein |
| *S. cerevisiae* | *Saccaromyces cerevisiae* |
| SSB | single strand binding protein |
| T | thymine |
| *trans*-DDP | *trans*-diamminedichloroplatinum(II) |
| TRCF | *E. coli* transcription-repair coupling factor |
| U | uracil |
| UV | ultra-violet |
| XP | xeroderma pigmentosum |

# INTRODUCTION

The working hypothesis of this research project is that mismatch repair proteins through their involvement in recombination modulate cellular responses to the anti-tumor drug cisplatin. The intellectual framework for this hypothesis lays in the following independent observations:

(i) Cisplatin (*cis*-diamminedichloroplatinum(II)) is a DNA damaging drug that has shown spectacular success in the treatment of testicular, ovarian and other tumors[1]. The detailed biochemical mechanism of action of cisplatin remains elusive and controversial, but most likely its therapeutic activity results from the formation of DNA adducts that block replication and elicit a variety of cellular responses including the triggering of apoptosis. The spectrum of cisplatin-DNA adducts has been well studied: cisplatin reacts with the N7 nitrogen of purines and forms predominantly intrastrand crosslinks (1,2-d(GpG) and 1,2-d(ApG)) and a small number of interstrand cross links[2]. The cisplatin adducts induce significant distortion of the double helix, bending towards the major groove (35 - 78°), narrowing of the major groove, and flattening and widening of the minor groove[3-5]. These distortions provide a structural signal for recognition for a variety of cellular proteins, including mismatch repair proteins[6,7].

It is useful to bear in mind the question that underlies most research on cisplatin - namely, why are tumors of the testis so singularly susceptible to the drug? The molecular mechanism that can account for the striking organotropism of cisplatin is yet to be discovered. The majority of testicular tumors (95%) derive from germ cells[1], which are unique in that they require recombination for meiotic crossing-over and proper chromosome segregation during cell division. It has been shown that cisplatin can induce high levels of recombination in mouse testicular germ cells[10]. Cisplatin also causes abnormal homologue pairing, and it disrupts the proper formation and resolution of recombination intermediates during testicular germ cell meiosis[11,12].

(ii) Resistance to a number of DNA damaging agents, including cisplatin and alkylators, correlates with the loss of mismatch repair proteins, both in *E. coli* and in eukaryotes[13-15]. Thus, mismatch repair proteins paradoxically seem to sensitize rather than protect cells from cisplatin and some other DNA damaging agents. How mismatch repair contributes to cisplatin toxicity is not understood, but it has been proposed that mismatch repair proteins initiate abortive repair opposite cisplatin adducts, or inhibit recombination-dependent bypass of the cisplatin-DNA adducts during replication. At least one apoptotic pathway for cisplatin induced cell death (that involving p73) requires an mismatch repair protein, MLH1[16]. Moreover, some mismatch repair proteins specifically recognize cisplatin damaged DNA[17,18].

(iii) Testicular tissues have been found to over-express several mismatch repair proteins including MSH2, MSH4, MLH1 and MSH5[17,19-24]. Mismatch repair proteins, aside from correcting replication errors, function to ensure the fidelity and regulate the levels of recombination, and to enable completion of meiotic cell division.

We propose that the relationships among these observations provide a framework within which we may begin to understand the molecular mechanism for the organotropic action of this drug. For example, high levels of cisplatin induced recombination could lead to cell death by triggering mismatch repair mediated damage signaling pathways that are specific to germ cells. The abundant mismatch repair proteins could also sensitize germ cells by interfering with the required high level of recombinational repair of cisplatin damage. Further exploration of the relationships between recombination, repair of DNA damage, and the roles of mismatch repair proteins in both of these processes are warranted.

# PART ONE: LITERATURE SURVEY

## Chapter 1. Historical Background

The coordination complex cis-diamminedichloroplatinum(II) or cisplatin was first synthesized in 1845[25], but it was not until a century later that the biological effects of Peyrone's chloride, which is the name that this square planar compound was known under, were serendipitously discovered. In 1965, Barnett Rosenberg during his studies on the effects of electrical current on bacterial growth noted that the application of an electric field caused *Escherichia coli* to halt division, but not growth, and to form long filaments that reached the size of up to 300 normal cells[26]. Further investigation revealed that platinum compounds produced at the electrodes during electrolysis were the active agent responsible for the observed phenomenon[27]. Consequently, a number of platinum complexes was tested for biological activity, and several of them including cisplatin, were able to induce filamentous growth in bacteria[28]. Interestingly, the trans isomer of cisplatin *trans*-diamminedichloroplatinum(II) (*trans*-DDP), did not induce filamentous growth, but merely acted as a bactericide. Since, *trans*-DDP has been routinely as a control compound in most experiments that involve cisplatin and other platinum compounds (including many of the experiments in this study).

The striking effectiveness of cisplatin in inhibition of bacterial cell division hinted that it could have potential value as an anticancer agent. Indeed, subsequent studies demonstrated that cisplatin inhibits the growth of solid sarcoma 180 cells[29], leukemia L1210 cells in mice[30], Dunning ascitic leukemia and Walker 256 carcinosarcoma[31], and in a separate study cisplatin inhibited the growth of dimethylbenzanthracene-induced mammary carcinoma in rats[32]. Following the demonstration of cisplatin's antitumor activity in a broad spectrum of cell lines and animal tumors, clinical studies were started that culminated with FDA approval of cisplatin in 1978. A detailed historical account of the discovery of cisplatin is available in a review by Rosenberg[33]. Today, cisplatin is one of the most widely used anticancer agents; cisplatin is used against cancers of the testis, ovary, cervix, bladder, lung, head and neck. The efficacy of cisplatin treatment against testicular cancer is one the success stories of modern medicine.

Testicular cancer has a low incidence of approximately 4.5 males in 100,000 and represents only a fraction 0.6% of all annual new cancer cases[34]. In the United States, about 6,000 men between the ages of 20 and 44 are diagnosed with the disease each year. Before the incorporation of cisplatin into combined therapies (most often with vinblastine and bleomycin), few patients with advanced nonseminomatous cancer were expected to survive beyond 1-2 years. Nowadays, following a combination of surgery and chemotherapy where the principal cytotoxic agent is cisplatin, it is estimated that testicular cancer is curable in 96% of the cases[34].

In spite of its tremendous clinical success, cisplatin, however, is far from being "the magic bullet". Aside from side effects that are usually related to chemotherapy, cisplatin is limited by effectiveness in a relatively small number of tumors and acquired drug tumor resistance. Treatment related side effects include severe gastrointestinal toxicity, renal failure, hearing loss and peripheral nerve damage[35]. Some of these side effects have been partially alleviated by mannitol pre-hydration of patients and careful dosage. The central drawbacks of cisplatin therapy remain its limited effectiveness to a relatively small subset of cancers and acquired drug tumor resistance. Ultimately, cisplatin therapy is very effective only against a small number of tumors including testicular and ovarian cancer. Resistance is a particular problem in the treatment of ovarian tumors, and it is a phenomenon where following initial sensitivity, the tumors become resistant to further cisplatin treatment. Cisplatin resistance has been associated with the mismatch repair status of the treated cancer cells; specifically MMR defective cells are resistant.

In spite of great scientific efforts, the detailed biochemical mechanisms that can account for the organospecificity or for the acquired resistance to cisplatin are not yet elucidated. These drawbacks underscore the ongoing need for further research in the area of cisplatin, and for the design and development of novel cisplatin-based anticancer agents. To date hundreds of platinum compounds have been synthesized and screened for antitumor activity. Only carboplatin has found limited use in the clinic. Another compound, oxaliplatin showed a great deal of promise in cross-resistant platinum cell-lines and tumors and is currently undergoing clinical testing. Achieving full understanding of the mechanism of action of cisplatin will facilitate the rational design of more selective compounds that are effective against a broader range of tumors.

# Chapter 2. DNA - The Ultimate Cellular Target Of Cisplatin

The success of cisplatin as an anticancer drug has stimulated a great deal of research interest in its biochemical mechanism of action. A search of the Pub Med database with a MeSH term "cisplatin" turns over 25000 hits, and about 2000 in the last year alone. Most of the research effort has been directed towards elucidating the interactions of cisplatin with DNA and its effects on DNA-dependent cellular functions. In recent years, it has become apparent that the interactions of proteins with cisplatin-DNA adducts can mediate the cellular responses to cisplatin and much research has been focused on elucidating these relationships. However, in spite of such an effort by the research community, to date, the detailed mechanism that can account for the cytotoxic specificity of cisplatin has remained elusive.

Cisplatin is a neutral, square planar coordination complex of platinum(II), coordinated by two chloride and two ammonia groups in cis geometry. The ammonia groups are strongly coordinated to platinum, while the chloride ligands can dissociate from the coordination sphere and in aqueous solution they are readily replaced by water or hydroxide ions. This dissociation is dependent upon the chloride concentration, and at low chloride concentrations the hydrated species predominates. The hydrated complex results in a reactive mono- or bifunctional species that react with various macromolecules inside the cell, including DNA, RNA, and proteins[36,37]. In addition, cisplatin interacts with phospohlipids and phosphatidylserine in memebranes[38,39], disrupts the cytosceleton[40], and affects the polymerization of actin[41]. It is widely believed, however, that the cytotoxic effects of cisplatin result from its capacity to react with nucleotide bases and form DNA crosslinks. Several lines of evidence strongly support this view.

An examination of the number of platinum atoms bound to DNA, RNA and protein molecules in HeLa cells treated with cisplatin at a 37% surviving fraction was determined to be 22 platinum atoms per DNA molecule (one platinum adduct per $1.3 \times 10^5$ nucleotides)[36]. In comparison, the study revealed that there was one cisplatin bound per 8 mRNA, 30 rRNA, 1500 tRNA, and 1500 protein molecules, respectively. A more recent study of HeLa cells treated with a mean lethal dose of radiolabeled cisplatin (2.8 μM), confirms the notion that relatively few protein and RNA molecules get damaged by cisplatin (one platinum adduct per 3,000-30,000, and 10-1,000 molecules, respectively). In comparison, the DNA was damaged by nine platinum adduct per molecule, or an adduct per $5.17 \times 10^4$ nucleotides[37]. A study which followed the levels of cisplatin-DNA adducts in peripheral blood leukocytes of cancer patients undergoing chemotherapy correlated the levels of cisplatin DNA-adducts with favorable response to treatment[42-45]. Because of these findings, it is has been reasoned that the damaged protein or RNA molecules are relatively low in numbers and in contrast to DNA, are expendable because they can be easily replaced. It could be argued, however, that some low-abundance regulator of a critical event, such as transcriptional regulator or an apoptotic effector protein may be the target of cisplatin. It is worth keeping an open mind for such possibilities.

The strongest evidence for cisplatin-DNA adducts as the primary cytotoxic lesions formed by cisplatin is the body of work that shows that both, eukaryotic and prokaryotic cells, deficient in nucleotide excision repair (NER), are strikingly sensitive to the drug[46-48]. This high sensitivity is probably due to an accumulation of a great number of cisplatin-DNA adducts. Significant effort has been focused on the details of the nature of these crosslinks as well as the cellular responses to this type of DNA damage.

**DNA adducts formed by cisplatin.** When administered, cisplatin is not reactive in the bloodstream because of the high chloride concentration (~100 mM). Upon diffusion in the cell, the low intracellular chloride concentration (~4 mM) facilitates hydrolysis of the two chloride ligands yielding a positively charged, bifunctional electrophilic derivative. The half-life ($t_{1/2}$) for

substitution of the first chloride ligand with a water molecule is about ~2 h[49,50]. The subsequent reaction of cisplatin with DNA is kinetically rather than thermodynamically controlled. The aquated species reacts readily with nitrogen at the N7 position of purines to form monofunctional cisplatin-DNA adducts ($t_{1/2}$ ~0.1 h)[49]. Subsequent reaction with a second nucleophile yields bifunctional intrastrand and interstrand crosslinks, as well as a small proportion of cisplatin DNA-protein crosslinks ($t_{1/2}$ ~2 h)[49]. The trans isomer of cisplatin, *trans*-DDP, undergoes a similar biotransformation, and the first hydrolysis step and the subsequent formation of monofunctional DNA adducts occur at a rate similar to that for cisplatin. The rate of formation of the bifunctional *trans*-DDP crosslinks however, is debatable. One report has measured the rate of formation of the bifunctional *trans*-DDP adducts to be similar to that of cisplatin ($t_{1/2}$ ~3 h)[49], while other studies have measured a much slower rate of formation ($t_{1/2}$ ~24 h)[51,52]. The differences in the reported rates of formation in these experiments could be due to differences in the experimental set-up such as the length and sequence of DNA used. However, the difference in the rate of formation of bifunctional adducts between cisplatin and *trans*-DDP could explain the different biological activities of the two isomers.

**Distribution of adducts and sequence specificity.** Cisplatin reacts with the nitrogen at the N7 position of purines and forms primarily intrastrand crosslinks: 1,2-d(GpG) ~65% of total adducts formed, 1,2-d(ApG) ~25%, and 1,3-d(GpNpG), where N is any nucleotide, ~8%[53]. Enzymatic digestion of cisplatin treated salmon sperm DNA followed by chromatographic separation and $^1$H NMR analysis confirmed that 70-88% of the DNA adducts formed by cisplatin are 1,2-intrastrand crosslinks, 8-10% are 1,3-intrastrand and interstrand crosslinks, and 2-3% are monofunctional guanine addcuts[2]. Subsequent studies have confirmed that cisplatin forms interstrand crosslinks between two guanines in opposing strands at d(GpC)/d(GpC) sites, although at a low frequency, < 2% of the total adducts[54,55]. The examination of cisplatin adducts in the DNA of mammalian cells grown in culture[56] and in circulating leukocytes in treated patients reveals adduct profiles similar to the ones found *in vitro*[57].

The trans isomer of cisplatin, *trans*-DDP, preferentially reacts with the N7 nitrogen of purines and the N3 of cytosine, and it forms a spectrum of monofunctional[51] and bifunctional adducts[58]. However, the trans isomer is stereochemically hindered from forming the 1,2-intrastrand crosslinks that comprise the majority of adducts formed by cisplatin[59,60] and instead forms predominantly intrastrand crosslinks at bases separated by one or more intervening nucleotides. The *trans*-DDP adduct spectrum is not as well studied as the adduct spectrum of cisplatin. Reaction of *trans*-DDP with single stranded DNA and subsequent analysis of enzymatic digestion products yields bifunctional crosslinks with the connectivity: dG-Pt-dG ~60%, dG-Pt-dA ~35% and dG-Pt-dC ~5%[58]. In congruence with these findings are the results of replication mapping studies that show a *trans*-DDP preference for d(GpNpG) sequences[61]. Bifunctional adducts formed by *trans*-DDP in duplex DNA exhibit a different distribution from that observed in single stranded DNA: dG-Pt-dC, dG-Pt-dG and dG-Pt-dA represent 50%, 40% and 10% of the total crosslinks, respectively[58]. A distinction between intrastrand adducts at nonadjacent bases and interstrand crosslinks could not be made by the methods used in these experiment. However, the preferential formation of dG-Pt-dC in duplex DNA suggests that it derived, at least in part, from an interstrand crosslink. Contrary to this extrapolation, it has been reported that the 3'-5' exonuclease activity of T4 DNA polymerase could detect no crosslinks on duplex DNA that was globally modified with *trans*-DDP[62]. However, the level of trans-DDP modification used in this experiment was low, and would have likely been below the limits of detection of the experimental system. More recently, interstrand crosslinks of *trans*-DDP have been unequivocally identified; they indeed occur at complementary guanine and cytosine bases, and comprise up to 20% of the total adduct profile[63]. Leng and colleagues have made the interesting observation that the 1,3-d(GpApG) intrastrand crosslink of *trans*-DDP present in a single stranded oligonucleotide undergoes isomerization to an interstrand crosslink when the oligonucleotide is paired with the complementary strand[64]. In addition, isomerization of the 1,3-d(GpCpG) *trans*-DDP adduct present in a single stranded nucleotide to a 1,4-d(CpGpCpG) intrastrand adduct has also been observed[65]. This suggests that at least the 1,3-intrastrand crosslinks of the trans isomer may be unstable, at least in some sequence

contexts. Because of its therapeutic inefficacy, the adduct profile of *trans*-DDP in genomic DNA following the treatment of cells has not been studied. The DNA adducts profiles of cisplatin and *trans*-DDP are summarized and compared in Table 2-1.

**Structures of cisplatin DNA adducts.** The formation of platinum-nucleotide crosslinks induces significant distortions of the double helix. These distortions have been studied in a great detail by numerous methods including gel electrophoresis, chemical probes, X-ray crystallography and nuclear magnetic resonance (NMR).

A gel electrophoretic study of multimers of dodecamer oligonucleotide that contained a single 1,2-d(GpG) intrastrand adduct demonstrated that the cisplatin adduct bends the DNA helix by ~40° towards the major groove[66]. Gel electrophoretic studies of DNA fragments containing site specific cisplatin adducts have demonstrated that the 1,2-intrastrand crosslinks impart a directed bend to the DNA helix by 32-34° towards the major groove[67]. The 1,2-d(GpG) and the 1,2-d(ApG) intrastrand adducts show comparable electrophoretic mobility[68] and they induce local unwinding of the duplex by 13°, while the 1,3-d(GpTpG) intrastrand crosslink causes unwinding of 23°[69] and a bend angle of 25-35°[67,70].

In addition to gel electrophoretic studies, X-ray crystalogrpahy has also been employed to study the structures of cisplatin DNA adducts. Analysis by X-ray crystallography of cisplatin coordinated to a d(GpG) dinucleotide have shown that the base stacking of the coordinated guanines is disrupted[71]. More recent, a 2.6 Å resolution X-ray structure of a 1,2-d(GpG) intrastrand adduct in a dodecamer duplex was reported[72]. The adduct causes a ~50° bend towards the major groove, thereby compressing the major groove and flattening and widening the minor groove (9.2-11.2 Å vs. 5.7 Å for the normal B-DNA). This flattened and widened minor groove is an important structural recognition element for protein binding. The guanine bases are destacked, and the dihedral angle between the bases is 30°. The base pairs at the platination site are propeller twisted, but they retain their hydrogen bonds. The conformation of the deoxyribose at the 5' position is C3'-endo, a finding in accordance with previous reports that the 5' G:T base pairing is disrupted for cisplatin intrastrand crosslinks[70,73]. One of the ammine ligands bound to platinum is hydrogen bonded to backbone phosphate oxygen. Overall, the distortions of the cisplatin crosslink induced a change of the B-type DNA architecture to one more resembling A-type, although it is possible that some of the described features are consequences of crystal packing forces.

There have been three high resolution NMR structures reported for an oligonucleotide modified to contain a 1,2-d(GpG) intrastrand cisplatin crosslink. The first reported study shows the structure of the 1,2-d(GpG) adduct present in an octamer DNA duplex[74]. The NMR study indicates even greater overall distortions in comparison to the crystallographic studies, such as bending of 58°, unwinding of 21°, and a dihedral angle between the guanine bases of 59°. This structure shows widening of the major groove and disruption of the 5' G:T base pair. The sugar pucker conformations are consistent with the ones reported in the crystal structure. It is of interest to note that there was on observation made in this study that the 1,2-d(GpG) intrastrand crosslink can undergo slow isomerization to an interstrand crosslink in the presence of a chloride ion. The significance of this isomerization and whether it occurs *in vivo* is currently unknown.

The structure of the identical dodecamer centrally modified with the 1,2-d(GPG) intrastrand adduct and used in the X-ray study was also resolved by NMR. This report presents an interesting comparison of the structures observed by the two experimental methods. The NMR structure reveals an overall helix bend of 78° and 25° unwinding of the helix at the site of platination[5]. The dihedral angle between the guanine bases is 47°. The DNA has a shallow, flat and wide minor groove. The overall distortions of the double helix, including the base pairing observed in the NMR study are more striking than in the previously discussed X-ray structure of the identical modified oligonucleotide.

The NMR solution structure of a palindromic dodecamer DNA probe modified to contain two 1,2-d(GpG) intrastrand adducts positioned to be 180° apart from each other was also determined[75]. Each adduct bends the DNA by ~40° and the overall helix axis is dislocated by ~13 Å. The structural features of the cisplatin DNA crosslinks are summarized on Table 2-2.

In the NMR studies described above the structure determinations are calculated from distance constraints obtained from nuclear Overhauser effect (NOE). The NOE data provides constrains for short-distance interactions (≤ 5 Å), but provides no information for long range interactions which could be of significance in determining the effects of cisplatin adducts on the helical structure away from the adduct site. Studies have been carried out in an effort to determine the effects of cisplatin beyond the range of NOE's. A cisplatin analog containing a 4-amino-TEMPO (4-amino-2,2,6,6-tetramethylpiperidinyloxy, free radical) ligand was employed to study the structure of an undecamer DNA duplex modified to contain a *cis*-[pt($NH_3$)(4-aminoTEMPO){d(GpG)}] adduct[76]. The observed helix bend angle is ~80°, and the minor groove is widened. The structure determined is similar to the previously discussed X-ray and NMR structures.

Because of its implied biological importance most structural studies of cisplatin-DNA adducts have focused on the 1,2-d(GpG) intrastrand adduct. Therefore there are no high resolution studies of the 1,2-d(ApG) intrastrand adduct. Molecular modeling studies based on the NMR data of an oligonucleotide containing a single 1,2-d(ApG) adduct indicate that the DNA is bent by 55° towards the major groove, suggesting that the two intrastrand crosslinks induce similar distortions in the DNA[76].

Two similar NMR solution structures of duplex containing a single 1,3-d(GpTpG) intrastrand adduct have been reported[77,78]. The overall structure is more distorted than the structure of DNA containing a single 1,2-d(GpG) adduct. The helix is unwound locally at the platination site by ~19°, it is bend towards the major groove by ~24°, and the minor groove is widened. Unlike the structures of the 1,2-intrastrand crosslinks the base pairing around the cisplatin adducts is severely disrupted. The base pairing is lost at the 5' platinated guanine as well as in the central thymine, which is flipped out and extruded in the minor groove. The striking structural differences between the two types of adducts could present basis for their differential biological processing.

The *trans*-DDP crosslinks also appear to induce less unwinding and rigid bending to DNA than the cis analog. Unwinding induced in plasmid DNA by global *trans*-DDP modification is reported to be about 9°. Global cisplatin modification was found to be twice as effective at unwinding supercoiled plasmid DNA as *trans*-DDP damage[79]. Gel electrophoretic mobility studies of the *trans*-DDP adducts and 1,3-d(GpTpG) intrastrand crosslink indicate that these lesions impart a nondirected bend, or a point of flexibility, to the DNA resembling a hinge joint[67,69]. This is in contrast to the rigid bend that is induced by the intrastrand adducts of cisplatin.

There are very limited structural data for the DNA adducts of other platinum compounds. For example, monofunctional adducts of the cisplatin analog $[Pt(DIEN)Cl]^+$, which has only one labile chloride and thus can only coordinate to only one nucleophile, unwind the helix by 6°[80].

Although less frequent in occurrence, the interstrand crosslinks of platinum compounds could have biological significance and structural studies have been carried out on these lesions as well. Both the cis- and trans- interstrand crosslinks appear to distort the double helix over a larger area than the intrastrand adducts[81]. The interstrand crosslink of cisplatin distorts the double helix by causing bending by 45-55° and unwinding by 79°[82,83]. Two NMR solution structures of a DNA decamer duplex crosslinked at a central GC:GC site by an interstrand cisplatin crosslink have been determined[84,85]. They show a double helix that is locally reversed to a left-handed form and unwound by ~80° for about four base pairs and bend by 20°-40° towards the minor groove. An unexpected feature of this structure is that the cisplatin bridge actually resides in the minor groove. Similar structural features are observed in the 1.63 Å crystal structure of the identical decamer duplex DNA modified to contain a cisplatin interstrand crosslink[86]. The DNA helix is bend

by 47° towards the minor groove and is unwound by 70°. The minor groove is enlarged and the complementary cytosines are extruded from the double helix and exposed to the solvent. The cisplatin bridge is again positioned in the minor groove. The minor groove positioning of the interstrand platinum ligand is in complete contrast to what is observed for the intrastrand adducts, and it further emphasizes the structural differences between the two types of crosslinks. It is interesting to note that the base excision of a self-complimetary oligonucleotide with a central G:T mismatch by the G:T/U-specific mismatch DNA glycosylase (MUG) generates an unusual DNA structure remarkably similar in conformation to a cisplatin-DNA interstrand crosslink[87]. The similarity of these structures suggests that cisplatin interstrand crosslinks could be substrates for proteins that recognize extrahelical nucleotides or abasic sites in DNA (*vide infra*).

The trans isomer of cisplatin also forms interstrand crosslinks. Electrophoretic mobility studies and reactivity assays using several different chemical probes indicate that the *trans*-DDP interstrand crosslink at a G/C base pair bends the helix towards the major groove by about 26° and it unwinds it by about 12°, and it suggests that the platinum coordinated nucleotides remain base paired[88]. The structure of a dodecamer DNA duplex containing a single GN7-CN3 interstrand crosslink of *trans*-DDP has also been resolved by NMR[89]. The duplex is distorted over two base pairs on either side of the adduct, and it is bend by 20° towards the minor groove. The platinated guanine adopts syn conformation. This rotation results in a Hoongsteen-type pairing between the complementary guanine and platinated cytosine residues.

Taken together the detailed high-resolution studies of the various platinum-DNA adducts begin to reveal the structural basis for the observed cellular responses to the different analogs. The signature distortions of major cisplatin adduct, the 1,2-intrastrand crosslink, including the bend, unwound duplex with a widened and flattened minor groove differentiate it from the other platinum-DNA adducts. The fact that *trans*-DDP is geometrically constrained from forming 1,2-intrastrand crosslink, which comprise about 90% of all adducts formed by cisplatin, has led to the proposal that the 1,2-intrastrand crosslinks are responsible for the therapeutic activity of cisplatin. This view has been supported by findings that a variety of cellular proteins specifically recognize and bind to DNA that is modified to contain 1,2-intrastrand crosslinks. By analogous reasoning, the interstrand crosslinks formed by cisplatin are thought not to be responsible for the cytotoxicity of cisplatin owing to the fact that the trans isomer forms significantly higher levels of this type of adduct. Such arguments rely on the assumption that the cisplatin and the *trans*-DDP interstrand crosslinks are structurally similar and that they occur in similar total numbers in the cellular environment. The discussion above indicates that this is not necessarily the case, and until a mechanism of action is fully elucidated, all cisplatin adducts formally remain potential candidates for the specific lesion(s) that mediate the cytotoxic and therapeutic activities of the drug.

**Alternative Cellular DNA Targets.** Genomic DNA (gDNA) in the nucleus is not the only cellular DNA target for cisplatin. Mitochondrial DNA (mtDNA) lacks histone and it also lacks excision repair of bulky lesions and as a result it accumulates DNA damage such as methylnitrosourea (MNU), aflatoxin B1[90], and bleomycin[91]. In a recent study, cisplatin-DNA adducts were measured in DNA from nuclear and mitochondrial fractions by dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA), accompanied by immunoelectron microscopy using the cisplatin-DNA antiserum and colloidal gold[92]. DELFIA analysis of cisplatin-DNA adducts in gDNA and mtDNA showed a six-fold higher incorporation of drug into mtDNA as compared to gDNA, while the morphometric studies of colloidal gold distribution in photomicrographs showed mtDNA to contain a four-fold higher concentration of cisplatin as compared to gDNA. Examination of rat[93] and monkey tissues[94] following transplacental exposure to cisplatin also showed higher distribution of cisplatin adducts in mtDNA in comparison to gDNA. A study that examined gene-specific DNA repair in Chinese hamster ovary (CHO) cells showed that there is minimal repair of cisplatin intrastrand crosslinks in mtDNA, but in contrast, there is efficient repair of cisplatin interstrand crosslinks in mtDNA as evidenced by approximately 70% of the lesions being removed by 24 h[95]. Similar results were observed in a parallel study, where preferential formation and decreased removal was recorded for mtDNA in comparison to gDNA in CHO cells[96]. The persistence of cisplatin crosslinks in

mtDNA that is seemingly due to the inability of mitochondria to repair cisplatin damage could lead to cellular responses that are of significance for the cytotoxic and anticancer mechanism of cisplatin. Clearly, further investigation of the role of cisplatin-mtDNA damage in the cellular responses to the drug is warranted.

Table 2-1. Comparison of adducts formed by cisplatin and *trans*-DDP

| Adduct | | Cisplatin | *trans*-DDP |
| --- | --- | --- | --- |
| Intra | 1,2-d(GpG) | 65% | --- |
| | 1,2-d(ApG) | 25% | --- |
| | 1,3-d(GpNpG) | 5-10% | 40% |
| Inter | d(G*pC)/d(G*pC) | 2% | --- |
| | d(G*pC)/d(GpC*) | --- | 20% |
| Monofunctional | | Yes | Yes |

--- not determined

Table 2-2. Structural Features of Cisplatin DNA adducts

| Adduct | Type | Pt Site | Bend angle | unwinding | Method[ref] |
|---|---|---|---|---|---|
| 1,2-d(GpG) | intrastrand | major groove | 32-40° | 18° | gel electrophoresis[66-68] |
| | | | 39-55° | --- | X-ray[72] |
| | | | 78° | --- | NMR[5] |
| | | | 58° | 21° | NMR[74] |
| | | | 40° | --- | NMR[75] |
| | | | ~80° | --- | paramagnetic NMR[76] |
| 1,2-d(ApG) | intrastrand | major groove | 34° | 13° | gel electrophoresis[68] |
| | | | 55° | --- | NMR/modeling[76] |
| 1,3-d(GpTpG) | intrastrand | major groove | 35° | 23° | gel electrophoresis[67,69,70] |
| | | | 20-24° | 19° | NMR[77,78] |
| d(G*pC)/d(G*pC) | interstrand | minor groove | 45° | 79° | gel electrophoresis[82,83] |
| | | | 47° | 70° | X-ray[86] |
| | | | 20° | ~80° | NMR[84,85] |
| | | | 40° | 76° | NMR[84,85] |

--- not determined

# Chapter 3. Cellular Responses to Cisplatin

Cisplatin Effects on DNA Replication. Cisplatin inhibits cellular replication and transcription. Replication is an essential cellular process that involves the synthesis of new DNA using the original strands as templates. Inhibition of DNA replication might very well be the primary mechanism of cisplatin cytotoxicity. Cisplatin induced inhibition of replication blocks cell division, which in turn, could trigger cell death. Of course, such as effect would be more pronounced in rapidly dividing cells such as cancer cells. Because inhibition of replication could provide such an elegant hypothesis for the anti-tumor effects of cisplatin, the effects of cisplatin and the other platinum analogs, including *trans*-DDP, on replication have been extensively studied *in vitro* and *in vivo*.

Globally modified single stranded templates have been used in studies that have examined the ability of the large (Klenow) fragment of *E. coli* DNA polymerase I to carry out second strand synthesis on platinated templates *in vitro*. Cisplatin adducts were found to block DNA polymerase I efficiently, and at sequences with known sites of adduction[61,97]. The adducts of *trans*-DDP also blocked synthesis, preferentially at d(GpNpG) sites. On the other hand, monofunctional adducts of cisplatin or the cisplatin analog $[Pt(DIEN)Cl]^+$ did not effectively block the polymerase[61].

Strong inhibition by cisplatin modifications has also been observed for eukaryotic polymerases. Early studies that employed salmon sperm DNA or poly[(dA-T):d(A-T)] as primer templates showed that partially purified calf thymus polymerase $\alpha$ and $\beta$ and Rauscher murine leukemia virus reverse transcriptase activities were inhibited when the templates were damaged with cisplatin or *trans*-DDP. The modification level by cisplatin and *trans*-DDP that reduced template activity by 50% was found to differ from 1.5-7 fold, indicating that the two isomers have comparable capacity to inhibit DNA synthesis[98]. Cisplatin bifunctional adducts, but not monofunctional adducts, blocked purified calf thymus DNA polymerase $\alpha$ efficiently, and at numerous sites along the template that again correlated well with probable sites of adduct formation[97,99]. In these systems additional cellular factors might be present that might aid the polymerases in translocation past damage. Early study in a T7 *in vitro* replication system revealed that cisplatin and *trans*-DDP both inhibited replication, with cisplatin showing at least a 5-fold better capacity for inhibition[100]. However, the DNA template for this study was incubated with the platinum agents for only 3 h at 37°C, an incubation that could be too short to allow for the formation of bifunctional adducts by *trans*-DDP. A study where SV40 chromosome treated with cisplatin and *trans*-DDP infected African green monkey CV-1 cells showed that equal inhibition of DNA synthesis by the two isomers when equal amounts of platinum adducts were present[101]. However 14-fold more *trans*-DDP was required to achieve comparable adduct levels to that of cisplatin. The two platinum isomers were also compared in a SV40-based *in vitro* replication system by DNA polymerases present in HeLa or human embryonic kidney 293 cell free extracts[102]. When double stranded plasmids were damaged with comparable levels of cisplatin or *trans*-DDP adducts ($r_b$ = 9 x $10^{-4}$), both compounds inhibited replication by ~95%. The same level of $[Pt(DIEN)Cl]^+$ damage, a platinum analog capable of only forming monofunctional adducts produced only ~20% inhibition of synthesis. Taken together, these studies suggest that, if they were present in equal number of DNA adducts, the two platinum isomers are equally effective at inhibiting DNA polymerases *in vitro*. An observation of relevance to this discussion was made in a study that examined the 5'-3' exonuclease repair activities of *E. coli* polymerase I[103]. Both isomers inhibited the total excision levels of nucleotides. In contrast to the proofreading activity, the 5'-3' exonuclease activity (repair) discriminated between DNA which had reacted with cisplatin and with *trans*-DDP. While both initial rates and total excision were inhibited for the cis isomer, they were almost not affected for the trans isomer. A follow-up study showed that in addition, monofunctional adducts of *trans*-DDP are preferentially removed by the exonuclease activity, while this activity did not react with bi- or monofunctional adducts of cisplatin[104]. Therefore even

though plasmids can be modified to contain equal amounts of cisplatin and *trans*-DDP adducts this might not present a realistic reflection of an cellular situation due to differential repair of the adducts as well as the different kinetics of formation.

The studies discussed above employed the use of DNA globally modified with platinum compounds, however it could be possible that the inhibitory effect is due only to a particular adduct. Site- and adduct- specifically modified DNA templates have been used to determine the relative capacities of individual platinum lesions to inhibit DNA polymerases. An early study investigated the effect of platinum modification on the GC box element of SV40 on the activity of DNA polymerase I[100]. The GC box regulatory sequence (GGGCGG), which is repeated six times is an important sequence for viral replication and an essential sequence for expression of the viral transforming gene. Cisplatin adducts efficiently blocked DNA polymerase I at the GC box. Sequences related to these GC box elements are known to be present in the flanking regions of many retroviruses and oncogenes, thus raising the possibility that the targeting of these sequences in tumor cells contributes to cisplatin activity. It is interesting to note that cisplatin-resistant mutants of SV40 have been isolated that had acquired specific deletions in the GC box region[105].

Comess and colleagues examined primer elongation on site specifically platinated M13 genome templates including 1,2-d(GpG), 1,2-d(ApG), and 1,3-d(GpG) cisplatin intrastrand crosslinks as well as a 1,4-d(CpGpCpG) trans-DDP crosslink, by four enzymes: *E. coli* DNA polymerase I (Klenow fragment), *E. coli* polymerase III holoenzyme, bacteriophage T7 polymerase and bacteriophage T4 polymerase[106]. Cisplatin intrastrand adducts inhibit with the following relative efficiencies: 1,2-d(GpG) > 1,2-d(ApG) > 1,3-d(GpG), with an average bypass efficiency of ~10%. Translesion synthesis was observed for each platinum adduct examined. The bacteriophage T4 DNA polymerase is the most strongly inhibited enzyme and interestingly it has the most active 3'-5' exonuclease activity from the enzymes that were examined. The *trans*-DDP 1,4-d(CpGpCpG) crosslink was found to be a poor block to DNA synthesis. Although this differential inhibition by the cis and trans isomer appears at odds with the results from the studies where globally modified templates were used (*vide supra*), it is important to note that the 1,4-d(CpGpCpG) crosslink is not a characteristic representative of the *trans*-DDP adduct spectrum.

Site-specifically platinated DNA templates have also been employed in studies with eukaryotic enzymes. Purified calf thymus polymerase $\varepsilon$ is completely inhibited by a cisplatin 1,2-d(GpG) adduct, as is the 3' - 5' proofreading exonuclease activity of the polymerase[107]. Progression of DNA polymerase $\varepsilon$ was also blocked by monofunctional cisplatin-guanine adducts. A more recent study compared the effect of the 1,2-d(GpG) crosslink (positioned on codon 13 within the human proto-oncogene *HRAS* sequence) on four eukaryotic polymerases. In an earlier study, the 1,2-d(GpG) adduct placed in the same sequence in an SV40 based shuttle vector was efficiently replicated in monkey COS-7 cells, leading to mutations at the lesion site[108]. Results revealed that the DNA polymerases $\alpha$, $\gamma$, and $\varepsilon$ are completely blocked at the site of the lesion, whereas polymerase $\beta$ is able to bypass the adduct efficiently[109]. Moreover, DNA polymerase $\beta$ is able to initiate elongation directly opposite the lesion and to compete at the replication fork with the other enzymes when stalled at the lesion. Interestingly the crystal structure of DNA polymerase $\beta$ shows structural similarity to *E. coli* DNA polymerase I[110,111], which also bypasses the cisplatin adducts efficiently (*vide supra*).

The ability of platinum adducts to inhibit DNA synthesis has also been examined *in vivo*. Treatment of mouse lymphoma cells grown in culture with cisplatin or *trans*-DDP revealed equal inhibition of DNA replication by the two compounds when serum was absent from the media[112]. This result is explained by the preferential sequestration of *trans*-DDP by the sulfur containing molecules in the serum media. In a separate study, treatment of L1210 leukemia cell line with platinum compounds shows that 50% inhibition of DNA synthesis was achieved when $1.8 \times 10^{-4}$, $2.4 \times 10^{-4}$, and $80 \times 10^{-4}$ platinum atoms are bound per nucleotide for cisplatin, *trans*-DDP and [Pt(DIEN)Cl]Cl, respectively[113].

Recent kinetic studies of the effects of cisplatin adducts on T7 DNA polymerase and HIV-1 reverse transcriptase suggest that the distortion of the DNA base pairs at the platination sites affects the alignment of the DNA in the binding site of the polymerase, slowing the protein conformational change necessary for polymerization and affecting the binding of the next correct nucleotide[114]. These results are in line with an earlier study that showed that platinum adducts inhibit DNA synthetic activity of DNA polymerase I through an increase in $K_m$ values and a decrease in $V_{max}$ values of the enzyme for platinated DNA; occurring as a consequence of lowered binding affinity between platinated DNA and DNA polymerase, and because of a platination-induced separation of template and primer strands[103].

Overall, the quantitative inhibition of DNA synthesis observed *in vivo* in these experimental systems does not appear to correlate with the cytotoxic and antitumor activities of cisplatin and *trans*-DDP, unless the small differences observed in these experimental systems reflect profound cellular effects. However, many factors such as adduct formation, processing by repair enzymes and recognition by cellular proteins could affect the capacity of the two isomers to inhibit DNA synthesis in living cells.

**RNA transcription.** The comparable inhibition of DNA synthesis by cisplatin and *trans*-DDP suggests that the antitumor activity of cisplatin is not derived solely from its ability to inhibit DNA replication. One possible way in which cisplatin could affect differential cytotoxicity is the inhibition of transcription. RNA synthesis, much like DNA replication, is more critical for rapidly dividing cells - tumor cells, for example[115]. Because of this possibility the effects of cisplatin and *trans*-DDP on RNA synthesis have been examined both *in vitro* and *in vivo*.

The examination efforts have focused on the capacity of cisplatin and *trans*-DDP to block RNA polymerases *in vitro*. A study that examined the transcription activity by T7 and SP6 RNA polymerases from a template DNA restriction fragment showed that both enzymes are blocked at platinated GG and AG sites[116]. Duplex DNA containing site-specific platinum adducts were multimerized and used as templates for transcription reactions catalyzed by *E. coli* RNA polymerase or the eukaryotic wheat germ RNA polymerase II[62,117,118]. The intrastrand 1,2-d(GpG), 1,2-d(ApG) and 1,3-d(GpTpG) adducts of cisplatin as well as the interstrand crosslinks by both compounds irreversibly blocked elongation of nascent RNA by both polymerases. By contrast, the 1,3-d(GpTpG) adduct of *trans*-DDP and the monofunctional adduct of $[Pt(DIEN)Cl]^+$, could be bypassed by RNA polymerases allowing elongation of nascent RNA. In responses to intrastrand adducts transcription stopped directly opposite the lesion, whereas elongation was blocked several nucleotides before the transcription complex reached an interstrand crosslink. Significantly, inhibition of the polymerases is only observed when a platinum lesion is present on the transcribed strand. In the same studies, the ability of RNA polymerase to add a single nucleoside triphosphate to a dinucleotide primer directly opposite a cisplatin lesion was examined. None of the platinum adducts are an absolute block to this priming activity. The 1,2-d(GpG) intrastrand cisplatin adduct inhibited the single-step addition reaction more effectively than the 1,2-d(ApG) intrastrand adduct, indicating that the polymerases could distinguish between the two structural crosslinks. This differential inhibition was attributed to a lower affinity of the polymerase for the 1,2-d(GpG)-adduct-containing template, as the apparent $K_M$ of the enzyme was increased by ~5 fold for this substrate compared to the one containing the 1,2-d(ApG) adduct. Taken together these results indicate that platinum lesions may not only provide a physical block to the progression of RNA polymerases, but may also alter the properties of the transcription complex through the distortions they introduce to the DNA duplex.

In addition to blocking RNA polymerase processivity, cisplatin adducts can also inhibit transcription at the level of initiation. Direct evidence for this conclusion comes from a study in which cisplatin treatment of cells inhibited binding of a transcription factor, NF1, to the mouse mammary tumor virus MMTV promoter present on a transiently introduced template[119]. In these same studies, cisplatin reduced the changes in nucleosomal organization required for transcription

factor access, but *trans*-DDP did not. However, the relative number of DNA adducts formed in cells after treatment with each platinum isomer was not determined in this experiment, and thus no direct comparisons between the two compounds can be made in this regard.

A more recent study examined the ability of cisplatin adducts to inhibit RNA polymerase II at the level of initiation and elongation[120]. RNA polymerase II transcription in human cell extracts directed from the adenovirus major late promoter was inhibited following treatment of the promoter-containing template with increasing concentrations of cisplatin. Transcription from an undamaged promoter fragment was depleted in the presence of increasing amounts of cisplatin DNA damage present on an exogenous plasmid. These results support a model for cisplatin toxicity where cisplatin damage hijacks essential factor(s) for transcription initiation. This study also examined the effect of site-specifically-placed cisplatin adducts on RNA polymerase II elongation. The 1,3-d(GpTpG) intrastrand adduct was an effective block to RNA polymerase II elongation, inhibiting the polymerase activity by 80%. In contrast, RNA polymerase II completely bypassed the 1,2-(GpG) cisplatin intrastrand adduct. This unexpected result certainly underscores the importance of further studies on the effects of cisplatin damage on RNA transcription.

The inhibition by cisplatin of bulk RNA synthesis in cultured human cells and in murine tumor cells has also been examined *in vivo*. Total RNA and mRNA production is markedly inhibited by cisplatin, although not to the same degree as DNA synthesis[121-123]. The effects of cisplatin on individual gene expression have also been monitored. A panel of chimeric protein markers, where the promoter and the reporter genes were independently varied, was transiently introduced into monkey CV-1 cells, and the cells were then treated with cisplatin or *trans*-DDP. Strong differential inhibition of gene expression is observed at pharmacologically relevant doses of the drug, and the greatest inhibition correlates with the strongest promoters[124]. This observation is probably a reflection of the fact that stronger promoters are probably associated with accessible chromatin and therefore more easily modified by DNA damage such as cisplatin. These differential effects were not observed for *trans*-DDP, which was only weakly inhibitory to transcription from all promoters examined. Inhibition of gene expression was greater for longer genes, which likely reflects the greater number of potential sites for cisplatin modification. In similar studies carried out in HeLa human cells, cisplatin caused a surprising induction of gene expression from certain promoters including the HIV-LTR (long terminal repeat) sequence, and inhibited gene expression from others[125]. Cisplatin-induced expression from the HIV-LTR promoter[126] and from the human *c-myc* promoter has been reported by others[127]. The expression of the chloramphenicol acetyl transferase (CAT) reporter gene from the human immunodeficiency virus 1 LTR sequences was stimulated by cisplatin in rat and human fibroblasts by 22- and 2.2-fold, respectively[126,127]. A later study in the same experimental system showed that the cisplatin analogue carboplatin does not show this effect[128]. As the mechanism responsible for this stimulation was not investigated, it remains unclear whether it was direct result of cisplatin modification of the gene, or was an indirect consequence of a general cellular response, such as induction of transcription regulatory factors, to cisplatin damage.

A study that provided a definitive answer to the differential capability of both isomers to inhibit RNA synthesis involved a system where a non-replicating plasmid harboring the β-galactosidase (β-gal) reporter gene was modified *in vitro* with either cisplatin or *trans*-DDP and transfected into human or hamster cell lines[129]. The use of nonreplicating plasmid and NER proficient and deficient cell lines allowed for examination of transcriptional bypass independent of replication or excision repair for each compound. A two to three fold higher level of transcription was observed in both cell lines from plasmids containing *trans*-DDP adducts as compared to plasmids modified with cisplatin, and this difference was independent of the NER status of the cell line. In addition, four-fold more *trans*-DDP than cisplatin adducts were required to inhibit transcription elongation by 63%, as measured by monitoring the elongation of nascent β-gal mRNA from the damaged templates. RNA polymerase II translocated past a single, representative DNA adduct of cisplatin and *trans*-DDP *in vivo* with an efficiency of ~16% and ~60-76% respectively.

These data support the view that inhibition of transcription may contribute to the greater toxicity of cisplatin in comparison to *trans*-DDP.

The effects of cisplatin on ribosomal RNA (rRNA) synthesis has been examined in a reconstituted system where a pBR322 plasmid modified with cisplatin was shown to inhibit rRNA transcription[130]. This inhibition was correlated with the removal of the transcription factor human upstream binding factor hUBF from its natural promoter binding sites to the cisplatin damaged plasmid, again providing support for the transcription factor hijacking model for cisplatin cytotoxicity.

In an interesting application of a translational opportunity the ability of cisplatin to inhibit transcription has been applied to screen a library of platinum compounds for potential drug candidates. There have been two such systems reported: the first employed an assay where the reporter gene was used in a Jurkat cell line to convert the fluorescent compound CCF2-AM to CCF2, changing the emission from green to blue light[131]. Cells treated with cisplatin have reduced expression of β-lactamase and revert to green light. The emission ratio of green to blue light can be used to quantitate the level of β-lactamase inhibition. The second involves an enhanced green fluorescence protein, EGFP, transfected in a HeLa cell line under a transcriptional control of tetracycline responsive element[132].

The observations discussed above support the possibility that inhibition of RNA synthesis may contribute to the selective cytotoxic and antitumor activities of cisplatin. Although bulk RNA synthesis is less affected by cisplatin than DNA synthesis, it is reasonable to speculate that even in the absence of measurable changes in RNA synthesis, changes induced in the delicate balance of cellular gene expression by cisplatin could be of significance for its cytotoxic mechanism. Of relevance in this context are studies showing that cisplatin treatment of L1210 cells causes arrest in G2 phase of the cell cycle, and that the arrested cells subsequently undergo apoptosis[133,134]. It has been proposed therefore that cisplatin adducts may trigger apoptosis by inhibiting either overall gene expression, or a critical gene required for passage to mitosis[135]. The effects of cisplatin on gene expression patterns are further discussed in Chapter 11.

**Cisplatin, Telomeres and Telomerase.** Telomeres are G-rich repeat sequences that appear at the ends of eukaryotic chromosomes whose function is to prevent the shortening of the chromosomes and their degradation during replication. Since DNA polymerases require a labile primer to initiate unidirectional 5'-3' synthesis, some bases at the 3' end of each template strand are not copied unless special mechanisms bypass this "end-replication" problem. During each cell division telomeres are shortened by 50-200 bp[136,137]. Eventually telomeres become critically shortened, and the cells become sentient and die. Immortal eukaryotic cells, including transformed human cells, apparently use the ribonucleoprotein telomerase, an enzyme that elongates telomeres, to overcome incomplete end-replication. Telomerase functions to synthesize and maintain the telomeric sequence at the ends of the chromosomes. Cells can become immortalized when the telomeres are not shortened and telomerase activity has been associated with cancerogenesis. Given that the telomeres are G-rich sequence (in humans and most vertebrates they have the sequence 5'-$(TTAGGG)_n$-3')[138,139]) they represent a potential target for cisplatin.

Few recent studies have examined some of the effects of cisplatin on telomeres or telomerase function. Telomeres of HeLa cells treated with cisplatin were shortened and degraded, causing lethal damage effects in ~61% of the population[140]. Another study compared the effects of a panel of DNA damaging agents including cisplatin, deoxorubicin, bleomycin and *trans*-DDP on the function of telomerase activity in testicular cancer cells[141]. Only cisplatin inhibited telomerase activity in a dose dependent manner while the other compounds in the panel had no effect. Given that cisplatin can not only modify the telomeric DNA but also directly damage telomerase, further

studies are required to elucidate fully this potentially very significant cellular response to platinum damage.

**Repair of Cisplatin Adducts.** The primary mechanism for repair of cisplatin DNA damage in prokaryotic and eukaryotic cells is nucleotide excision repair (NER). Because of this central importance, the mechanism and efficiency of repair of the various cisplatin adducts by NER has been carefully studied; however at times, the results have been conflicting and the precise role of NER in cisplatin resistance and organospecificity remains somewhat controversial.

Since cisplatin-DNA adducts greatly if not singularly contribute to the cellular toxicity of this drug, the repair of these lesions is certainly an important way for a cell to increase its probability for survival. Indeed, from early on in the cisplatin literature studies in *E. coli* have demonstrated that strains deficient in NER (*uvrA, uvrB, uvrC*) and strains deficient in the SOS response to DNA damage (*lex1, recA*) are hypersensitive to cisplatin toxicity[142,143]. These strains are also hypersensitive to high doses of *trans*-DDP, indicating that NER pathways also play a role in repair of *trans*-DDP damage. Survival of cisplatin modified plasmids was greater in *recA* mutant strains rather than *uvrB* mutant strains, indicating that perhaps that recA dependent pathways play a lesser role in repair of cisplatin damage[144,145]. In the same studies the induction of the SOS response, which also serves to increase the expression of excision repair proteins, increased survival of cisplatin- but not *trans*-DDP- modified plasmid, indicating that the two isomers at least to some extent might be differentially repaired in *E. coli*.

NER acts on a broad range of DNA damage including bulky adducts formed by psoralen, benzo[a]pyrene, and UV light. The mechanism of Uvr(A)BC excision repair in *E. coli* is well understood[146]. A dimer of UvrA in complex with UvrB binds to the site of DNA damage, followed by ATP-dependent conformational change that leads to dissociation of UvrA and the formation of stable UvrB-DNA complex. UvrC is recruited by this complex and together UvrBC incise the eight phosphodiester bond 5' and the fourth or fifth phosphodiester bond 3' to the cisplatin adduct[147]. UvrD (helicase II) subsequently facilitates the release of the 12-13 nucleotide fragment, DNA polymerase I fills the gap, and the remaining nick is sealed by ligation. This so called excinuclease activity of Uvr(A)BC on platinum damage has been examined *in vitro*. Plasmid DNA globally modified with cisplatin or *trans*-DDP was a substrate for incision by the Uvr(A)BC excinuclease, although the excinuclease was more active on cisplatin modified plasmids[145,147]. The relative activity of Uvr(A)BC for individual platinum adducts was examined using substrates containing the site-specific adducts of $[Pt(DIEN)Cl]^+$; the relative rates of excision by Uvr(A)BC were found to be in the order 1,3-d(GpNpG) > monofunctional adducts > 1,2-d(ApG) > 1,2-d(GpG) adducts[148]. A more recent study that employed site specific adducts of cisplatin, the 1,2-d(GpG) crosslink was reported to be incised 3.5-fold more efficiently than a 1,3-d(GpCpG) crosslink[149]. This inconsistency may be a reflection of the different platinum complexes used in the two studies.

In mammalian cells as well as in *E. coli*, NER is believed to be the primary mechanism for repair of platinum damage. NER in mammalian cells is far more complex than in *E. coli;* 13-16 proteins are involved in the excision step and a total of about ~30 peptides are involved in the entire process[146,150]. The autosomal recessive disorder xeroderma pigmentosum (XP) is caused by defects in NER and is characterized by extreme UV sensitivity and a high predisposition to skin cancers. Mammalian NER genes include those that complement the seven XP complementation groups A to G, as well as ERCC (excision repair cross-complementing). The basic mechanism of NER in mammalians cells also involves recognition, dual incisions on the damaged strand, excision of an oligomer and resynthesis through the resulting gap. Specifically, XPA protein, in complex with single strand binding protein (RPA), is responsible for damage recognition. Recognition signals for recruitment of TFIIH, a protein complex that contains XPB and XPD and plays a dual role in transcription and NER and the XPC-HR33B protein joins the complex as well. The role in NER for TFIIH involves a helicase role that opens the lesion at the damage site. The XPG and ERCC1-XPF heterodimer makes incisions 3-9 phosphodiester bonds 3' and 16-25 phosphodiester bonds 5' to the

lesion, respectively, yielding a repair patch of 25-30 nucleotides long. DNA polymerase δ or ε carries out the gap filling repair synthesis with the aid of proliferating cell nuclear antigen (PCNA), an accessory factor that likely assists in initiation of synthesis at the 3'-OH of the gap. This reaction has been reconstituted *in vitro*[151].

Mammalian cells deficient in NER are also hypersensitive to cisplatin[46,48,152]. XPA deficient cells are 3-4 fold more sensitive to cisplatin compared to repair proficient cells as measured by the dose required to reduce survival to 37% of control untreated cells[48,152]. A NER-deficient rodent cell line UV5 is similarly 3-fold hypersensitive to cisplatin, while the rodent UV20 cell line, which is deficient in the ERCC1 gene product, is 50-fold more sensitive to cisplatin than the repair proficient cell line as measured by the lowest concentration of drug that produced measurable loss in survival[46]. Studies monitoring repair activity through the reactivation of a cisplatin modified reporter gene transfected into mammalian cells found less gene reactivation in excision repair deficient cells than in normal cells, suggesting that less efficient repair of cisplatin adducts occurred[47,153]. Experiments in which the level of cisplatin DNA adducts present in the genomic DNA of cisplatin treated cells was monitored directly over time has provided demonstration that XPA cells are indeed deficient in repair of cisplatin intrastrand addcuts[48]. The rodent UV20 cell line defective in the ERCC1 gene product was less efficient than normal cells at removal of the minor interstrand crosslink[154].

The rate of NER of cisplatin adducts has also been examined. Global removal of intrastrand crosslinks in repair proficient cells occurs most rapidly in the first 4-6 hours after treatment, followed by slower removal over time, and repair kinetics for the individual crosslinks were found to be similar[48,155]. NER deficient XPA cells are lacking in this fast process, although some slow repair is detected over a 24 h time period[48].

The relative repair efficiency of cisplatin in comparison to *trans*-DDP has been examined in several studies. *In vitro* repair assays carried out on globally damaged plasmid DNA using human cells extracts demonstrated that both cisplatin and *trans*-DDP DNA damage stimulated repair synthesis. Extracts of XP cells were deficient in repair synthesis for either compound, indicating that excision repair operates on DNA adducts formed by both compounds[156,157]. Interestingly, greater repair synthesis was stimulated by the trans isomer in this system. A study examining the inhibitory effects of platinum adducts on DNA replication *in vitro* found that pre-incubation of platinum modified substrates with cell extracts resulted in 30% restoration of DNA replication for the *trans*-DDP modified template, but not for cisplatin damaged DNA[102]. These results suggest that adducts of *trans*-DDP may be preferentially repaired over those of cisplatin, and it has been postulated that *trans*-DDP might be less toxic for this reason. However, *in vivo* studies have failed to confirm this hypothesis unequivocally. A study in monkey cells in which the levels of cisplatin and *trans*-DDP adducts following treatment were followed over time found results suggesting that indeed *trans*-DDP adducts are preferentially repaired[101]. Later studies challenged these conclusions, proposing that the appearance of differential repair was caused by the differential reactivities of the two isomers with cellular DNA, and by the subsequent greater inhibitory effects of cisplatin to DNA synthesis and cell growth[158]. This study however, was carried out in an environment in which the nature of the platinum compounds interacting with cells was uncertain and as consequence, the studies may not be directly comparable[159]. Whether the cisplatin and the *trans*-DDP adducts are differentially repaired remains an unresolved issue in the cisplatin literature.

The repair of individual adducts formed by cisplatin has also been examined. Results from early *in vitro* repair assays indicate that repair synthesis carried out on cisplatin modified DNA resulted form removal of the minor adducts of cisplatin[160]. Consistent with this prediction, a circular DNA duplex modified to contain a site-specific 1,3-d(GpTpG) intrastrand adduct was repaired by human cell extracts, while no repair activity was detected for the major 1,2-d(GpG) adduct[161]. In independent studies, excision by human cell extracts of the 1,2-d(GpG) as well as the 1,2-d(ApG) cisplatin crosslink was observed, but consistent with the previous report the 1,3-

d(GpTpG) intrastrand adduct was repaired the most efficiently[162,163]. These results were confirmed in a later study where a repair synthesis assay where the 1,3-d(GpTpG) intrastrand cisplatin crosslink was repaired ~15-20 fold better than the 1,2-intrastrand adducts[164]. Similar propensities have been observed for the repair of adducts by the cisplatin analogs [Pt(DACH)$Cl_2$] and [Pt(EN)$Cl_2$][148].

A site-specific interstrand cisplatin crosslink was not excised by the human exinuclease in an *in vitro* system. A reconstituted repair system containing highly purified repair components yielded similar results to those obtained with human extracts[163]. Further analysis of the human excinuclease activity *in vitro* revealed incision at the $16^{th}$ phosphodiester bond 5' to the adduct and at the $9^{th}$ phosphodiester bond 3' to the cisplatin lesion, resulting in an excised oligomer 26 nucleotides in length[165]. Taken together, these results suggest that the structural distortions induced by the cisplatin DNA adducts may determine their relative rates of repair. Moreover, these results suggest that the antitumor activity of cisplatin could, at least partially, be due to the inefficient repair of the major 1,2-d(GpG) adducts.

A decade ago it was revealed that transcribed DNA is repaired more efficiently than nontrascribed DNA, and that this effect is predominantly due to preferential repair of the transcribed strand[166]. This phenomenon, known as transcription coupled repair, has been the subject of reviews[167,168]. The major factor contributing to this process is believed to be the blocking of RNA polymerase II at inhibitory DNA lesions. In *E. coli,* the transcription-repair coupling factor (TRCF) mediates such repair by specifically recognizing the stalled polymerase and recruiting the $UvrA_2B$ complex to the site of blockage[169]. In humans, the CSA and CSB gene products are required for transcription-coupled repair, and a defect in either gene results in Cockayne's syndrome[170]. Although the detailed mechanism of transcription coupled repair in humans is not known, it is believed that CSB may perform a function analogous to TRCF in *E. coli*. Interestingly, some mutations in XPB and XPD, proteins that play dual roles in transcription and repair as components of TFIIH, can also give rise to Cockayne's syndrome.

Several studies have demonstrated that cisplatin DNA damage is a substrate for transcription coupled repair. Cisplatin intrastrand crosslinks are repaired more efficiently from actively transcribed genes and also from the transcribed versus nontranscribed strand[171-173]. More efficient repair of cisplatin interstrand crosslinks from an actively transcribed gene was observed when cells were treated with low doses of the drug[173]. It is noteworthy that in these studies cleavage by Uvr(A)BC exinuclease was used to monitor the presence of cisplatin intrastrand adducts in DNA. Hence, it remains possible that only those intrastrand adducts efficiently detected by the enzyme are in fact substrates for this repair process.

# Chapter 4. Interactions of Proteins with Cisplatin-DNA Adducts

A variety of cellular proteins specifically interact with the distortions induced by the major cisplatin adduct, the 1,2-d(GpG) intrastrand crosslink. These observations have led to the hypothesis that the differential cytotoxicity and clinical efficacy between cisplatin and the other platinum analogs are a result of the specific interactions between the cisplatin crosslinks and cellular proteins. As a result, the interactions of cellular proteins with cisplatin adducts, particularly the intrastrand crosslinks, have been extensively studied in the recent years. From the perspective of this study, the most significant interactions are those between the proteins involved in mismatch repair proteins and their homologous and cisplatin crosslinks. These interactions are discussed in great detail in Chapter 4, and in the introductions to the chapters in Part II where it was relevant.

## 4.1 Cellular proteins that recognize cisplatin adducts

**Base Excision Repair Proteins.** The hAAG protein is involved in the first step of base excision repair, where AAG catalyzes the cleavage of the *N*-glycosylic bond between the damaged base and the deoxyribose phosphate backbone. AAG acts on a variety of DNA damage including 3-methyladenine, 3-methylguanine and hypoxanthine. The X-ray crystal structure of hAAG complexes to a double stranded DNA containing an abasic nucleotide site, shows that the DNA is kinked at the abasic nucleotide site and that a tyrosine residue intercalates into the DNA[174]. Given the similarities between the DNA kinking and the intercalation as a mode of binding between this structure and the reported crystal structure of an HMG box protein bound to a cisplatin crosslink, it was reasonable to speculate that perhaps cisplatin adducts would be substrates for AAG recognition as well. Indeed, recently it was discovered that AAG has an affinity for DNA modified to contain cisplatin adducts[175]. AAG recognizes the 1,2-d(ApG) intrastrand crosslink with highest affinity ($K_d$ = 71 nM), followed by the 1,2-d(GpG) and the 1,3-d(GpTpG) intrastrand crosslinks ($K_d$ = 115 nM and 144 nM, respectively). The hAAG protein however cannot excise cisplatin adducts from DNA, although it has been proposed that it could possibly facilitate their removal by nucleotide excision repair (via hHR23 interactions)[175]. Moreover, cisplatin adducts inhibit the excision of 1,*N*6-ethenoadenine (εA) by AAG[175]. This result suggests that cisplatin could hijack DNA repair factors from their "natural" lesion substrates, leading to cytotoxicity because of their persistence in the DNA. Consistent with this hypothesis, cisplatin and MMS showed synergistic effect in killing mouse cells (M. Kartalou, unpublished results).

**NER Proteins including XPE, XPA and RPA.** Given the high sensitivity of NER deficient mutants to cisplatin, it would be expected that various proteins involved in NER interact and recognize cisplatin-DNA adducts. These proteins include XPE, XPA and RPA. The exact function of xeroderma pigmentosum (XP) complementation group E (XPE) is unknown, however, it is considered that this protein participates in DNA damage recognition. XPE is the least pronounced form of the XP disorder; XPE deficient cells retain about 50% of their DNA repair capacity. It has been speculated that XPE is the human homologue of the *S. cerevisiae* photolyase[176]. Human cell extracts contain a factor that binds specifically to cisplatin damaged DNA and this activity is absent in XPE deficient cells[177]. Moreover, purified XPE recognizes DNA modified to contain cisplatin adducts, whereas it has no affinity for DNA modified with *trans*-DDP[178]. Interestingly, XPE expression is induced following cisplatin treatment[179], and human tumor cell lines selected for resistance to cisplatin show more efficient DNA repair and increased expression of XPE[180]. Although it is very tempting to attribute the increased repair of cisplatin adducts to the higher levels of XPE, a study showed that microinjection of XPE protein in XPE deficient cells restores UV damage repair to wild type levels but injection of higher levels gives no further stimulation of repair[181].

Other proteins involved in nucleotide excision repair interact with cisplatin adducts as well. XPA protein is involved in the damage recognition step of NER and it interacts with ERCC1, the p34 subunit of RPA and TFIIH. Both the DNA recognition domain of XPA and the full length protein have affinity for cisplatin damaged DNA[182-184] and XPA can be crosslinked to DNA containing a single 1,3-d(GpTpG) cisplatin adduct[185]. Moreover, *XPA* cell lines are hypersensitive to cisplatin[48,152,186] and enhanced expression of XPA mRNA is observed in tumor tissues from ovarian cancer patients that are resistant to platinum based chemotherapy compared to levels in tissues of patients that responded favorably to chemotherapy[187,188]. The interaction of XPA with ERCC1 increases the binding affinity of XPA for UV damaged DNA[189], indicating that ERCC1 might also be involved in the damage recognition step of NER. Moreover, there is a statistically significant correlation between the relative expression of XPA and ERCC1 mRNA's in ovarian tumors[190]. ERCC1 mRNA levels correlate with response to platinum based chemotherapy with the higher mRNA levels being observed in tumors refractory to chemotherapy[187,191]. It is of interest to note that testicular tumors have low levels of XPA protein and the ERCC1-XPF complex[192].

RPA, single stranded DNA binding protein, is a heterodimeric protein composed of p70, p24 and p14 subunits, and it is involved in DNA replication, repair and recombination. Even though RPA can bind to DNA damage alone, it has been implicated in stabilizing the opened DNA duplex in cooperation with XPA, TFIIH, and XPC. Moreover, RPA interacts with XPA, XPG and XPF-ERCC1, indicating that it is involved in the damage recognition and excision steps of NER. RPA has been identified in protein complexes bound to cisplatin damaged DNA by Western Blot analysis[193], and purified RPA binds with higher affinity to cisplatin damaged DNA than unmodified DNA[185,194,195]. Moreover RPA recognizes a single 1,2-d(GpG) and a single 1,3-d(GpTpG) intrastrand adduct[195], and it shows higher affinity for the later. The relative binding affinities of RPA to the different cisplatin adducts correlate with the repair of the adducts observed in an *in vitro* repair assay[163]. A DNA substrate containing a single interstrand crosslink is poorly recognized[195]. The binding affinity of an XPA-RPA complex for a DNA substrate containing a single 1,3-d(GpTpG) adduct is greater than that of RPA alone[185]. Furthermore, photo-crosslinking studies demonstrated that the p70 subunit of RPA can be crosslinked with high efficiency to DNA containing a single 1,3-d(GpTpG) intrastrand crosslink[185]. This is a particularly interesting finding given that when RPA and XPA are both present in reactions, only the RPA protein gets crosslinked to DNA[185]. These results suggest that RPA protein could play a major role in cisplatin adduct recognition. The amount of RPA binding to cisplatin modified DNA correlates with the ability of the protein to denature DNA[195]. RPA binds with higher affinity to unmodified single stranded DNA than to DNA containing a single 1,2-d(GpG) adduct. These results indicate that RPA binds to duplex DNA, causes denaturation of the DNA helix, and then binds preferentially to the undamaged strand. Studies have demonstrated that RPA can enhance the binding and excision activities of XPG and XPF-ERCC1 to bubble and loop structures[196], and it has been suggested that the proteins protect the undamaged strand from excision[197,198]. The preferential binding of RPA to the unmodified strand provides a structural basis for the direction of excision repair to the damaged strand.

**T4 endonuclease VII.** T4 endonuclease VII resolves branched DNA structures, such as four-way junctions and D-loops. T4 endonuclease VII recognizes and cleaves DNA containing a single 1,2-d(GpG) or 1,2-d(ApG) intrastrand cisplatin crosslink[199]. The same study shows that the 1,2-d(GpG) crosslink is the preferred substrate over the 1,2-d(ApG) crosslink, while the 1,3-d(GpTpG) adducts of *trans*-DDP are not recognized at all by the enzyme. T4 endonuclease VII also cleaves the interstrand crosslinks of both cisplatin and *trans*-DDP, however, the cisplatin interstrand crosslinks are cleaved more efficiently[200].

**Human Ku Antigen.** Ku is a DNA binding protein with affinity for the ends of double stranded DNA and DNA substrates containing small gaps and nicks that plays a role in double strand break (DSB) repair and V(D)J recombination. The Ku-DNA complex stimulates the catalytic subunit of the human DNA activated protein kinase (DNA-PK), whose substrates include RPA, p53, c-Jun, HMG1, and a variety of transcription factors. As it would be expected, cells deficient in DNA-PK activity are hypersensitive to cisplatin[201], and murine leukemia cells resistant to cisplatin have high

levels of Ku expression[202]. Biochemical studies have demonstrated that cisplatin intrastrand crosslinks inhibit the ability of Ku to stimulate DNA-PK in dose dependent manner, and the 1,2-d(ApG) adduct causes the greatest inhibition in comparison to the other crosslinks[203,204]. Adducts of *trans*-DDP are also capable of inhibiting Ku dependent DNA-PK catalyzation of target proteins *in vitro*[205]. From this perspective it is interesting to note that treatment with cisplatin prior to irradiation results in decrease in the repair of double strand breaks[206]. These observations have led Turchi *et al.* to propose that the antitumor activity of cisplatin is due to the fact that cisplatin sensitizes cells to ionizing radiation because the repair of the double strand breaks in impaired due to DNA-PK inhibition[205].

**HMG Box Proteins.** The high mobility group (HMG) domain is the common structural element of a large family of DNA binding proteins. Although they can be roughly divided into two groups based on their sequence specificities, common features of these proteins include the capacity to bend the DNA and their high affinity for non-canonical DNA structures. The first group includes HMG1, HMG2, the upstream binding factor (UBF), and the mitochondrial transcription factor (mtTFA), which all contain multiple HMG domains and recognize DNA with no sequence specificity. The second group contains sequence specific binding proteins such as the lymphoid enhancer-binding factor LEF-1 and the sex determining factor SRY.

Several of the HMG proteins, as well as the purified HMG domains of these proteins, recognize cisplatin adducts and they display selective affinity for the clinically effective platinum analogs. Moreover, they selectively bind the 1,2 intrastrand crosslinks and show no affinity for the 1,3-intrastrand cisplatin crosslinks. HMG box proteins that recognize cisplatin damage include the human and the *Drosophila* structure specific recognition protein 1 (SSRP1)[207-210], the non histone, chromatin associated calf HMG1[211-213], and HMG2[211,212], the rat HMG1[214], the *Drosophila* homologue of HMG1, HMG-D, the *Schizosaccharomyces pombe* Cmb1[215], UBF[216], mtTFA[217], the yeast transcription factor Ixr1[218,219], the mouse testis specific tsHMG[220], and the sex determining factor SRY[221]. The apparent binding affinities of these proteins for the various cisplatin adducts have been determined and they range for a single 1,2d-(GpG) adduct from 60 pM (UBF) to 370 nM (rat HMG1). Direct comparison of the binding affinities however can not be made because the $K_d$ values are sensitive to sequence context, the $K_d$ of HMG1 domain A for a single 1,2-d(GpG) adduct ranged from 1.67 nM to 517 nM depending on the sequence context[222].

HMG box proteins distort the DNA upon binding and they stabilize bend and supercoiled DNA. The HMG domain has an L-shaped fold involving three $\alpha$ helices. The same fold is observed in the NMR solution structures of LEF-1 and SRY bound to their cognate recognition sequences[223,224]. The domain binds in the minor groove and causes bending and unwinding of the DNA helix, resulting in the widened minor groove and a compressed major groove. An amino acid side chain, methionine and isoleucine respectively, intercalates into the DNA helix from the minor groove side at the site of the bend and stabilizes it. The complexes of *S. cerevisiae* HMG non histone protein 6A in complex with DNA containing the recognition sequences of SRY and LEF-1 have also been studied by NMR. In these complexes, the DNA architecture is distorted, and methionine and phenylalanine residues intercalate between adjacent base pairs, generating two kinks in the DNA. Finally, isoleucine intercalation is observed in the structure of the HMG domain of SRY in complex with a four-way DNA junction[225]. Taken together these results suggest that the intercalation of a hydrophobic residue into the DNA helix might be a common structural determinant for the interactions of HMG box proteins with DNA.

The crystal structure of rat HMG domain A in complex with DNA containing a single 1,2-d(GpG) intrastrand adduct was also solved[226]. The DNA is bend by 61° towards the major groove, and the minor groove is widened. Moreover, a phenylalanine side chain, Phe 37, intercalates through he minor groove into a hydrophobic notch generated by the destacking of the platinated guanines. A Phe37Ala mutation greatly reduced the affinity for the cisplatin modified DNA, consistent with the observation that intercalation plays an critical role in substrate recognition.

The structure of rat HMG1 domain A in complex with the 1,2-d(GpG) adduct might explain the previously puzzling observation that HMG1 recognizes the interstrand crosslink formed by cisplatin[200]. The structure of an interstrand crosslink of cisplatin reveals that the cytosines complementary to the platinated guanines are extrahelical[84,85]. It is possible that the HMG1 binds to the cisplatin interstrand crosslinks by intercalation in the DNA duplex in the space originally occupied by the cytosines.

**Histone H1.** Histone H1 binds to linker DNA in chromatin, and like HMG proteins have an affinity for bend and branched DNA structures. Recently it was shown that histone H1 also recognizes DNA modified with cisplatin. Histone H1 binds more strongly to cisplatin modified DNA that to DNA modified with *trans*-DDP, and with much higher affinity in comparison to HMG box proteins[227]. Most studies of cisplatin DNA damage to date have excluded chromatin modeling of DNA, but these results show that further experiments in this direction are clearly warranted.

**Photolyase.** Photolyase is a flavoprotein that uses UV or visible light (300-500 nm) to reverse the *cis-syn* pyrimidine dimers produced in DNA following UV irradiation. In the absence of photoreactivating light, photolyase binds to pyrimidine dimers and stimulates their repair by the Uvr(A)BC excinuclease[228]. An observation has been made in *E. coli* that suggests that photolyase could play a role in repair of cisplatin adducts. Cells expressing photolyase are more resistant to cisplatin treatment in comparison to photolyase deficient cells[229]. Accordingly, the *E. coli* photolyase binds to duplex DNA containing a single 1,2-d(GpG) intrastrand cisplatin adduct with high affinity ($K_d$ = 50 nM), and stimulates *in vitro* repair of this adduct by the Uvr(A)BC excinuclease[229]. Since photolyase bends the DNA helix by 36° when bound to UV damaged sites[230], it is likely that photolyase recognizes the bending in the DNA induced by the cisplatin adducts.

The DNA binding surface of the *Saccharomyces cerevisiae* photolyase has 50% homology with the *E. coli* enzyme. Yeast photolyase also recognizes cisplatin adducts, but it has no affinity for DNA modified with *trans*-DDP[231]. However, in contrast to the genetic results obtained in *E. coli*, the same study shows that *S. cerevisiae* photolyase deficient mutants are more resistant to cisplatin. Consistent with the lack of affinity of photolyase for *trans*-DDP, these cells are not differentially sensitive to *trans*-DDP. These results suggest that in yeast, photolyase might contribute to cisplatin toxicity, perhaps by a mechanisms similar to the abortive repair *(vide infra)*.

**TATA Binding protein.** The TATA binding protein (TBP) is a transcription factor required for initiation of transcription by all three eukaryotic RNA polymerases. The association of TBP with promoter sequences is slow and it may be the rate-limiting step in transcriptional activation. The crystal structures of human, yeast and *Arabidopsis Thaliana* TBP, in complex with their cognate TATA boxes reveal that TBP bends DNA by 80° towards the major groove. TBP recognizes UV or cisplatin damaged DNA[232,233]. Consistent with a transcription factor hijacking model, the presence of UV adducts inhibits transcription *in vivo*, and this inhibition is reversed by microinjection of TBP into cells[232]. Recently it was reported that the presence of a platinum adduct in the TATA box sequence significantly increases the affinity of TBP binding, presumably because of a reduced $K_{off}$ rate[233]. As it could be expected, the enhancement in binding affinity is maximized when the sites of platination and TBP intercalation overlapped. It follows that platination of promoter regions could result in upregulated transcription, or alternatively platination sites could interfere with transcription. For example, the presence of a single 1,2-d(GpG) intrastrand adduct in the estrogen response element decreases the affinity of the estrogen receptor for that sequence.

**Y Box binding protein.** The Y box protein is a transcription factor that binds to the inverted CCAAT element (Y box) in DNA. The Y box is located in the promoter sequences of many genes, such as PCNA, polymerase $\alpha$, and the multi-drug resistance gene 1 (*mdr1*). Cisplatin induces *mdr1* expression, and this induction can be attenuated by reducing cellular YB-1 levels[234]. Moreover YB-1 is over-expressed in cisplatin resistant cell lines, and reduction of YB-1 expression sensitizes cells to cisplatin[235]. In contrast to HMG proteins, YB-1 recognizes both the 1,2- and the 1,3-intrastrand crosslinks of cisplatin[236]. Because of the interaction of YB-1 with PCNA, it has been

speculated that YB-1 could mediate responses to cisplatin by interacting with the cellular repair machinery.

The structural distortions induced by cisplatin adducts provide a recognition signal for many cellular proteins. For many of these proteins roles have been assigned in which they modulate cellular responses in the wake of cisplatin damage including transcription factor hijacking, repair shielding and abortive repair. Many of these roles and models will be discussed in the following chapters.

## 4.2 Roles for cisplatin damage recognition proteins

**Transcription Factor Hijacking.** The human ribosomal RNA (rRNA) transcription factor UBF binds to a 1,2-d(GpG) cisplatin crosslink with a high affinity, $K_d$ = 60 pM[216]. The dissociation constant of UBF for its cognate promoter is 18 pM. The high affinity of hUBF for cisplatin adducts is attributed to the presence of multiple HMG boxes that contribute to binding in an additive manner[130]. The high affinity suggests that levels of cisplatin adducts that are well bellow those found in patients treated with the drug could be able to compete with the rRNA promoters for hUBF binding. hUBF binds specifically to DNA modified with clinically effective platinum drugs (cisplatin, $Pt(EN)Cl_2$, $Pt(DIEN)Cl_2$) and not to DNA modified with the ineffective *trans*-DDP and [Pt(DIEN)Cl]Cl[130]. Cisplatin modified DNA inhibits rRNA synthesis in a reconstituted system, and this inhibition can be reversed by the addition of excess of hUBF[216]. Cisplatin causes a redistribution of hUBF in the nucleolus of human cells similar to that observed after inhibition of rRNA synthesis, whereas *trans*-DDP does not[237]. The transcription factor hijacking model proposes that cisplatin adducts sequester hUBF away from its promoter, thereby disrupting the transcription of ribosomal genes that may be critical for cell survival. This model was tested *in vivo* using *S. cerevisiae* cells. The Ixr1 HMG box protein inhibits transcription of cytochrome *c* oxidase subunit V by binding to the Cox5b promoter. Cisplatin treatment does not affect transcription from the promoter, indicating that cisplatin adducts can not titrated away Ixr1 from the Cox5b promoter[238]. It is noteworthy, however, that the dissociation constant for Ixr1 binding to a single cisplatin adduct is 250 nM (about 4000-fold higher than hUBF), therefore the binding affinity for cisplatin adducts might not be able to compete with the Ixr1-Cox5b interaction.

**Repair Shielding.** *In vitro* repair assays have demonstrated that the excision of the 1,2-d(GpG), but not the 1,3-d(GpTpG) intrastrand crosslink is inhibited by the presence of HMG proteins (HMG1, mtTFA, tsHMG, SRY)[163,221,239]. The repair shielding model proposes that HMG box proteins mediate cisplatin toxicity by binding to cisplatin adducts, specifically the 1,2-intrastrand crosslinks, and shielding them from repair. As a consequence, the adducts persist in the DNA thereby potentiating their cytotoxicity. Consistent with this model, *S. cerevisiae* strains deficient in the HMG protein Ixr1 are 2-6 fold more sensitive to cisplatin and accumulate fewer cisplatin adducts[218,240]. The differential sensitivity to cisplatin is abolished in an excision repair deficient background, suggesting that Ixr1 can shield cisplatin adducts from repair *in vivo*. In contrast, *cmb1*deficient *S. pombe* cells are more sensitive to cisplatin than wild type cells[215]. Therefore, there is no unified mechanism for the role of HMG box proteins in cisplatin toxicity, some such as Ixr1 appear to potentiate toxicity, whereas others such as Cmb1 appear to play a protective role.

## 4.3 Resistance to cisplatin

One of the most significant drawbacks to cisplatin therapy is the development of clinical resistance. There are two types of resistance to cisplatin, one is an acquired phenomenon that occurs in tumors following exposure to the drug, and the second is an intrinsic resistance of tumors from the very onset of the cisplatin treatment. Numerous cisplatin resistant cell lines, most of which have been developed by repeated exposure to cisplatin, as well as resistant tumors isolated from patients have been studied and have revealed a variety of molecular mechanisms that

contribute to this phenomenon including[241]: altered drug uptake levels, inactivation of cisplatin by cellular thiols, and enhanced repair of cisplatin adducts. [242-244]

**Altered drug uptake as a determinant of cisplatin cellular sensitivity.** Reduced intracellular accumulation of cisplatin, which may arise because of decreased uptake or increased efflux, is frequently observed in cisplatin resistant cell lines[245-247]. To date the exact mechanism by which cisplatin is taken up by the cells is not fully understood[248,249]. The rate limiting factor for cisplatin uptake is its concentration and uptake is not inhibited by structural analogs and it is can not be saturated, suggesting that cisplatin enters the cells by passive diffusion. In contrast, a variety of pharmacological agents that do not alter the permeability of the membrane inhibit cisplatin uptake. The sodium-potassium ATPase inhibitor ouabain inhibits uptake, and the cisplatin accumulation is potassium dependent, even though cisplatin is not transported into the cells through the sodium-potassium pump, indicating that accumulation is dependent on cell membrane potential[250-252]. Moreover, a number of aldehydes inhibit uptake, presumably by forming Schiff bases with membrane proteins.

The level of platinum accumulation has also been examined in several different cell lines with acquired cisplatin resistance, but the results have been inconsistent. A variety of cell lines that have acquired resistance to cisplatin have shown increased accumulation of the drug. Other studies have shown enhanced efflux of cisplatin for resistant cell lines. For example, a study showed that resistant epidermoid KB carcinoma cells have higher efflux of cisplatin[253]. Along the same lines intracellular accumulation was 1.6-fold greater in a cisplatin sensitive testicular nonseminomatous germ cell line[254]. In contrast, for small cell lung carcinoma sublines no difference in intracellular accumulation was found between cisplatin sensitive and resistance sublines[255]. Human head and neck squamous cell carcinoma the resistant cells had a reduced capacity to take up cisplatin, whereas release of the drug was similar to the original cell line[256]. Some murine leukemia L1210 cells displayed a 40-50% reduction in drug accumulatin[155,257], while in other drug uptake was reduced[258,259]. To complicate the matter further, a study demonstrated that there was essentially no difference in the amount of cisplatin taken up by the nucleous and the amount of cisplatin bound to DNA was similar in sensitive and resistant L1210 cells[260]. Inconsistencies in platinum accumulation levels have also been observed in ovarian cell lines: one study showed a 50% decreased level of accumulation of cisplatin in a resistant cell line [261], while another showed a decrease of accumulation parallel with the level of resistance[262]. A study that examined varied selection conditions for the generation of cisplatin resistant ovarian sublines, observed that the resulting resistant sublines varied by 48% in their capacity to accumulate cisplatin depending upon the selection used[263]. Yet another study made the observation that although the rate of drug accumulation was similar between the resistant and sensitive sublines the resistant subline was better at effluxing cisplatin, possibly as the outcome of enhanced repair capacity[246]. Taken together, these studies make it difficult to draw a decisive conclusion on the level of cellular uptake as a determinant of cisplatin cytotoxicity.

**Inactivation of cisplatin by cellular thiols.** Resistance of cisplatin because of increased inactivation by intracellular proteins has also been reported and recently reviewed[244,249]. Glutathione (γ-glutamylcysteinylglysine, GSH) is the most abundant thiol in cells present in 0.5-10 mM concentrations[241]. Cisplatin can be covalently linked to GSH after a nucleophilic attack of the thiolate anion, and this complex can be transported out of the cell by an ATP-dependent pump[264]. Conjugation with GSH inhibits the conversion of monoadducts to crosslinks, thereby reducing the cytotoxic potential of the adducts. In addition, GSH might protect cells from cisplatin toxicity by maintaining the dNTP pool size needed for DNA repair and by maintaining functional repair enzymes such as polymerase $\alpha$[265]. Interestingly, elevated GSH levels have been found in some cisplatin resistant cell lines and depletion of GSH by D,L-buthione-(*S*,*R*)-sulfoxime (BSO) increased cisplatin sensitivity in some, but not all cell lines tested[255,266-268]. (BSO inhibits the enzyme γ-glutamylcysteinylglysine synthetase responsible for GSH synthesis.) Experiments in several cisplatin-resistant cell lines, including human small cell lung carcinoma[255], various ovarian tumor sublines[263,269-271], murine leukemia L1210 cells[257,268], and human colon carcinoma line[272] have

determined increased cellular levels of GSH and the total amount of sulfhydryl compounds that correlated well with the cisplatin-resistance. In some cases the resistance to cisplatin could be reversed by treatment with BSO[263,268], however in other cases the addition of BSO had no effect on the resistance of others[257,267]. Finally studies with human testicular nonseminomatous germ cells observed no difference in GSH levels between resistant and sensitive cells[273]. Taken together this inconsistent data obtained with GSH studies suggests that although GSH levels are of importance for the cellular resistance to cisplatin they are unlikely the determinant.

Metallothioneins are a family of cyteine rich proteins involved in $Zn^{2+}$ homeostasis and in the detoxification of heavy metals such as cadmium[241]. Metallothioneins bind to cisplatin in a ratio of 1:10 and may modulate the cellular responses to the drug. Metallothionein deficient mouse fibroblasts are more sensitive to cispaltin[274], over expression of metallothionein can sometimes cause resistance to cisplatin[275], and conversely cell lines that have acquired resistance to cisplatin over express metallothionein[276]. Moreover, cadmium resistant cell lines over express metallothionein and are cross resistant to cisplatin[277,278]. In contrast, cisplatin resistant cell lines are slightly cross resistant to cadmium or show no resistance. In addition, analysis of the amount of metallothionein content is not a major determinant of sensitivity to cisplatin based chemotherapy[279]. Much like the situation with GSH there are various cisplatin-resistant cell lines with elevated metallothionein levels[254,256], and also there are cisplatin-resistant cell lines where there seems to be no correlation between metallothionein levels and cisplatin resistance[258,280].

**Regulatory proteins.** Alterations in the expression of oncogenes (such as *fos, ras, jun, v-abl, myc,* etc.) and tumor suppressor genes (p53) have also been implicated in the cellular resistance to cisplatin. Since a change in the expression of these genes can have pleiotropic effects on cellular homeostasis, the mechanism underlying resistance is not entirely understood. Overexpression of *ras, fos, c-jun* and *myc* increases resistance to cisplatin, and down-regulation of *c-jun* sensitizes cells to cispaltin[242]. *c-fos* modulates the expression of genes that have the AP-1 (fos/jun complex) binding domain, such as *c-myc*, metallothionein, and DNA polymerase β. The expression of metallothionein and DNA polymerase β can also be modulated by *H-ras*.

Because of its association with high frequencies of mutations in the p53 gene in human cancers the transcription factor p53 has been well studied[281,282]. The tumor suppressor gene p53 is involved in cell cycle control, DNA repair and apoptosis. p53 also acts as a transcriptional regulator for a number of genes including MDM2, Bax, GADD45, possibly p48, cyclin G and p21. Activation of p53 by DNA damage can lead to cell cycle arrest at G1 and G2/M phases and it can trigger apoptosis. These mechanisms help maintain genomic stability presumably by extending the time available to repair the damage[283]. p53 mutations occur in about half of human cancers and loss of p53 mediated apoptosis can lead to cancer genesis. It is of interest to note that testicular tumors do not contain mutated p53 genes[282,283]. Consequently, a defect in p53 can have pleiotropic effects in the cellular sensitivity to cisplatin. Lymphoma cells, ovarian cancer cells, and lung cancer cells mutated in p53 are more resistant to cisplatin[284-286], presumably because of the inactivation of p53 related apoptotic responses. In contrast, $p53^{-/-}$ mouse fibroblasts are more sensitive to cisplatin than wild type cells[287], and p53 inactivation of p53 in human foreskin cells, breast cancer MCF-7 cells, and colon cancer cells sensitizes them to cisplatin[287,288], presumably because these cells are not as susceptible to apoptosis and p53 can facilitate repair and extend the time available for repair. However, there are studies that suggest that p53 and cisplatin cytotoxicity are unrelated, the cisplatin sensitivity of a panel of nine ovarian cancer cell lines[289] and a mouse testicular teratoma[290] did not correlate with their p53 status.

The regulatory protein p21 (WAF1/Cip1) is under regulatory control of p53 and it is involved in negative regulation of G1 cell cycle arrest[281,282]. Overexpression of p21 in glioblastoma cells conferred resistance to cisplatin and the alkylating agent 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) presumably because it allowed for enhanced repair of the DNA damage[291]. Cisplatin sensitivity was also observed in p21 deficient human colon cancer cells and mouse embryonic

fibroblasts[292] and p21 loss was associated with debilitated capacity for repair of cisplatin DNA lesions.

GADD45 is another gene product that is regulated by p53 and GADD45 is associated with G1 cell cycle arrest as well as DNA repair because of its association with PCNA[281,282]. A study where GADD45 expression was blocked by antisense vectors revealed that the cells exhibited altered levels of DNA repair and hypersensitivity to cisplatin[293].

A prominent cellular role for p53 is the triggering of apoptosis. p53 can stimulate the expression of Bax and promote apoptosis, and it can repress the expression of Bcl-2, a protein that inhibits apoptosis, and by affecting the relative ratios of these proteins affect apoptosis[281,294]. Cisplatin resistant ovarian cell lines have reduced levels of Bax mRNA[286]. A study showed that cisplatin treatment upregulates the expression of a 21 kDa Bax isoform while the levels of Bcl-2 and a 24 kDa Bax isoform remained unchanged[295]. The 21kDa isoform of Bax is not constitutively expressed and it could be expressed or stabilized as a direct response to DNA damage. As expected, overexpression of Bcl-2 confers cisplatin resistance, most likely due to its capacity to inhibit apoptosis[285,296,297].

P53 could be involved in mediating cisplatin cellular responses by interacting with proteins that recognize cisplatin damage. Such as interaction could possibly trigger downstream signaling cascades and apoptotic responses. P53 interacts with HMG1 protein as well as TATA binding protein (TBP)[298,299].

**Enhanced DNA repair as a mechanism for acquiring cisplatin resistance.** Cell lines selected for resistance to cisplatin after prolonged culture in the presence of cisplatin have significantly higher levels of repair than the corresponding parental cell lines, indicating that DNA repair is an important determinant of cisplatin resistance[246,247,300,301]. Differential capacity to repair cisplatin adducts is postulated to be responsible for the variability in clinical response to cisplatin based chemotherapy[302]. However, protein extracts from ovarian tumor biopsies vary in their abilities to repair cisplatin adducts by up to 10 fold, and this variability in repair capacity is an intrinsic property of the tumor and does not correlate to the repair capacity of the non-tumor cells from the same individual[303]. In general, even though ovarian cancer patients have initially high response rates to chemotherapy, frequently resulting in complete remission, they often relapse and their tumors become refractory to subsequent chemotherapy. Interestingly, the sensitivity of ovarian carcinoma xenographs established from the same patients at different stages of the disease reflected the responsiveness of the patient to chemotherapy[304], underscoring the usefulness of cell culture studies. Along the same lines, a cell line established from the tumor of an ovarian cancer patient that was not responding to chemotherapy had a three fold higher repair synthesis activity than the cell line established from the tumor of the patient prior to the onset of resistance[305]. A similar increase in repair is observed in cells of an oligodendroglioma obtained after the onset of resistance as compared to tumor cells obtained before therapy. The increase in repair is correlated with higher expression levels of DNA polymerase $\beta$[306].

Cell lines established from testicular tumors appear to be more sensitive to cisplatin than the other cultured cell lines, reflecting the clinical responsiveness of these tumors to treatment with the drug. For example, testicular tumor cells are, on the average, 4 fold more sensitive to cisplatin than bladder tumor cell lines[307]. Moreover, following 18 h of incubation after cisplatin treatment, five out of six testicular teratoma cell lines (including the SuSa call line) had adduct levels similar to those observed immediately after treatment, indicating that these cell lines have a significantly reduced capacity to remove cisplatin adducts[307,308]. The repair proficient line 833K was established from a patient that had received platinum based chemotherapy and had higher polymerase $\beta$ levels. Similar experiments from a different group indicate that the 833K cell line is repair deficient, and that the SuSa cell line is repair proficient[309]. Accordingly, SuSa cells and repair proficient cells were capable of reactivating adenovirus DNA modified with cisplatin to a similar extent[310]. These differences may be attributed to the different concentrations of cisplatin

used in the first two experiments (17 μM vs. 50 μM) and/or the different time of analysis (18 h vs. 48-72 h). Similar observation was made in a testicular nonseminomatous germ cell line where the observed difference in repair between the cisplatin resistant and sensitive sublines was attributed to an inherent rather acquired reduced capacity for repair[254]. Consistent with the hypothesis that testicular tumors have low capacity for repair of cisplatin adducts, extracts from three testicular tumor cell lines (including 833K) support low levels of excision of a 1,3-d(GpTpG) cisplatin adduct[192]. Western analysis indicated that even though the testicular tumors have high levels of most repair proteins, such as RPA, XPG and XPC, they have low levels of XPA and ERCC1-XPF. Moreover, addition of these proteins in the reaction stimulated repair of the adduct, suggesting that testicular tumors are deficient in nucleotide excision repair and therefore less able to tolerate cisplatin induced damage. Studies parallel to this work have shown that DNA repair proteins, such as XPA, XPE, ERCC1 and the aforementioned DNA pol β are overexpressed in resistant cell lines[180,191,311,312].

Even though small cell lung cancer (SCLG) has a very aggressive clinical course with median survival after diagnosis of only two to four months, it is more responsive to chemotherapy than non-small cell lung cancer. Accordingly, primary and established non-small cell lung cancer cell lines are more resistant to cisplatin, and they have a higher overall capacity to repair cisplatin adducts as measured by the their capacity to reactivate cisplatin damaged plasmid DNA[313-315].

**Adduct tolerance and replication bypass.** A study of a panel of human ovarian cell lines derived from patients who were or were not treated with cisplatin based chemotherapy revealed that adduct level tolerance correlated well with sensitivity to cisplatin[316,317]. Moreover, a report has demonstrated that cisplatin resistant cells have a 2.3-4.5 fold higher capacity for replicative bypass and adduct tolerance than the corresponding cisplatin sensitive parental cells[318]. A study in murine leukemia L1210 cells showed that resistant cells have capacity for replication bypass and adduct tolerance[319]. Enhanced replicative bypass and adduct tolerance could lead to a requirement for higher levels of adducts in order to trigger apoptotic responses or other cell death triggering mechanisms.

From the presented discussion is apparent that cisplatin resistance is a consequence of complex cellular interactions that involve many factors. Perhaps the best conclusion to the complex cellular responses described above is the result of a study in EMT-6 murine mammary tumors that were isolated *in vivo* as cisplatin-resistant clones[320]. When this subline was established *in vitro* the cisplatin-resistance was abolished. However, when the tumors were implanted back into mice the resistance in these tumors was reintroduced. These results clearly indicate that some mechanisms of resistance clearly depend on factors that are only present *in vivo*.

## Chapter 5. Mismatch Repair and Cisplatin

Mismatch repair (MMR) is a specialized DNA correction system that plays several distinct roles in the maintenance of genomic integrity. MMR corrects polymerase errors such as mismatches and insertion or deletion loops that arise during replication[20,321]. In addition, MMR proteins ensure the fidelity of recombination events by preventing recombination between heterologous DNA sequences, and by correcting mispairs that arise during recombination[20,321,322]. In eukaryotes, mismatch repair proteins also play a role in apoptotic signaling and cell cycle regulation[16,323].

Although the most extensively studied mismatch repair system to date is the *E. coli* MutHLS-dependent pathway - the first evidence for the mismatch correction was obtained in studies with *Streptococcus pneumoniae,* where a series of *hex* mutants were isolated that allowed high-efficiency recipients in transformations with any DNA donor marker and that were deficient in mismatch correction. It is believed that during DNA replication the interruptions present on the nascent DNA strand are signals for the Hex MMR system to target removal of misincorporated bases in the newly synthesized strand.

A different mode of strand discrimination characterized and understood more in detail is employed in *E. coli* by the MutHSL system. In 1975, Marinus and Morris found a spontaneous mutator phenotype to be associated with inactivating mutations in the DNA adenine methylase (*dam*) gene of *E. coli*[324]. This gene encodes for a DNA methyltransferase that methylates adenine in GATC sequences. Therefore, transiently unmethylated GATC sites in the nascent strand present immediately after DNA synthesis could serve a signal for the post-replicative MMR apparatus to discriminate between template and the newly synthesized DNA strand. A number of observations support this hypothesis. Genome-wide alteration of GATC methylation in *E. coli* results in increased spontaneous mutation rates and *in vitro* experiments have shown that repair is strongly biased towards the unmethylated strand[325,326].

The discovery of protein factors involved in MMR were elucidated by detailed genetic characterization of mutants that showed mutator phenotypes. Mutations that inactivated four genes in *E. coli, mutS, mutH, mutL*[327], and *uvrD*[328] correlated with a deficiency in MMR and were found to give rise to high spontaneous mutability in an epistatic manner. Later, an *in vitro* MMR assay developed by Modrich and co-workers allowed the biochemical dissection of the pathway and of the protein functions involved which culminated with the reconstitution of the of the entire methyl directed mismatch repair reaction with purified proteins[329,330]. The understanding gained from these studies has given rise to the at present most comprehensive current model for MMR discussed in the following paragraphs.

A key step in the mismatch repair mechanism of action involves the recognition of the mispair and, in bacteria, where mismatch repair is best understood, this task is accomplished by the homodimeric MutS protein[321]. The binding of a MutS dimer is followed by nucleotide hydrolysis, and experimental evidence suggests a scenario where the ATP binding and hydrolysis is required for the induction of conformational changes that lead to the association with a homodimer of the MutL protein and the translocation of DNA along or through the MutS-MutL complex[331-333]. This translocation has been visualized by electron microscopy as the formation of protein stabilized $\alpha$-shaped double stranded DNA loop structures in which MutS colocalizes with MutL at the base of the nascent loop[333]. In the presence of ATP the MutS-MutL complex protects about a 100 bp region from digestion by DNase I, which is considerably larger than the MutS homodimer alone[331]. The ATP dependent translocation mechanism might allow coordinated interaction between the MMR recognition complex and the nearest hemi-methylated GATC site. This results in association with, and the activation of a latent MutH endonuclease, which will incise at unmethylated GATC sites and thus initiate the excision process[334]. A significant observation regarding strand discrimination

by the MutHLS system is that the requirement for MutH endonuclease can be obviated *in vitro* by the introduction of strand-specific nick located up to 1000 bp from the mismatched site[335]. Once initiated by the MutS, MutL, and MutH proteins the repair reaction proceeds by exonucleolytic degradation of the nicked DNA strand form the incised GATC site towards and past the mismatch, followed by DNA resynthesis and ligation. *In vitro* reconstitution experiments have shown that the excision and resynthesis steps can be bi-directional and require the functions of UvrD (MutU) helicase II, exonuclease I, exonuclease VII or RecJ, DNA polymerase III holoenzyme, single stranded DNA binding protein (SSB), and DNA ligase[330,332,336].

The identification of MutS and MutL homologues in eukaryotes from unicellular yeast to mammals, suggests that the key components of the bacterial mismatch correction system have been conserved from throughout evolution, and it is thought that the mechanistic principles of post-replicative MMR mirror those of the bacterial prototype. The major differences lie in the multiplicity and heterodimeric organization of the MutS and the MutL factors, indicating a higher complexity of the eukaryotic system. Mismatch recognition in eukaryotes is mediated by either of two heterodimers of MutS homologues (MSH): MutS$\alpha$, a complex formed by MSH2 and MSH6, and MutS$\beta$, a complex formed by association of MSH2 and MSH3 homologues. The eukaryotic mismatch recognition complexes are lesion specific, MutS$\alpha$ preferentially recognizes one base mismatches, while MutS$\beta$ is primarily involved with the recognition of insertion and deletion loops (IDL's)[20,321]. The MSH1, MSH4 and MSH5 homologues do not contribute to mismatch correction in nuclear DNA. MSH1 is involved with MMR correction in mitochondria. The MSH4 and MSH5 homologues have diverged to play a role in meiotic recombination and crossover [323]. The functions of MSH4 and MSH5 are discussed in more detail in Chapter 12.

The role of ATP resembles observations made with the bacterial pathway, indicating that a similar strategy of initial mismatch processing, including the formation of an $\alpha$-loop structure, might be employed by the eukaryotic system. In this scenario, the $\alpha$-loop structure would be stabilized at its base by MutS$\alpha$ or MutS$\beta$ in complex with MutL$\alpha$, which is a heterodimer of two MutL homologues (MLH1 and PMS2 in humans or PMS1 in yeast). The lack of evidence for eukaryotic homologues of MutH and the absence of DNA methylation in yeast and *D. melanogaster*, coupled with the irregular distribution of cytosine methylation in higher eukaryotes, suggests a strand discrimination mechanism distinct from the methylation-directed mechanism described for *E. coli*. As in *Strep. Pneumoniae*, directionality appears to be imparted by the presence of DNA strand-specific nicks insuring that, during DNA replication, mismatch correction would be directed by DNA ends in leading stand synthesis or nicks between Okazaki fragments in lagging strand DNA synthesis[337-339]. Exonucleolytic degradation of the incised strand can be bi-directional, and it involves either a 5'-3' or 3'-5' exonucleases[330,339]. One 5'-3' exonuclease, the *exo I* product in *S. pombe* and its homologues in *S. cerevisiae* could be genetically and physically associated with the mismatch repair process[340]. The gap filling reaction is most probably carried out by DNA polymerase $\delta$[341], and the nick is sealed by DNA ligase I. In addition, proliferating cell nuclear antigen (PCNA), has been shown to be involved in steps proceeding DNA synthesis in mismatch correction, which may indicate an association of mismatch repair components with the replication apparatus[342], although the nature of this interaction is unclear.

A common parameter for the recognition of mispairs by the MMR cellular apparatus is the nature of the DNA structural alterations imposed by mispairs. This is particularly important because of the discussion of the nature of interactions of MMR proteins with DNA modified to contain cisplatin lesions. With the caveat that MMR efficiencies measured *in vitro* and *in vivo* truly reflect the mismatch recognition capacities, the mismatch repair systems has demonstrated to correct G/T, A/C, G/G, and A/A mismatches and IDL's consisting up to four unpaired bases with high efficiency, and T/T, C/T and G/A mismatches with intermediate and variable efficiencies, while C/C mismatches and larger IDL appear to be very poor substrates for MMR[343]. Thus, allowing for some sequence context dependent variability purine-purine, purine-purimidine and small IDL's are more effective substrates for MMR rather than pyrimidine-pyrimidine mismatches and larger IDLs. This observations seems to be universal, a similar general trend has been observed for the *E.*

*coli* MutHLS system, the Hex-pathway in *Strep. Pneumoniae,* for eukaryotic MMR systems in yeast[344], and for the activity present in mammalian cell extracts[337-339,345]. The best repaired mispairs form Wobble base pairs which may cause a rigid deformation of the helix (note the similarity to cisplatin adducts), whereas the most poorly repaired mispairs fall into the group of open or unstacked mismatches, local instabilities are poorly recognized.

Since the primary role of MMR is to correct polymerase errors that occur during replication, a reasonable expectation would be that the profile of affinity of MMR for mispairs should correlate with the spectrum of mistakes generated by DNA polymerase during replication. Indeed, the mutational spectra displayed by the *E. coli mutH, mutS, mutL* mutants are similar to those derived from errors of the DNA polymerase III holoenzyme, and mispairs that are most frequently generated by DNA polymerase III are repaired with the highest efficiency. The multiplicity of MutS-related proteins in eukaryotic cells suggests that during evolution the mismatch recognition function has been refined to accommodate the demands of the increasingly complex genomes. The features of the *E. coli* MutHLS system are well preserved in eukaryotes with two major differences. The first concerns the strand discrimination function. Unlike the methylated GATC sites there appears to be no signal in eukaryotic cells that could direct the MMR machinery towards the nascent strand. There are however two possibilities that are being pursued in the literature, one involves PCNA which could physically link the mismatch and the replication proteins and the other, at are nick and gaps in the nascent strand switch could direct repair in a Hex-like fashion. The second important difference is that the MutS and MutL homologues in eukaryotes are hetero rather than homodimeric. However, following the publication of the crystal structure of MutS it was revealed that MutS is a structural heterodimer, with both monomers performing different functions. In yeast and mammalian cells there are six known MutS homologues and three have been shown to engage in pairwise interactions that relevant for mismatch correction. The eukaryotic mismatch recognition complexes are lesion specific, MutSα preferentially recognizes one base mismatches, while MutSβ is primarily involved with the recognition of insertion and deletion loops [20,321].

**Mismatch repair modulates cellular responses to cisplatin.** It is becoming evident that the mismatch repair correction system also addresses chemically induced DNA adducts or lesions that mimic the structure of mispaired Watson-Crick bases. A strong stimulus for investigating the impact of cellular DNA repair activities on the various types of chemically induced DNA adducts has come from the development and application of genotoxic agents for cancer chemotherapy. The central observations in this regard were positive correlations between mismatch repair deficiency and tolerance to several DNA damaging agents, the most important of which is cisplatin. These observations were made in both prokaryotic and eukaryotic systems. In 1982, Karran and Marinus reported that the hypersensitivity of *E. coli dam* (methylation deficient) mutants to alkylating agents was abrogated by the introduction of additional mutations in the mismatch repair genes MutS or MutL[13]. Later, in 1985 this phenomenon was reported for cisplatin as well[14]. In parallel, in 1986, Goldmacher *et al*[346] demonstrated that a human cell line TK6, can be induced to alkylation tolerance by treatment with acrydine. They speculated that this acquisition of alkylation tolerance could be a result of deficiency in mismatch repair. The hypothesis formulated by these studies was verified later and it has been established that that tolerance to cisplatin and alkylation agents (and other DNA damaging drugs) seems to be a basic characteristic of MMR deficient cells.

Ovarian carcinoma cell lines selected *in vitro* for cisplatin resistance are defective in mismatch repair, with the same phenotypic consequences described for cell tolerant to methylating agents[347-349]. The acquired resistance caused by inactivation of mismatch repair appears to be clinically relevant, as MSH2$^{-/-}$ human xenograft tumors were shown to be significantly less responsive to cisplatin treatment than MSH$^{+/+}$ tumors [350].

Biochemical observations have indicated that human mismatch repair proteins, the purified native heterodimer hMutSα[18] and the over-expressed hMSH2 subunit alone[17] might specifically recognize the major cisplatin adduct, the 1,2-d(GpG) intrastrand crosslink. Interestingly, the hMSH2[17] and some of the other mammalian MutS homologues are overexpressed in testicular and

ovarian tissue, the tumors of which are most responsive to cisplatin treatment. If indeed, the levels of mismatch repair reflect the cells capacity to interact with cisplatin adducts and thus interfere with their repair, these data might support the idea that cisplatin kills cells by either provoking mismatch repair or because MMR proteins shield cisplatin adducts from nucleotide excision repair.

Nucleotide excision repair is more efficient when the guanines from the cisplatin intrastrand adduct are mispaired with thymines (one or both)[164]. This stimulation of NER repair efficiency was observed with hMutS$\alpha$-deficient cell extracts, arguing against direct involvement of the MMR system in the processing of such lesions. These observations were corroborated by another study in which hMutS$\alpha$ was found to have reduced affinity for a G:T mismatch in the context of a cisplatin crosslink[351]. This is an apparent contrast to reports regarding the binding of hMutS$\alpha$ to matched platinated DNA[17,18,352] and would suggest that although mismatch repair recognition factors interact with cisplatin adducts they seem to be unimportant for processing of the lesions by NER.

Another proposed mechanism by which MMR proteins could modulate cisplatin cytotoxicity involves MMR as a form of interference *in vivo* in a replication-associated physical competition between MMR proteins and other cisplatin recognizing factors including HMG box proteins. It is not clear if and how, MMR, HMG-box or other proteins or other cellular factors could modulate NER, but they could either facilitate lesion processing and removal by attracting repair factors or inhibit correction by shielding the adducts. Another possibility is that MMR proteins once they interact with the cisplatin adducts during the process of replication could block translesion synthesis by directly or indirectly staling the polymerase.

Since replication bypass at the sites of cisplatin DNA lesions has been described, mismatch repair could enter the scene following replication, after a DNA polymerase bypasses a cisplatin adduct and incorporates a mismatch opposite the crosslink. MMR proteins would then bind this compound lesion and attempt repair of the mismatch. However, their activity would be directed to the newly synthesized strand - the cisplatin adduct would remain opposite and a new cycle of synthesis would again result in the incorporation of the mismatch opposite the cisplatin crosslink. Following the new synthesis MMR proteins would again attempt repair of the lesion, leading to a cycle of futile repair attempts that would ultimately result in strand breaks and cell death. One prediction based on this model is that inactivation of MMR should lead to an increase in cellular tolerance to cisplatin adducts because of improved, but more promiscuous translesion synthesis (and more efficient repair by NER) which should be manifested by a cisplatin induced hyper-mutability phenotype. This hypothesis is supported by the evidence that human cells lines, especially ovarian cancer cells, acquire resistance to cisplatin concomitantly with the appearance of spontaneous or selected MMR inactivating mutations[347-349].

The main trust of the work in this thesis focused on elucidating yet another cellular mechanism by which mismatch repair could modulate the cellular responses to cisplatin, namely through its role in recombination.

# Chapter 6. Recombinational Repair of Post-Replicative DNA Damage

Recombinational DNA repair represents cross-roads where virtually every aspect of DNA metabolism comes together. Homologous genetic recombination is an essential biological process that involves the pairing and the exchange of DNA between two homologous chromosomes or DNA molecules. It is of fundamental importance to the preservation of genomic integrity, the production of genetic diversity and the proper segregation of chromosomes. Because our studies involving recombination were carried out with prokaryotic enzymes this survey will focus on bacterial recombination, particularly from the perspective of recombinational repair of DNA damage. In *E. coli* the RecA protein is essential to recombination, and biochemical analysis demonstrate that it is responsible for the crucial steps of homologous pairing and DNA strand exchange. The presence of RecA-like proteins, or their functional equivalents, in all organisms from bacteriophage to mammals confirms that the mechanisms of homologous pairing and strand exchange is conserved through out all forms of life.

General genetic recombination involves the exchange of homologous regions between two chromosomes of double-stranded DNA molecules. The resulting recombinant DNA contains genetic information originally present in each of the parental molecules. Genetic studies have demonstrated that in *E. coli* there are several recombination pathways with many proteins involved in the process. One of these, the RecA protein is conserved from bacteriophage to humans and it plays a central role in the process. Initially the RecA gene was discovered by virtue of the strong effects of *recA* mutations on conjugal recombination. Subsequent to this discovery, the RecA protein was shown to be essential for homologous recombination and for induction, following DNA damage, of the SOS response.

Given that cisplatin adducts present a strong block to replication, of particular interest for the work in this thesis is the role of recombination in the repair of replication forks halted at DNA damage. The first suggestion that replication forks might collapse at the site of a DNA strand break came in 1974[353]. The general idea that replication fork progress is halted by various types of DNA damage is now supported by an array of experimental observations[354]. The response to a UV challenge, for example, provides ample evidence that DNA damage halts the progress of replication forks. UV triggers a transient pause in DNA synthesis[355], and DNA fragments produced after UV irradiation have sizes that correspond to the average inter-dimer distance in the template strands, as though the replication forks halted and then started up again to leave discontinuities[356].

The recombinational pathways in *E. coli* summarized on Figure 6-1. The pathways shown are an oversimplification in more than one respect. There are more than two pathways of recombinational DNA repair, along with overlapping pathways and pathway variants. There are also many more steps and proteins involved in the individual pathways. The recombinational functions of recombinational repair can be viewed as an adaptable and changing assemblage that can address a wide variety of DNA structural realities. The hierarchy of pathways and enzymatic activities defined to date for conjugational and transductional recombination reflect the DNA substrates presented to the cell under those specialized conditions, and need not be exactly replicated in recombinational repair.

Once a replication fork halts at a DNA lesion it is believed to disassemble[9]. Direct evidence for this outcome is limited. DNA polymerase are halted by a variety of DNA lesions *in vitro*, and this interruption is followed by a polymerase dissociation[357]. However, these are simple models that do not reproduce a complete replication fork. At a minimum, the disassembly of a stalled replication fork is logical, but the available evidence is insufficient to preclude the possibility that stalled replication forks remain partially or entirely intact under some circumstances. The repair of DNA gaps which are generated when a replication fork encounters a DNA lesion follows a pathway dependent on the RecF, RecO, and RecR proteins. At least one major function of these

proteins is to modulate the assembly of the RecA protein filaments in the single-stranded gap. RecA filaments assemble and disassemble 5' to 3' in an end-dependent fashion, with a protein being added at one end and deleted at the other[358]. Certain mutants of RecA protein suppress the defects of recFOR mutants[359-361]. *In vitro* work to date indicates that the RecR protein forms alternative complexes with RecO and RecF, and these complexes perform different functions. The RecOR complex facilitates the binding of the RecA protein to SSB-coated DNA[362] and prevents the end-dependent disassembly of the RecA filament[363]. The recFR complex binds primarily to double-stranded DNA and can prevent excessive extension of the filament into the adjoining duplex DNA[364]. If this activity of RecFR complexes near the gaps where they are needed. Neither RecF protein nor RecFR complexes bind specifically to the ends of DNA gaps *in vitro*[364]. A stalled replication complex would be positioned in part in the exact position where the RecFR complex would be required to modulate RecA filament assembly, and an interaction of RecFR with replication proteins is an intriguing possibility. The importance of the of the RecFOR proteins in a RecA filament assembly can be seen in the RecA-mediated induction of the SOS response, which is delayed in *recFOR* strains[365,366].

Repair of double-strand breaks resulting from an encounter of the fork with a nick or direct chemical damage is dependent on the RecBCD enzyme and follows a pathway outlined in Figure 6-1. Large parts of this pathway have been reconstituted *in vitro* by Kowalczykowski and his coworkers[367-369]. In short, the RecBCD enzyme binds to a double-stranded DNA end, unwinds the DNA and degrades the two strands asymmetrically, with a 5'-end remaining intact. Upon encountering a octamer sequence named *chi*, the polarity of the nuclease changes and now the 5'-tail is preferentially degraded. The result of the RecBCD activity is the formation of a 3' single-stranded DNA tail. RecBCD facilitated the loading of RecA protein on the prepared single strand[368]. A RecA mediated strand invasion and strand exchange then follows.

The *chi* sites recognized by the RecBCD enzyme function in only one orientation relative to the RecBCD enzyme unwinding and degrading a linear DNA from one end[370]. In the *E. coli* genome, the *chi* sites are highly over-represented[371-373]. Furthermore, most of the *chi* sites are oriented so that they would alter the activity of RecBCD enzymes moving only in the direction toward oriC[371,372,374]. The *chi* sites are therefore positioned to function in recombinational DNA repair[354], and this is true regardless of which template strand is broken. The *chi* sites can modulate the activity of a RecBCD enzymes entering a linear DNA molecule at the site of a replication generated double-strand break, and are spaced to prevent extensive degradation of the chromosome by RecBCD. The *chi* sites also appear to be located within islands of sequences shown to be the preferred DNA binding sites for the RecA protein[373]. The evolution and conservation of this highly facilitative positioning of *chi* sites in the *E. coli* genome can be viewed as indirect evidence that most double-strand breaks, subject to recombinational repair in bacteria, are generated in the course of replication.

Following RecA-mediated DNA strand invasion and strand exchange, the resulting crossover is resolved by some combination of the RuvABC, RecG, and perhaps other enzymes[375]. The RuvABC proteins and the RecG protein provide alternative pathways for the resolution of Holliday junction intermediates[376]. The RuvC protein is a Holliday junction resolvase[375], and it is one of several enzymes with this activity in *E. coli*[377]. A deficiency in RecG protein greatly increases the sensitivity to DNA damage and the recombination defects conferred by RuvABC mutations[376,378]. The RecG protein has helicase activity that promotes the migration of a DNA branch or crossover in the direction of opposite to that promoted by the RecA protein[376,379,380]. The action of RecG following RecA-mediated DNA strand exchange and DNA repair could move the crossover backwards and ultimately reconstruct the framework of a replication fork without the action of RuvC or a similar Holliday junction resolvase[376]. The RuvA and RuvB proteins also displace RecA protein from DNA under some *in vitro* conditions, suggesting additional functions for these proteins *in vivo*[381]. However, the RecFOR proteins also appear to modulate RecA assembly and disassembly, and the fate of the RecA filament s may turn out to be a more complex affair involving interactions with the RuvAB, RecFOR, and perhaps other proteins.

Two additional points are worth noting with respect to Figure 6-1 and the above discussion. First, the pathways outlined in the figure are not necessarily as distinct as shown. For example, some evidence exists that the RecF pathway functions may participate in RecBCD-mediated recombination pathways under at least some conditions[382]. Second, the resolution of the recombination crossover in either pathway can occur in at least two ways. One of the possibilities leads to the formation of a chromosome dimer. If recombinational DNA repair is required as often as already postulated, than the formation of dimeric chromosomes should represent a barrier to the segregation of chromosomes at cell division in a large fraction of cells, even under normal growth conditions. This is actually observed, and the problem is addressed by the XerCD site-specific recombination system that functions in the resolution of dimeric genomes to monomers.

The role of recombination in repair of cisplatin-DNA damage has not been studied in great amount of detail. It has been shown that cisplatin induces recombination in *Candida albicans*[383], *D. melanogaster*[384], and also that it induces meiotic crossing-over in germ cells of mice[10]. Recombination deficient mutants, such as *recA* and *recBC* in *E. coli*[142,143,385], *RAD52* in *S. cerevisae*[240,386], and *RAD21* and *RAD22* in *S. pombe*[387], display sensitivity to cisplatin. Remarkably, despite these observations, there has been no systematic analysis to date of recombination as a strategy for managing cisplatin DNA damage. One of the main goals of this thesis work to further elucidate the role of recombination in mediating cellular responses to cisplatin damage particularly at the intersection with mismatch repair.

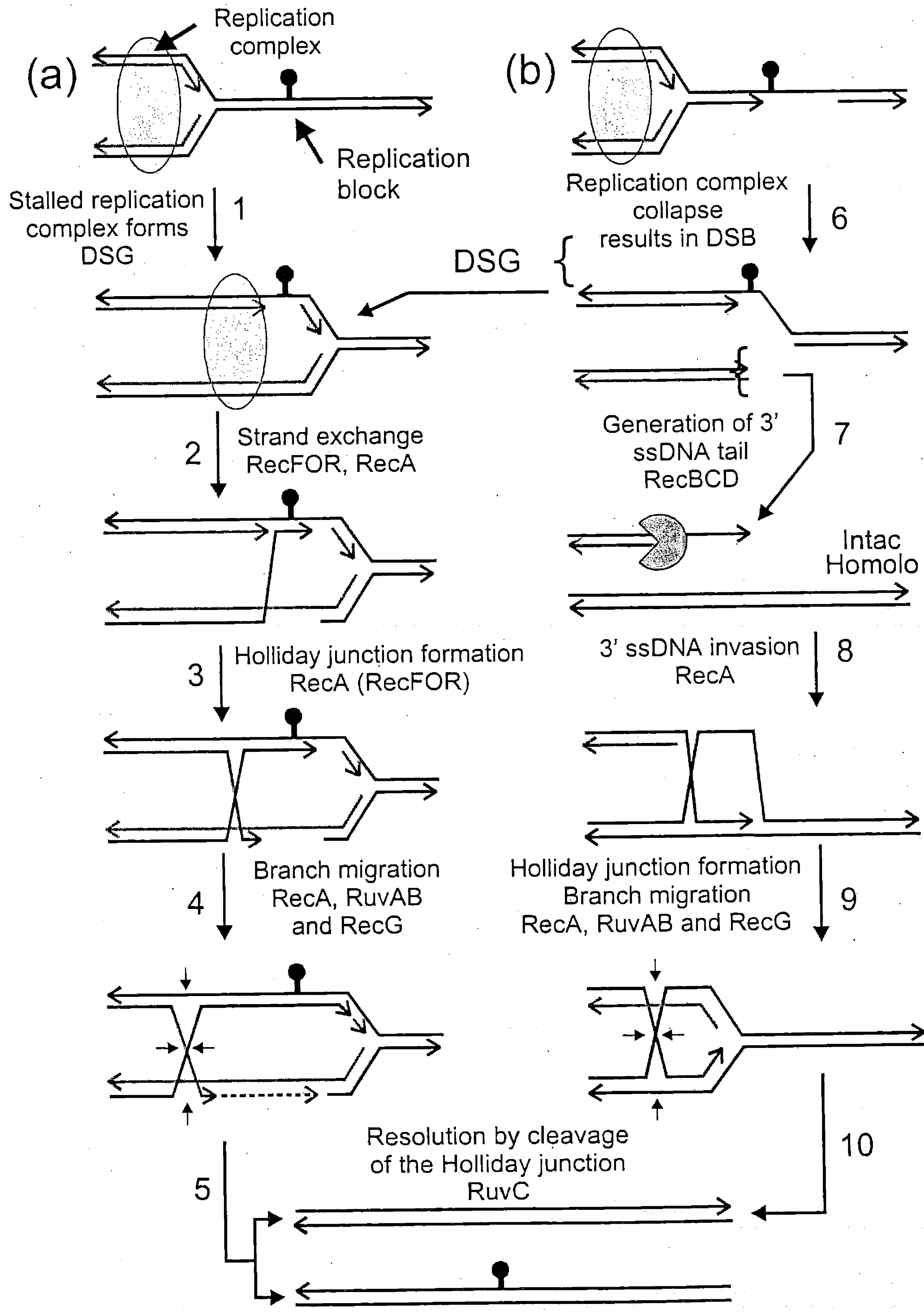

(a)
Replication complex
Replication block
Stalled replication complex forms DSG
1
DSG
2
Strand exchange RecFOR, RecA
3
Holliday junction formation RecA (RecFOR)
4
Branch migration RecA, RuvAB and RecG
5
Resolution by cleavage of the Holliday junction RuvC
(b)
Replication complex collapse results in DSB
6
Generation of 3' ssDNA tail RecBCD
7
Intac Homolo
3' ssDNA invasion RecA
8
Holliday junction formation Branch migration RecA, RuvAB and RecG
9
10

**Figure 6-1. Models for recombinational repair of secondary DNA lesions (daughter strand gaps and double strand breaks) induced by DNA damage.** Models based upon references[388,389]. *(a) Daughter Strand Gap Pathway.* (Step 1) The replication complex encounters a replication block. Stalled replication results in the formation of a daughter strand gap. (Step 2) Interactions between the proteins of the RecFOR pathway and the replication fork initiate RecA nucleation and strand exchange. (Step 3) The ensuing RecA catalyzed strand exchange (with the aid of the RecFOR accessory proteins) results in the formation of a Holliday junction. (Step 4) Branch migration of the Holliday junction catalyzed by the RecA, RuvAB or RecG proteins results in the repair of the daughter strand gap and restoration of the replication fork. (Step 5) Resolution of the Holliday junction by RuvC restores two double stranded DNA molecules. This could be a mechanism of damage tolerance as the replication blocking lesion is bypassed by recombinational repair and persists in the DNA. *(b) Double Strand Break Pathway.* (Step 6) The replication complex encounters an unrepaired daughter strand gap or a nick opposite the adduct. Collapse of the replication fork forms a double strand break and a daughter strand gap; the daughter strand gap portion of the collapsed replication fork is processed by the daughter strand gap pathway (a). There are other mechanisms by which the double strand breaks could arise, and we have presented only one scenario. *By the proposed scheme, repair of the double strand breaks requires an intact homologue of the damaged duplex.* (Step 7) The RecBCD complex (shown in red) binds the free end of the double strand break and generates ss DNA that is a substrate for RecA nucleation. (Step 8) RecA nucleoprotein filaments catalyze the invasion of the RecBCD generated ss tail into the homologous duplex. (Step 9) RecA catalyzed strand exchange and branch migration results in the formation of a Holliday junction and restoration of the replication fork. (Step 10) Resolution of the Holliday junction by RuvC yields two intact duplexes (only one molecule is shown).

# PART TWO: EXPERIMENTAL RESULTS AND DISCUSSION

## Chapter 7. Multiple Pathways of Recombination Define Cellular Responses to Cisplatin

The cytotoxicity of many DNA damaging agents is believed to result from the formation of lesions that block the processivity of DNA polymerases and cause replication arrest[390]. Replication arrest, in turn, may lead to the formation of secondary DNA damage such as daughter strand gaps and double strand breaks[9]. If uncorrected, daughter strand gaps and double strand breaks can be lethal, owing to the loss of essential genes and faulty chromosomal segregation; therefore all organisms have developed strategies for repair of these types of damage. In *E. coli*, the principal mechanism for repair of daughter strand gaps and double strand breaks is recombination, where the injured DNA strand is paired with an intact homologous strand that provides a template for repair of the secondary lesion[9,390,391].

The widely used chemotherapeutic drug cisplatin (*cis*-diamminedichloroplatinum(II)) (Figure 7-1) is toxic to cells and it is strikingly effective against testicular tumors[35]. Although the cytotoxicity of cisplatin is attributed to its capacity to damage DNA, the detailed molecular mechanism to account for the therapeutic efficacy and organotropic specificity of this drug remains elusive. Cisplatin binds to the N7 atom of purine bases in DNA to form predominantly 1,2-d(GpG), 1,2-d(ApG) and 1,3-d(GpNpG) (where N is any nucleotide) intrastrand crosslinks, and a small percentage of interstrand crosslinks (between two guanines in complementary strands)[2,53]. These DNA adducts elicit a variety of cellular responses, including inhibition of DNA synthesis. The 1,2-intrastrand crosslinks, in particular, are strong blocks to replication *in vitro* and *in vivo*[8,392]. Cisplatin induces recombination in *Candida albicans*[383], *D. melanogaster*[384], and it induces meiotic crossing-over in germ cells of mice[10]. Recombination deficient mutants, such as *recA* and *recBC* in *E. coli*[142,143,385], *RAD52* in *S. cerevisae*[240,386], and *RAD21* and *RAD22* in *S. pombe*[387], display sensitivity to cisplatin. Remarkably, despite these observations, there has been no systematic analysis to date of recombination as a strategy for managing cisplatin DNA damage. To address this gap in understanding, we assembled a series of *E. coli* strains deficient in the major pathways of recombination and studied their responses to treatment with the drug. We report that recombination deficient mutants showed exceptionally high sensitivity to cisplatin in comparison to their parental strain. Indeed, most recombination deficient mutants were as sensitive to cisplatin as mutants lacking nucleotide excision repair (NER). Recombination/NER deficient double mutants produced increased sensitivity to cisplatin indicating that these two pathways act independently in the cellular defenses against the drug. In addition, we found that even modestly toxic doses of cisplatin were potently recombinogenic compared to other DNA damaging agents. The results suggest a model for cisplatin cytotoxicity that can accommodate the currently known cellular effects of the drug and may account for the therapeutic specificity of cisplatin.

### Materials and methods

*Chemicals.* Methylmethane sulfonate was obtained from Eastman-Kodak, and mitomycin C, streptozotocin, *N*-Methyl-*N*'-nitro-*N*-nitrosoguanidine, *cis*- and *trans*-diamminedichloroplatinum(II) were obtained from Sigma-Aldrich.

*Bacterial strains.* The strains used in this study are listed in Table 7-1. All the strains used for cytotoxicity studies are derivatives of AB1157. The auxotrophic phenotype of all mutant strains was confirmed by growth on the appropriate supplemented minimal medium.

*Cytotoxicity assay.* Overnight cultures were diluted one thousand-fold and grown in Luria-Bertani (LB) medium[393] until the density of the populations reached 2 x $10^8$ cells/ml as determined by $OD_{600}$. The exponentially growing cells were resuspended in M9 minimal medium[393] and treated with drug dissolved in $H_2O$ for 2 hr at 37 °C. Appropriate dilutions in M9 medium were plated on LB plates and incubated at 37 °C until colonies could be scored. Results from three to six independent experiments plated in duplicate were averaged and plotted versus drug concentration.

*Drug-induced recombination assay.* Strain GM7330 carries a specially constructed non-tandem duplication of partially deleted *lac* operons (*lacMS286ϕ80dIIlacBK1*). *ϕ80dIIlacBK1* has a small deletion in the proximal portion of the *lacZ* gene, whereas *lacMS286* contains a distal deletion. The deletions are non-overlapping, so functional Lac$^+$ revertants result only after a recombination event, and spontaneous recombinants are rare. The construction and properties of *lac* duplication strains have been described elsewhere[394].

Strain GM7330 was grown overnight in L-broth and diluted ten-fold in minimal salts without glucose[395]. Diluted cells (1.5 ml) were added to MacConkey agar plates (Difco; supplemented with 1% lactose), the cells were allowed to settle for 10 min, and then the excess medium was removed by aspiration. This procedure produced a uniform lawn of cells on the plate. Sterile 6.35 mm disks (Difco) were placed on each dry plate and aliquots of drug were added to the disks. Not more than 10 μl were spotted on the disks at one time and the disks were allowed to dry before further addition of drug. In this manner, the drug was delivered by diffusion from the disk, yielding a gradient of drug concentration that decreased with distance from the disk. The low solubility of *trans*-diamminedichloroplatinum(II) (*trans*-DDP) precluded testing at higher doses than those presented. The plates were then incubated for 48 hr at 37 °C. Plates were scanned (bottom down) with a Umax 1220 scanner and CorelDraw software.

## Results

**Mutants deficient in the initiation of the daughter strand gap or the double strand break pathways of recombination are hypersensitive to cisplatin.** Two pathways can initiate recombinational repair in *E. coli*: the RecFOR pathway for the repair of daughter strand gaps and the RecBCD pathway for the repair of double strand breaks. Daughter strand gaps are formed when the processivity of the replication fork is interrupted by a non-coding DNA lesion, such as a UV-induced dimer, in the template strand, and the lesion is left opposite a single stranded (ss) gap in the nascent strand[396]. Genetic evidence implicates proteins of the RecFOR pathway in the recombinational repair of UV induced daughter strand gaps[397]. Biochemical studies demonstrate that the RecOR complex promotes the binding of RecA protein to ss DNA (in the presence of ss DNA binding protein), and it facilitates the homologous pairing by RecA[398]. The RecFR complex is thought to interact directly with the stalled replication fork, and it may function in fork disassembly or reassembly during recombination and repair[364,399]. To assess the importance of the RecFOR pathway in the cellular response to cisplatin DNA damage, we examined the survival of *recF*, *recO* and *recR* mutants after cisplatin treatment (Figure 7-2a). At the highest cisplatin dose (100 μM), the surviving fraction for each mutant was approximately three orders of magnitude lower than that for the isogenic wild type strain. The high sensitivity of these mutants is consistent with a role of the RecFOR gene products in recombinational repair of daughter strand gaps produced as a consequence of replication blockage by cisplatin adducts.

In *E. coli* the RecBCD pathway is essential for recombinational repair of X-ray induced double strand breaks[400]. The RecBCD complex combines helicase and nuclease functions that simultaneously unwind and asymmetrically degrade double strand breaks (the strand with the 3' terminus is nicked more frequently than the strand with the 5' end). Once the enzyme complex encounters a *chi* sequence (5'-GCTGGTGG-3') from the 3' direction, it pauses and nicks the DNA to generate a 3' ss DNA tail that serves as a substrate for RecA polymerization and initiation of recombination[368,374,401,402]. To determine if the RecBCD pathway participates in the cellular

processing of cisplatin induced DNA damage, we examined the two major phenotypes displayed by *recBCD* mutants[403]. The *recBC* mutant is deficient in normal helicase and nuclease activities and it is sensitive to DNA damaging treatments[404]. In agreement with previous reports[142], the *recBC* mutant displayed high sensitivity to cisplatin (Figure 7-2b). The surviving fraction for the *recBC* strain at a cisplatin dose of 75 μM was approximately four orders of magnitude lower than for the parental wild type strain. The *recD* mutant is defective for normal nuclease activity and it exhibits wild type sensitivity to DNA damaging agents. In contrast to the results with the *recBC* strain, the *recD* mutant showed little or no sensitivity to cisplatin. These data provided genetic evidence that cisplatin DNA damage resulted in the formation of double strand breaks.

**Mutants deficient in branch migration and resolution of recombination intermediates are also hypersensitive to cisplatin.** Both the RecFOR and RecBCD pathways mediate the formation of RecA nucleoprotein filaments on ss DNA. These filaments catalyze the pairing and the strand exchange reactions between the damaged DNA molecule and an intact homologous duplex. The cisplatin hypersensitivity of *recA* mutants is well-documented[143,385] and was confirmed in this investigation (data not shown). The ensuing crossover and branch migration converts the damage-containing strand into duplex DNA and results in the formation of a four-way Holliday junction. In the late steps of recombination, the Holliday junction is subjected to the branch migration activities of either the RuvAB complex or the RecG protein[379,405], and it is cleaved by the RuvC resolvase[369]. Accordingly, we tested individual *ruvA, ruvC* and *recG* mutants, as well as a *ruvC recG* double mutant, for sensitivity to cisplatin. It should be noted that the transposon insertion in the *ruvA60* mutant has a polar effect on *ruvB* expression[406]. As shown in Figure 7-3, the individual *ruvA* and *ruvC* mutants displayed a striking sensitivity to cisplatin that was equal or greater in magnitude to that observed for the mutants deficient in the RecBCD and RecFOR pathways of recombination. At a cisplatin concentration of 80 μM, the *ruvA* and *ruvC* strains exhibited approximately four orders of magnitude decreased survival in comparison to the wild type strain. The sensitivities of these mutants indicated that branch migration and resolution of Holliday junctions by the RuvABC pathway were of critical importance, along with the earlier stages of recombination, for the post-replicative repair of cisplatin DNA damage. In contrast to the RuvABC deficient strains, the *recG* mutant was found to be only 10-fold more sensitive to cisplatin than the parental strain at a cisplatin dose of 80 μM. The *ruvC recG* double mutant, deficient for both pathways of branch migration and resolution, displayed an additive effect, exhibiting higher sensitivity than either individual mutant strain. This observation is consistent with previous suggestions that the RecG and RuvABC pathways do not significantly overlap[378]. Taken together, these results indicate that RuvABC function is as important as RecBCD function for cell survival following cisplatin DNA damage, and that the RecG pathway plays a comparatively minor role that is independent of RuvABC in the processing of cisplatin damage.

**Recombination deficient and nucleotide excision repair (NER) deficient strains are equally sensitive to cisplatin.** In order to appraise the significance of the results of the previous experiments, we compared the cisplatin sensitivity of recombination deficient mutants to a strain deficient in NER. NER acts on a broad range of DNA damages and has been assigned the central role in modulating the sensitivity of eukaryotic and prokaryotic cells to cisplatin. Cisplatin intrastrand adducts are removed from DNA by the NER repair system *in vivo* and by a reconstituted NER system *in vitro*[407]. Mutations that impair the function of this system cause hypersensitivity to cisplatin that is held as a benchmark for mutant susceptibility to the drug. Accordingly, we compared survival following cisplatin treatment of the NER deficient strain *uvrA* with that for representative recombination deficient strains: *recF, recBCD* and *ruvABC* (Figure 7-4). The NER deficient strain showed hypersensitivity to cisplatin as previously described[142,144] but, interestingly, not higher than mutants deficient in the RecBCD or RuvABC pathways. The survival curves for *uvrA, recBCD* and *ruvABC* strains essentially overlapped, while only the *recF* mutant was slightly less sensitive than *uvrA*. The comparable sensitivities of these mutants establish a crucial role for recombination alongside NER in determining cell survival following cisplatin DNA damage.

**Recombination/nucleotide excision repair (NER) deficient double mutants show increased sensitivity to cisplatin.** The comparable sensitivity of the recombination and NER deficient single mutants presented in Figure 7-4 posed the question of whether or not the two pathways (recombination and NER) act independently in the processing of cisplatin induced DNA damage. We addressed this question by comparing the effects of cisplatin on the survival of recombination and NER single and double mutants. If a double mutant showed an increased sensitivity to cisplatin in comparison to the parental single mutants, this would suggest that recombination and NER are non-overlapping pathways for the repair of cisplatin damage. We constructed a series of recombination/NER deficient double mutants: *recF uvrA*, *recBCD uvrA*, *ruvA uvrA*, and *ruvC uvrA*, and tested them for sensitivity to cisplatin. As shown in Figure 7-4, all of the tested double mutants showed decreased survival. The *recF uvrA* and the *recBCD uvrA* double mutants showed comparable sensitivities, and both showed higher sensitivity than the corresponding single mutants (Figure 7-4a). In the same manner, *ruvA uvrA* and *ruvC uvrA* double mutants also showed increased sensitivities in comparison to the analogous single mutants (Figure 7-4b). At the relatively low cisplatin dose of 10 μM, all of the recombination/NER double mutants tested showed a striking reduction in survival that equaled approximately four orders of magnitude in comparison to the parental wild type strain. Taken together, these results suggest that the recombination and the NER pathways act independently of each other in protecting the cell from cisplatin damage.

**Recombination deficient mutants show low sensitivity to *trans*-DDP.** The trans isomer of cisplatin, *trans*-diamminedichloroplatinum(II) (*trans*-DDP) (Figure 7-1a), also reacts with DNA to generate a spectrum of N7 intrastrand and interstrand crosslinks[58,63], but it is far less cytotoxic than cisplatin and it is ineffective against tumors. Consequently, *trans*-DDP is a useful reference compound for calibrating the relative significance of various cellular responses to cisplatin. To determine if the extreme sensitivities of recombination mutants were unique to the therapeutically active cis isomer, we tested the same panel of isogenic mutants (*recF, recBCD, ruvABC* and *uvrA*) for survival after *trans*-DDP treatment (Figure 7-5). The *uvrA* strain displayed slightly higher sensitivity to *trans*-DDP in comparison to the wild type, as previously reported[143]. The recombination deficient mutants *recF, recBCD*, and *ruvABC* displayed similarly modest sensitivity (again, in comparison to the wild type), even at *trans*-DDP concentrations of 150 μM. The lack of sensitivity of these mutants suggested that, in contrast to cisplatin, *trans*-DDP did not result in significant levels of either daughter strand gaps or double strand breaks that require homologous recombination for their repair.

**Cisplatin is highly recombinogenic.** The extreme cisplatin sensitivity of recombination deficient strains underscores the importance of recombination strategies for cell survival following cisplatin exposure. These observations suggested that cisplatin might induce high levels of recombination events in surviving populations. Therefore, we next examined the relative amounts of drug-induced recombination for a panel of compounds including cisplatin, the alkylating agents *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG), methylmethane sulfonate (MMS), streptozotocin (STZ), and the bifunctional crosslinking agents mitomycin C (MMC) and *trans*-DDP (for chemical structures of the compounds Figure 7-1c). An assay was used in which inverted inactive *lac* operons could be made functional only through a recombination event (Figure 7-6). Induced Lac$^+$ recombinants appeared within a lawn of Lac$^-$ cells as concentrated zones of red colonies around a drug-containing disk, while spontaneous recombinants appeared as sparse red colonies over the entire plate. The cytotoxicity of the drug was visible as a clear cell-free zone surrounding the disk. As shown in Figure 7-7, at approximately equal cytotoxic doses (determined by the approximate radius of the zone of killing) cisplatin stimulated an extremely high number of Lac$^+$ recombinants as compared to other DNA damaging agents. The alkylating agents MNNG, MMS, and STZ induced some recombinants, but they showed high levels of cytotoxicity without stimulating correspondingly high levels of recombination. The therapeutically inactive trans isomer of cisplatin displayed almost no induction of Lac$^+$ recombinants, even at the highest dose tested (120 nmol; 3 o'clock in Figure 7-7). At this *trans*-DDP dose the level of toxicity achieved was roughly equal to that of the lowest dose of cisplatin (30 nmol; 9 o'clock in Figure 7-7). This result correlated with

our observation that recombination deficient mutants showed little sensitivity to the trans isomer. Only MMC, which forms covalent adducts with the exocyclic amines of guanines and abundant interstrand crosslinks[408], showed comparable recombinogenicity to cisplatin. This result poses the possibility that the interstrand crosslinks of cisplatin and MMC may be the lesions that induce recombinogenicity. It must be noted, however, that the levels of interstrand crosslinks in our experiments were not measured and therefore we cannot make a correlation between recombinogenicity and interstrand crosslinks at this time. We also note that *trans*-DDP forms interstrand crosslinks *in vitro*[58], but this compound did not induce a significant number of recombinants in our assay. This result possibly reflects the fact that the interstrand crosslinks of *trans*-DDP may form less frequently *in vivo* than they do *in vitro* (i.e., few interstrand lesions may have been formed at the concentrations of *trans*-DDP used)[36,409]. Regardless of which lesion induces recombination, the high ratio of recombination to cytotoxicity for cisplatin and MMC, when compared to that found for the other DNA damaging drugs and *trans*-DDP, may provide an important key to understanding the therapeutic activities of these two compounds.

## Discussion

This study was an analysis of the role of recombination as a cellular defense against cisplatin. The results showed that *E. coli* recombination deficient mutants: *recF, recO, recR, recBC, recBCD, ruvA, ruvC, ruvABC, recG,* and *ruvC recG,* were strikingly sensitive to the drug. The sensitivities of the recombination deficient mutants were comparable to the cisplatin sensitivity of the NER deficient strain (*uvrA*). This result is significant because, until this work, NER was considered the pathway of greatest importance as a cellular defense against cisplatin damage. Recombination/NER deficient double mutants (*recF uvrA, recBCD uvrA, ruvA uvrA, ruvC uvrA)* produced increased sensitivity to cisplatin underscoring the possibility that recombination and excision repair pathways may be independent strategies for managing the DNA damage induced by this drug.

Our results indicated that recombination proteins are required for survival following cisplatin induced DNA damage. Based on current models, there are two major pathways for recombinational repair and homologous recombination in bacteria[9,390,391]. The daughter strand gap repair pathway requires the RecFOR and the RecA, RuvABC and/or RecG gene products (Figure 7-8a), and the double strand break repair pathway requires the RecBCD and RecA, RuvABC and/or RecG gene products (Figure 7-8b). Since mutants deficient in the gene products involved in both pathways showed high sensitivity to cisplatin we can make the conclusion that cisplatin DNA damage led to the formation of both daughter strand gaps and double strand breaks. While the formation of daughter strand gaps (Figure 7-8a) as a result of replication blocks is consistent with the knowledge that cisplatin inhibits DNA synthesis, the induction of double strand breaks is not widely associated with the activities of the drug. Cisplatin does not react with DNA in a manner that would lead directly to strand breaks or abasic sites, and thus double strand breaks must arise following cisplatin exposure as indirect, secondary DNA lesions. DNA damage could lead to the formation of double strand breaks following the encounter of a replication fork with an unrepaired daughter strand gaps caused by a cisplatin adduct in the previous round of replication (Figure 7-8b). An unrepaired daughter strand gap could also lead to the formation of double strand breaks due to the activities of single strand endonucleases[390]. Alternatively, double strand breaks could be formed by cisplatin adducts via a recently proposed model in which induced replication arrest results in a double strand breaks through the annealing of the ends of the complementary, newly synthesized daughter strands[410].

It has been discovered that cisplatin-DNA crosslinks are uniquely recognized by a variety of cellular proteins (Adduct Binding Proteins, or ABPs in Figure 7-8), and many of these interactions have been proposed to play a key role in the mechanism of action of the drug[241,407]. In the context of our present findings, protein recognition of cisplatin crosslinks may contribute to the formation of daughter strand gaps and double strand breaks. For example, an ABP could contribute to a

replication arrest by providing an exceptionally strong block to the processivity of DNA polymerases, as has been shown for the rat high mobility group protein HMG-1[411] (Figure 7-8, Step 1). Alternatively, specialized ABPs could introduce strand breaks via enzymatic nicking activities at sites of cisplatin crosslinks. For example, T4 endonuclease VII nicks DNA site-specifically at a cisplatin 1,2-d(GpG) crosslink[199] and it is possible that other proteins possess similar activities. It has also been proposed that mismatch repair proteins, which selectively recognize cisplatin-DNA adducts[17,18,352], could initiate repair events targeted to the newly synthesized strand opposite a cisplatin crosslink, leaving the offending lesion intact and leading to an iterative process of excision and resynthesis. In these cases, such errant nucleolytic activities would result in direct or post-replicative formation of double strand breaks that would require recombination for their repair. We do not know if there are ABPs that recognize MMC adducts but, given the similarities in recombinogenicity of cisplatin and MMC, it would be interesting to examine cellular extracts for such proteins.

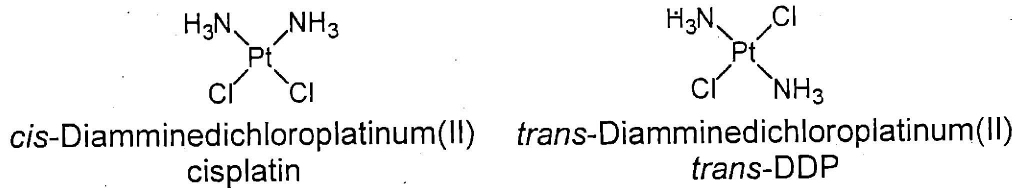
Cisplatin forms a variety of DNA adducts and the specific lesion responsible for cisplatin cytotoxicity remains undefined. In the context of this study, it is reasonable to speculate that the highly abundant 1,2-intrastrand crosslinks (~90% of all adducts formed *in vitro*) led to frequent replication arrests and contributed significantly to formation of daughter strand gaps and double strand breaks. This interpretation is based on several lines of reasoning (reviewed in [8]): (i) the 1,2-intrastrand cisplatin-DNA crosslinks are inefficiently repaired by NER compared to the minor 1,3-d(GpNpG) crosslink (6-8% of all adducts) and are therefore persistent; (ii) the 1,2-crosslinks inhibit phage and *E. coli* polymerases *in vitro* and *in vivo* more strongly than the 1,3-intrastrand crosslinks; and (iii) the recombination mutants in our study exhibited low sensitivity to *trans*-DDP, which does not form 1,2-intrastrand crosslinks due to geometric constraints. It is noteworthy that a single 1,2-d(GpG) intrastrand crosslink does not inhibit the DNA unwinding or the ATPase activities of RecA, but it inhibits both the helicase and DNA dependent ATPase activities of the RecB protein[412]. It would be interesting to investigate further the effect of cisplatin DNA crosslinks on the *in vitro* activities of the RecBCD holoenzyme and the other recombinases (RuvABC and RecG).

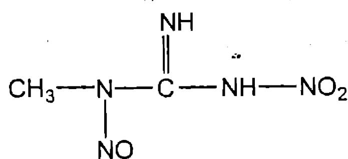
We must note that the <u>inter</u>strand crosslink, although a minor adduct formed by cisplatin (~2% of all adducts), is also a viable candidate for the lethal lesion. The precise mechanism for repair of interstrand crosslinks is not yet understood, but it is believed to involve recombination and excision repair[390]. It is thus possible that the interstrand crosslinks also contributed to the cisplatin sensitivity of the various recombination mutants. Although we observed increased sensitivity to cisplatin by the recombination/NER double mutants, we can not exclude the possibility that there is partial overlap in activities of the two pathways in repair of this (or other minor) subset of cisplatin adducts. A further understanding of how the individual cisplatin crosslinks are processed by specific recombination and repair strategies could provide insights into identification of the specific adduct(s) responsible for the therapeutic activity of the drug.

While our study is a genetic analysis of recombinational pathways of tolerance/repair of cisplatin DNA damage in bacteria, it is useful to bear in mind the question that underlies most research on cisplatin - namely, why are tumors of the testis so singularly susceptible to the drug? High levels of cisplatin induced recombination could lead to cell death by triggering mismatch repair mediated damage signaling pathways that are specific to germ cells. Certain mismatch repair proteins are overexpressed in testicular tissues including MSH2, MSH4, MLH1 and MSH5[21-24] and, these proteins could sensitize germ cells by interfering with the required high level of recombinational repair of cisplatin damage. Further exploration of the relationships among recombination, repair of DNA damage, and the role of mismatch repair proteins in both of these processes are warranted.

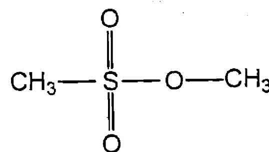
Finally, in our study of DNA damaging agents that induce recombination (Figure 7), only MMC rivaled cisplatin as a recombinogen. It is noteworthy that this drug, like cisplatin, is differentially toxic to testicular cancer cells *in vitro*[413]. It is tempting to speculate that induced

recombination might be the common denominator in the mechanism of action of a specific class of anticancer agents. Therefore, understanding the role of recombination in genome maintenance could be of great significance for future tissue-specific drug design efforts. Since the publication of these results a study showed that a similar panel of recombination deficient mutants was very sensitive to nitric oxide further underscoring the importance of recombinational repair pathways in mediating cellular responses to a variety of chemical factors[414].

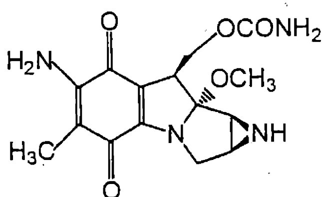


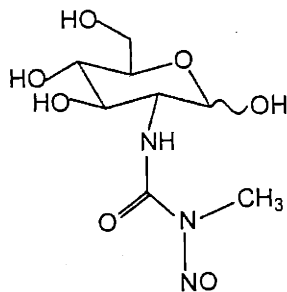

*N*-Methyl-*N'*-nitro-
*N*-nitrosoguanidine
(MNNG)




Methylmethane
sulfonate (MMS)




Mitomycin C
(MMC)




Streptozotocin (STZ)

**Figure 7-1.** (a) Structures of diamminedichloroplatinum(II) isomers. (b) Structures of cisplatin DNA crosslinks. (c) Chemical structures of other DNA damaging agents used in this study.

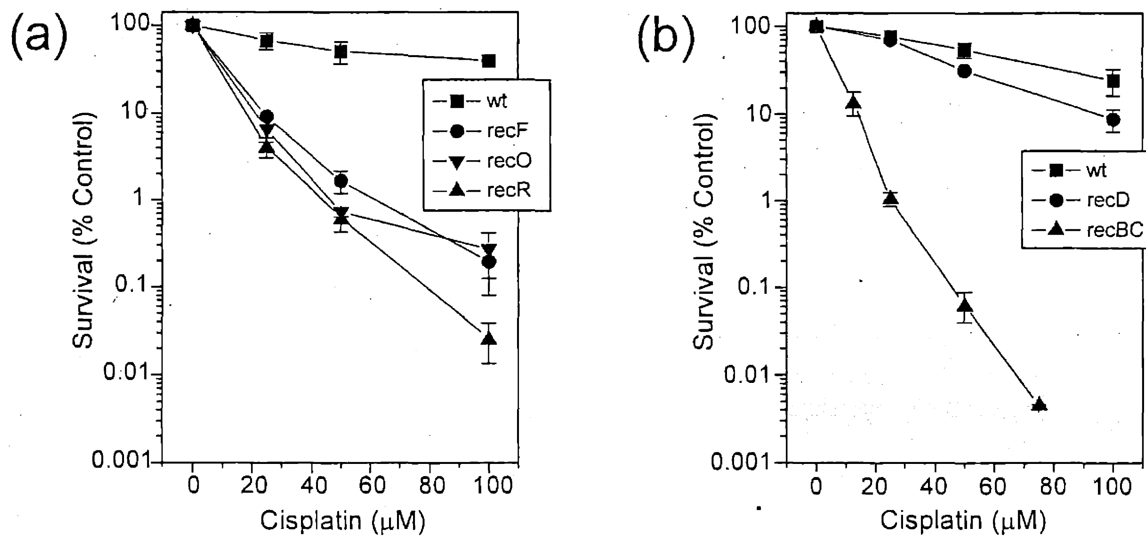



**Figure 7-2. Survival of *E. coli* strains treated with cisplatin.** For each data point, results shown are the mean of at least three independent experiments plated in duplicate, ± SEM. (a) Effects of *recF*, *recO*, and *recR* mutations on cisplatin sensitivity. (b) Effects of *recBC* and *recD* mutations on cisplatin sensitivity.

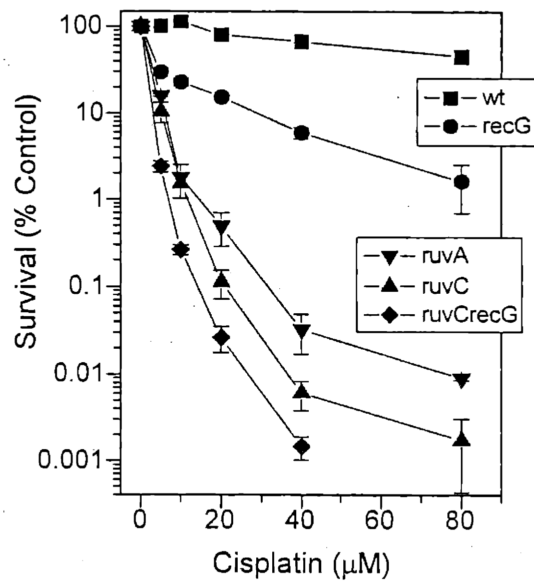



**Figure 7-3. Effects of *recG*, *ruvA*, *ruvC* and *ruvC recG* mutations on cisplatin sensitivity in *E. coli*.** For each data point, results shown are the mean of at least three independent experiments plated in duplicate, ± SEM.

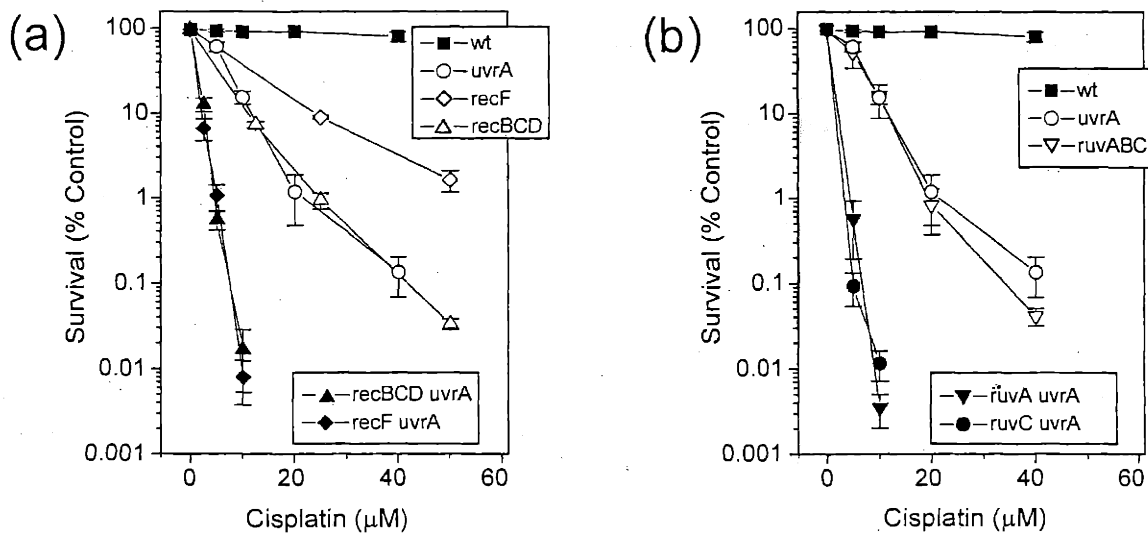



**Figure 7-4. Comparison of cisplatin sensitivities in *E. coli* recombination and NER single mutants and recombination/NER double mutants.** For each data point, results shown are the mean of at least three independent experiments plated in duplicate, ± SEM. (a) Effects of *uvrA*, *recF*, *recBCD*, *recF uvrA* and *recBCD uvrA* mutations on cisplatin sensitivity (*recF* survival profile from Figure 2a is shown for comparison). (b) Effects of *uvrA*, *ruvABC*, *ruvA uvrA* and *ruvC uvrA* mutations on cisplatin sensitivity.

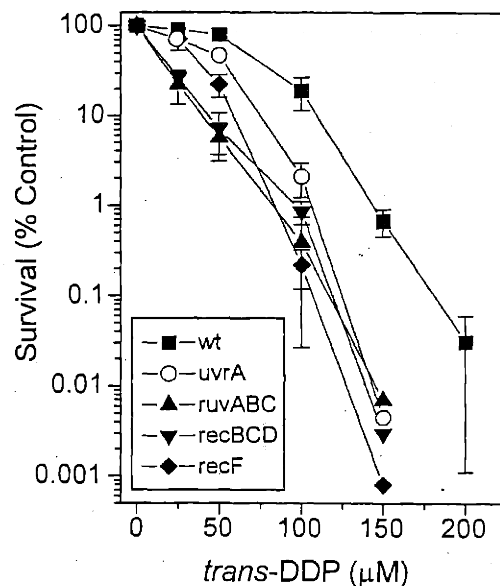



**Figure 7-5.** Survival of *uvrA*, *ruvABC*, *recBCD*, and *recF E. coli* strains treated with *trans*-DDP. For each data point, results shown are the mean of at least three independent experiments plated in duplicate, ± SEM.

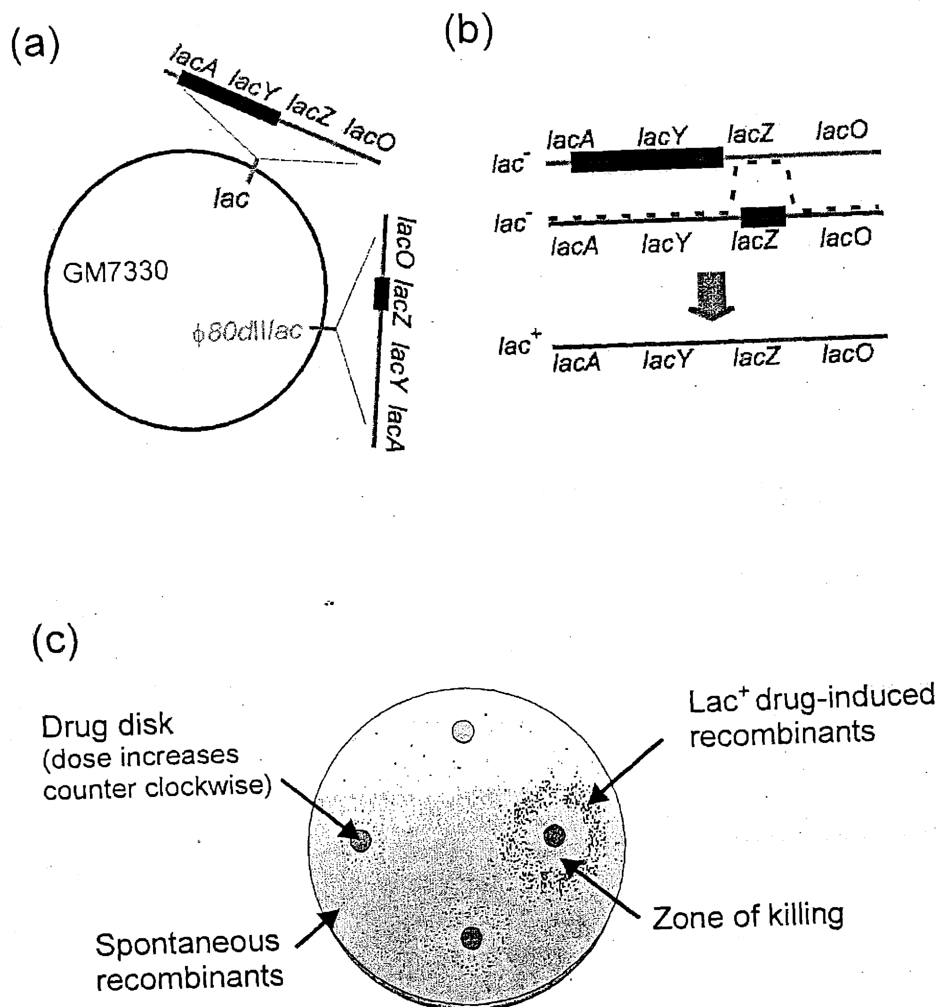



**Figure 7-6. Assay for drug-induced recombination.** (a) Schematic of the chromosome of the *lac* diploid strain GM7330 showing the normally present *lac* locus (blue) and the inserted duplicate but reverse, *ϕ80dIIlac* locus (green). The black boxes represent the deletions that render the strain *lac*⁻. (b) A recombination event between the two incomplete *lac* loci yields a functional *lac*⁺ product. (c) Schematic of the experimental set up: drug was applied to filter disks, in increasing amounts counter clockwise, to a lawn of GM7330 on MacConkey agar plates. The clear zone surrounding the disks is the zone of killing by the drug. The *lac*⁺ recombinants grow as concentrated zones of red colonies around the drug disks (or the zone of killing). The sporadic red colonies over the entire plate are spontaneous recombinants.

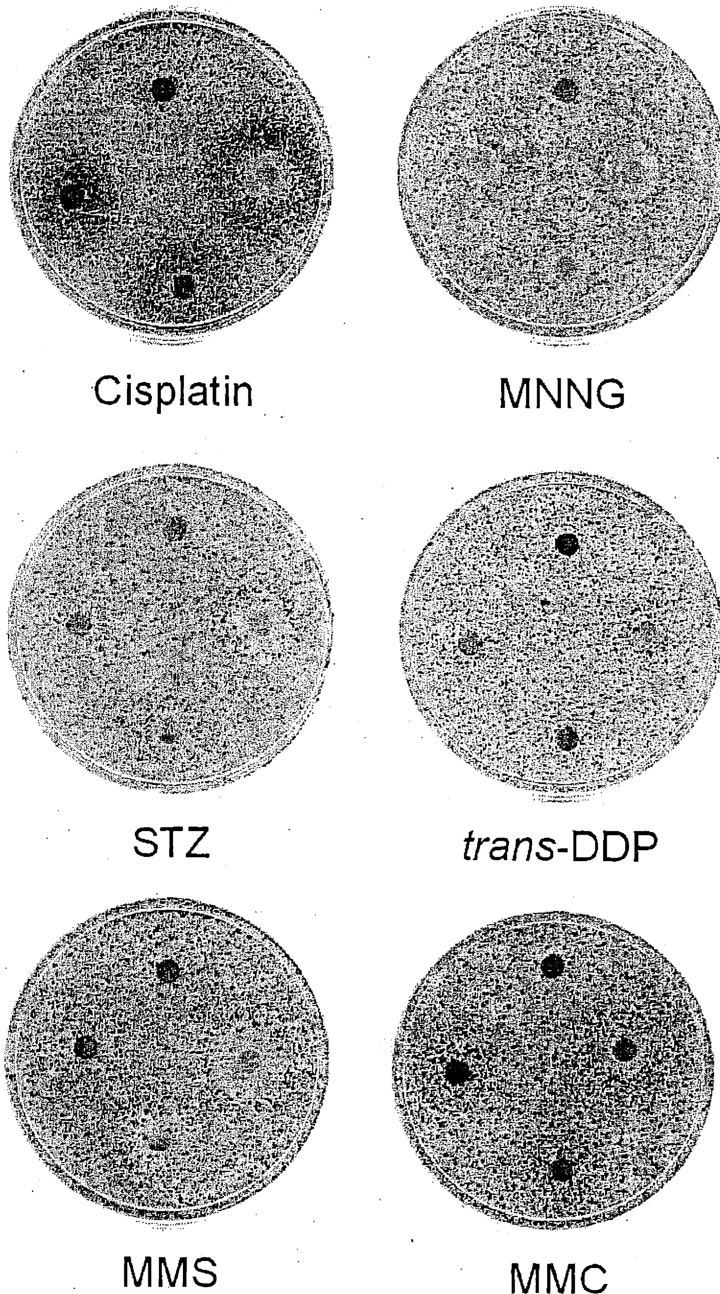



**Figure 7-7.** **Lac⁺ recombinants induced by DNA damaging agents in the *E. coli* strain GM7330.** Doses applied to filter disks increase counter clockwise from 12 o'clock position for all compounds: cisplatin: 0, 30 60, 120 nmoles; *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG): 0, 5, 10, 20 μg; streptozotocin (STZ): 0, 10, 20, 40 μg; *trans*-DDP: 0, 30, 60, 120 nmoles; methylmethane sulfonate (MMS): 0, 0.65, 1.3, 2.6 μg; and mitomycin C (MMC): 0, 0.05, 0.1, 0.2 μg.

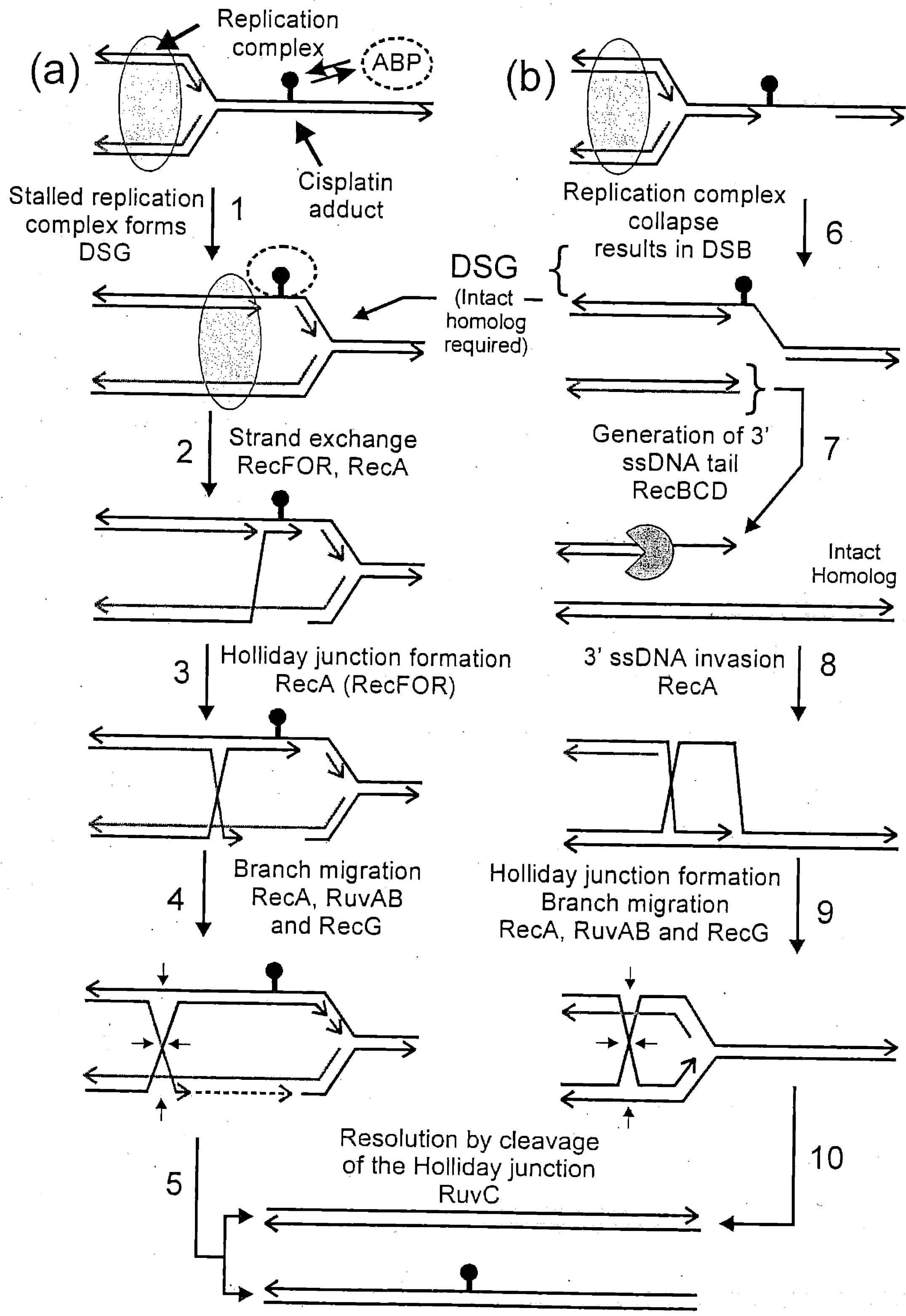

(a)
Replication complex
ABP
Cisplatin adduct
Stalled replication complex forms DSG
1
DSG
(Intact homolog required)
2
Strand exchange RecFOR, RecA
3
Holliday junction formation RecA (RecFOR)
4
Branch migration RecA, RuvAB and RecG
5
Resolution by cleavage of the Holliday junction RuvC
(b)
Replication complex collapse results in DSB
6
7
Generation of 3' ssDNA tail RecBCD
Intact Homolog
3' ssDNA invasion RecA
8
Holliday junction formation Branch migration RecA, RuvAB and RecG
9
10

**Figure 7-8. Models for recombinational repair of secondary DNA lesions (daughter strand gaps and double strand breaks) induced by cisplatin damage.** Models based upon references [388,389]. _(a) Daughter Strand Gap Pathway_. (Step 1) The replication complex encounters persistent cisplatin DNA adducts (perhaps due to poor NER of the 1,2 intrastrand crosslink). Stalled replication results in the formation of a daughter strand gap opposite the adduct. The presence of an adduct binding protein (ABP) may present an even stronger block to replication than the adduct alone. (Step 2) Interactions between the proteins of the RecFOR pathway and the replication fork initiate RecA nucleation and strand exchange. (Step 3) The ensuing RecA catalyzed strand exchange (with the aid of the RecFOR accessory proteins) results in the formation of a Holliday junction. (Step 4) Branch migration of the Holliday junction catalyzed by the RecA, RuvAB or RecG proteins results in the repair of the daughter strand gap and restoration of the replication fork. (Step 5) Resolution of the Holliday junction by RuvC restores two double stranded DNA molecules. This could be a mechanism of damage tolerance as the cisplatin adduct is bypassed by recombinational repair and persists in the DNA. _(b) Double Strand Break Pathway_. (Step 6) The replication complex encounters an unrepaired daughter strand gap or a nick opposite the adduct. Collapse of the replication fork forms a double strand break and a daughter strand gap; the daughter strand gap portion of the collapsed replication fork is processed by the daughter strand gap pathway (a). There are other mechanisms by which the double strand breaks could arise, and we have presented only one scenario. *By the proposed scheme, repair of the double strand breaks requires an intact homologue of the damaged duplex*. (Step 7) The RecBCD complex (shown in red) binds the free end of the double strand break and generates ss DNA that is a substrate for RecA nucleation. (Step 8) RecA nucleoprotein filaments catalyze the invasion of the RecBCD generated ss tail into the homologous duplex. (Step 9) RecA catalyzed strand exchange and branch migration results in the formation of a Holliday junction and restoration of the replication fork. (Step 10) Resolution of the Holliday junction by RuvC yields two intact duplexes (only one molecule is shown).

Table 7-1. Genotypes of *E. coli* K-12 strains.

| Strain | Genotype | Source |
|---|---|---|
| AB1157 | *thr-1 ara-14 leuB6* – (*gpt-proA*)62 *lacY1 tsx-33 glnV44*(AS) *galK2*(Oc) *hisG4*(Oc) *rfbD1 mgl-51 rpoS396*(Am) *rpsL31*($Str^R$) *kdgK51 xylA5 mtl-1 argE3*(Oc) *thi-1* | E.A. Adelberg |
| AB2500 | As AB1157 but *uvrA6 deoB16 thyA12* | W.D. Rupp |
| AM207 | As AB1157 but *recR252*::mTn*10* | R.G. Lloyd |
| AM547 | As AB1157 but Δ*ruvABC65* | R.G. Lloyd |
| C266 | As AB1157 but *recG258*::Kan | F. Stahl |
| CS85 | As AB1157 but *ruvC53 eda51*::Tn*10* | R.G. Lloyd |
| GM5560 | As AB1157 but *recA56 srl300*::Tn*10* | Lab stock |
| GM5593 | As AB1157 but *uvrA6 ruvA60*::Tn10 | Lab stock |
| GM5598 | As AB1157 but *uvrA6 ruvC64*::Kan | Lab stock |
| GM7330 | Δ*lacMS286*ϕ*80*dII*lacBK1 ara thi*(?) | Lab stock |
| GM7522 | As AB1157 but *uvrA6 recBCD*::Kan | Lab stock |
| JC5519 | As AB1157 but *recB21 recC22* | A.J. Clark |
| JC3913 | As AB1157 but *uvrA6 recF143* | M. Volkert |
| JC9239 | As AB1157 but *recF143* | A.J. Clark |
| KM21 | As AB1157 but Δ*recBCD*::Kan | K.M. Murphy |
| KM353 | As AB1157 but *recD1901*::Tn*10* | K.M. Murphy |
| N2057 | As AB1157 but *ruvA60*::Tn*10* | R.G. Lloyd |
| N2445 | As AB1157 but *recO1504*::Tn5 | R.G. Lloyd |
| N3398 | As AB1157 but *recG258*::Kan *ruvC53 eda51*::Tn*10* | R.G. Lloyd |

All strains are $F^-$. Abbreviations used: Am, *amber* mutation; AS, *amber* suppressor; Δ, deletion; Oc, ochre mutation; Str, streptomycin; Kan, kanamycin; Tn*5* and Tn*10* encode kanamycin and tetracycline resistance respectively; mTn*10*, miniTn*10*.

# Chapter 8. MutS Preferentially Recognizes Cisplatin Over Oxaliplatin Modified DNA

Cisplatin (*cis*-diamminedichloroplatinum(II), Figure 8-1) is a DNA damaging drug that has shown success in the treatment of testicular, ovarian and other tumors[35]. The detailed biochemical mechanism underlying the clinical effectiveness of cisplatin is incompletely understood, but most likely it results from the formation of DNA adducts that block replication and elicit a variety of cellular responses including nucleotide excision repair[3,8], recombinational repair[415], and the triggering of apoptosis [16]. Cisplatin forms predominantly 1,2-d(GpG), 1,2-(ApG) and 1,3-d(GpNpG, where N is any nucleotide) intrastrand adducts (>90%), and a small number of monofunctional adducts and interstrand crosslinks[2,53]. The 1,2-intrastrand cisplatin-DNA adducts induce significant distortions of the double helix and provide a structural signal for specific recognition by a variety of cellular proteins, including those involved in mismatch repair[6,8,175,241].

Mismatch repair maintains genomic integrity by correcting polymerase replication errors and by ensuring the fidelity and frequency of recombination events[20,321,322]. In eukaryotes, mismatch repair also plays a role in apoptotic signaling and cell cycle regulation[16,323]. It has been established that mismatch repair proteins mediate the cellular responses to cisplatin damage, but paradoxically they seem to sensitize rather than protect the cell. In both, *E. coli* and eukaryotes, loss of mismatch repair confers cellular resistance to cisplatin cytotoxicity[8,347,350,416,417]. Cisplatin-resistance by tumors (mismatch repair deficient) presents a serious clinical problem[418], and it has stimulated a great deal of interest in the design of novel platinum compounds that would overcome this drawback. One of the earliest leads involved complexes with diammiocyclohexane (DACH) carrier ligand[419], such as oxaliplatin ((*trans-R,R*)-(DACH)oxalatoplatinum(II), Figure 8-1) and Pt(DACH)$Cl_2$ ((1,2-DACH)dichloroplatinum(II), Figure 8-1). Loss of mismatch repair does not seem to confer resistance to oxaliplatin[416], and in recent years, oxaliplatin has shown great potential for clinical use[419,420]. Oxaliplatin and Pt(DACH)$Cl_2$ form a similar DNA adduct profile to cisplatin[421,422], and modeling studies have suggested that the adducts of both, cisplatin and DACH, could induce similar distortions of secondary DNA structure[423]. Adducts of the DACH compounds differ from cisplatin by their bulky, nonpolar ligand that probably protrudes in the major groove. The presence of the nonpolar cyclohexane ligand in the mostly polar major groove would certainly present a distinct recognition environment for the mismatch repair proteins or any other cellular proteins that interact with platinum adducts. For example, high mobility group 1 (HMG-1) box proteins, which recognize cisplatin-DNA adducts with great affinity[3], poorly recognize DACH-DNA adducts[424].

We set out to examine if the differential mismatch repair-mediated cellular responses to the cisplatin and DACH compounds result from differential recognition of their platinum-DNA adducts by mismatch repair proteins. The eukaryotic mismatch repair proteins hMSH2[17] and MutS$\alpha$[18] bind to oligonucleotides modified to contain the major cisplatin-DNA adduct, an 1,2-d(GpG) intrastrand crosslink. To date, however, there have been no studies of the interaction of their bacterial homologue, MutS, with DNA modified with cisplatin or DACH compounds. To address this gap in knowledge, we examined the interactions of MutS with oligonucleotides differentially modified with platinum compounds. In addition, we assembled a panel of *E. coli* mutants deficient in the major mismatch repair and recombination pathways and we compared their sensitivity to treatment with the cisplatin and DACH compounds.

## Materials and Methods

*Preparation of platinum-modified DNA probes.* Platinum compounds were purchased from Sigma-Aldrich, except for $Pt(EN)Cl_2$ (*cis*-ethylenediammine dichloroplatinum(II)) and $[Pt(DIEN)Cl]^+$ (diethylenetriamine platinum(II)chloride), which were synthesized as previously described[425,426]. Oxaliplatin was a generous gift from Dr. S.B. Howell, UCSD. Platinum-modified DNA probes were prepared as previously described[17]. In brief, restriction enzyme digests of pSTR3 with *Cla*I and *Eco*RV yielded 162-bp and 4205-bp restriction fragments. DNA probes of 162-bp were purified from the 4205-bp restriction fragment on native 5% polyacrylamide gels. Platination reactions of the restriction fragment were carried out in a 3 mM NaCl, 1mM $Na_2HPO_4$ (pH 7.4) with 100 µg per ml DNA and appropriate platinum compound:DNA molar ratios by incubating at 37 °C for 16 h. Unreacted platinum compounds were removed by dialysis (24 h) against 10 mM Tris-HCl buffer (pH 8.0), 1 mM EDTA (TE). Levels of platinum modification were determined by flameless atomic absorption spectroscopy on a Varian AA1475 instrument equipped with a GTA95 graphite furnace. DNA probes of 162-bp were radiolabeled with $[\gamma\text{-}^{32}P]$dATP (6000 Ci $mmol^{-1}$, New England Nuclear) and resuspended in TE to 5000-10000 counts per minute (cpm) per µl. It should be noted that for oligonucleotide modifications we used *(trans R,R)*-$Pt(DACH)Cl_2$ whose chloride leaving groups differ from the oxalato group of oxaliplatin. However, following biotransformation both compounds should form identical adducts with DNA. $^1H$-NMR spectroscopic analysis of the $Pt(DACH)Cl_2$ compound was used to demonstrate that the compound was in the *trans-R,R* conformation.

*Protein Purification.* MutS was purified as previously described[427]. The host strain was BL21 (λDE3) (pLysS) and the plasmid used was pMQ372[428]. In brief, the strain was transformed with pMQ372 and grown at 37 °C to an $A_{600}$ of 0.8, shifted to room temperature, and isopropyl-1-thio- -D-galactopyranoside (IPTG) was added to 50 µM final concentration. Incubation was continued for 2 h at room temperature, and the cells were harvested and lysed in a French pressure cell (Aminco). The lysate was treated with streptomycin sulfate and ammonium sulfate as described[427]. We used a heparin agarose column (Sigma) instead of heparin Sepharose. Two fractions (IVa and IVb) from the hydroxylapatite chromatography were saved and stored at -70 °C. The IVb fraction was used in the binding assays. Protein concentration was assayed using the Bradford reagent (Bio-Rad).

*Binding assays.* Binding assays contained radiolabeled 162-bp DNA probes (present at 100-200 pM, 5000-10000 cpm) either unmodified or modified with platinum compounds, and purified MutS present at 0-300 nM concentration. Binding reactions were carried out in a 15 µl volume containing 20 mM Tris base, 5 mM $MgCl_2$, 2.5 mM $CaCl_2$, 0.1 mM DTT, 0.01 mM EDTA, and 50 ng of nonspecific competitor chicken erythrocyte DNA. The binding reactions were incubated for 30 min on ice. Samples were then loaded onto 4% (29:1 acrylamide:bis) native gels containing TAE buffer (90 mM Tris base (pH 8.0), 2.0 mM EDTA, 90 mM boric acid) and 5% sucrose, and separated by electrophoresis at room temperature in TAE buffer at ~25 mA (140V) for 2 h. Amounts of bound and unbound radiolabeled probe were determined by quantitative analysis of gels using a Molecular Dynamics Storm system and ImageQuant software. The $K_{d(app)}$ was determined by a nonlinear least squares fitting of the binding data to the standard Hill equation. In the reactions that contained nucleotides, ADP or ATP (Roche) was added to a 100 µM reaction concentration. Titration of increasing amounts of ADP (up to 300 µM) did not further increase the percentage of MutS bound to the modified probes.

*Bacterial Strains.* The strains used in this study are listed in Table 8-1. The strains are derivatives of GM112, used in the toxicity experiments with the mismatch repair and methylation deficient mutants, or AB1157, used in the experiments with the recombination deficient mutants. The auxotrophic phenotype of each mutant was conformed by growth on the appropriate supplemented minimal medium.

*Cytotoxicity analysis*. Overnight cultures were diluted 1000-fold and grown in Luria-Bertani (LB) medium until the density of the population reached 2 x $10^8$ cells/ml as determined by $OD_{600}$. The exponentially growing cells were resuspended in M9 minimal medium[393] and treated with drug dissolved in $H_2O$ for 2 h at 37 °C. Appropriate dilutions in M9 medium were plated on LB plates and incubated at 37 °C until colonies could be counted. Results from three to six independent experiments plated in duplicate were averaged and plotted against drug concentration, ± SEM (standard error of the mean). $IC_{37}$ (inhibitory concentration of 37%) was determined as the drug concentration where there was 37% of survival in comparison to the untreated control.

## Results

**MutS preferentially binds to DNA globally modified with cisplatin.** To examine if the bacterial MutS binds to DNA modified to contain cisplatin adducts, purified *E. coli* MutS was used in an electrophoretic mobility shift assay with DNA globally modified by cisplatin. Three types of globally modified cisplatin duplexes were constructed that differed in the level of modification: (i) Cisplatin-3 had, on the average, three cisplatin adducts per oligonucleotide molecule (drug-to-nucleotide ratio ($r_b$) = 0.0009), (ii) Cisplatin-7 had seven adducts per oligonucleotide ($r_b$ = 0.0021), and (iii) Cisplatin-11 had eleven adducts per oligonucleotide ($r_b$ = 0.0033). Binding of MutS to these radiolabeled 162-base pair (bp) probes was readily observed by the retarded band migration that represented the bound probe (Figure 8-2). The fraction of bound probe increased proportionately as the cisplatin modification level increased, 4.9% for Cisplatin-3, 12% for Cisplatin-7, and 30% for Cisplatin-11. The increased fraction of shifted material was probably due to an increasing population of modified DNA, reinforcing the specific nature of the interaction.

In the same assay, we examined the ability of MutS to recognize DNA modified with DACH adducts. The probe DACH-9 had on the average nine DACH adducts per DNA molecule ($r_b$ = 0.0027). MutS showed affinity for the DNA modified with DACH adducts, but the fraction of the shifted material was lower in comparison to the cisplatin-modified probes, showing only 2.9% bound probe for DACH-9 (Figure 8-2). Under identical conditions the MutS protein did not cause a shift of the corresponding control unmodified homoduplex. To assess if the recognition of the globally modified cisplatin duplex were a consequence of nonspecific MutS interactions, we examined the interaction of MutS with the identical DNA modified by the panel of platinum compounds shown on Figure 8-1. It is of interest to note that the electrophoretic mobility of the modified probes in the absence of MutS reflects the differential structural distortions the respective adducts induce to the double helix[3,80]. As mentioned, cisplatin induces strong directional bend and distortion of the double helix, and higher levels of modification with cisplatin result in significantly altered electrophoretic mobility of the oligonucleotide. Other platinum compounds do not induce strong bending and unwinding of the double helix and, as a result, even high levels of modification do not alter the mobility of the oligonucleotide: *trans*-DDP (*trans*-diamminedichloroplatinum(II)) adducts induce a hinge-like bend in the DNA, while $[Pt(DIEN)Cl]^+$ produces only minimally disruptive monofunctional adducts. MutS showed affinity for the DNA modified with adducts of the cisplatin analog $Pt(EN)Cl_2$, an analog with an ethylenediammine (EN) ligand. The $Pt(EN)Cl_2$ modified 162-bp probe had on the average seven EN adducts ($r_b$ = 0.0021) and the fraction of the MutS bound probe was 3.4%. This result is in line with previously published data that have shown that $Pt(EN)Cl_2$ modified DNA is recognized by the MutS homologue hMSH2[17]. In contrast, MutS had low affinity for DNA that contained adducts of the clinically inactive platinum complexes *trans*-DDP and the monofunctional $[Pt(DIEN)Cl]^+$ (1.1% and 0.4% bound probe, respectively) even though, on the average, the *trans*-DDP modified oligonucleotide contained ten ($r_b$ = 0.0030) and the DIEN-modified oligonucleotide contained thirteen platinum adducts ($r_b$ = 0.0039). The specificity of the interactions of MutS with the cisplatin-, EN-, and DACH-modified oligonucleotides was confirmed by competition band-shift experiments (described in detail[17], data not shown).

**Specificity of MutS binding to cisplatin- and DACH- DNA adducts.** To characterize the nature of the interaction between MutS and cisplatin- or DACH-modified DNA further, MutS protein

was titrated into binding reactions containing a constant concentration of duplex DNA modified by adducts of the two drugs (Figure 8-3a). The 162-bp oligonucleotide used in this experiment contained, on the average, seven cisplatin adducts (Cisplatin-7) or nine DACH adducts (DACH-9) per duplex DNA molecule (one cisplatin adduct per 23 bp, and one DACH adduct per 18 bp). The addition of increasing amounts of protein caused the complex to be proportionally shifted through the gel, presumably because multiple protein complexes bound to the multi-platinated probes. The binding isotherm (Figure 8-3b) reveals that the fraction of bound platinated DNA increases to saturation over a narrow range of MutS concentrations, consistent with positive cooperative binding (Hill coefficient, $n_H = 2.9$ for Cisplatin-7; $n_H = 2.7$ for DACH-9). The observed apparent cooperative binding behavior may be a consequence of multiple platinum sites situated in close proximity in the duplex DNA. MutS produces a 20 bp DNaseI footprint at a mismatch site[427] and, the crystal structure reveals protein DNA contacts that extend to thirteen nucleotides proximal to the mismatch[429,430]. The binding of a MutS dimer to an adduct may render the subsequent binding of a second MutS dimer to a nearby platinum adduct more favorable or it may facilitate the formation of higher-ordered MutS complexes (tetramers and higher oligomers) that have been observed in experiments with high MutS (or MutSα) concentrations (unpublished data,[431]). Generation of the binding isotherm yielded a $K_{d(app)} = 57$ nM for the cisplatin-modified probe and $K_{d(app)} = 120$ nM for the DACH-modified probe. Neither the active fraction of our MutS preparation nor the aggregation state of the protein were established; thus, our estimation of the dissociation constant assumes that MutS binds as a dimer and that 100% of the protein is active in binding. These considerations, taken together with the observed complex nature of the MutS-DNA interactions, dictate that the dissociation constant should be considered an approximation of the affinity of MutS for the platinum modified DNA. However, the value obtained for the interaction of MutS cisplatin-modified DNA is in accordance with the previously reported value for the interaction of hMSH2 with a cisplatin-modified probe of similar size and level of modification [17]. No previous reports of MutS binding to DNA modified with DACH adducts exist for comparisons.

**Nucleotide effects on MutS binding to DNA modified to contain platinum adducts.** Nucleotide (ATP or ADP) binding to MutS mediates the conformation of the protein dimer and its binding affinity for DNA and mismatches. Addition of ATP to mismatch-bound MutS can cause the protein to dissociate or translocate from the mismatch, whereas addition of ADP stimulates MutS binding[431-433]. To investigate the effects of nucleotides on the interaction of MutS with platinum-modified DNA, ATP or ADP was added to a binding reaction containing MutS and the previously described platinum modified probes (Figure 4a). In the binding reactions that contained DNA probes modified with cisplatin adducts, the addition of ADP increased the proportion of the shifted probe, while the addition of ATP caused a decrease in the portion of the shifted probe (Figure 8-4b). For the Cisplatin-7 probe, the addition of ADP increased the amount of the shifted probe 1.8 fold, from 13 ± 2.1% to 23.9 ± 1.5%, while addition of ATP decreased the amount of shifted probe by a factor of 2, from 13.5 ± 2.1% to 7.4 ± 1.3%. Similar nucleotide effects were observed with the Cisplatin-3 and the Cisplatin-11 probe (Figure 8-4b). In contrast to the results with cisplatin-modified probes, addition of ADP to the binding reactions that contained DNA modified with DACH- or EN-adducts did not increase the percentage of binding observed; actually, it slightly decreased it from 4.6 ± 0.65% to 3.4 ± 0.54% and from 4.2 ± 0.30% to 3.5 ± 0.95%, respectively. The addition of ATP to the binding reaction containing the DACH- and EN- modified probes also resulted in a decrease of the fraction of the bound probe.

**Sensitivity of methylation and mismatch repair deficient mutants to cisplatin analogs.** Methylation deficient (*dam*) mutants in *E. coli* show high sensitivity to cisplatin, and this sensitivity is abrogated by additional mutations in either of the mismatch repair genes MutS or MutL (repeated in Figure 8-5b,[14]). The biochemical basis for this observation is not known, but it is has been proposed that it involves mismatch repair initiated cycles of futile repair of cisplatin adducts (due to the absence of a strand discrimination signal in the *dam* mutants). We examined the survival of *dam, dam mutS,* and *dam mutL* mutants following treatment with increasing concentrations of $Pt(DACH)Cl_2$ (Figure 8-5a). The wild type showed higher sensitivity to equimolar $Pt(DACH)Cl_2$ than cisplatin, which was expected since higher toxicity for DACH compounds has been previously

reported in other systems[419]. The methylation deficient *dam* mutants demonstrated high sensitivity to both drugs in comparison to the wild type. When compared, the wild type/*dam* $IC_{37}$ ratios for both compounds revealed that the *dam* mutants were ~2 fold more resistant to $Pt(DACH)Cl_2$ than cisplatin. The $IC_{37}$ ratio was 1.4 for $Pt(DACH)Cl_2$ ($IC_{37\ wild\ type}$= 21 μM, $IC_{37\ dam}$= 15 μM) and 2.7 for cisplatin ($IC_{37\ wild\ type}$= 73 μM, $IC_{37\ dam}$= 27 μM). This difference could reflect the degree of sensitivity added by the *dam* mutation, presumably because of the previously discussed abortive repair model. Introduction of an additional mutation in the mismatch repair gene MutS or MutL (*dam mutS, dam mutL*) abrogated the *dam* sensitivity to $Pt(DACH)Cl_2$ and cisplatin to similar levels. Similar results were observed in experiments where oxaliplatin was used in place of $Pt(DACH)Cl_2$ (data not shown).

**Recombination deficient mutants are equally sensitive to cisplatin and DACH compounds.** Cisplatin-DNA adducts present strong blocks to replication *in vitro* and *in vivo*[8,392], and these frequent replication blocks require various recombination pathways for their repair or tolerance[415]. DACH adducts also present replication blocks, and it has been shown *in vitro* and *in vivo* that the DACH-DNA adducts are bypassed more efficiently than cisplatin adducts by various polymerases[319,434,435]. We examined if there would be a difference in *E. coli* in the capacity of the two drugs to induce replication-blocking lesions that would require recombination for their repair. We determined the sensitivity of a panel of mutants deficient in the major pathways of recombination to increasing concentrations of DACH compounds. The *recF* mutant is deficient in repair of daughter strand gaps that follow replication blocks and it is sensitive to UV treatment[397]. The *ruvABC* mutant is deficient in branch migration and resolution of various recombination intermediates such as Holliday junctions, and these mutants are sensitive to certain types of DNA damage, including UV treatment, cisplatin and gamma irradiation[406]. The *recBCD* mutants are deficient in the repair of double strand breaks and are sensitive to gamma irradiation[400]. As shown on Figure 8-6a, all of the mutants tested showed sensitivity to treatment with $Pt(DACH)Cl_2$. These results are comparable to the cisplatin sensitivity previously reported for this panel of mutants, shown here in Figure 8-6b for better comparison[415]. Taken together these data suggested that cisplatin and DACH compounds require recombinational repair for cellular survival, presumably because in *E. coli* both types of adducts present replication blocks. A similar pattern of sensitivity was observed when the strains were treated with oxaliplatin (data not shown).

## Discussion

Mismatch repair deficient cells have shown differential sensitivity to the two platinum analogs, cisplatin and oxaliplatin, and several mutually non-exclusive mechanisms have been proposed that account for this observation. Mismatch repair could initiate abortive repair of the cisplatin-DNA adducts, selectively inhibit their replicative or recombinational bypass, or directly trigger apoptotic signaling. A key common upstream event in these proposed mechanisms is the recognition of platinum-DNA adducts by mismatch repair proteins. Our hypothesis is that mismatch repair proteins preferentially recognize cisplatin over oxaliplatin DNA adducts and that this preferential recognition leads to the observed cellular responses. Because of the differential responses to the two drugs, it has been assumed that mismatch repair proteins do not interact with DNA modified to contain DACH adducts.

Our results showed that MutS recognized both types of adducts, but it recognized DNA modified with cisplatin with a 2-fold higher affinity than DNA modified with DACH. This 2-fold difference could be clinically significant, especially when it is considered that mismatch repair proteins have only 10-20 fold higher affinity for mismatches than they have for homoduplex DNA[436]. The recently reported crystal structure of MutS may provide clues to explain the weaker MutS interactions with DACH-modified DNA[429,430]. While the bending and unwinding caused by a cisplatin adduct would favor MutS recognition and possibly intercalation of MutS residues in the double helix, the non-polar DACH ligand would likely protrude into the major groove where it could disrupt

the non-specific, polar major-groove interactions between the positively charged surface of the clamp portion of MutS and the phosphate backbone.

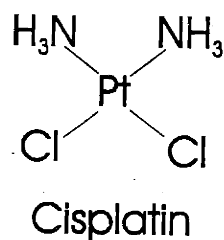
Another difference, specific for the MutS interaction with cisplatin-modified DNA, was observed when nucleotides were added to the binding reaction. Addition of ADP increased the MutS affinity for the cisplatin modified DNA, but it did not have an observable effect on the affinity of MutS for DNA modified with DACH- or EN-adducts. The function of nucleotide hydrolysis in the function of MutS, or its mammalian homologues, is currently unclear. It could provide the energy for bi-directional DNA scanning[333] or it could form a molecular switch, signaling between ADP bound/ON and ATP bound/OFF states to downstream components[431,437]. These downstream components include the remainder of the mismatch repair machinery and, in eukaryotes, possibly apoptotic pathways as well. It has been shown that cisplatin-DNA damage can trigger c-Abl/p73 mismatch repair mediated apoptosis[16]. This response is absent in mismatch repair deficient cells, and oxaliplatin failed to show detectable activation of JNK or c-Abl kinases regardless of the mismatch repair status of the cells[438]. It is possible that the selective ADP modulation of MutS binding to cisplatin adducts underlies a potential mechanism of specific, damage recognition signaling.

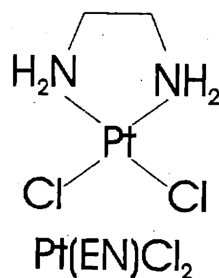
In parallel to the MutS binding assays, survival experiments showed that the methylation deficient mutants *dam* were more sensitive to cisplatin than DACH compounds. This comparison was made at doses of cisplatin and $Pt(DACH)Cl_2$ that were equally toxic to wild type cells. In *dam* mutants, where the strand discrimination signal is absent, mismatch repair could in principle initiate futile cycles of abortive repair opposite platinum adducts[14]. In support of this model, an additional mutation in mismatch repair genes abrogates the cisplatin sensitivity. This model has been extrapolated to account for the cisplatin resistance of eukaryotic mismatch repair deficient cells as well[17]. If abortive repair were operational, preferential recognition of cisplatin in comparison to DACH adducts should lead to higher level of abortive repair in *dam* mutants. The abortive repair phenomenon would lead to enhanced toxicity. Our results support this model to the extent that the 2-fold higher sensitivity of the *dam* mutants to cisplatin in comparison to $Pt(DACH)Cl_2$, parallels the 2-fold higher affinity of MutS for cisplatin over DACH-modified DNA. These results are also in line with studies done in mismatch repair deficient cells lines where it has been observed that defects in mismatch repair result in increased cisplatin, but not oxaliplatin, resistance[350].

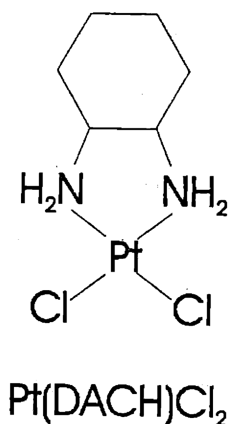
It is also possible that mismatch repair proteins could mediate cisplatin toxicity by inhibiting replication or recombination dependent bypass of platinum DNA adducts. Studies have shown that DACH compounds are more efficiently bypassed by eukaryotic polymerases in comparison to cisplatin adducts[434,435]. Our survival experiments showed that recombination deficient mutants were strikingly, but equally sensitive to both cisplatin and DACH compounds. This result suggests that the primary mechanism of cytotoxicity for both types of compounds, at least in *E. coli*, involves the formation of DNA adducts that form replication blocks requiring recombination for repair. In this respect, it is possible that in eukaryotic cells other factors, such as protein binding, significantly contribute to the selective inhibition of replicative bypass by cisplatin adducts. For example, the mammalian HMG-1 box protein can selectively inhibit translesion synthesis of cisplatin over oxaliplatin damaged templates, presumably because of a stronger affinity of HMG-1 for cisplatin over oxaliplatin DNA adducts[424], and the replicative bypass of cisplatin adducts is enhanced when a mismatch repair inactivating mutation is introduced[439]. It is possible that in our study the replication blocks, at least in part, were also a consequence of preferential interactions of cellular proteins, such as MutS, with cisplatin adducts.

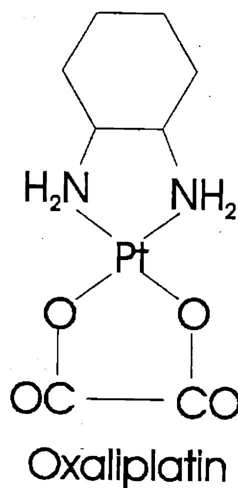
In addition to the models for mismatch repair mediated responses to cisplatin and oxaliplatin discussed above, other, yet undiscovered mechanisms by which these compounds contribute to cellular toxicity could exist. Since oxaliplatin and $Pt(DACH)Cl_2$ are more toxic than cisplatin for equimolar doses yet have a substantially lower rate of formation of DNA adducts in comparison to cisplatin[421], it is possible that the cellular responses to the DACH compounds are

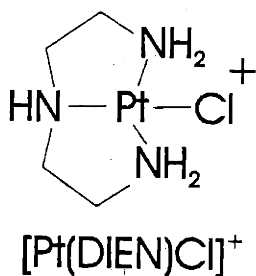
significantly modulated by their interactions with proteins or other cellular components. Our results add information to the biochemical framework within which the differential cellular responses to the two platinum analogs can be viewed. Further biochemical elucidations within this framework could have clinical importance in that they may lead to the development of novel successful anti tumor drugs based on the parental structure of cisplatin.



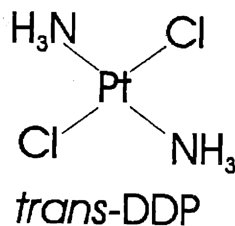




**Figure 8-1. The structures of cisplatin and cisplatin analogs used in this chapter.** Cisplatin, $Pt(EN)Cl_2$, oxaliplatin and $Pt(DACH)Cl_2$ are therapeutically active platinum complexes and they all have chloride ligands in cis geometry. Oxaliplatin and $Pt(DACH)Cl_2$ have different leaving groups, but they form identical DNA adducts. The trans isomer of cisplatin, *trans*-DDP and $Pt(DIEN)Cl_2$, are clinically ineffective cisplatin analogs.

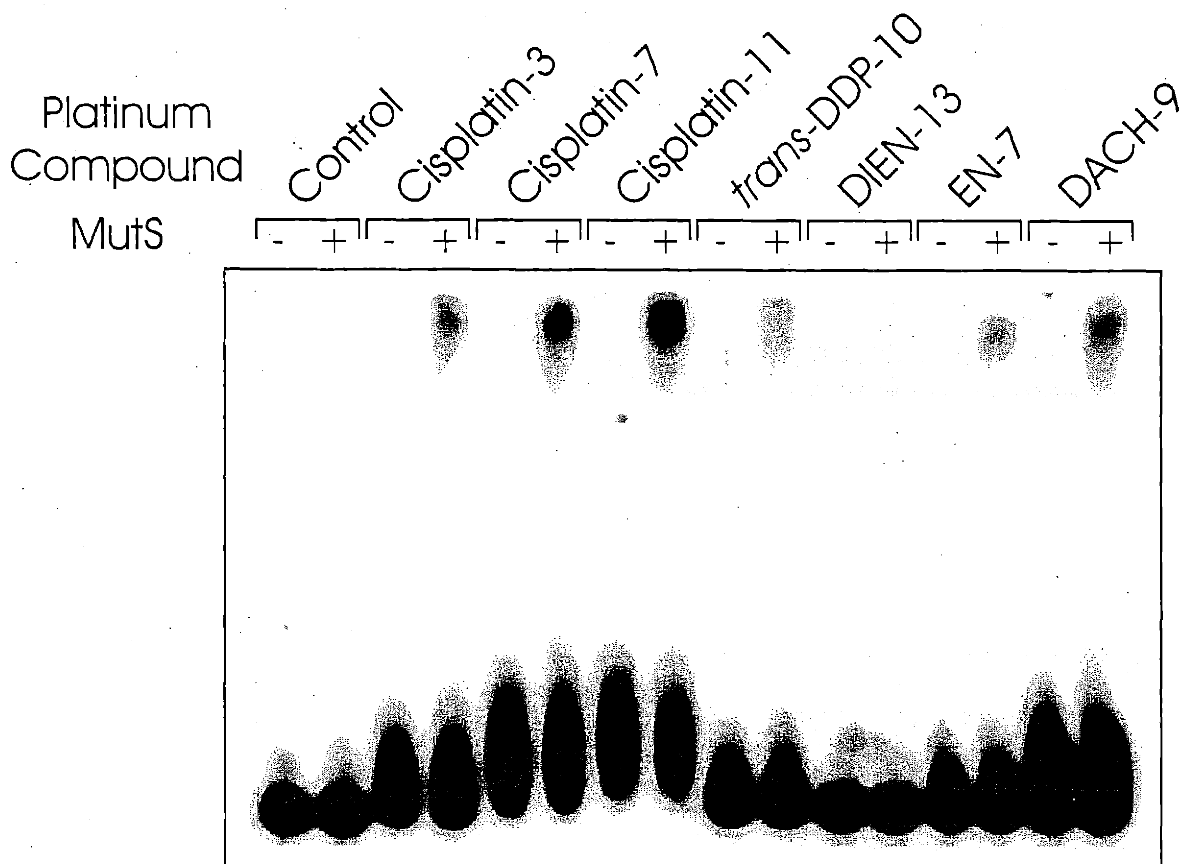
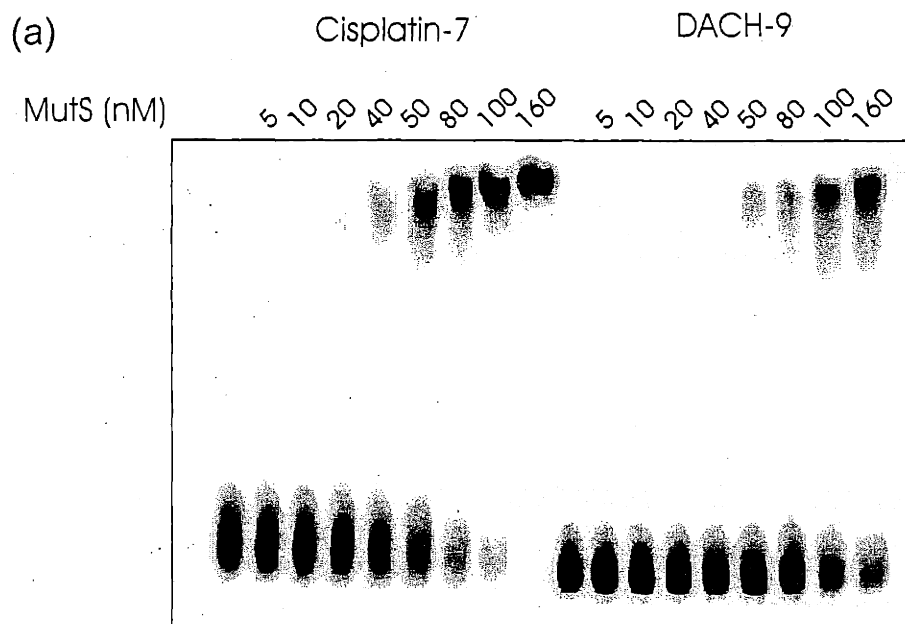



**Figure 8-2. Selectivity of MutS for DNA modified with therapeutically active platinum compounds.** A radiolabeled 162-bp probe was modified to contain 3, 7, and 11 cisplatin adducts, 10 *trans*-DDP adducts, 13 DIEN adducts, 7 EN, and 9 DACH adducts. Unmodified 162-bp probe was used as a control. DNA probes were incubated in the absence (-) or presence (+) of MutS (40 nM). Discrete, shifted bands were observed only when MutS was incubated with DNA modified by the therapeutically active complexes cisplatin, $Pt(EN)Cl_2$ and $Pt(DACH)Cl_2$. The binding of MutS to the cisplatin modified probes increased as the degree of cisplatin modification increased.



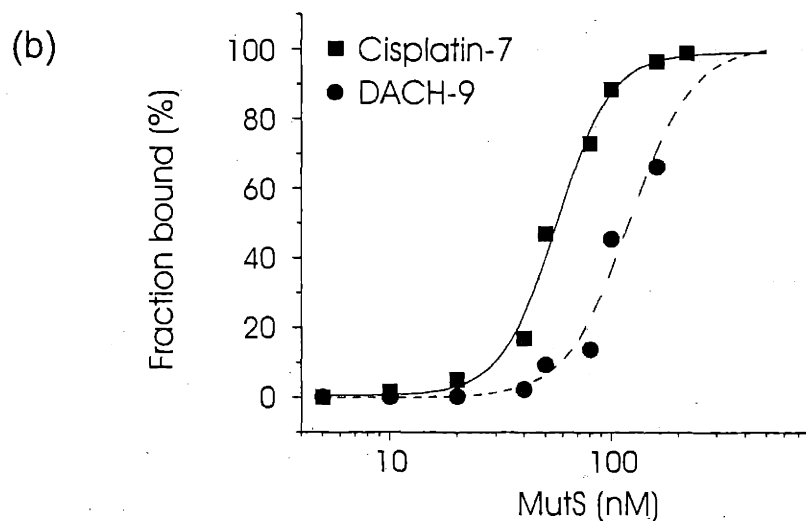
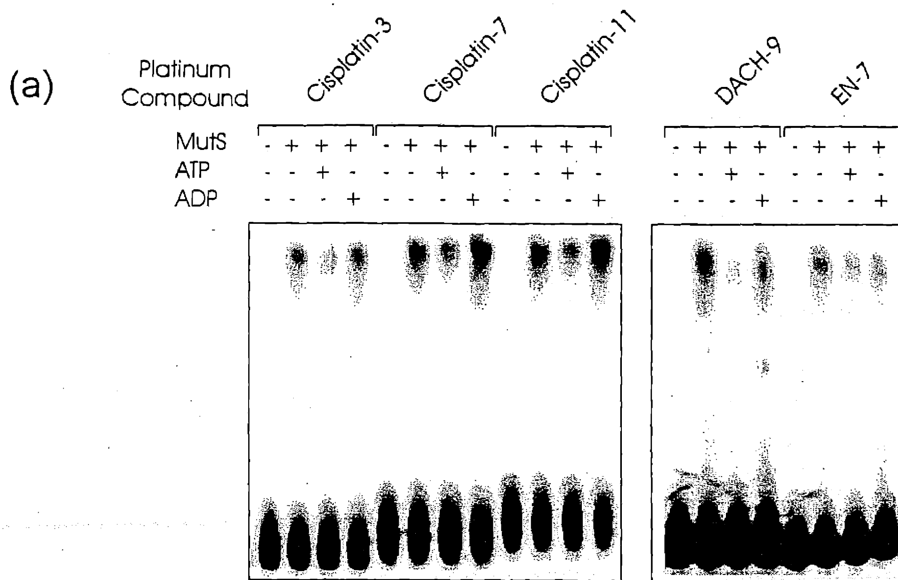




**Figure 8-3. Binding isotherm describing the interaction between MutS and cisplatin- and DACH-modified DNA.** *(a)* MutS protein was titrated into binding reactions containing radiolabeled 162-bp probe that contained an average of seven cisplatin adducts or nine DACH adducts. *(b)* The fraction of bound probe in each lane was quantitated by Storm Phoshopimager analysis and is presented as a function of the concentration of MutS present in the binding reactions. Fitting these binding data to the Hill equation generated the binding curve.



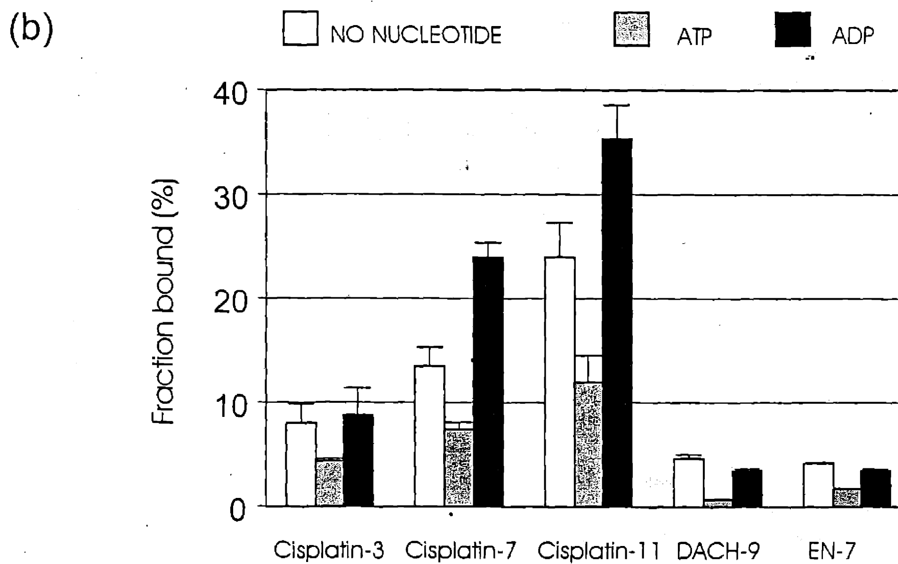
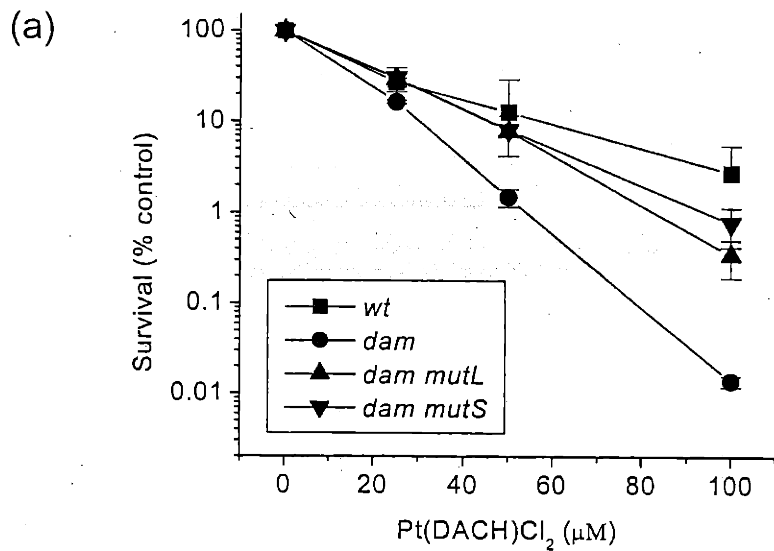




**Figure 8-4. Effects of nucleotides on binding of MutS to platinated DNA.** A radiolabeled 162-bp probe modified to contain three, seven and eleven cisplatin-adducts, nine DACH-adducts and seven EN-adducts was incubated with MutS (40 nM). ATP or ADP was added to the binding reaction to a final concentration of 100 μM. *(A)* Retarded bands were observed similar to the ones in Fig. 1. *(B)* Specific binding diminished with the addition of ATP, while it increased with the addition of ADP to significant levels only when MutS was incubated with cisplatin-modified probes. Mean ± standard deviation (n = 3).



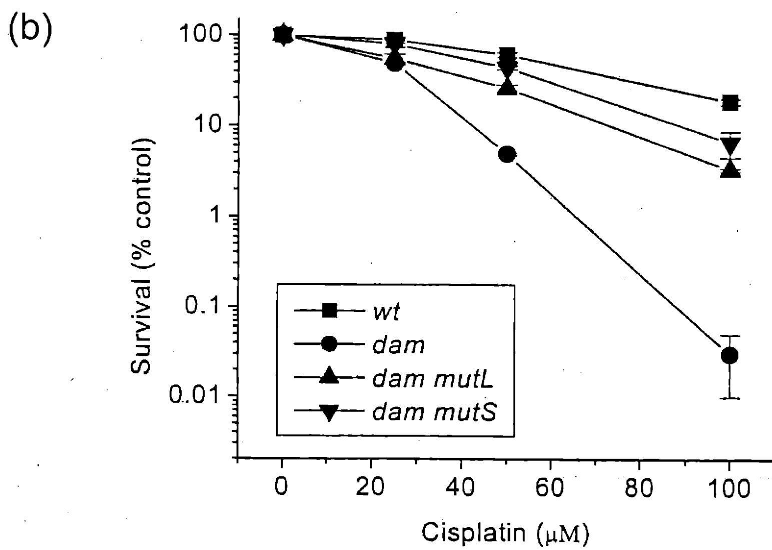
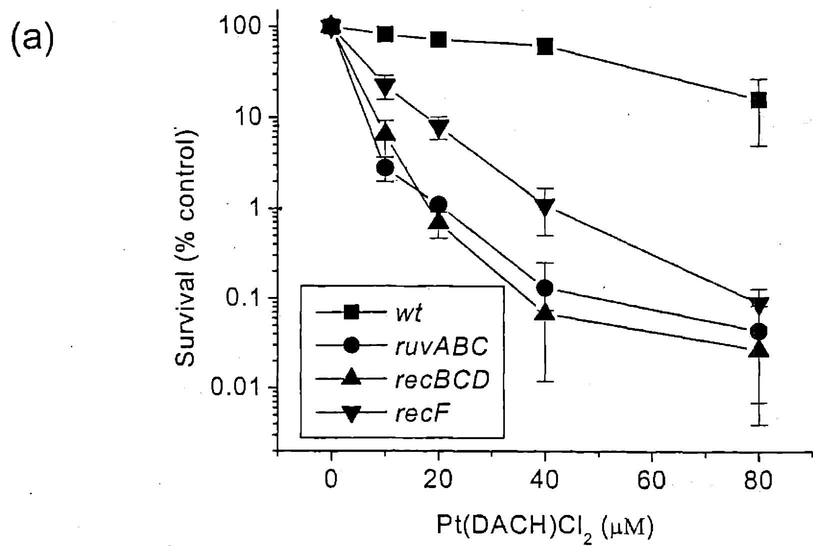




**Figure 8-5. Survival of mismatch repair deficient *E. coli* strains treated with $Pt(DACH)Cl_2$ and cisplatin.** For each data point, results shown are the mean of at least three independent experiments plated in duplicate, ± SEM.



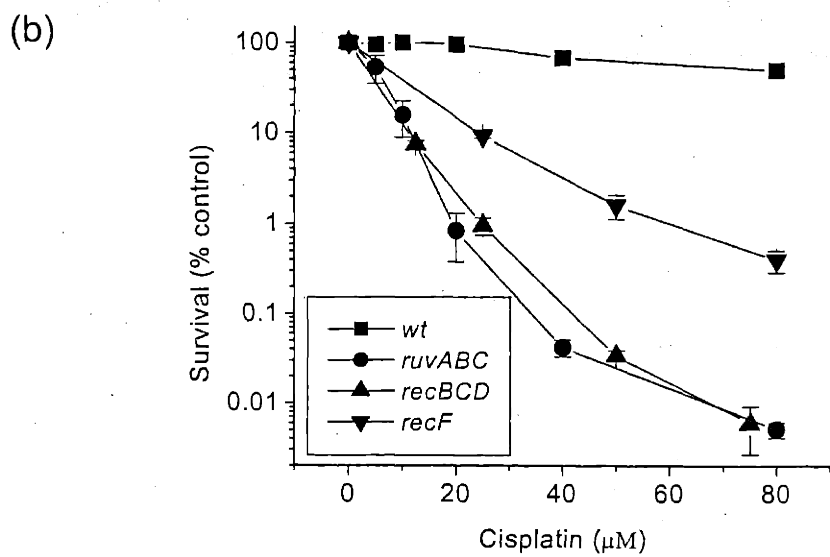




**Figure 8-6. Survival of recombination deficient *E. coli* strains treated with $Pt(DACH)Cl_2$ and cisplatin.** For each data point, results shown are the mean of at least three independent experiments plated in duplicate, ± SEM.

Table 8-1. Genotypes of *E. coli* K-12 strains used in this chapter.

| Strain | Genotype | Source |
|---|---|---|
| AB1157 | *thr-1 ara-14 leuB6* – (*gpt-proA*)62 *lacY1 tsx-33 glnV44*(AS) *galK2*(Oc) *hisG4*(Oc) *rfbD1 mgl-51 rpoS396*(Am) *rpsL31*($Str^R$) *kdgK51 xylA5 mtl-1 argE3*(Oc) *thi-1* | E.A. Adelberg |
| GM112 | F- thr-1 ara-14 leuB6 DE(gpt-proA)62 lacY1 tsx-33 supE44 galK2 hisG4 metB1 rfbD1 mgl-51 rpsL31 kdgK51 mtl-1 thi-1 thyA12 deoB16 | Lab stock |
| GM113 | As GM112 but dam-3 | Lab stock |
| GM150 | As GM112 but mutL451 dam-3 | Lab stock |
| GM169 | As AB1157 but mutS453 dam-3 | Lab stock |
| AM547 | As AB1157 but Δ*ruvABC65* | R.G. Lloyd |
| JC9239 | As AB1157 but *recF143* | A.J. Clark |
| KM21 | As AB1157 but Δ*recBCD*::Kan | K.M. Murphy |

All strains are $F^-$. Abbreviations used: Am, *amber* mutation; AS, *amber* suppressor; Δ, deletion; Oc, ochre mutation; Str, streptomycin; Kan, kanamycin; Tn5 and Tn*10* encode kanamycin and tetracycline resistance respectively.

# Chapter 9. Interactions of the Mismatch Repair Protein MutS With an Oligonucleotide Modified to Contain the Major Cisplatin Adduct, a Single 1,2-d(GpG) Intrastrand Crosslink

Cisplatin (*cis*-diamminedichloroplatinum(II), Figure 9-1) is a successful DNA damaging drug that is used in the treatment of testicular, ovarian and other tumors[35]. Cisplatin forms DNA adducts that block replication and elicit a variety of cellular responses including nucleotide excision repair[3,8], recombination[415], and the triggering of apoptosis[16]. The spectrum of cisplatin-DNA adducts has been well documented: cisplatin reacts with the N7 nitrogen of purines and forms predominantly 1,2-d(GpG) (65% of all adducts), 1,2-d(ApG) (25%), and 1,3-d(GpNpG) (where N is any nucleotide, 5-10%) intrastrand crosslinks and a smaller number of mono-adducts and interstrand crosslinks[2,53]. The 1,2-intrastrand crosslinks induce significant distortions of the double helix, that include unwinding and bending towards the major groove by 35-78°, and flattening and narrowing of the minor grove[5,72]. These distortions provide a structural signal for recognition by a variety of cellular proteins, including those involved in mismatch repair[6,7,241].

Mismatch repair proteins maintain genomic integrity by correcting polymerase errors[20,321] and by ensuring the fidelity and frequency of recombination events[20,321,322]. Mismatch repair is best understood in *E. coli*, where recognition of mispairs is accomplished by the homodimeric complex of the MutS protein[321]. MutS displays variable affinity for the different mispairs and it preferentially recognizes G/T mismatches with affinity that is 10-20 fold higher than that of binding to a homoduplex[427]. In eukaryotes there is a number of MutS homologues that form function specific heterodimers; MutS$\alpha$, a complex formed by MSH2 and MSH6 homologues preferentially recognizes one base mismatches, MutS$\beta$, a complex formed by the association of MSH2 and MSH3 homologues is primarily involved with the recognition of insertion and deletion loops[20,321], and the MSH4 and MSH5 homologues have diverged to play a role in meiotic recombination and crossover[323].

It has been established that mismatch repair proteins mediate the cellular responses to cisplatin damage, but paradoxically they seem to sensitize rather than protect the cell. In both *E. coli* and in eukaryotes, loss of mismatch repair confers cellular resistance to cisplatin cytotoxicity[8,347,416,417]. How mismatch repair proteins contribute to cisplatin toxicity is not understood, but a key step probably involves the recognition of one or more cisplatin-DNA adducts by these proteins. It has been shown that MutS[440] and hMSH2[17] can recognize DNA globally damaged with cisplatin. In addition, it has been shown that hMSH2[17] and hMutS$\alpha$[18] can specifically recognize an oligonucleotide modified with a single 1,2-d(GpG) cisplatin adduct. However, to date there have been no reports of interactions between bacterial MutS and DNA modified to contain a single, site-specific cisplatin adduct. In order to address this gap in knowledge, we constructed oligonucleotides modified to contain a single 1,2-d(GpG) intrastrand cisplatin crosslink (Figure 9-1b),and we examined the interactions of the purified *E. coli* mismatch repair protein, MutS, with the modified probe. MutS specifically recognized the oligonucleotide modified to contain a single 1,2-d(GpG) cisplatin crosslink and, furthermore, MutS recognized the oligonucleotide modified to contain the major cisplatin crosslink with comparable affinity to that shown for an oligonucleotide with a G/T mismatch. These interactions of MutS with DNA modified by cisplatin could underlie physiologically relevant molecular events.

## Materials and Methods

*Preparation of platinum-modified DNA probes.* Oligonucleotides were purchased from Research Genetics and purified by gel electrophoresis to remove failure sequences. Platination

reactions were carried out in 5 mM $Na_3PO_4$ buffer, pH 7.4, at 37 °C for 18-21 h, and the platinated DNA was purified on denaturing polyacrylamide gels. The platination sites were confirmed by Maxam-Gilbert sequencing. The complementary strands (bottom strands in Figure 9-1b) were radiolabeled with [$\gamma$-$^{32}$P] dATP (6000 Ci mmol$^{-1}$, New England Nuclear). The DNA duplexes were hybridized by heating the top and bottom strands for 5 min at 80 °C and then allowing the mixture to cool 14-20 h. The sequences of the DNA duplexes are shown in Figure 9-1b. Concentrations were determined by measuring $A_{260}$.

*Protein purification.* MutS was purified as previously described[427]. The host strain was BL21 ($\lambda$DE3) (pLysS) and the plasmid used was pMQ372[428]. In brief, the strain was transformed with pMQ372 and grown at 37 °C to an $A_{600}$ of 0.8, shifted to room temperature, and isopropyl-1-thio-$\beta$-D-galactopyranoside (IPTG) was added to 50 µM final concentration. Incubation was continued for 2 h at room temperature, and the cells were harvested and lysed in a French pressure cell (Aminco). The lysate was treated with streptomycin sulfate and ammonium sulfate as described[427]. We used a heparin agarose column (Sigma) instead of heparin Sepharose. Two fractions (IVa and IVb) from the hydroxylapatite chromatography were saved and stored at -70 °C. The IVb fraction was used in the binding assays. Protein concentration was assayed using the Bradford reagent (Bio-Rad). The active concentration during this study was determined by comparison with previous band shift experiments and was approximately 10% of the total protein concentration. The inactive protein was removed prior to binding assays by centrifugation (30 sec, 14000 min$^{-1}$).

*Binding assays.* Binding assays contained radiolabeled DNA probes (as indicated, present at 0.1-2.0 nM, 5000-60000 cpm), either unmodified or modified with cisplatin, and purified MutS present at 0-800 nM. Binding reactions were carried out in 15 µl reactions containing 20 mM Tris, 5 mM $MgCl_2$, 2.5 mM $CaCl_2$, 0.1 mM DTT, 0.01 mM EDTA, and 50 ng of nonspecific chicken erythrocyte competitor DNA. Binding was performed for 30 min on ice. Samples were than loaded onto 4% (29:1 acrylamide:bis) native polyacrylamide gels containing TAE buffer (90 mM Tris (pH 8.0), 2.0 mM EDTA, 90 mM boric acid) and 5% sucrose, and separated by electrophoresis at room temperature in TAE buffer at ~ 25 mA (140V) for 2 h. Quantitative analysis was determined by Molecular Dynamics Storm system and ImageQuant software.

## Results

**MutS binds to the major cisplatin adduct.** The observation that MutS binds to DNA globally modified with a low number of cisplatin adducts (three on the average per 162-bp oligonucleotide) [440], suggests that MutS may recognize an oligonucleotide modified with a single cisplatin adduct as well. We constructed a 24-bp probe containing a single, centrally located 1,2-d(GpG) cisplatin crosslink, the major and presumably most cytotoxic cisplatin-DNA adduct (Figure 9-1b), and we examined the binding by purified *E. coli* MutS to the modified probe by a DNA-retardation band shift assay (Figure 9-2). The binding of MutS to the radiolabeled probe modified to contain a 1,2-d(GpG) cisplatin crosslink was readily observed by a discrete, retarded band in the polyacrylamide gel specific to the lanes that included MutS and the platinated probe. The fraction of the retarded band shifted for the platinated probe increased with the increase of MutS concentration. For example, the percentage of the shifted probe doubled (from .6% to 1.2%, relative to the amount of total probe in each lane) when the MutS concentration was increased from 5 nM to 10 nM. Under identical conditions, MutS did not cause a shift of the unmodified control homoduplex 24-bp probe. This result extends our previous reports that showed that the human MutS homologue hMSH2 binds to a 100-bp probe site specifically modified with one 1,2-d(GpG) intrastrand cisplatin crosslink[17], and that the hMutS$\alpha$ complex can recognize a 32-bp probe modified with a single 1,2-d(GpG) intrastrand crosslink [18].

**MutS recognizes the major cisplatin adduct with comparable affinity to a G/T mismatch.** The overall weak nature of the interaction of MutS with the cisplatin-modified oligonucleotide prohibited a more detailed investigation and calculation of the specific apparent dissociation

constants. To evaluate further the significance of the observed interaction we compared the binding affinity of MutS for the major cisplatin adduct to the binding affinity of MutS for a G/T mismatch, the mismatch best recognized by MutS[427]. For this purpose, we constructed a 24-bp oligonucleotide identical to the cisplatin-modified probe, except that it contained a G/T mismatch instead of a cisplatin crosslink (Figure 9-1b). Increasing amounts of MutS were titrated into a binding reaction that contained the radiolabeled mismatch- and cisplatin-modified oligonucleotide and the resulting interactions were examined by a DNA-retardation band shift assay (Figure 9-3). As expected, MutS showed affinity for the oligonucleotide modified to contain a G/T mismatch, as demonstrated by the retarded band in the lanes where MutS and the mismatch-modified oligonucleotide were present (Figure 9-3a). The portion of the shifted band increased with the increase of MutS concentration reinforcing the specific nature of this interaction (Figure 9-3a & 9-3c). At active MutS concentrations higher than 30 nM, multiple retarded bands were observed. Similar multiple bands have been observed previously in band shift experiments with mismatch repair proteins, and their significance is currently unknown[17,431]. MutS showed concentration dependent affinity for the cisplatin modified oligonucleotide as well (Figure 9-3b). The MutS affinity for the probe modified with the 1,2-d(GpG) cisplatin crosslink was comparable to the affinity shown for the probe that contained the G/T mismatch, as illustrated by the binding isotherms shown on Figure 9-3b. Assuming that all of the shifted probe resulted form lesion-specific interaction, it can be estimated that 50% of the probe was bound at MutS concentration of approximately 80 nM for the G/T probe and 600 nM for the 1,2-d(GpG) cisplatin modified probe, respectively. These values are higher in comparison to specific dissociation constant ($K_d$) values previously reported for the MutS interaction with DNA that contains a G/T mismatch ($K_d \approx$ 20-40 nM) and various other mismatches ($K_d \approx$ 50 - 500 nM)[427]. No reports of the MutS $K_d$ for DNA modified with single cisplatin adduct exist for comparison. The $K_d$ for the identical protein preparation and a 162-bp globally modified probe to contain seven cisplatin adducts on the average was determined to be approximately 57 nM[440]. It should be noted that the functional aggregation of the protein was not determined; these calculations assumed a dimer functional unit of active protein whose specific interactions result in all of the shifted probe in the gel. Due to these assumptions, these values could be in error. However, this approach provides a clear comparison of the relative affinities of MutS for the two types of DNA damage, the adduct and the G/T mismatch.

**MutS-IVa fraction binds specifically to 1,2-d(GpG) intrastrand cisplatin crosslink.** During purification, MutS activity co-purifies with two 97kD peptide fractions, IVa and IVb, identical with respect to size[427]. The fraction IVb is routinely used in MutS studies. The IVa fraction elutes at lower salt concentrations and it has approximately a third of the specific activity of the IVb fraction, probably due to varying degrees of proteolysis prior or subsequent to isolation[427]. Using a band-shift assay we examined the binding of MutS-IVa fraction to the set of 24-bp DNA probes site-specifically modified with a single lesion, including an A/G mismatch, a 1,2-d(ApG), a 1,2-d(GpG), and a 1,3-d(GpTpG) cisplatin intrastrand crosslink. Binding of the MutS-IVa fraction to the radiolabeled oligomers was readily observed by the retarded migration of the labeled probe through the gel (Figure 9-4). The MutS-IVa appeared to bind the probes in multiple forms reflected in the presence of multiple bands observed in the polyacrylamide gel. The slowest migrating band was labeled as the upper band (UB), and this band increased with the increase of the MutS-IVa concentration for all of the probes examined. The lower migrating band, labeled LB (Lower Band) on Figure 9-4, did not show dependence on the protein concentration, regardless of the type of probe employed. Multiple bands like UB and LB were not observed with the MutS-IVb fraction and they could have resulted from various products of MutS-IVa proteolytic complexes. Since these bands (UB and LB) were present for all of the probes, they probably represented non-specific interactions between MutS-IVa fraction and the oligonucleotides. A similar pattern of bands was observed for all types of probes except the probe modified with an 1,2-d(GpG) cisplatin crosslink, where an additional, fastest-migrating band was observed (band labeled S for Specific, Figure 9-4). This band was not visible in reactions with the IVb fraction (Fig. 2). The amount of shifted material in the 1,2-d(GpG) specific fastest-migrating S band increased with the increase of MutS concentration, the relative amount of probe shifted in this band increased approximately two-fold (from .4% to .9% relative to the amount of total probe in each lane) when the MutS concentration

used was increased from 10 nM to 20 nM. This result was further confirmed in experiments where larger range of MutS concentrations were used (data not shown). No studies of the interactions of the MutS-IVa fraction with (modified) DNA exist for comparison.

**Specificity of MutS-IVa fraction binding to the major cisplatin adduct.** To characterize further the unique nature of the interaction of the MutS-IVa fraction and the 1,2-d(GpG) adduct, we examined its specificity by a competition assay. In this assay, increasing concentrations of unlabeled competitor DNA containing a 1,2-d(GpG) cisplatin crosslink or a G/T mismatch were added to a binding reaction that contained a fixed concentration of MutS-IVa and labeled probe modified with a single 1,2-d(GpG) cisplatin intrastrand crosslink. A representative DNA-retardation band shift experiment is shown on Figure 9-5a. MutS-IVa at a fixed concentration (20 nM) was incubated with the radiolabeled cisplatin-modified oligonucleotide (1.1 nM). The interaction between MutS-IVa and the radiolabeled probe resulted in a 1,2-d(GpG) specific, faster migrating band and two slower migrating bands (*vide supra*). Increasing amounts of unlabeled competitor DNA (0.5 to 53 nM) also modified to contain a 1,2-d(GpG) cisplatin crosslink were titrated into the binding reaction. As the amount of the unlabeled cisplatin-modified competitor DNA in the reaction increased, the size of the bands decreased, indicating that an increasing amount of MutS-IVA was binding to the unlabeled substrate. The size of the 1,2-d(GpG) cisplatin-specific band also decreased gradually until it nearly vanished. A 20-fold higher molar excess of competitor cisplatin-modified DNA reduced the MutS-IVa 1,2-d(GpG) cisplatin specific binding by 50%, as evaluated by the amount of probe present in the S-band. Similarly, when unlabeled DNA modified with the G/T mismatch was added to the binding assays, the size of all bands gradually decreased as the amount of unlabeled DNA in the reaction increased. Unlike the reaction with the cisplatin-modified competitor, however, the specific S-band decreased but did not vanish. In comparison, 20-fold excess of competitor mismatch-modified DNA reduced only about 20% of the 1,2-d(GpG) cisplatin crosslink specific S-band. A similar experiment was performed using unmodified, homoduplex competitor DNA with the same outcome as above: only the 1,2-d(GpG) cisplatin modified probe itself was effective at competing for MutS-IVa binding as reflected in the reduction of the percentage of retarded probe in the specific (S) band.

**Nucleotide effects on MutS-IVA binding to DNA modified with platinum adducts.** Addition of ATP to mismatch-bound MutS can cause the protein to dissociate from a mismatch, while addition of ADP seems to stimulate MutS binding[431-433]. Addition of ADP to the binding reaction between MutS and DNA modified to contain a 1,2-d(GpG) cisplatin adduct or a G/T mismatch increased the amount of shifted probe, while the addition of ATP to the binding reaction had the opposite effect (data not shown). To investigate the effects of nucleotides on the interaction of MutS-IVa with platinum-modified DNA, we titrated increasing amounts of ATP or ADP (50-200 μM) into a binding reaction containing MutS-IVA (20 nM) and the 24-bp probe modified with a single 1,2-d(GpG) cisplatin crosslink (1.1 nM). Addition of ADP to the binding reaction had small effects on the outcome, it only slightly increased the previously observed faster migrating 1,2-d(GpG) specific S-band (Figure 9-6). Addition of increasing amounts ATP resulted in a significant decrease of MutS bound to DNA in the faster-migrating, lower band (LB), but interestingly it did not affect the slower-migrating upper band (UB) or the fastest-migrating 1,2-d(GpG) specific band (S). This result suggests that the interaction between MutS-IVA fraction and the probe modified with a 1,2-d(GpG) cisplatin crosslink cannot be completely modulated by the presence of nucleotides.

## Discussion

We report that the *E. coli* mismatch repair protein MutS recognizes DNA site specifically modified with a single 1,2-d(GpG) cisplatin intrastrand crosslink, the major DNA adduct of this anticancer drug. Furthermore, MutS recognized DNA modified with the major cisplatin adduct and a G/T mismatch with comparable affinity. Interestingly, MutS-IVa fraction also interacted with the cisplatin modified DNA, and it showed a unique, faster-migrating band when incubated with DNA modified to contain the 1,2-d(GpG) intrastrand crosslink. This interaction was resistant to

competition by unmodified or mismatched DNA and was unaffected by the addition of ATP to the binding reaction.

Our results show that MutS can recognize a 24-bp probe modified with a single 1,2-d(GpG) adduct. The 1,2-d(GpG) intrastrand crosslink is the major cisplatin-DNA adduct; it accounts for ~65% of all adducts, and together with the other two types of intrastrand crosslinks, the 1,2-d(ApG) and the less abundant 1,3-d(GpNpG) (where N is any nucleotide), it comprises ~90% of all cisplatin DNA adducts formed[2,53]. Because the 1,2-intrastrand crosslinks are inefficiently repaired by nucleotide excision repair in comparison to the 1,3-intrastrand crosslinks, and they inhibit phage and *E. coli* polymerases *in vitro* and *in vivo* more strongly (reviewed in[8]), they are considered to be the DNA lesions responsible for the cytotoxicity and the unique anti-tumor activity of cisplatin. In addition, *trans*-DDP, the therapeutically ineffective isomer of cisplatin, does not form 1,2-intrastrand crosslinks due to geometric constraints. It has been demonstrated that the mismatch repair proteins (MutS, hMSH2, hMutS$\alpha$) preferentially recognize DNA globally damaged with cisplatin and other platinum analogs (such as oxaliplatin), which have cis ligand geometry and form intrastrand crosslinks[17,18,440]. Given that mismatch repair proteins play a role in mediating cisplatin toxicity, the selective recognition by mismatch repair proteins for DNA modified to contain platinum intrastrand crosslinks further supports the proposed central role of these crosslinks in cisplatin cytotoxicity.

The basis of interaction of MutS with the oligonucleotide modified to contain a single 1,2-d(GpG) crosslink can be extrapolated from the recently published crystal structure of MutS bound to a mismatch. In this respect, an interesting comparison can be drawn between the structure of DNA distorted by the 1,2-d(GpG) cisplatin adduct and the distortions of mismatched DNA bound by MutS as reported in the crystal structure. In the crystal structure of MutS bound to a G/T mismatch, MutS distorts the duplex by inducing a 60° kink propagated by C3'-endo deoxyribose conformation that results in widening of the minor groove and deepening of the major groove[429,430]. In the crystal structure, a phenylalanine residue wedges into the DNA and stacks in the double helix with the mismatched thymine residue. The X-ray and NMR structural data for a dodecamer duplex containing a single 1,2-intrastrand cisplatin adducts show a bend towards the major groove of 35-78°, compression of the major groove, C3'-endo conformation of the 5' nucleotide, and widening and flattening of the minor groove including 25° unwinding of the double helix at the site of platination[5,72]. It is possible that the bending and unwinding induced by cisplatin and the other cis platinum analogs mimic the structure of a mismatch and allow for efficient MutS binding, perhaps by intercalation of an amino acid residue, such as a phenylalanine. At least one other class of cellular proteins, those containing HMG1 domains, binds to the site of 1,2-d(GpG) intrastrand cisplatin adducts by intercalation of a phenylalanine residue[226]. Alternatively, recognition of cisplatin DNA adducts by MutS could occur by other biochemical mechanisms. One such possibility could involve the recognition of the base incorporated opposite the cisplatin-nucleotide crosslink as a mismatch.

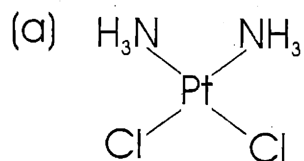
The overall weak protein-DNA interactions and the high level of non-specific binding at higher MutS concentrations precluded us from carrying out thermodynamic analysis with confidence even though we tested a variety of experimental conditions. The MutS concentrations required for the interaction with the mismatched oligonucleotide was somewhat higher than expected and higher than some of the values previously reported in the literature. DNase I footprinting study on a 120-bp oligonucleotide has reported a $K_d$ for a G/T mismatch of 20 nM[427], and a later DNase I study that employed a 143-bp oligonucleotide reported a MutS $K_d$ for a G/T mismatch of 39 ± 4 nM. These differences could be due to the experimental conditions used, such as the probe length or context effects. As it was discussed in Chapter 4, the $k_d$ values for the interaction of HMG1 protein for DNA modified with a single 1,2-d(GpG) adduct ranged from 1.67 nM to 517 nM depending on the sequence context. When MutS protein from a previous preparation was used in experiments with globally modified 162-bp cisplatin probes, the $K_d$ was estimated to be 57 nM[440]. However, even though more rigorous quantitative results could not be obtained at this time, we believe that the comparisons between the protein interactions with the cisplatin- and mismatch-modified

oligonucleotides clearly illustrate the comparable affinity of MutS for both types of DNA damage, the cisplatin adducts and the G/T mismatch.

The purification of MutS results in two fractions IVa and IVb which are essentially homogeneous with respect to size [427]. The fraction IVb is routinely used in MutS studies, while the fraction IVa is discarded on the account of low stability and auto-proteolysis. In our experiments, the MutS-IVa fraction showed a specific faster-migrating band when incubated with the probe that contained the1,2-d(GpG) cisplatin crosslink. Since the 1,2-d(GpG) cisplatin crosslink specific band S was unaffected by large quantities of competitor mismatch-containing DNA but vanished quickly with the addition of a competing cisplatin-modified probe, it must be the result of a specific MutS-IVa - 1,2-d(GpG) crosslink interaction. In addition, this band was resistant to an ATP challenge. The S band could represent protein species smaller in size, such as a MutS monomer or a MutS proteolytic product with altered electrophoretic mobility. If, indeed, the 1,2-d(GpG) specific band is a MutS monomeric species, this presents an interesting model by which mismatch repair proteins could mediate cisplatin cytotoxicity. It is possible that monomers of MutS or its eukaryotic homologues bind the 1,2-d(GpG) cisplatin crosslinks, get hijacked from the formation of functional mismatch repair dimers, and consequently become involved in mediating cellular responses to cisplatin, such as the triggering of apoptosis.

The comparable affinity of MutS for DNA modified to contain a cisplatin adducts and a G/T mismatch is perhaps the greatest significance of these findings. Our results suggest that in the cellular environment mispairs and cisplatin-DNA adducts could compete for recognition by mismatch repair proteins. The consequence of such a competition could lead to a number of scenarios outlined in the proposed models by which mismatch repair proteins could mediate cisplatin toxicity. Mismatch repair proteins bound to cisplatin adducts could (i) directly trigger apoptosis[16], (ii) initiate abortive repair opposite cisplatin adducts[441], (iii) interfere with recombination required for survival following cisplatin damage[415], (iv) shield cisplatin adducts from excision repair[17], or (v) inhibit replication dependent bypass of adducts[442].

The findings presented here demonstrate that mismatch repair proteins have the capacity to recognize cisplatin-DNA adducts with an affinity high enough to present this interaction in the cell as a likely event. Work is underway to further define these interactions and narrow down the number of plausible models by which mismatch repair can mediate the cellular responses to cisplatin. The understanding of the interaction between this DNA repair system and the DNA damaging drug could ultimately lead to the design of novel, more effective antitumor drugs.




(b)

| | |
|---|---|
| 1,2-d(GpG) | 5'-CCTCTCCTT**GG**TCTTCTCCTCTCC-3'<br>3'-GGAGAGGAACCAGAAGAGGAGAGG-5' |
| G/T | 5'-CCTCTCCTT**G**GTCTTCTCCTCTCC-3'<br>3'-GGAGAGGAA**T**CAGAAGAGGAGAGG-5' |
| 1,2-d(ApG) | 5'-CCTCTCCTT**AG**TCTTCTCCTCTCC-3'<br>3'-GGAGAGGAATCAGAAGAGGAGAGG-5' |
| A/G | 5'-CCTCTCCTT**A**GTCTTCTCCTCTCC-3'<br>3'-GGAGAGGAA**G**CAGAAGAGGAGAGG-5' |
| 1,3-d(GpTpG) | 5'-CCTCTCCTT**G**T**G**TCTTCTCCTCTCC-3'<br>3'-GGAGAGGAACACAGAAGAGGAGAGG-5' |

**Figure 9-1.** ***(a)*** **Chemical structure of cisplatin.** ***(b)*** **Sequences of the DNA duplexes used in this study.** The pyrimidine rich strand is designated as the top strand and the complementary strand is designated as the bottom strand. The bases involved in adduct formation are located in the top strand and are shown in boldface type.

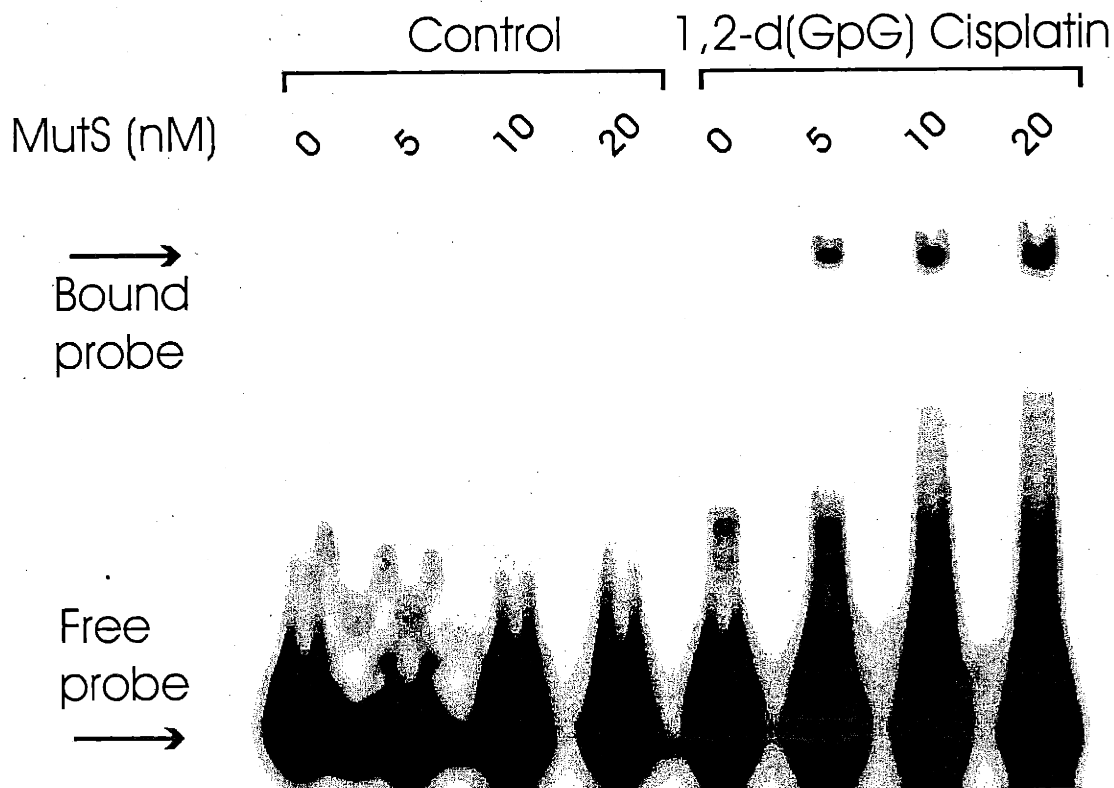



**Figure 9-2. Binding of MutS to a 24-bp probe containing the major cisplatin adduct.** Increasing concentrations of MutS (0-20 nM) were titrated into a binding reaction that contained probe modified with a single, site-specific 1,2-d(GpG) cisplatin intrastrand crosslink or its unplatinated control. A discrete, shifted band was visible which was specific for the platinated probe that increased with the amount of added protein. No shifted band was observed for the control oligonucleotide at the equivalent MutS concentrations.

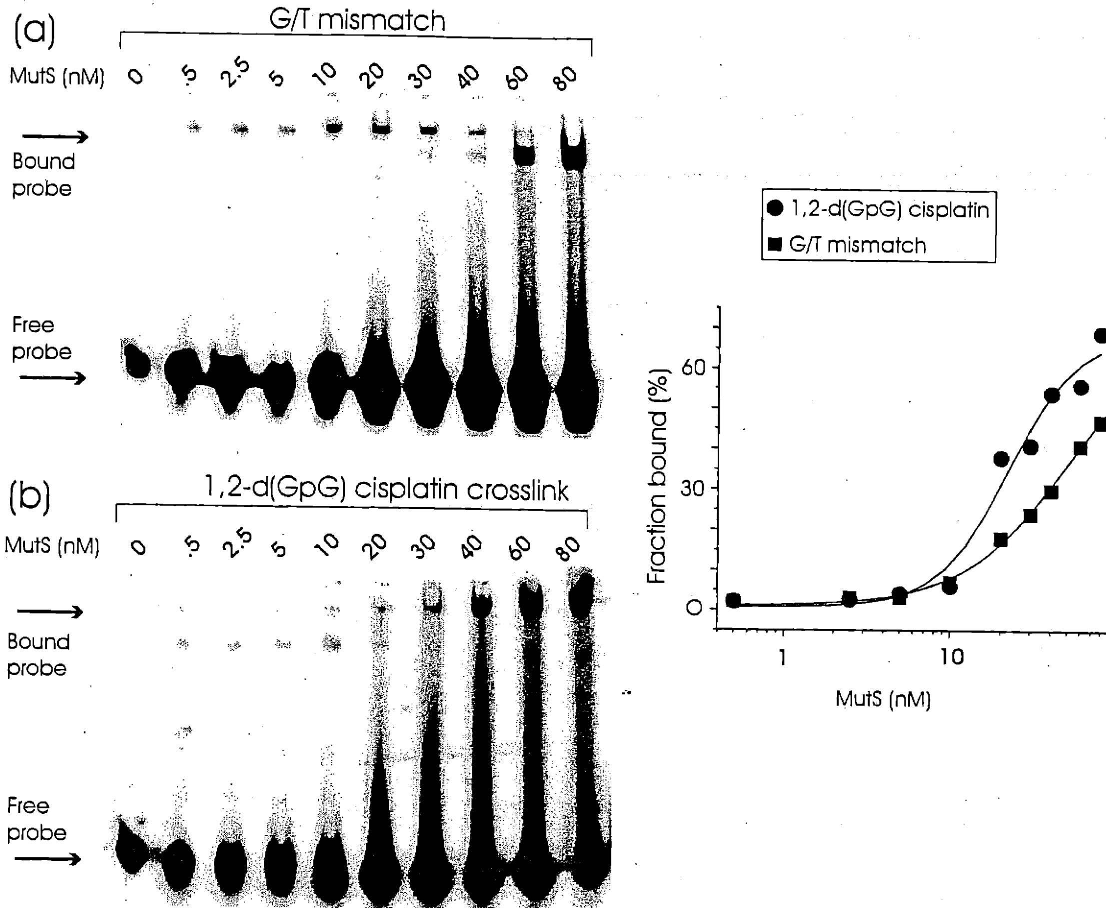



**Figure 9-3. Comparison of MutS binding to a 24-bp probe containing a G/T mismatch or the major cisplatin adduct 1,2-d(GpG) cisplatin intrastrand crosslink.** *(a)* MutS (0-80 nM) was titrated into a reaction containing radiolabeled 24-bp probe (1.1 nM) that contained single centrally located G/T mismatch. *(b)* MutS (0-80 nM) was titrated into a binding reaction that contained a 24-bp probe modified with a single 1,2-d(GpG) cisplatin intrastrand crosslink (1.1 nM). *(c)* Binding isotherm describing the interaction between MutS and the modified probes. The fraction of bound probe (%) in each lane was quantitated and is presented as a function of MutS concentration present in the binding reactions.

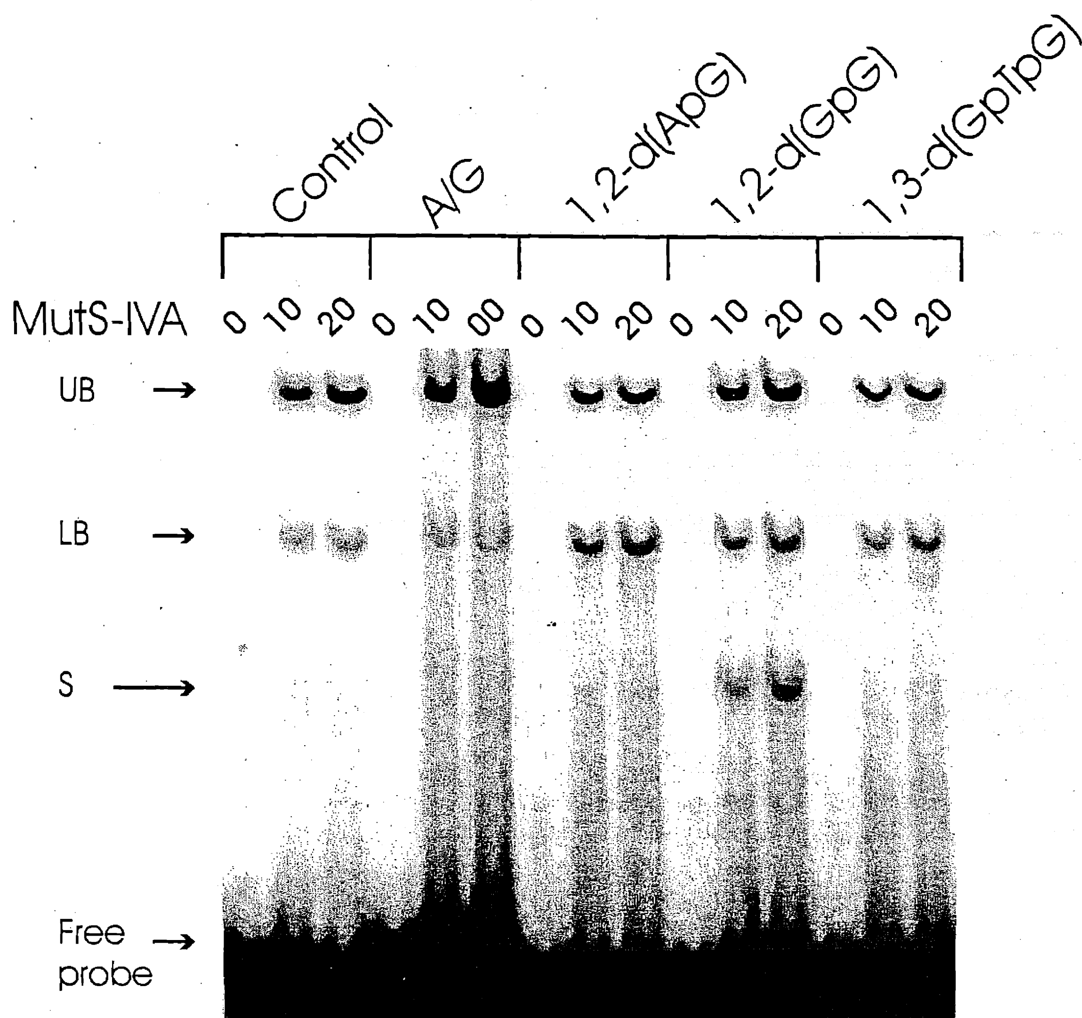



**Figure 9-4. Binding of MutS-IVa fraction to cisplatin and mismatch modified DNA.** Radiolabeled 24-bp probes modified with an A/G mismatch, a 1,2-d(ApG), a 1,2-d(GpG), and a 1,3-d(GpTpG) cisplatin intrastrand crosslink were incubated in the absence (0) and presence of MutS (10 and 20 nM). Unmodified probe was used as a control. Two slower migrating bands were observed for all the probes probably due to non-specific MutS DNA interactions, upper band (UB) and lower band (LB). A discrete, shifted, fastest-migrating band was observed when MutS was incubated with the probe modified with a 1,2-d(GpG) cisplatin crosslink, labeled S for specific. The relative proportion of the S band increased as the MutS concentration increased.

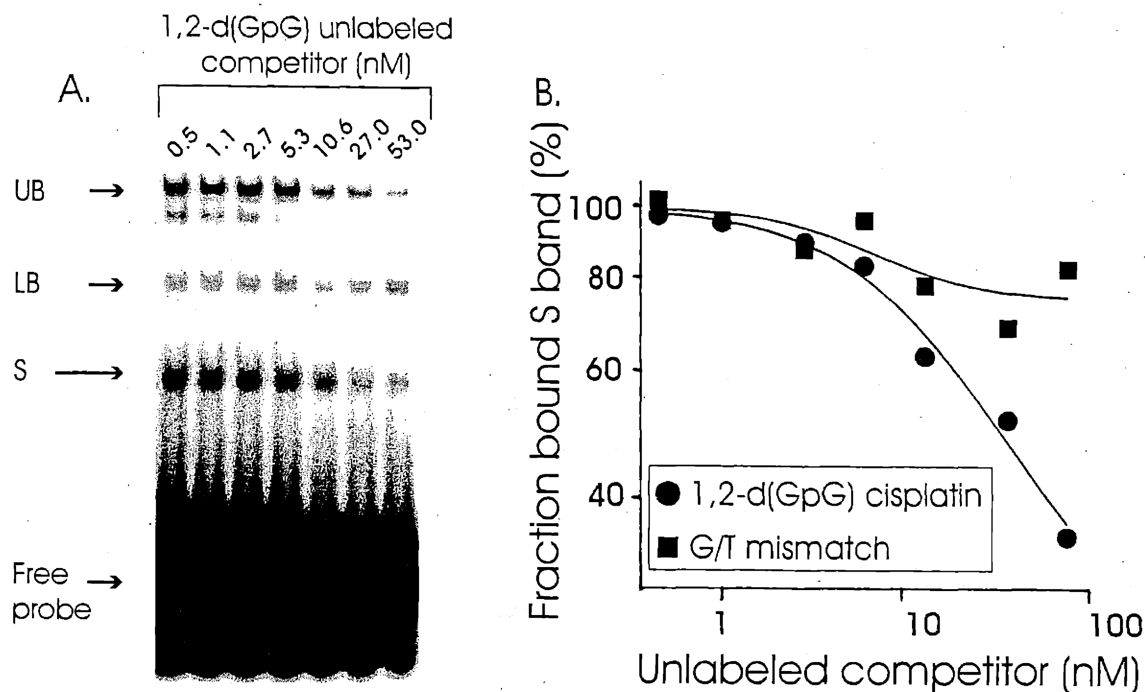



**Figure 9-5. Specificity of MutS-IVa fraction binding to DNA modified with the major cisplatin adduct.** *(a)* Unlabeled, cisplatin-modified duplex DNA (0.5-53.0 nM) was used to compete with a radiolabeled probe modified to contain a 1,2-d(GpG) cisplatin crosslink (1.1 nM) for association with MutS. *(b)* The fraction of bound probe in the S band in each lane was quantitated and is presented as a function of the concentration of the competitor DNA present in the binding reactions. In addition, this data represent a competition experiment where the competitor DNA used was modified to contain a G/T mismatch (0.5-53.0 nM).

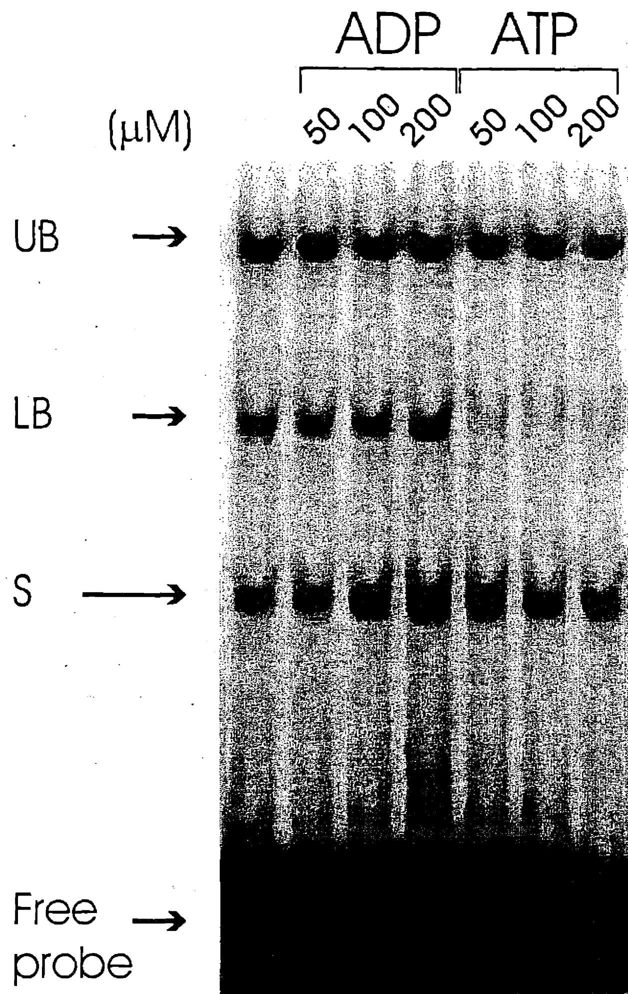



**Figure 9-6. The effects of nucleotides (ATP and ADP) on the binding of MutS-IVa fraction to DNA modified to contain the major cisplatin adduct.** A radiolabeled 24-bp probe modified with a single 1,2-d(GpG) cisplatin adduct (1.1 nM) was incubated with the MutS-IVa fraction (20 nM) in the presence ATP or ADP (50-200 μM). The far left-hand lane contains the binding reaction without any nucleotide added. Only the LB band was affected by the addition nucleotides to the binding reaction. The UB and the 1,2-d(GpG) specific S band were unaffected by the addition of ATP to the binding reaction.

# Chapter 10. The Mismatch Repair Protein MutS Inhibits the RecA Catalyzed Strand Exchange Reaction of DNA Modified to Contain Cisplatin Intrastrand Crosslinks

The *recA* gene of *E. coli* plays an essential role in promoting cell survival following exposure to agents that damage chromosomal DNA. The RecA protein is central in the processes of recombinational DNA repair, homologous recombination, reinitiating of DNA replication on collapsed replication forks, induction of SOS damage response, and the partitioning of chromosomes during cell division. RecA structural and functional homologous are well preserved in all bacteria and eukaryotes. The eukaryotic homologue Rad51 is responsible for the initiation of strand exchange between homologous DNA molecules crucial in recombination and repair of certain types of DNA damage.

*In vitro*, RecA protein promotes a set of DNA strand exchange reactions that mimics its presumed roles *in vivo*. The catalysis of recombination by RecA requires the formation of nucleoprotein filament consisting of RecA, ss DNA, and ATP[358,358,367,388,388,443]. In a typical strand exchange reaction (schematically represented on Figure 10-1), RecA protein first forms a nucleoprotein filament on circular ss DNA with a stoichiometry of one RecA monomer per three nucleotides in a 5' to 3' direction. The rate of this process in certain experimental conditions can exceed 1000 RecA monomers $min^{-1}$ $filament^{-1}$[444]. RecA does not readily bind to ds DNA at neutral pH due to a very slow nucleation step. RecA filaments disassemble in an end-dependent manner from the filament end opposite to that at which assembly occurs and RecA molecules are replaced by SSB. When the RecA:ss DNA complex is paired with a linear duplex DNA, RecA stabilizes a triplex hybrid and promotes a homology search between the two sequences and alignment that results in a strand exchange. The newly formed duplex DNA extends unidirectionaly, 5' to 3' relative to the ss DNA in the original filament. At the end of the reaction, one of the strands of the duplex is completely replaced by the circular ss DNA and RecA remains bound to the product. RecA is able to promote this strand exchange reaction past some lack of perfect structural complementarity between the two DNA species. For example, it can drive the strand exchange past up to 30 UV-induced pyrimidine dimers[445,446] and inserts from 500-1300 heterologous bases in the circular DNA[447] and 4-38 deletions and insertions[446]. However, RecA is unable to promote strand exchange past psoralen monoadducts or interstrand crosslinks[446].

Given the established importance of recombination for cellular survival following cisplatin damage we set out to examine if RecA could promote the strand exchange reaction past cisplatin crosslinks. For this purpose we modified circular ss $\phi$X174 virion DNA to contain varying number of cisplatin intrastrand crosslinks, and we examined the capacity of RecA to promote strand exchange between the cisplatin-modified DNA and complementary linearized ds $\phi$X174 DNA. In addition, we examined the effect of the mismatch repair protein MutS on the RecA catalyzed strand exchange reaction. One of the functions of mismatch repair proteins is to monitor recombination frequency and fidelity. *In vitro*, MutS impedes the RecA-mediated homeologous exchange as a distinct mismatch-provoked event and blocks branch migration, presumably in response to occurrence of mispairs within newly formed heteroduplex[448,449].

## Materials and Methods

*Preparation of platinum-modified DNA probes.* Cisplatin was purchased from Sigma-Aldrich. The platination of $\phi$X174 single stranded circular virion DNA (New England Biolabs) was carried in a 3 mM NaCl, 1 mM $Na_2HPO_4$ (pH 7.4) for 16 h, at 37 °C, with the appropriate cisplatin:DNA molar ratios. Unreacted platinum compounds were removed by dialysis (24 h) against

10 mM Tris-HCl buffer (pH 8.0), 1 mM EDTA (TE) followed by ethanol precipitation. The resulting modified-DNA was resuspended in TE buffer and stored at -20 °C.

*Protein Purification.* MutS was purified as previously described[427]. The host strain was BL21 (λDE3) (pLysS) and the plasmid used was pMQ372[428]. In brief, the strain was transformed with pMQ372 and grown at 37 °C to an $A_{600}$ of 0.8, shifted to room temperature, and isopropyl-1-thio-β-D-galactopyranoside (IPTG) was added to 50 μM final concentration. Incubation was continued for 2 h at room temperature, and the cells were harvested and lysed in a French pressure cell (Aminco). The lysate was treated with streptomycin sulfate and ammonium sulfate as described[427]. We used a heparin (Sigma) agarose column instead of heparin Sepharose. Two fractions (IVa and IVb) from the hydroxylapatite chromatography were saved and stored at -70 °C. The IVb fraction was used in the strand exchange reactions. Protein concentration was assayed using the Bradford reagent (Bio-Rad).

RecA was purified as previously described[450]. All cultures were grown in 2 L LB containing 3.8 mg/ml glucose and 100 μg/ml ampicillin. Four 1.5-liter cultures were inoculated with 50 ml of an overnight culture grown at 37 °C. Incubation at 37 °C was continued until $A_{600}$ ~ 0.8, at which time isopropyl-1-thio-β-D-galactopyranoside was added to a final concentration of 5 mM. Incubation was continued for 3.5 h, cells were harvested by centrifugation, and pellets resuspended (25 ml/1.5-liter culture) in a buffer containing 0.25 M Tris-HCl, pH 7.5, 25% sucrose. Cell suspensions were quick frozen using liquid nitrogen and stored at -70 °C. Cell lysis and extraction of the RecA protein using polyethylenimine was performed as described to generate fraction II. Fraction II was dialyzed extensively against R buffer (20 mM Tris-HCl, pH 7.5, 5% glycerol, 5 mM β-mercaptoethanol, 0.1 mM EDTA) containing 50 mM $NH_4Cl$, loaded onto a DE-52 column (30-ml bed volume) equilibrated in the same buffer, and proteins were eluted with a linear gradient (300 ml) of 50-500 mM $NH_4Cl$. RecA protein eluted at approximately 180-280 mM $NH_4Cl$. Fractions containing RecA protein were pooled and proteins precipitated by addition of ammonium sulfate. The resulting protein pellet was dissolved in 3 ml of R buffer, 30 mM $NH_4Cl$ and dialyzed extensively against the same to generate fraction III. $MgCl_2$ was then added to a final concentration of 15 mM, and the sample was loaded onto a Sephacryl S-1000 gel filtration column (1.5 x 120 cm) equilibrated in R buffer, 50 mM $NH_4Cl$, 15 mM $MgCl_2$. RecA proteins elute in pure form in the void volume of this column. Fractions containing RecA were pooled and protein precipitated as above. The precipitate was dissolved in R buffer (200-400 μl) and dialyzed extensively against the same. Glycerol was added to a final concentration of 25%, and 20 μl aliquots were quick frozen and stored at -70°C. RecA was judged to be at least 95% pure in silver-stained SDS-polyacrylamide gels. The RecA concentration was determined spectrophotometrically using an extinction coefficient of $\varepsilon_{280} = 0.59\ mg^{-1}ml$.

*DNA strand exchange reaction.* DNA strand exchange activity was measured as follows: Reactions (120 μl) were performed in buffer containing 25 mM Tris-acetate (pH 7.5), 10 mM Mg-acetate, 1 mM DTT, and 5% (w/v) glycerol. RecA protein was incubated with both ss- and ds- ϕX174 DNA (20 μM each) in reaction buffer for ten minutes at 37° C. Reactions were started by simultaneous addition of 3 mM dATP and 2 μM SSB. Aliquots (9 μl) were removed at the indicated times and added to stop solution such that the final concentrations of SDS, glycerol and EDTA were 1% (w/v), 5% (w/v) and 10 mM, respectively. Samples were electrophoresed on a 0.8% agarose gel in TAE buffer and DNA was visualized by staining with ethidium bromide. Gels were displayed using a FluorS MultiImager (BioRad).

## Results

The results from the RecA catalyzed strand exchange experiment are shown on Figure 10-2. In addition to unmodified ss DNA control, we constructed three modified probes that contained on the average 6, 12 and 24 cisplatin intrastrand crosslinks per ss ϕX174 molecule (a cisplatin adduct

per 900, 450, and 224 nucleotides, respectively). In addition, for each set of probes we titrated increasing amounts of MutS (0-300 nM) in the strand exchange reaction.

The first left hand lane in each set represents the RecA catalyzed reaction with unmodified virion ss DNA. For the unmodified control in the reaction time of 60 min RecA converts all of the ss and ds substrates into a nicked circle (NC) product molecules, as indicated by the absence of substrates or joint molecules (JM). For the ss DNA modified with 6 cisplatin adducts there is significant amount of NC products, although not all of the ds substrate is converted to products as indicated by the visible substrate band. With the increase of the level of cisplatin modification of the ss DNA the amount of nicked circle product decreases; for the reaction with the ss DNA modified with 12 cisplatin adducts there is more ds substrate than product, and for the highest level of platinum modification where there are 24 platinum adducts there is no detectable products following the 60 min incubation. These results suggest that RecA is capable of promoting strand exchange past intrastrand cisplatin crosslinks, but not with an unlimited capacity. One cisplatin adduct per 224 nucleotides seems to abolish completely the recA strand exchange reaction.

Next, we examined the effect of addition of MutS to the RecA catalyzed strand exchange reaction. Increasing amounts of MutS were titrated into the binding reactions with the unmodified and the cisplatin modified ss DNA. Overall, the addition of MutS inhibited the strand exchange reaction in a concentration dependent manner. However, in the reactions with the unmodified probe as well as the ss DNA modified with 6 cisplatin adducts there were still observable nicked circle products even at the highest MutS concentration. The best illustration of the effects of MutS on the RecA catalyzed strand exchange with platinated DNA is the set of reactions with the Cisplatin-12 probe. With the addition of increasing amounts of MutS both the substrates and the nicked circle product bands fade, while the amount of joint molecules increases indicating that in the presence of MutS and cisplatin adducts RecA is prevented from completing the strand exchange. Presumably the RecA strand exchange was halted at a cisplatin adduct site. MutS could have prevented the completion of the strand exchange reaction because it recognized the newly formed duplex that contains the strand modified by cisplatin adducts as a mispair.

## Discussion

We have shown that the presence of cisplatin adducts can inhibit the RecA catalyzed strand exchange reaction. Addition of the mismatch repair protein MutS resulted in inhibition of the formation of the nicked circle strand exchange products, but it increases the number of joint molecule intermediates. MutS presumably inhibited the completion of the strand exchange because it recognized the newly formed duplex that contains cisplatin adducts as a mispair. These results are of significance because recombination and mismatch repair pathways have been shown to have opposite effects on the cellular responses to cisplatin. Recombination deficient mutants show high sensitivity, while mismatch repair deficient mutants show resistance to the drug. The two pathways overlap at the processing of recombination intermediates and there are two general, mutually non-exclusive models (discussed in greater detail in Chapters 5 and 6) that have been proposed to account for the interactions of the two pathways that would lead to the observed cellular responses.

In brief, mismatch repair proteins could attempt abortive repair of cisplatin lesions that would eventually result in double strand breaks that are substrates for recombinational repair. This study did not examine this model, although this *in vitro* system with the appropriate modification could be used to ask the question if cisplatin adducts are indeed substrates for the reconstitute mismatch repair reaction.

The alternative model involves the inhibition of recombinational bypass of cisplatin adducts by mismatch repair proteins. This model has been extrapolated from *in vivo* results in prokaryotic

as well as eukaryotic genetic studies[415,442]. In the later report, inactivation of mismatch repair genes (MLH1, MLH2, MSH2, MSH3, and MSH6) in isogenic strains of *S. cerevisiae* led to increased resistance to the cisplatin, but inactivation of MLH1, MLH2 or MSH2 had no significant effect on drug sensitivities in the *rad52* or *rad1* mutant strains that are defective in mitotic recombination and the removal of unpaired DNA single strands, respectively. Here we have presented *in vitro* results that support this model. MutS most likely prevented the completion of the reaction by interfering with the recA promoted strand exchange as a response to the formation of DNA duplex that contained intrastrand cisplatin crosslinks. The majority of the intrastrand crosslinks formed *in vitro* are the 1,2-d(GpG) crosslinks, the adducts that induce the most significant structural distortions in the DNA and are held to be the most important cytotoxic lesions (Chapter 2). It is unlikely that MutS interacted with the cisplatin modified DNA beforehand, given that only ss DNA was modified with cisplatin and MutS has no known affinity for ss DNA. The interactions of MutS with cisplatin modified duplex DNA were discussed in detail in the previous two chapters.

In *E. coli*, once initiated by recA, the strand exchange reaction and branch migration is further promoted by the RuvAB complex or alternatively by the recG protein (see Chapters 5 and 7 for details). It has been reported that MutSL complex can inhibit the formation of full-length heteroduplex DNA between M13-fd DNA in the presence of RuvAB, such that less than 2% of the linear substrate is converted to product[451]. The observed Inhibition required the formation of base-base mismatches and ATP utilization. From the perspective of our findings it can be speculated that the high levels of recombination intermediates such as branch migration molecules induced by cisplatin could become substrates for similar MutS(L) inhibition. We are in the process of optimizing the addition RuvAB as well as MutL to our experimental system, and we hope that further experiments could provide additional insight to the interactions between recombination and mismatch repair.

Currently we can only support a simple model where the unrepaired cisplatin adducts that persist during recombination are recognized by mismatch repair proteins and the completion of branch migration and strand exchange reactions is inhibited (Figure 10-3). The resulting joint molecules could result in strand breaks that ultimately would accumulate and lead to cell death. In eukaryotes, the recognition of cisplatin adducts during recombination processes by mismatch repair proteins could lead to the triggering of cell signaling pathways and apoptosis. As a concluding remark, it should be noted that although this discussion focused on the role of the mismatch repair proteins in recombination, cisplatin adducts, when present at high enough number, completely abolished the recA catalyzed strand exchange, even in the absence of MutS. Therefore, it would seem that at high enough damage level cisplatin could lead to the accumulation of strand breaks by similar mechanisms to the ones illustrated in Figure 10-3 that do not necessarily involve mismatch repair proteins.

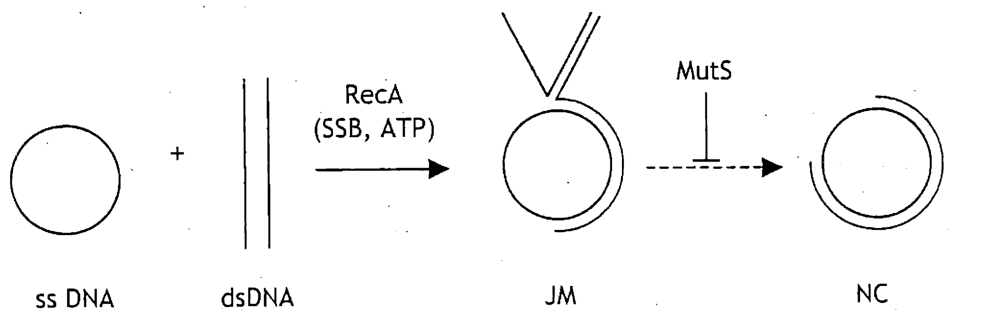



**Figure 10-1. RecA mediated DNA strand exchange reaction.** ss DNA and ds linear complimetary DNA are incubated with RecA, SSB and ATP. RecA catalyzes the homologous strand exchange reaction where one of the stands of the linearized duplex is replaced by the circular ss DNA (with a homologous sequence). The resulting products are triplex joint molecules (JM) of varying configuration. Completion of the strand exchange reaction by RecA results in nicked circle (NC) molecules (accompanied by the resulting complimetary ss linear DNA). If heterologies are to result in the newly formed duplex, MutS could prevent the completion of the strand exchange reaction and the conversion of the JM into a NC.

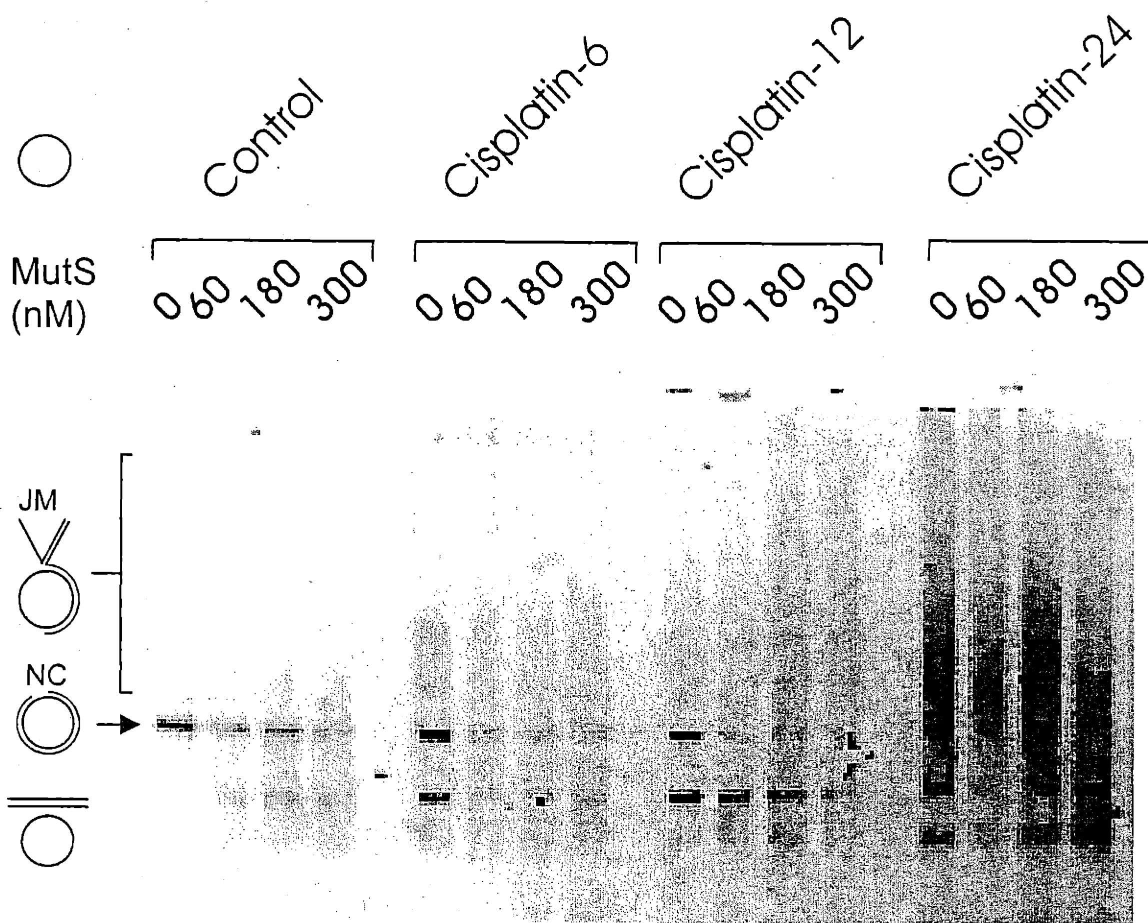



**Figure 10-2. RecA catalyzed strand exchange reaction with platinated substrates in the presence of MutS.** Reaction time 60 min. The left hand lane is each set represents the control reaction and does not contain any MutS. Details are discussed in the text. NC, nicked circle; JM, joint molecule.

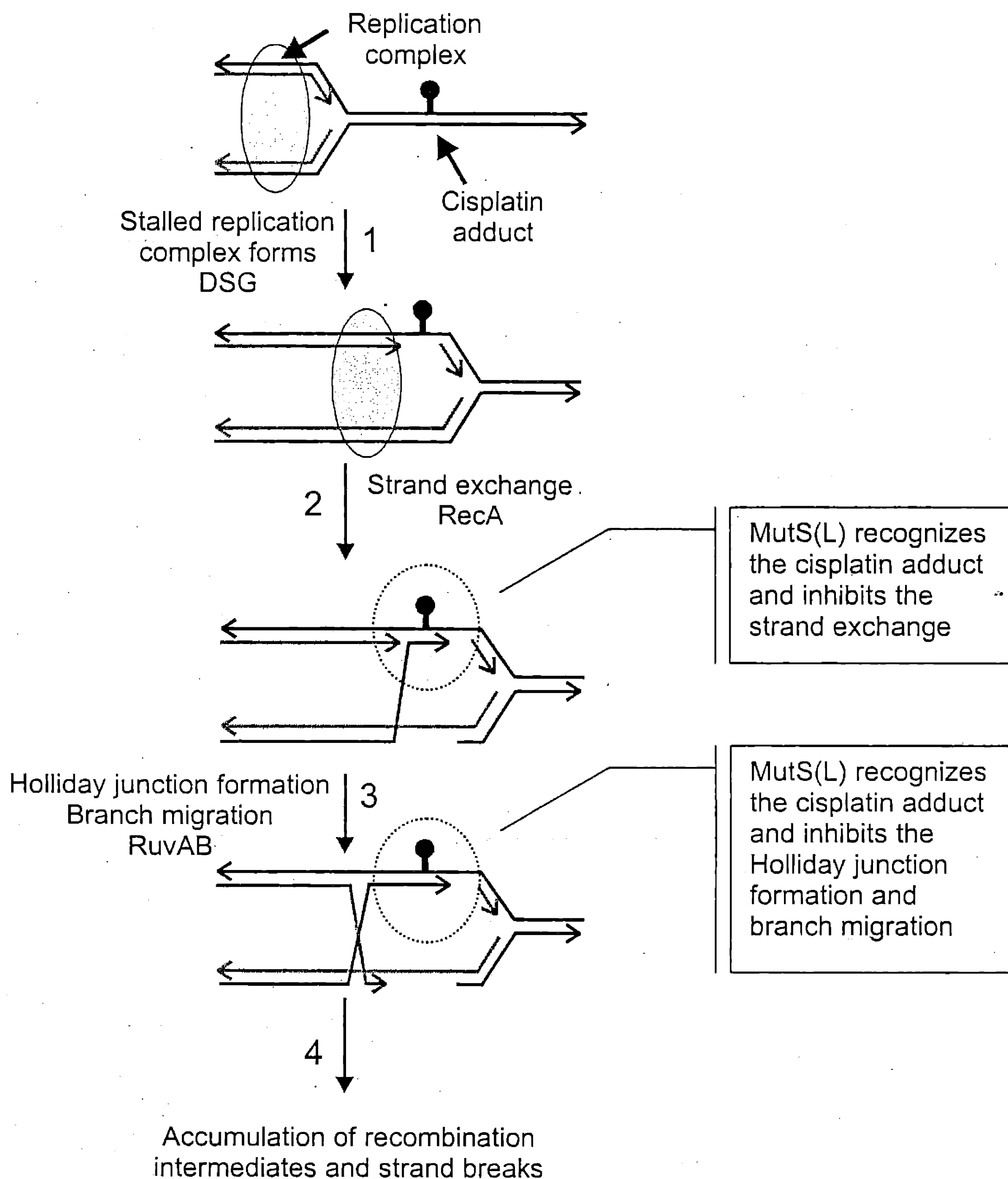



**Figure 10-3. Model for MutS inhibition of recombinational bypass of cisplatin DNA damage.** (Step 1) The replication complex encounters persistent cisplatin DNA adducts. Stalled replication results in the formation of a daughter strand gap opposite the adduct. In this figure only the RecFOR initiation pathways is illustrated. This model, however, is just as valid for the RecBCD pathway of initiation of recombination. (Step 2) Interactions between the proteins of the RecFOR pathway and the replication fork initiate RecA nucleation, strand exchange and the formation of a Holliday junction. This step could be inhibited by the MutS recognition of cisplatin adducted DNA as a mispair. (Step 3) Branch migration of the Holliday junction catalyzed by the RuvAB or RecG proteins results in the repair of the daughter strand gap and restoration of the replication fork. This step could also be inhibited by MutS recognition of cisplatin crosslinks. (Step 4) The MutS inhibition results in accumulation of recombination intermediates and strand breaks.

# Chapter 11. Cisplatin Toxicogenomics: Mismatch Repair-Methylation Deficient *E. coli* Mutants Show Low Sensitivity to Cisplatin, Yet They Do Not Induce DNA Repair Responses

The phenomenon of cisplatin resistance in mismatch repair deficient cells was initially discovered in *E. coli*[14], where methylation deficient *dam* mutants show high sensitivity to cisplatin, and this sensitivity is abrogated by the introduction of additional mutation in the mismatch repair genes *mutS*, *mutL* or *mutH*. The prevalent explanation that accounts for this observation is the abortive repair model which proposes that in *dam* mutants, where the strand discrimination signal is lost, mismatch repair attempts futile cycles of repair opposite cisplatin adducts. The results presented in the previous few chapters support this model to the extent that MutS, the *E. coli* mispair recognition protein, specifically recognizes DNA modified with cisplatin.

It is possible, however, that the abrogated sensitivity of the methylation-mismatch repair deficient mutants is due to cellular mechanisms that are yet undescribed, such as the upregulation or downregulation of specific cellular responses to cisplatin damage that would allow this mutant to tolerate or repair the adducts and show cisplatin resistance and high survival rate. Therefore, it is of interest to learn if the expression of certain genes is uniquely regulated in these mutants in comparison to wild type and the methylation deficient mutants. The changes in gene expression in the entire genome can be measured simultaneously using high-density DNA microarrays, and the use of this method is rapidly contributing to an improved understanding of coordinated cellular events in response to a variety of DNA damage[76,227,452-455]. These studies have demonstrated that global changes in the expression of individual mRNA's are sufficiently distinct, robust and reproducible. We used DNA microarrays to compare the changes in gene expression patterns induced by cisplatin damage between wild type, methylation deficient (*dam*) and methylation-mismatch repair deficient (*dam mutS*) *E. coli* strains. The purpose of comparison was two fold: to examine the effect of cisplatin damage on the expression of genes involved in known DNA repair and recombination responses and to examine if there are genes whose expression was significantly altered following cisplatin damage that were unique for the mismatch repair deficient mutants.

## Materials and Methods

*Chemicals.* Cisplatin was obtained from Sigma-Aldrich and dissolved in $ddH_2O$. The chemicals used as part of the Affymetrix GeneChip protocol were obtained from the suggested vendors.

*Cisplatin cytotoxicity.* Overnight cultures were diluted 1000-fold and grown in 50 ml Luria-Bertani (LB) medium until the density of the population reached ~$2 \times 10^8$ cells/ml as determined by $OD_{600}$. The exponentially growing cells were resuspended in M9 minimal medium for 45 min and then in a 15 ml volume incubated with 150 µM cisplatin at 37 °C for 2 h, unless otherwise noted. Following the appropriate incubation time the cells were resuspended in LB medium and allowed to replicate for 90 min. Appropriate dilutions in M9 medium were plated on LB plates and incubated at 37 °C until colonies could be counted. Results from three to six independent experiments plated in duplicate were averaged and plotted against drug concentration to determine the cytotoxicity level to cisplatin exposure in the particular experimental set up.

*RNA isolation and microarray hybridization.* The total RNA was isolated from the treated cells, and the mRNA was enriched as described in the Affymetrix GeneChip protocol. In brief, RNA-DNA hybrids were generated by cDNA synthesis using primers for 16S and 23S RNA and reverse transcriptase (MMLV, Epicentre). The RNA-DNA hybrids were digested by RNase H and DNaseI. The

enriched mRNA was fragmented by heat (95 °C for 30 min) and the fragments were tagged with biotin (following functionalized 5' addition of γ-S-ATP that was reacted with PEO-Iodoacetyl-Biotin). The Biotin tagged fragments (1.5 to 4.0 μg) were hybridized with an *E. coli* GeneChip array (Affymetrix) for 16 hrs at 45 °C. The hybridized array was incubated with streptavidin-phycoerythrin conjugate and scanned according to the manufacturers specifications. The microarray contained 7312 gene probes, represented by oligonucleotides 25 bases in length. There were ~15 probe pairs per gene, each pair consisting of an oligonucleotide perfectly matched to the mRNA sequence and a second oligonucleotide containing a single base mismatch.

*Statistics on Data.* The fold change in gene expression between the cisplatin induced and the untreated baseline levels was calculated using the Affymetrix GeneChip Analysis Suite that employs the following equation:

$$\text{FC (Fold Change)} = \text{Avg Diff Change}/\max[\min(\text{Avg Diff}_{\text{Cisplatin}}, \text{Avg Diff}_{\text{Untreated}}), Q] + x$$

Where Avg Diff Change = $\text{Avg Diff}_{\text{Cisplatin}} - \text{Avg Diff}_{\text{Untreated}}$, Q is the background noise in the particular array, and x = +1 if $\text{Avg Diff}_{\text{Cisplatin}} > \text{Avg Diff}_{\text{Untreated}}$ or -1 if $\text{Avg Diff}_{\text{Cisplatin}} < \text{Avg Diff}_{\text{Untreated}}$. The fold changes obtained from two independent experiments for each strain were averaged and are shown in Table 11-1.

In addition, the relative differences between gene expression for the treated and untreated samples were determined according to a statistical method that accounts for the gene specific fluctuations in expression level, called Significance Analysis of Microarrays (SAM) and developed by G. Chu and coworkers[76]. The software, as well as further details on the SAM method can be obtained on the web site: http://www-stat-class.stanford.edu/SAM. In brief, the ratio of relative change for each gene was calculated as a value based on the ratio of change in gene expression to the standard deviation in the data for that gene. The formula used to calculate the relative difference, *d(i),* in gene expression was:

$$d(i) = \frac{x_{\text{Cisplatin}}(i) - x_{\text{Untreated}}(i)}{s(i) + s_o}$$

Where $x_{\text{Cisplatin}}(i)$ and $x_{\text{Untreated}}(i)$ were defined as the average levels of expression for gene *(i)* in cultures exposed to Cisplatin and Untreated, respectively. The gene specific scatter, *s(i),* was the standard deviation of the repeated expression measurements:

$$s(i) = \text{SQRT}(a\,\{\Sigma_m[x_m(i) - x_{Cisplatin}(i)]^2 + \Sigma_n[x_n(i) - x_{Untreated}(i)]^2\})$$

Where $\Sigma_m$ and $\Sigma_n$ were summations of the expression measurements for the Cisplatin and Untreated experiments, respectively, $a = (1/n_1 + 1/n_2)/(n_1 + n_2 - 2)$, and $n_1$ and $n_2$ are the numbers of measurements in the Cisplatin and Untreated experiments, respectively. The value of the constant $S_o$ was determined to be 2.8, and is intended to minimize the coefficient of variation of the data required to ensure that at low expression levels the variance of *d(i)* is independent of gene expression. Because gene expression was computed from differences in hybridization to matched and mismatched probes, expression levels were sometimes reported by the Affymetrix GeneChip Analysis Suite software as negative numbers. These value were reset to 1.0 before they were used in our calculations. The relative difference in expression *d(i)* was calculated from three independent experiments for the two mutant strains and two independent experiments for the wild type.

*Bacterial strains.* The wild type AB1157 (*thr-1 ara-14 leuB6* – (*gpt-proA*)62 *lacY1 tsx-33 glnV44*(AS) *galK2*(Oc) *hisG4*(Oc) *rfbD1 mgl-51 rpoS396*(Am) *rpsL31*($Str^R$) *kdgK51 xylA5 mtl-1 argE3*(Oc) *thi-1*) was kindly provided by E.A. Adelberg. The strains GM3819 (*dam*), GM5556 (*dam*

*mutS*) are derivatives of AB1157. The auxotrophic phenotype of each mutant was conformed by growth on the appropriate supplemented minimal medium.

## Results

**Overall changes in gene expression in *E. Coli* strains treated with cisplatin.** We examined the gene expression responses of the *E. coli dam* and *dam mutS* mutant strains following a 2 h exposure to a 150 μM dose of cisplatin. These results were compared with the expression pattern of the parental wild type. These experimental conditions were selected following a set of pilot microarray experiments where the wild type strain was treated with 150 μM cisplatin at exposure times that varied from 0 h, 2 h, and 4 h, in replicating and non replicating conditions. At the 2 h time point followed by 90 min replication there was a robust expression response with a reasonable survival rate, a combination that we determined suitable for this experiment. At the cisplatin dose of 150 μM and 2 h incubation time the survival was determined to be ~15.6% of the untreated control for the wild type. As expected and previously discussed, the *dam* mutant showed high sensitivity to cisplatin (~.04% survival), and this sensitivity was abrogated by the introduction of an additional mutation in the mismatch repair gene *mutS* (~2.3% survival) as shown on Figure 11-1.

To examine the changes in gene expression in response to cisplatin damage we compared samples of total RNA taken from the cisplatin and the sham treated cultures for all three strains and we determined the relative changes in the transcript levels for each gene in the *E. coli* chromosome based on the two statistical methods described above. The values obtained for the fold change (FC) and the relative difference *d(i)* are listed alphabetically in Table 11-A. In addition to the known ~4200 open reading frames (ORF), the probes included ORF for hypothetical proteins as well. Significant FC value for expression in microarrays is considered to be 2-fold change in expression, FC > 2, or FC < -2[456-458]. The employment of FC analysis however, can yield a very high false discovery rate (~70-81%)[459], and we accompanied our FC calculations by SAM analysis to ensure accurate interpretation of the data.

The overall expression of genes for the three experiments is illustrated in Figure 11-2. The scatter plot shows the relative difference in expression *d(i)* vs. the gene specific scatter *s(i)* (the standard deviation of repeated expression measurements). The scatter for most of the gene probes shows that most values align along the x-axis showing low *d(i)/s(i)* ratios. The values denoted with open diamonds depict genes with potentially significant changes of expression, with a symmetric horizontal cutoff *d(i)* > 5 for induced genes, and *d(i)* < -5 for repressed genes. The most striking feature depicted on Figure 11-2 is the number of genes with significant changes in expression for the three different strains used, the wt and the *dam* mutant show high levels of modified expression while the *dam mutS* strain shows overall a very low number of genes with changes in expression.

**Expression of genes involved in DNA damage repair, the SOS response and recombination.** We focused our comparison on genes involved in DNA repair and recombination. Many changes to gene expression in the wake of DNA damage in *E. coli* are regulated by the SOS response, which is negatively regulated by the LexA repressor. Following DNA damage, activated RecA can cleave the LexA repressor resulting in transcription from as many as 30 genes LexA repressed genes[390]. Many, but not all of the proteins involved in recombinational repair such as RuvA, RuvB, and RecN are regulated by LexA. We selected two panels of genes that are central to the DNA damage responses in *E. coli* and carefully compared their changes in expression in the three strains. The first panel was composed of genes known to be part of the inducible SOS response: *recA, umuD, sulA, uvrA, recN* and *dinJ* (Figure 11-3).

RecA is the central protein in recombination as well as the induction of the SOS damage response, and most of its functions have been discussed in great details in previous chapters.

There was a significant induction of RecA expression in wild type and the *dam* strain (FC = 16.5 and 4.27, and *d(i)* = 2.22 and 4.47, respectively), however there was a very small significant change in the level of RecA expression for the *dam mutS* mismatch repair deficient mutant (FC = 2.4, *d(i)* = 1.06). These results are in line with reports where induction of *recA* expression was shown to range 6-12 fold as determined by microarrays for UV DNA damage[452]. The gene *umuD* codes for the subunit of UmuD'C, a polymerase involved in translesion synthesis, and is also induced as a part of the SOS response. In this study significant cisplatin-induced changes of *umuD* expression were observed for the wild type and the *dam* mutant (FC = 4.0 and 1.60, and *d(i)* = 2.52 and 2.84, respectively) while again no significant induction was observed for the mismatch repair deficient mutant, actually there was 1.65 fold repression in expression (*d(i)* = -1.37). The SulA protein is a SOS inducible transcriptional suppressor of *lon,* it possibly inhibits cell division and *ftsZ* ring formation and it induces the filamenation that is a hallmark of cisplatin treatment of *E. coli* (see Chapter 1). In confirmation of previous studies with certain DNA damaging agents we found that *sulA* was induced in the wild type strain following cisplatin damage (FC = 12.75, *d(i)* = 1.96). There was a borderline induction of *sulA* for the *dam* mutant (FC = 2.17, *d(i)* = 1.99). Again there was no significant response for the *dam mutS* double mutant.

The importance of NER for dealing with cisplatin DNA damage was already discussed in previous chapters. Both the *uvrA* and the *uvrB* transcripts were highly induced in the wild type and the *dam* strain (FC = 3.4 and 3.3, *d(i)* = 15.5 and 5.67, respectively), surprisingly there was no noticeable induction of *uvrA* or *uvrB* in the mismatch repair deficient strain. In addition, while *uvrC* gene was not significantly induced in any of the strains, it was significantly repressed in the *dam mutS* strain (FC = -1.2, *d(i)* = -1.2). RecN is a SOS inducible protein that has a putative role in recombinational repair of double strand breaks[9,460]. A significant induction for *recN* was observed for the wild type and *dam* mutant (FC = 5.9 and 3.23, *d(i)* = .99 and 3.48, respectively. The induction of *recN* in the *dam* mutants could be interpreted to support the abortive repair model, where the result of errand excisions would lead to increased number of double strand breaks. The *din* ORF's encode DNA damage inducible genes of unknown function that are under SOS regulation, and *dinJ* was also induced in the wild type and the *dam* mutant, but not in the mismatch repair mutant. Overall, the selection of genes discussed in this panel revealed a surprising finding that in spite of high survival the *dam mutS* mutants do not induce a high DNA damage response.

The high rate of survival of the *dam mutS* double mutants could be due to upregulation of recombination pathways that are relatively or completely independent of the SOS DNA damage response. To consider this possibility we examined another panel of genes involved in recombinational repair including *mutL, recO, ruvA, recG, ruvC and rus* (Figure 11-4). It was of particular interest to study the changes in expression of genes involved in the various steps of recombination since we had established their importance for survival of cisplatin damage in our genetic studies. However, there was no significant induction of any known recombination genes in the *dam mutS* strain. For the wild type there was induction of expression of transcripts for the initiation protein RecO as well as the branch migration protein RuvA (FC = 2.75 and 2.85, *d(i)* = 4.79 and .72, respectively). This result is consistent with the notion that cisplatin adducts could cause frequent replication blocks that would require RecO initiated repair of the daughter strand gaps. Another interesting observation was the induction of *rus* and the repression of *ruvC* for the wild type, and just the opposite pattern was observed for the *dam* mutant. Both Rus and RuvC are resolvases of recombination intermediates and it has been speculated that the Rus resolvase is possibly a suppressor of the *ruv* operon[390]. This observation begs the question: is one resolvase would be favored in conditions where the strand discrimination signal is absent? Given that in the *dam* mutant there was no observable induction of the expression of *ruvAB* or *recG* it is possible that the RuvC protein can play a role in the repair of double strand breaks that is independent of the interactions with RuvAB promoted branch migration. An uncoupled role for RuvAB and RuvC in the processing of double strand breaks has been previously elucidated by genetic analysis[461]. The alternative branch migration and resolution protein RecG showed little difference in expression in the three phenotypes, a finding consistent with constitutive expression of this gene and the modest phenotype of *recG* deficient mutants following cisplatin exposure[415].

Another interesting observation was the finding that in the wild type there was a strong repression of *mutL* expression (FC = -1.60 and *d(i)* = -5.27). This pattern was mildly mimicked by the *dam* strain. It is possible that *mutL* repression facilitates recombinational bypass of cisplatin damaged intermediates that are induced at high levels in surviving populations (see Chapter 7). Increased transcription was observed in the *dam* strain for the *recD* gene (FC = 2.13, *d(i)* = 3.91) that encodes for the regulatory subunit of the RecBCD recombinase, a complex that functions in the repair of double strand breaks. This is consistent with the idea that a high number of double strand breaks form in the methylation deficient mutants because of abortive repair.

**Top 30 genes with significant changes in gene expression.** The 30 genes with highest changes of expression (induction or repression) for the three strains are listed in Tables 11-1, 11-2 and 11-3. The inspection of these results reinforces the previously discussed results, the tables for the wild type and the *dam* mutant are dominated by proteins involved in DNA repair and recombination, while these proteins are conspicuously absent in the *dam mutS* data. Interesting follow-up work to this study would involve the dissection of the repressed and induced genes presented on these tables for representatives of transcriptional regulators and other significant modulators of cellular responses.

## Discussion

In this study we compared the transcriptional responses to cisplatin by *E. coli* wt, methylation deficient (*dam*), and methylation-mismatch repair deficient (*dam mutS*) mutant strains. The most surprising feature of the results is that the methylation-mismatch repair deficient mutant showed no induction of DNA damage responses, and yet it displayed a relatively high survival rate.

These results imply that loss of mismatch repair in a *dam* background can lead to tolerance of DNA damage by a lack of repair response. One possible explanation for this is provided by the abortive repair model, in the *dam* strain components of the observed DNA damage response could have been induced by errand excision activity of the mismatch repair machinery. The second possibility is that mismatch repair proteins act as sensors of damage in *E. coli*. The major mechanism of cytotoxicity for cisplatin involves the replication blocking activity by the adducts. In non-replicating cells there is a significantly lower number of cisplatin induced strand breaks (pulse-field gel electrophoresis results, data not shown) and in a microarray experiment where non replicating wild type strain was treated with cisplatin there was very low induction of a DNA damage response (microarray results, data not shown). Therefore, while mismatch repair proteins are associated with the replication machinery, it is conceivable that they could encounter the cisplatin adducts and subsequently initiate adduct-repair or a more general DNA damage response. This is a provocative role for mismatch repair, but it would be parallel to signal transduction roles that are known for eukaryotic mismatch repair proteins.

The study we have presented should be the starting point for follow up projects. These results provide some generalizations with respect to the role of mismatch repair in the cellular responses to cisplatin in *E. coli*. Surprisingly it shows that in the absence of mismatch repair in methylation deficient background there are no major DNA repair responses. It remains to be determined whether these observations are significant in terms of a new role for mismatch repair for induction of DNA damage responses.

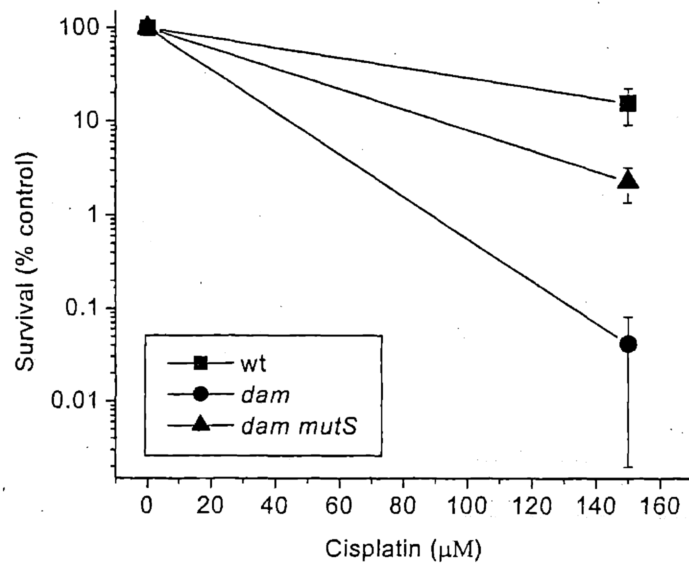



**Figure 11-1. Survival of wt, *dam*, and *dam mutS E. coli* strains treated with cisplatin and used in the microarray experiments.** For each data point, results shown are the mean of at least three independent experiments plated in duplicate, ± SEM.

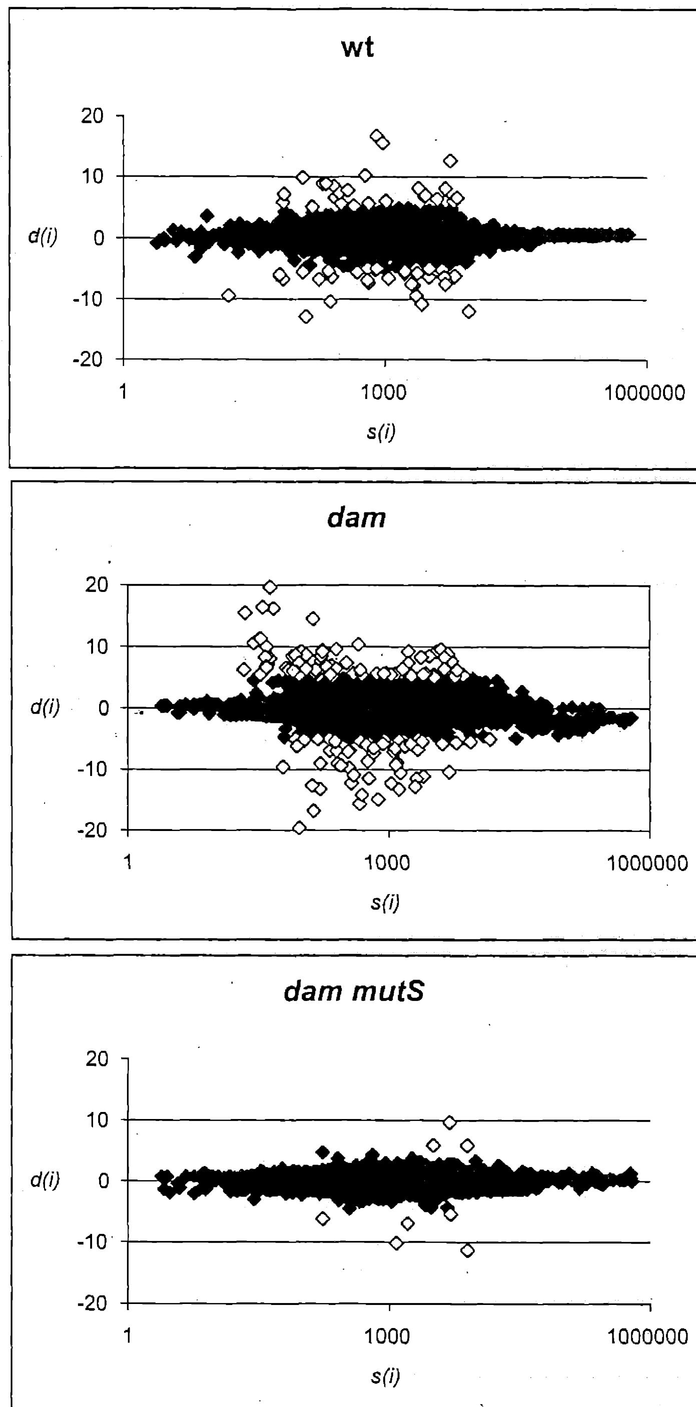



**Figure 11-2. Gene expression of wt, *dam* and *dam mutS E. coli* strains measured by microarrays.** Scatter plot of the relative difference of gene expression *d(i)* *vs*. the gene specific scatter *s(i)*. The genes with open diamonds represent genes with potentially significant changes in expression where $d(i) > 5$, and $d(i) < -5$.

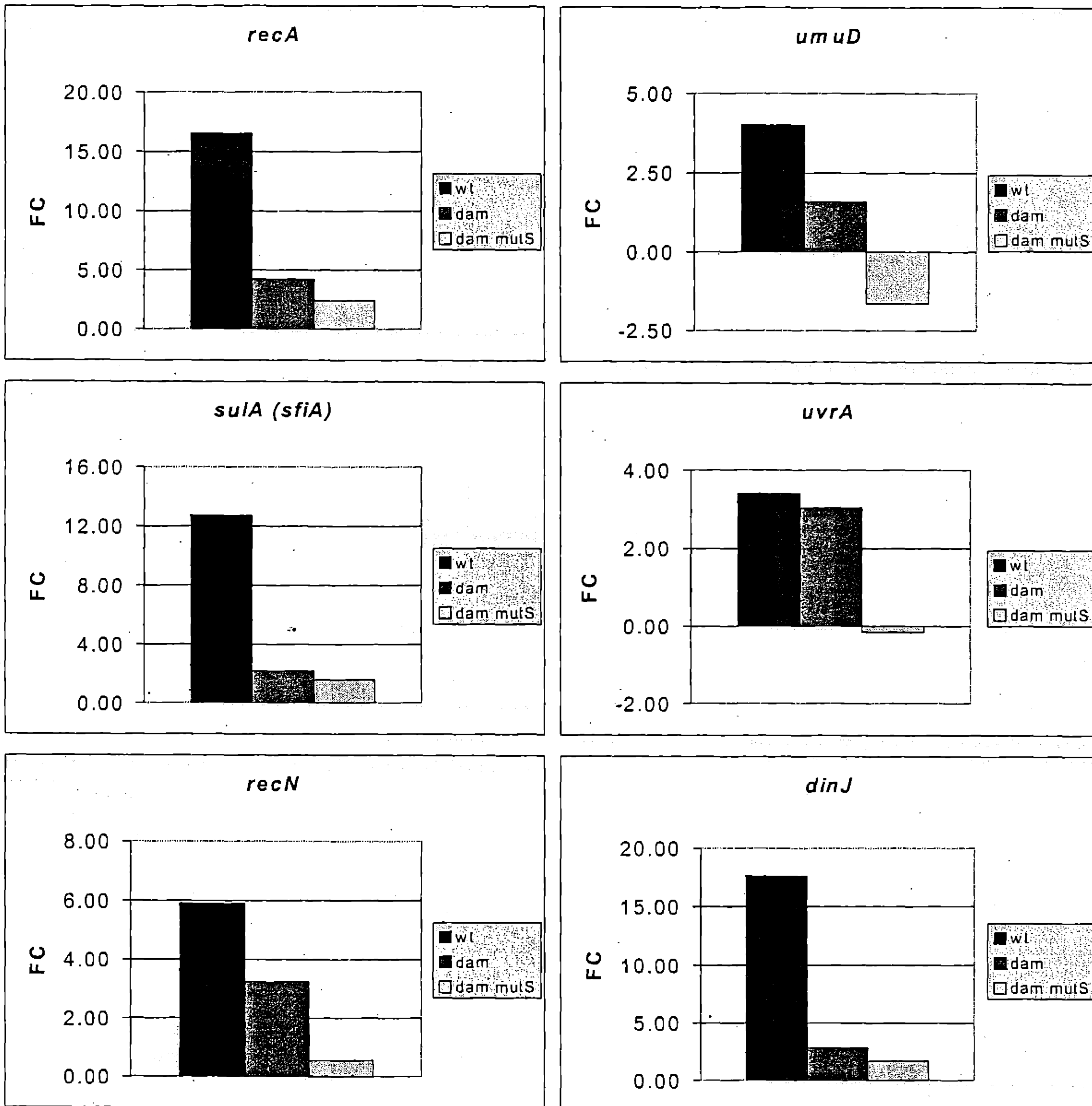



**Figure 11-3. Examples of expression profiles of genes involved in SOS damage responses.** The fold change FC in gene expression for a panel of genes between treated and untreated samples is presented for the three strains used in this study. Details in the text.

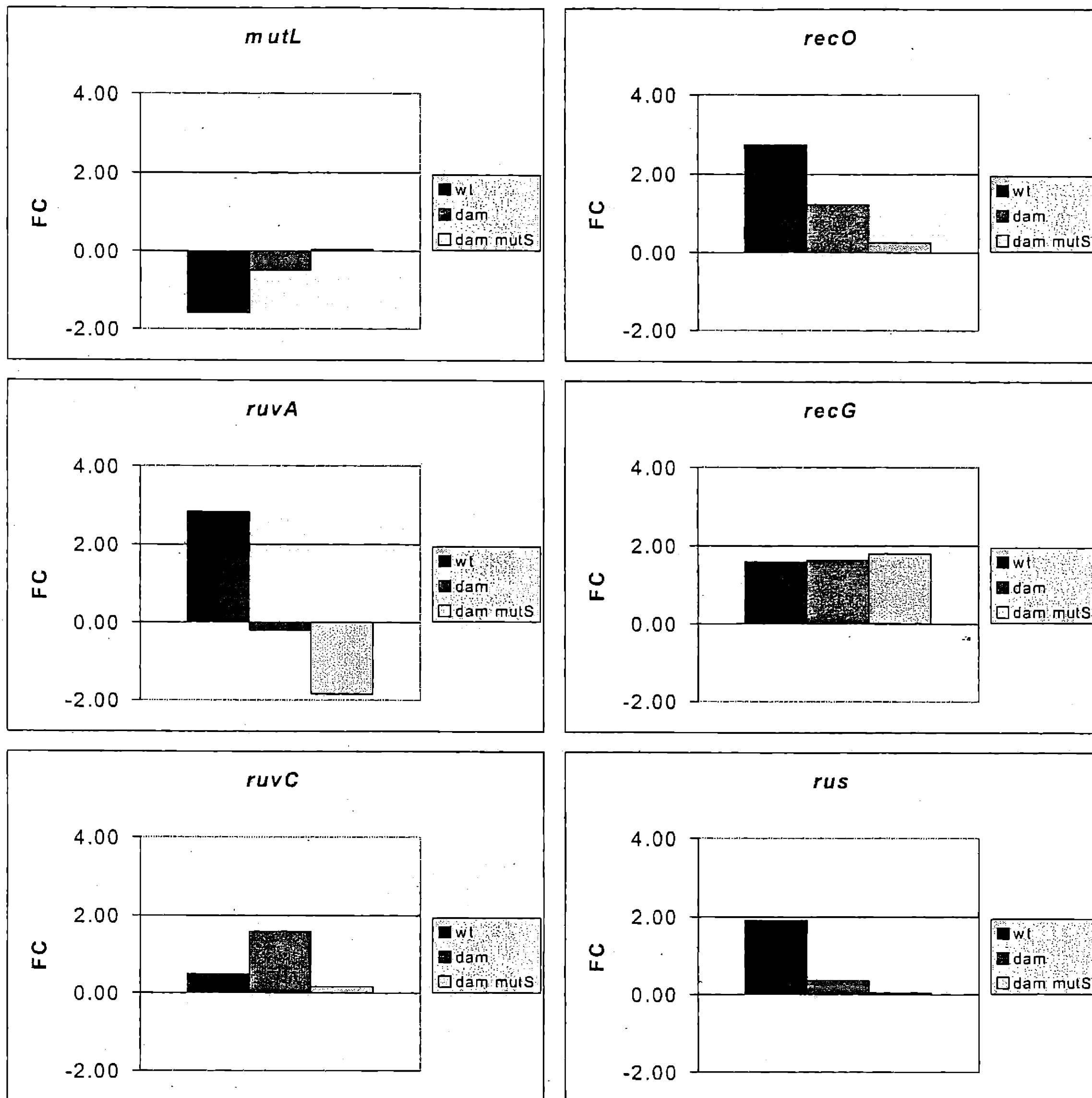



**Figure 11-4. Examples of expression profiles of genes involved in recombination.** The fold change FC in gene expression for a panel of genes between treated and untreated samples is presented for the three strains used in this study. Details in the text.

Table 11-1. Genes with significant changes of expression following cisplatin treatment of *E. coli* wild type strain.

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| dinI | **17.65** | 2.83 | **1.70** | 1.36 | 9.20 | 1.23 | damage-inducible protein I |
| ymfJ | **17.15** | 2.10 | **1.25** | 2.34 | 1.97 | 0.91 | orf, hypothetical protein |
| recA | **16.50** | 4.27 | **2.40** | 2.22 | 4.47 | 1.06 | DNA strand exchange and renaturation |
| lldD | **14.60** | **-1.57** | **-1.05** | 0.33 | -1.79 | -0.46 | L-lactate dehydrogenase |
| sulA | **12.75** | 2.17 | **1.55** | 1.96 | 1.99 | 1.25 | suppressor of lon; inhibits cell division and ftsZ ring formation |
| lldR | **9.40** | **-1.37** | **0.00** | 0.40 | -2.15 | -0.59 | transcriptional regulator |
| yjiY | **9.10** | **1.47** | **1.25** | 0.40 | 6.38 | 0.89 | putative carbon starvation protein |
| ymfH | **8.50** | **0.53** | **-0.10** | 1.06 | 2.33 | 0.06 | orf, hypothetical protein |
| yaaH | **6.30** | **-1.97** | **-2.05** | 0.96 | -1.63 | -1.37 | orf, hypothetical protein |
| ymfL | **6.20** | **-0.03** | **1.25** | 1.85 | -0.79 | 0.43 | orf, hypothetical protein |
| recN | **5.90** | 3.23 | **0.55** | 0.99 | 3.48 | 0.51 | protein used in recombination and DNA repair |
| dinF | **4.60** | **-0.27** | **0.20** | 0.63 | -0.97 | 0.06 | DNA-damage-inducible protein F |
| yebG | **4.40** | 3.60 | **1.80** | 2.37 | 8.21 | 1.73 | orf, hypothetical protein |
| intE | **4.25** | **-0.20** | **0.25** | 1.66 | -0.57 | 0.52 | prophage e14 integrase |
| araJ | **4.05** | **1.43** | **1.25** | 1.05 | 0.75 | 1.29 | involved in either transport or processing of arabinose polymers |
| aceA | **-6.60** | **-1.37** | **-0.30** | -2.21 | -1.91 | -1.30 | isocitrate lyase |
| ygiW | **-6.60** | **-1.00** | **-0.15** | -1.29 | -1.22 | -0.32 | orf, hypothetical protein |
| bfr | **-6.80** | -3.03 | **1.05** | -1.18 | -3.35 | 0.57 | bacterioferrin, an iron storage homoprotein |
| glcF | **-7.10** | **-0.23** | **-0.05** | -0.64 | -1.12 | -0.77 | glycolate oxidase iron-sulfur subunit |
| rmf | **-7.45** | -4.45 | 6.50 | -0.90 | -3.82 | -0.06 | ribosome modulation factor |
| cysM | **-8.40** | **0.60** | **-0.20** | -0.79 | -0.06 | -1.07 | cysteine synthase B, O-acetylserine sulfhydrolase B |
| fliC | **-9.15** | -7.10 | **-0.35** | -1.16 | -3.59 | -1.09 | flagellar biosynthesis; flagellin, filament structural protein |
| glcD | **-9.15** | **-1.10** | **1.25** | -1.25 | -1.79 | 0.57 | glycolate oxidase subunit D |
| cysN | **-10.15** | **-2.70** | **-0.15** | -0.99 | -0.55 | 0.73 | ATP-sulfurylase (ATP:sulfate adenylyltransferase) |
| yhaE | **-10.15** | **1.37** | **-0.25** | -0.11 | 0.64 | 0.04 | putative dehydrogenase |
| glpK | **-11.75** | -6.87 | **-1.25** | -1.92 | -21.68 | -1.24 | glycerol kinase |
| glcG | **-12.20** | **-2.07** | **0.05** | -1.25 | -1.55 | -0.08 | orf, hypothetical protein |
| dps | **-13.55** | -3.47 | **-1.80** | -1.46 | -4.80 | -1.23 | global regulator, starvation conditions |
| glcB | **-15.55** | **-1.33** | **-0.30** | -1.61 | -1.52 | -1.34 | malate synthase G |
| yi21 | **-18.15** | **-0.73** | **1.45** | -0.47 | -0.95 | 0.79 | IS2 hypothetical protein |
| cysA | **-22.25** | **-2.77** | **0.00** | -0.74 | -1.81 | -0.16 | ATP-binding component of sulfate permease A protein |

FC, fold change; *d(i)* relative difference in gene expression

Table 11-2. Genes with significant changes of expression following cisplatin treatment of *E. coli dam* strain.

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| recA | 16.50 | 4.27 | 2.40 | 2.22 | 4.47 | 1.06 | DNA strand exchange and renaturation |
| yebF | 3.95 | 4.10 | 0.20 | 2.62 | 8.91 | 0.27 | orf, hypothetical protein |
| bisZ | -1.70 | 3.80 | 0.15 | -1.33 | 2.80 | 0.12 | biotin sulfoxide reductase 2 |
| cmtA | 1.90 | 3.73 | -1.10 | 0.73 | 2.79 | -1.01 | PTS system, mannitol-specific enzyme II component, cryptic |
| yebG | 4.40 | 3.60 | 1.80 | 2.37 | 8.21 | 1.73 | orf, hypothetical protein |
| sodA | 2.35 | 3.57 | 1.55 | 0.27 | 2.56 | 0.59 | superoxide dismutase, manganese |
| deaD | 2.65 | 3.50 | -1.55 | 1.19 | 2.29 | -1.49 | inducible ATP-independent RNA helicase |
| rplW | 0.75 | 3.47 | 0.10 | -0.15 | 3.69 | 0.40 | 50S ribosomal subunit protein L23 |
| rplQ | 2.20 | 3.40 | 0.10 | 0.42 | 4.91 | 0.66 | 50S ribosomal subunit protein L17 |
| yfjA | 0.80 | 3.37 | 0.10 | 0.32 | 6.18 | -0.15 | orf, hypothetical protein |
| recN | 5.90 | 3.23 | 0.55 | 0.99 | 3.48 | 0.51 | protein used in recombination and DNA repair |
| rplA | 1.50 | 3.23 | 0.60 | 0.48 | 2.76 | 0.45 | 50S ribosomal subunit protein L1, regulates synthesis of L1 and L11 |
| yecA | -1.15 | 3.23 | 1.55 | -0.43 | -0.45 | 1.05 | orf, hypothetical protein |
| oraA | 3.50 | 3.20 | 1.80 | 2.06 | 3.40 | 1.01 | regulator, OraA protein |
| uvrA | 3.40 | 3.03 | -0.15 | 15.52 | 5.67 | 0.65 | excision nuclease subunit A |
| | | | | | | | |
| mdh | -3.05 | -4.70 | -0.15 | -4.51 | -11.51 | -1.20 | malate dehydrogenase |
| rbsD | -0.90 | -4.83 | 0.25 | 0.03 | -1.47 | 0.06 | D-ribose high-affinity transport system |
| galE | -4.95 | -4.93 | -0.05 | -2.56 | -0.83 | 1.19 | UDP-galactose-4-epimerase |
| ptsG | -2.45 | -4.97 | 0.25 | -1.63 | -12.78 | -0.19 | PTS system, glucose-specific IIBC component |
| fkpA | 1.40 | -5.10 | 1.30 | 0.37 | 0.55 | 1.44 | FKBP-type peptidyl-prolyl cis-trans isomerase (rotamase) |
| cspG | -0.45 | -5.10 | 1.45 | -1.14 | -1.71 | 2.58 | homolog of Salmonella cold shock protein |
| mtlA | -2,80 | -5.10 | 0.10 | -0.35 | -4.54 | 0.10 | PTS system, mannitol-specific enzyme IIABC components |
| pflB | -0.10 | -5.27 | 0.55 | -0.61 | -1.91 | 0.92 | formate acetyltransferase 1 |
| lamB | -1.80 | -5.63 | 0.05 | -0.40 | -1.48 | 0.67 | phage lambda receptor protein; maltose high-affinity receptor |
| glpB | -2.80 | -5.80 | -1.25 | -2.24 | -3.38 | -1.10 | sn-glycerol-3-phosphate dehydrogenase (anaerobic) |
| glpK | -11.75 | -6.87 | -1.25 | -1.92 | -21.68 | -1.24 | glycerol kinase |
| fliC | -9.15 | -7.10 | -0.35 | -1.16 | -3.59 | -1.09 | flagellar biosynthesis; flagellin, filament structural protein |
| malE | -3.20 | -7.93 | 1.15 | -2.46 | -1.50 | 0.72 | periplasmic maltose-binding protein |
| udp | -1.60 | -10.97 | -0.10 | -1.60 | -10.29 | -1.05 | uridine phosphorylase |
| ybaT | 1.75 | -12.30 | -0.15 | 0.72 | -1.34 | -1.08 | putative amino acid |
| yfiD | 0.05 | -12.63 | 0.05 | 0.13 | -1.46 | -0.60 | putative formate acetyltransferase |

FC, fold change; *d(i)* relative difference in gene expression

Table 11-3. Genes with significant changes of expression following cisplatin treatment of *E. coli dam mutS* strain.

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| carA | 1.50 | -0.83 | 7.10 | 1.40 | -0.90 | 0.45 | carbamoyl-phosphate synthetase, glutamine (small) subunit |
| rmf | -7.45 | -4.45 | 6.50 | -0.90 | -3.82 | -0.06 | ribosome modulation factor |
| rpsT | 2.15 | 1.50 | 4.20 | 1.49 | 2.20 | 0.53 | 30S ribosomal subunit protein S20 |
| dnaK | 0.00 | -2.27 | 3.85 | -0.06 | -2.48 | 0.40 | chaperone Hsp70; DNA biosynthesis |
| rpmJ | 1.45 | 1.25 | 3.65 | 0.73 | 0.74 | 0.81 | 50S ribosomal subunit protein L36 |
| gef | 0.30 | -1.70 | 3.60 | 0.47 | -1.36 | 0.66 | Gef protein interferes with membrane function when in excess |
| ygeK | -0.10 | -1.33 | 3.35 | -0.57 | -1.34 | 0.34 | putative 2-component transcriptional regulator |
| ybgI | -1.25 | 2.23 | 3.20 | -1.28 | 1.50 | 0.82 | orf, hypothetical protein |
| yadT | -0.05 | -0.60 | 2.80 | -1.05 | -1.15 | 0.14 | orf, hypothetical protein |
| ylbF | -0.25 | -0.30 | 2.60 | 0.89 | -0.57 | 0.61 | putative carboxylase |
| rpoB | 1.95 | 2.23 | 2.55 | 1.06 | 5.52 | 0.59 | RNA polymerase, beta subunit |
| recA | 16.50 | 4.27 | 2.40 | 2.22 | 4.47 | 1.06 | DNA strand exchange and renaturation |
| yddB | -1.95 | 1.30 | 2.35 | -1.91 | 1.71 | 0.92 | orf, hypothetical protein |
| uidA | 2.80 | -0.80 | 2.35 | 0.73 | -1.35 | 0.77 | beta-D-glucuronidase |
| yjfQ | 1.45 | -1.47 | 2.35 | 3.28 | -1.49 | 0.88 | putative DEOR-type transcriptional regulator |
| yhhA | 0.25 | -0.40 | -2.15 | -0.07 | -1.19 | -1.37 | orf, hypothetical protein |
| yaaJ | -0.10 | -0.53 | -2.15 | -0.56 | -0.95 | -1.31 | inner membrane transport protein |
| secF | -0.05 | -1.87 | -2.20 | -0.43 | -1.61 | -1.37 | protein secretion, membrane protein |
| tktA | -1.15 | -0.03 | -2.25 | -0.36 | 0.32 | 0.07 | transketolase 1 isozyme |
| htgA | 0.25 | -0.63 | -2.30 | 0.50 | -1.36 | -1.26 | positive regulator for sigma 32 heat shock promoters |
| lspA | -0.05 | -1.27 | -2.35 | -0.05 | -1.04 | -1.29 | prolipoprotein signal peptidase (SPase II) |
| lytB | 1.55 | -1.97 | -2.45 | 0.96 | -0.88 | -1.34 | control of stringent response; involved in penicillin tolerance |
| yicO | 2.10 | -1.00 | -2.65 | 0.71 | -1.36 | 0.09 | orf, hypothetical protein |
| yaaI | 0.20 | 1.07 | -2.75 | 0.47 | 0.87 | -1.35 | orf, hypothetical protein |
| ybeM | 2.00 | 1.10 | -3.00 | 0.34 | -0.44 | -1.31 | putative amidase |
| carB | 1.40 | -1.43 | -3.10 | 0.45 | -1.14 | -1.24 | carbamoyl-phosphate synthase large subunit |
| ybbO | 2.85 | 0.40 | -3.30 | 0.41 | -1.13 | -1.33 | putative oxidoreductase |
| yi22 | 0.10 | -2.37 | -3.45 | -0.14 | -1.61 | -1.33 | IS2 hypothetical protein |
| ylbB | -0.30 | 0.33 | -4.85 | -0.96 | 0.76 | -1.33 | putative hydantoin utilization protein |
| murG | -2.10 | -1.93 | -5.20 | -3.13 | -1.56 | -1.12 | UDP-N-acetylglucosamine |

FC, fold change; *d(i)* relative difference in gene expression

# Chapter 12. Mismatch Repair Proteins Involved in Meiosis But Not in the Correction of Replicative Errors Sensitize Eukaryotic Cells to Cisplatin

In eukaryotes there are two lineages of MutS homologues, the first one includes MSH2, MSH3, and MSH6 and these proteins form complexes involved in the repair of replication errors, such as mismatches and insertion/deletion loops. The second lineage includes MSH4 and MSH5, and these proteins are involved in meiotic recombination processes. MSH4 and MSH5 orthologues have been identified in most eukaryotic organisms including yeast, humans, mice and worms[22,462,463]. The MSH4 and MSH5 proteins are associated with chromosomes during the pachytene stage of meiosis I and are required for reciprocal recombination during crossing-over and proper chromosome segregation[464]. Accordingly, high levels of coregulated *hMSH4* and *hMSH5* transcripts have been found in meiotic tissues such as the testis, and in particular during spermatogenesis between the late primary spermatocytes and the elongated spermatid phase[24,456].

The MSH4 and MSH5 proteins form a heteroduplex complex, and neither MSH4 or MSH5 has been shown to interact with MSH2 or MSH6, further reinforcing the notion that MSH4 and MSH5 constitute a class of MutS homologues that are functionally different from the proteins that participate in mismatch repair[457]. Fittingly, MSH4 and MSH5 interact with proteins involved in meiosis, such as Zip3, a protein that promotes the late steps of meiotic synapsis[458], and with MLH1 during the crossing-over and reciprocal recombination[465].

Yeast *msh4* mutants display reduced crossing over frequency, meiosis I-homologous nondisjunction and spore inviability, but they do not display any mismatch repair defects in either vegetative or meiotic cells[464,466]. The role of MSH4 could be in determining whether some recombination intermediates are resolved as crossover events and in generating crossover interference[467].

It was previously discussed that cells deficient in proteins involved in mismatch repair proper, *msh2, msh3*, and *msh6* are in general, more resistant to cisplatin than wild type[442]. The responses to DNA damage of the MSH4 and MSH5 deficient cells have not been studied in detail yet. In one report, the methylating agent MNNG was used to treat a panel of *S. cerevisiae* mismatch repair deficient mutants in a methyltransferase (*mgt1*) deficient background, and the results revealed that an additional *msh5* mutation could abrogate the sensitivity of the *mgt1* mutants to MNNG, while mutations in *msh2, msh3*, and *msh6* did not[468]. Given that the majority of testicular tumors (95%) derive from germ cells that are pre-meiotic in origin[1], the extrapolations of these observations as well as the results discussed in the previous chapters raised the possibility that cisplatin could uniquely affect testicular cancer cells due to interactions with MSH4/MSH5 proteins and the meiotic processes that occur specifically in these cells. To probe this hypothesis further, we set out to examine if mutants deficient in the two different lineages of mismatch repair proteins show differential sensitivity to cisplatin.

## Materials and Methods

*Cytotoxicity analysis. S. cerevisiae* cultures (RKY3109 isogenic strains, provided by Dr. R. Kolodner *via* Prof. L. Samson's laboratory) were grown in YPD medium until the density of the population reached log phase 1 x $10^7$ cells/ml as determined by counting. The exponentially growing cells were treated with cisplatin (dissolved in $H_2O$) for 1.5 h at 30 °C. Appropriate dilutions in were plated on YPD plates and incubated at 30 °C until colonies could be counted. Results from three to six independent experiments plated in duplicate were averaged and plotted

against drug concentration, ± SEM (standard error of the mean). $IC_{37}$ (inhibitory concentration of 37%) was determined as the drug concentration where there was 37% of survival in comparison to the untreated control.

## Results

To assess the importance of the meiotic pathways of recombination and possible role for the MSH4 and MSH5 proteins in the cellular responses to cisplatin DNA damage, we examined the survival of *msh4* and *msh5* *S. cerevisiae* mutants following cisplatin treatment (Figure 12-1). Both, the *msh4* and the *msh5* mutants showed higher survival to cisplatin in comparison to the isogenic wild type strain. The $IC_{37}$ was determined to be 670 μM, 520 μM, and 360 μM for the *msh4, msh5* and the wt, respectively (Table 12-1). This approximately two-fold difference in $IC_{37}$ was well illustrated at the highest cisplatin dose (1000 μM), where the surviving fraction for the *msh4* and *msh5* mutants was ~10-20 fold higher than that for the isogenic wild type strain.

## Discussion

We report that inactivation of the mismatch repair genes MSH4 and MSH5 in isogenic strains of *S. cerevisiae* led to increased resistance to cisplatin. These findings suggest a model of cisplatin organospecificity where the MSH4/MSH5 proteins could specifically sensitize meiotic testicular cells to cisplatin by interfering with cisplatin-induced recombination events.

Recent studies have shown that the production of crossovers in meiotic recombination is independent of Spo11 generated double strand breaks, and it can be induced by a site specific HO endonuclease[469], or γ irradiation[470]. Cisplatin is highly recombinogenic in bacteria[415], as well as in mouse testicular germ cells [10], and it is possible that this induction of recombination occurs by a Spo 11 independent mechanism. These high levels of recombination probably have to be sanctioned by interactions with MSH4/MSH5. For example Him14, a *Caenorhabditis elegans* MSH4 orthologue, promotes crossing over by interfering with Holliday junction branch migration[471]. As discussed in the introduction, the *msh4* mutants have decreased levels of crossing-over events. We propose a model where MSH4/MSH5 inhibition of the high levels of cisplatin-induced recombination specifically sensitizes meiotic cells to this drug.

In support of such a model for the role of MSH4/MSH5 in mediating cisplatin cytotoxicity, cisplatin has been shown to cause abnormal homologue pairing, and disruption of the proper formation and resolution of recombination intermediates during testicular germ cell meiosis [11,12]. It is an interesting question if these events are mediated by direct interactions of MSH4/MSH5 with cisplatin-modified DNA. In this regard, it is to noteworthy that in parallel experiment where isogenic strains that had inactivated *MSH2, MSH3,* and *MSH6,* under the identical conditions, these mismatch repair mutants showed comparable or higher sensitivity in comparison to the wild type (data not shown). It is probable that these discrepancies with the literature result from the different experimental conditions used.

We propose that the relationships among these observations provide a framework within which we may begin to understand the molecular mechanism for the organotropic action of this drug. High levels of cisplatin induced recombination could lead to cell death by triggering MMR mediated damage signaling pathways that are specific to germ cells. The abundant MMR proteins could also sensitize germ cells by interfering with the required high level of recombinational repair of cisplatin damage. Clearly, further exploration of the relationships among recombination, repair of DNA damage, and the roles of MMR proteins in both of these processes are warranted, and hopefully this thesis will contribute to this growing body of knowledge.

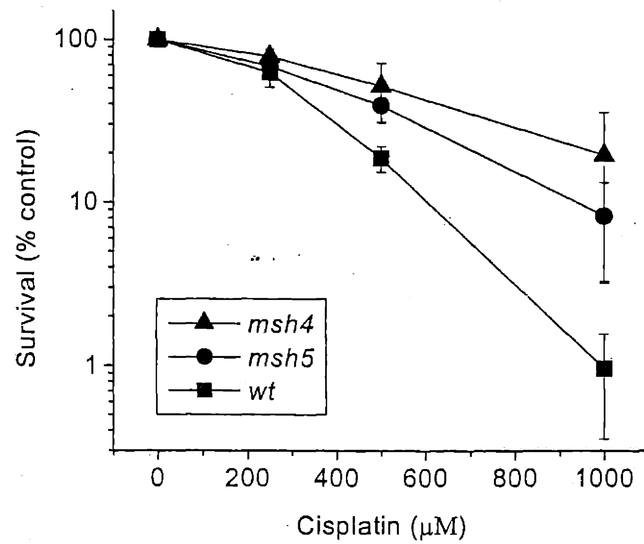



**Figure 12-1. Effects of *msh4* and *msh5* mutations on cisplatin sensitivity in *S. cerevisiae*.** For each data point, results shown are the mean of at least three independent experiments plated in duplicate, ± SEM.

Table 12-1. Sensitivities of mismatch repair mutants to cisplatin

| Genotype | $IC_{37}$ (cisplatin, μM) | $RF_{37}$ | $RF_{1000}$ |
|---|---|---|---|
| wt | 360 | 1 | 1 |
| *msh4* | 670 | 1.9 | 20.2 |
| *msh5* | 520 | 1.4 | 8.6 |

All strains are isogenic derivatives of a *Mat*$\alpha$ wild-type strain. $IC_{37}$ concentration of cisplatin inducing 37% survival of untreated control. $RF_{37}$, resistance factor relative to wild type strain compared at the $IC_{37}$. $RF_{1000}$, resistance factor relative to wild type compared at cisplatin dose of 1000 μM.

## CONCLUSIONS

Although this study involved analysis of the role of recombination and mismatch repair process in mediating cellular responses to cisplatin, it is useful to bear in mind the question that underlies most research on cisplatin- namely, why are tumors of the testis so singularly susceptible to the drug? It is possible that there is an important connection between the capacity of cisplatin to induce robust levels of recombination and the therapeutic specificity of this drug for testicular tumors. Testicular tumors derive from germ cells, cells that are unique in that they undergo meiotic recombination as an essential step during cell division. Meiotic recombination is a highly regulated and a precise event and, if disrupted, germ cells enter apoptosis. Cancer cells derived from germ cells might inherit such regulatory mechanisms specific for meiotic recombination, which may be triggered by cisplatin induced recombination events. Thus, while recombination is a powerful protective pathway against cisplatin damage, it may actually selectively sensitize germ cells and germ cell tumors to the drug.

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## Biographical note

Zoran Zdraveski was born on September 25, 1969 in Skopje, Macedonia. Following his graduation at the Medical High school Center in Skopje, Zoran continued his education in the United States. He awarded scholarships to attend Southern Methodist University, in Dallas, Texas, where he graduated with degrees in Chemistry and Studio Art. During his undergraduate studies Zoran was the recipient of the Algur H Meadows Merit Artistic Award and The Dorothy Aman Award for Contribution to Student Life. Following his undergraduate carrier Zoran worked for one year in the laboratory of Dr. Louis Picker at the University of Texas Southwestern Medical Center where he conducted research in the area of cytokine expression kinetics. This research experience was crucial in Zoran's decision to continue with a scientific education. In 1994 he returned to SMU to obtain a Masters Degree in Chemistry in the laboratory of Mark Schell, under the thesis: *Mechanistic Significance of Universal and Nonuniversal Behavior Accompanying Chemical Instabilities In The Voltammetric Oxidation of Ethylene Glycol and Butan-1-ol.* During this time Zoran discovered a love for teaching and became a Science Teacher for a Dallas Upward Bound Program.

In 1996, following the competition of his masters studies, Zoran joined the laboratory of John Essigmann at the Chemistry Department at the Massachusetts Institute of Technology and began working toward a Ph. D. in Biological Chemistry with a focus on the cellular responses to the anticancer cisplatin. For this research project, in 1999, Zoran was the recipient of the Anna Fuller Fund Graduate Fellowship in Molecular Oncology from the MIT Center for Cancer Research. During his graduate studies Zoran continued to fulfill his love for teaching as well, he was a Teaching Assistant for Introductory Chemistry 5.11, Advanced Biochemistry Lab 5.071J and the Head Teaching Assistant for Biochemistry 5.07 and in 1997-98 he was a Chemistry Tutor at the Phillips Academy in Andover. In addition, he was an organizing member of the MIT Chemistry Dept Graduate Student Committee. Zoran was involved with extracurricular activities outside of the Chemistry Department, as well. From 1998 to 2000, Zoran was a Macedonian Language Instructor at the Slavic Languages Dept. at Harvard University. In the spring of 2000 as one of the founders of the biotech start-up company EyeGen, Zoran was the winner of the 2000 MIT$50K Entrepreneurial Contest and the Stanford Global Entrepreneurial Challenge. Following his graduation Zoran will be engaged full time with EyeGen now renamed Genigma. Zoran is the first citizen of Macedonia to receive a doctorate from MIT.

Appendix A.

Table 11-A. Complete Alphabetical Data for Microarray Gene Expression Following Cisplatin Treatment of *E. coli* wt, *dam* and *dam mutS* Strains (FC, fold change; *d(i)* relative change on gene expression)

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| aas | -0.94 | 1.42 | -0.27 | -0.30 | 1.70 | 0.10 | 2-acyl-glycerophospho-ethanolamine acyltransferase; acyl-acyl-carrier protein synthetase |
| aat | 0.00 | 0.00 | -0.60 | -1.95 | 0.33 | 0.05 | leucyl, phenylalanyl-tRNA-protein transferase |
| abc | -0.74 | -0.83 | -0.38 | -0.05 | -1.47 | -1.50 | ATP-binding component of a transporter |
| abrB | -1.41 | 0.77 | 0.48 | -1.45 | 1.47 | 0.35 | putative transport protein |
| accA | 0.27 | 0.99 | 0.24 | -0.35 | 0.47 | -1.30 | acetylCoA carboxylase, carboxytransferase component, alpha subunit |
| accB | 0.07 | 0.67 | -0.64 | -0.20 | 0.13 | -1.20 | acetylCoA carboxylase, BCCP subunit; carrier of biotin |
| accC | -0.21 | 0.45 | -1.29 | -1.15 | 0.10 | -1.70 | acetyl CoA carboxylase, biotin carboxylase subunit |
| accD | 0.12 | 0.79 | -0.24 | 1.20 | 0.57 | 0.15 | acetylCoA carboxylase, carboxytransferase component, beta subunit |
| aceA | -2.21 | -1.91 | -1.30 | -6.60 | -1.37 | -0.30 | isocitrate lyase |
| aceB | -6.14 | 0.67 | -0.05 | -2.20 | 1.27 | 0.20 | malate synthase A |
| aceE | -0.45 | 1.76 | 0.91 | 0.00 | 1.67 | -0.35 | pyruvate dehydrogenase (decarboxylase component) |
| aceF | -0.33 | 2.81 | 2.40 | -0.70 | 2.50 | 2.25 | pyruvate dehydrogenase (dihydrolipoyltransacetylase component) |
| aceK | 0.94 | -1.03 | 0.91 | 1.70 | -0.07 | 1.20 | isocitrate dehydrogenase kinase |
| ackA | -0.09 | 0.13 | 0.25 | 0.05 | -0.43 | -1.25 | acetate kinase |
| acnA | -1.39 | -0.01 | -1.20 | -2.05 | 1.37 | -1.20 | aconitate hydrase 1 |
| acnB | -4.38 | -3.07 | 0.23 | -1.60 | -1.67 | 0.50 | aconitate hydrase B |
| acpD | 0.19 | -1.64 | -1.32 | 0.15 | -1.43 | -1.55 | acyl carrier protein phosphodiesterase |
| acpP | 0.61 | -5.74 | -1.06 | 0.70 | -1.67 | -0.30 | acyl carrier protein |
| acpS | -1.18 | 0.86 | 2.05 | -0.65 | 0.33 | 1.30 | CoA:apo-[acyl-carrier-protein] pantetheinephosphotransferase |
| acrA | -0.20 | -0.84 | -1.12 | -1.55 | -0.67 | -0.15 | acridine efflux pump |
| acrB | -2.47 | 0.81 | 0.22 | -1.75 | 0.03 | 0.00 | acridine efflux pump |
| acrD | -0.85 | 5.83 | 0.84 | 0.05 | 1.27 | 1.45 | sensitivity to acriflavine, integral membrane protein, possible efflux pump |
| acrE | 1.51 | -0.97 | 0.72 | 0.50 | 1.10 | 1.00 | transmembrane protein affects septum formation and cell membrane permeability |
| acrF | 2.34 | 0.80 | -0.74 | 0.45 | 1.23 | -0.05 | integral transmembrane protein; acridine resistance |
| acrR | -1.02 | 0.58 | -0.60 | -1.70 | 1.30 | -0.10 | acrAB operon repressor |
| acs | -0.48 | 0.14 | -0.08 | -1.55 | -1.13 | 0.05 | acetyl-CoA synthetase |
| ada | 0.68 | 1.15 | -0.89 | -0.45 | 1.07 | 0.00 | O6-methylguanine-DNA methyltransferase; transcription activator |
| add | 1.19 | -1.24 | 0.75 | 1.45 | -0.57 | 0.00 | adenosine deaminase |
| adhC | 0.29 | 1.14 | -0.53 | 0.15 | 0.57 | 0.00 | alcohol dehydrogenase class III; formaldehyde dehydrogenase, glutathione-dependent |
| adhE | -0.42 | 0.10 | -0.84 | -1.20 | -0.40 | 0.00 | CoA-linked acetaldehyde dehydrogenase and iron-dependent alcohol dehydrogenase |
| adhP | -0.32 | 1.18 | -1.30 | -1.15 | 1.30 | -0.05 | alcohol dehydrogenase |
| adiA | 0.05 | 1.14 | -1.37 | 0.55 | 1.43 | -1.40 | biodegradative arginine decarboxylase |
| adiY | -0.46 | 0.03 | -1.31 | -0.15 | 0.53 | -1.25 | putative ARAC-type regulatory protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| adk | 0.38 | 0.71 | 1.46 | 1.90 | 0.57 | 1.30 | adenylate kinase activity; pleiotropic effects on glycerol-3-phosphate acyltransferase activity |
| aefA | -1.31 | 0.89 | -0.38 | -2.00 | 1.27 | -1.20 | putative alpha helix protein |
| aer | -0.77 | 0.74 | 0.12 | -2.25 | 1.27 | -0.05 | aerotaxis sensor receptor, flavoprotein |
| afuC | 0.45 | -1.43 | -1.44 | 1.50 | -1.27 | -1.35 | putative ATP-binding component of a transport system |
| agaA | 0.09 | 1.30 | 0.78 | 0.65 | 1.57 | 1.35 | putative N-acetylgalactosamine-6-phosphate deacetylase |
| agaB | 0.23 | 0.31 | -0.58 | 1.20 | 1.23 | 0.05 | PTS system, cytoplasmic, N-acetylgalactosamine-specific IIB component 1 (EIIB-AGA) |
| agaC | -0.92 | -0.56 | -1.33 | 0.30 | 0.07 | -0.05 | PTS system N-acetylgalactosamine-specific IIC component 1 |
| agaD | -0.50 | -0.15 | 0.70 | 0.05 | 1.43 | 1.60 | PTS system, N-acetylglucosamine enzyme IID component 1 |
| agaI | 1.09 | 0.89 | -1.33 | 2.35 | 1.47 | -0.20 | putative galactosamine-6-phosphate isomerase |
| agaR | -0.66 | -1.30 | -0.39 | -0.80 | -0.70 | 0.15 | putative DEOR-type transcriptional regulator of aga operon |
| agaS | 2.04 | 1.43 | 0.10 | 0.60 | 1.10 | 0.15 | putative tagatose-6-phosphate aldose |
| agaV | -1.38 | -1.31 | 0.74 | 0.00 | -1.20 | 1.45 | PTS system, cytoplasmic, N-acetylgalactosamine-specific IIB component 2 (EIIB-AGA) |
| agaW | 0.40 | -1.31 | -1,03 | 1.65 | -0.37 | -1.65 | PTS system N-acetylgalactosameine-specific IIC component 2 |
| agaY | 0.50 | 1.13 | 0.69 | 0.80 | 1.47 | 0.00 | tagatose-bisphosphate aldolase 2 |
| agaZ | -0.80 | -1.28 | 1.11 | 0.10 | -1.33 | 1.20 | putative tagatose 6-phosphate kinase 2 |
| agp | -1.02 | -1.69 | -0.04 | -2.75 | -1.43 | 1.10 | periplasmic glucose-1-phosphatase |
| ahpC | -2.52 | -0.76 | -0.32 | -1.55 | -1.50 | 0.00 | alkyl hydroperoxide reductase, C22 subunit; detoxification of hydroperoxides |
| ahpF | -0.10 | 1.15 | 0.56 | -1.70 | 1.23 | -0.25 | alkyl hydroperoxide reductase, F52a subunit; detoxification of hydroperoxides |
| aidB | 0.49 | -0.46 | 0.68 | 1.10 | 1.17 | 0.05 | putative acyl coenzyme A dehydrogenase |
| ais | 2.10 | -1.09 | -0.79 | 1.70 | -0.17 | -0.05 | protein induced by aluminum |
| alaS | -1.53 | 0.91 | 1.05 | -2.80 | 0.53 | 1.60 | alanyl-tRNA synthetase |
| alaT | 0.44 | -0.12 | -0.28 | 1.50 | 39.77 | 17.60 | Alanine tRNA 1B; rrnA operon |
| alaU | 0.45 | -1.93 | 0.27 | 1.50 | 18.07 | 21.70 | Alanine tRNA 1B; rrnD operon |
| alaW | 0.52 | -3.42 | 0.16 | 0.45 | 9.97 | 21.80 | Alanine tRNA 2; tandemly duplicated |
| alaX | 0.48 | -4.28 | -0.16 | 0.35 | 11.43 | 6.90 | Alanine tRNA 2; tandemly duplicated alaW |
| aldA | -0.08 | 1.45 | 1.17 | -1.25 | 1.93 | 1.70 | aldehyde dehydrogenase, NAD-linked |
| aldB | 0.71 | -1.49 | 0.82 | 0.35 | -0.23 | 1.05 | aldehyde dehydrogenase B (lactaldehyde dehydrogenase) |
| aldH | 0.00 | 0.00 | -1.34 | -1.75 | 1.23 | -0.45 | aldehyde dehydrogenase, prefers NADP over NAD |
| alkA | 0.41 | -2.41 | 0.00 | -0.55 | -1.30 | -1.40 | 3-methyl-adenine DNA glycosylase II, inducible |
| alkB | 0.26 | -1.05 | 0.81 | 1.15 | 1.17 | 1.25 | DNA repair system specific for alkylated DNA |
| alpA | 8.54 | 0.78 | 0.46 | 0.35 | 1.30 | 0.00 | prophage CP4-57 regulatory protein alpA |
| alr | 1.72 | 2.17 | 0.32 | 1.40 | 1.47 | 0.20 | alanine racemase 1 |
| amiA | 1.29 | -1.20 | -0.55 | 1.40 | -0.50 | -1.25 | N-acetylmuramoyl-l-alanine amidase I |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| amiB | -0.60 | -0.47 | 0.74 | -0.20 | 0.50 | 1.30 | N-acetylmuramoyl-l-alanine amidase II; a murein hydrolase |
| amn | -0.08 | -0.50 | 0.79 | 0.15 | 1.40 | 1.40 | AMP nucleosidase |
| ampC | -0.19 | -1.39 | -0.91 | 0.50 | -1.43 | -0.05 | beta-lactamase; penicillin resistance |
| ampD | 0.53 | -1.40 | 0.74 | 0.00 | -1.37 | -0.10 | regulates ampC |
| ampE | 0.47 | -1.39 | -1.27 | 0.20 | -1.53 | -0.25 | regulates ampC |
| ampG | 0.74 | -1.24 | -1.28 | 1.50 | -0.40 | -0.25 | regulates beta-lactamase synthesis |
| amtB | 1.03 | -1.13 | -0.07 | 1.30 | -0.17 | 0.15 | probable ammonium transporter |
| amyA | -1.21 | -1.22 | 0.59 | -4.05 | -1.13 | 0.20 | cytoplasmic alpha-amylase |
| ansA | 0.06 | 1.01 | 0.78 | -0.15 | 1.80 | 1.45 | cytoplasmic L-asparaginase I |
| ansB | -1.23 | -2.89 | 0.13 | -1.50 | -4.43 | -0.05 | periplasmic L-asparaginase II |
| ansP | 2.24 | -0.97 | 0.80 | 1.55 | -0.47 | 0.30 | L-asparagine permease |
| apaG | 0.22 | -1.05 | -0.70 | 1.20 | -1.37 | -0.05 | orf, hypothetical protein |
| apaH | 0.63 | 1.11 | 1.46 | 2.20 | 0.43 | 0.05 | diadenosine tetraphosphatase |
| apbA | -0.81 | -0.55 | 0.43 | -0.15 | 0.17 | 0.05 | involved in thiamin biosynthesis, alternative pyrimidine biosynthesis |
| aphA | -0.09 | -3.15 | 0.24 | -1.25 | -2.57 | 0.30 | diadenosine tetraphosphatase |
| appA | 1.55 | 0.07 | -0.88 | 1.35 | 1.17 | -1.15 | phosphoanhydride phosphorylase; pH 2.5 acid phosphatase; periplasmic |
| appB | -0.70 | 0.56 | 0.32 | 0.00 | 1.30 | 0.15 | probable third cytochrome oxidase, subunit II |
| appC | 0.93 | 0.48 | 0.62 | 1.85 | 1.90 | -1.10 | probable third cytochrome oxidase, subunit I |
| appY | 0.03 | -0.02 | -1.35 | 0.15 | 0.40 | -1.45 | regulatory protein affecting appA and other genes |
| apt | 0.42 | -0.80 | 0.14 | 1.45 | 1.30 | 0.35 | adenine phosphoribosyltransferase |
| aqpZ | -0.55 | -1.94 | 0.74 | -0.20 | -1.33 | 1.45 | transmembrane water channel; aquaporin Z |
| araA | -0.27 | -1.19 | 0.19 | -0.30 | -1.33 | -0.65 | L-arabinose isomerase |
| araB | 0.49 | -1.33 | -0.82 | 0.05 | -0.77 | 0.00 | L-ribulokinase |
| araC | -0.08 | -4.37 | -1.22 | 0.00 | -1.67 | -1.40 | transcriptional regulator for ara operon |
| araD | -1.44 | -0.62 | 0.03 | -2.20 | -1.27 | -0.20 | L-ribulose-5-phosphate 4-epimerase |
| araE | -0.38 | 0.14 | 0.74 | 0.00 | -0.37 | 1.40 | low-affinity L-arabinose transport system proton symport protein |
| araF | 0.87 | -0.40 | -0.87 | 1.90 | 0.10 | -0.05 | L-arabinose-binding periplasmic protein |
| araG | 0.76 | 0.38 | -1.09 | 1.30 | 0.00 | -0.05 | ATP-binding component of high-affinity L-arabinose transport system |
| araH | -0.81 | -1.36 | -1.44 | -0.05 | 0.33 | 1.40 | high-affinity L-arabinose transport system; membrane protein, fragment 1 |
| araH | -1.00 | -1.73 | 0.75 | -0.60 | -0.67 | -1.70 | high-affinity L-arabinose transport system; membrane protein, fragment 2 |
| araJ | 1.05 | 0.75 | 1.29 | 4.05 | 1.43 | 1.25 | involved in either transport or processing of arabinose polymers |
| arcA | -0.26 | -0.77 | 1.44 | -0.25 | -1.57 | 1.50 | negative response regulator of genes in aerobic pathways, (sensors, ArcB and CpxA) |
| arcB | -1.69 | -1.55 | 0.53 | -1.40 | -0.37 | 0.20 | aerobic respiration sensor-response protein; histidine protein kinase |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| arcC | 0.95 | -0.68 | -0.99 | 0.20 | -0.10 | -0.10 | putative carbamate kinase (EC 2.7.2.2) |
| argA | 0.71 | 0.64 | -1.33 | 1.30 | 0.37 | 0.10 | N-acetylglutamate synthase; amino acid acetyltransferase |
| argB | -0.53 | -0.39 | 0.69 | 0.15 | 0.17 | 1.25 | acetylglutamate kinase |
| argC | -0.13 | -1.55 | -1.23 | 1.35 | -1.63 | 0.30 | N-acetyl-gamma-glutamylphosphate reductase |
| argD | 0.77 | -0.34 | 0.71 | 0.35 | -0.10 | 1.20 | acetylornithine delta-aminotransferase |
| argE | -0.27 | -0.11 | -1.35 | 0.30 | 0.17 | -1.35 | acetylornithine deacetylase |
| argF | 0.00 | -3.13 | 0.74 | -1.80 | -1.40 | 1.95 | ornithine carbamoyltransferase 2, chain F |
| argG | 1.92 | 1.66 | 0.75 | 1.15 | 1.27 | 1.30 | argininosuccinate synthetase |
| argH | 0.49 | -3.15 | -1.18 | 0.65 | -2.03 | -1.45 | argininosuccinate lyase |
| argI | -0.88 | -1.22 | 1.18 | 0.00 | -0.50 | 1.15 | ornithine carbamoyltransferase 1 |
| argQ | 0.51 | 0.26 | 1.25 | 0.45 | 1.97 | 4.10 | Arginine tRNA2 tandem quadruple genes |
| argR | -1.81 | -1.31 | -1.09 | -1.75 | -1.37 | -0.20 | repressor of arg regulon; cer-mediated site specific recombination |
| argS | -0.04 | 0.53 | 1.15 | -0.40 | -0.13 | 1.45 | arginine tRNA synthetase |
| argT | 0.27 | -1.22 | -1.31 | 0.15 | -0.33 | -1.70 | lysine-, arginine-, ornithine-binding periplasmic protein |
| argU | 0.43 | -1.78 | -1.15 | 1.65 | -1.50 | -1.70 | Arginine tRNA4 |
| argV | 0.49 | 0.58 | 0.56 | 0.40 | 2.73 | 2.00 | Arginine tRNA2; tandem quadruplicate genes |
| argW | 0.22 | 2.84 | 0.70 | 2.40 | 2.43 | 1.45 | Arginine tRNA5 |
| argX | 0.21 | -0.76 | 0.53 | 0.10 | -0.15 | 6.60 | Arginine tRNA3 |
| argZ | 0.53 | -4.87 | 0.57 | 0.55 | -2.00 | 11.50 | Arginine tRNA2; tandem quadruplicate genes |
| aroA | -0.83 | 0.83 | 0.81 | -0.60 | 1.33 | 1.10 | 5-enolpyruvylshikimate-3-phosphate synthetase |
| aroB | 0.01 | -0.70 | 1.58 | -0.20 | -1.30 | 1.30 | 3516124.00 |
| aroC | -0.36 | -1.19 | -1.08 | 0.15 | -0.67 | 0.00 | chorismate synthase |
| aroD | 0.37 | -1.40 | 0.34 | 2.15 | -1.40 | 0.00 | 3-dehydroquinate dehydratase |
| aroE | 0.10 | -1.35 | -1.33 | 0.10 | -1.20 | -1.10 | dehydroshikimate reductase |
| aroF | 0.67 | -1.18 | -1.38 | 0.40 | -0.37 | -1.40 | 3-deoxy-D-arabinoheptulosonate-7-phosphate synthase (DAHP synthetase, tyrosine repressible) |
| aroG | 1.19 | 1.06 | 0.84 | 1.55 | -1.17 | 1.45 | 3-deoxy-D-arabinoheptulosonate-7-phosphate synthase (DAHP synthetase, phenylalanine repressible |
| aroH | 0.03 | -1.13 | 1.15 | -0.05 | -1.13 | -0.10 | 3-deoxy-D-arabinoheptulosonate-7-phosphate synthase (DAHP synthetase, tryptophan repressible) |
| aroK | 1.44 | 1.16 | -0.72 | 1.30 | 0.67 | -1.35 | shikimate kinase I |
| aroL | -7.28 | 0.16 | -1.23 | -1.60 | -0.10 | -1.45 | shikimate kinase II |
| aroM | 0.77 | -1.58 | 1.36 | 0.40 | -1.27 | 1.20 | protein of aro operon, regulated by aroR |
| aroP | -0.23 | -0.41 | -0.76 | 0.15 | -1.20 | -1.25 | aromatic amino acid transport protein |
| arp | 0.35 | 0.76 | -1.30 | 0.45 | 1.27 | -0.30 | regulator of acetyl CoA synthetase |
| arsB | 0.40 | 1.64 | 0.77 | 0.45 | 1.70 | 1.50 | arsenical pump membrane protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| arsC | 0.67 | -1.24 | 1.13 | 2.05 | -0.13 | 1.45 | arsenate reductase |
| arsR | 0.17 | -1.28 | 0.70 | -0.25 | 0.47 | 1.15 | transcriptional repressor of chromosomal ars operon |
| artI | -5.22 | -4.14 | 0.75 | -2.75 | -1.67 | 0.55 | arginine 3rd transport system periplasmic binding protein |
| artJ | -3.87 | 0.00 | 0.77 | -2.80 | 0.83 | -0.10 | arginine 3rd transport system periplasmic binding protein |
| artM | -1.06 | -1.02 | 0.66 | -2.05 | 0.20 | 0.35 | arginine 3rd transport system permease protein |
| artP | 0.26 | 1.01 | 0.88 | -0.05 | 0.37 | 1.60 | ATP-binding component of 3rd arginine transport system |
| artQ | -1.38 | 0.66 | -1.03 | -0.75 | 1.70 | -1.45 | arginine 3rd transport system permease protein |
| ascB | -0.45 | -1.37 | -1.39 | 0.05 | -0.40 | -1.35 | 6-phospho-beta-glucosidase; cryptic |
| ascF | -0.31 | 0.37 | 0.32 | 0.65 | 1.93 | 0.10 | PTS system enzyme II ABC (asc), cryptic, transports specific beta-glucosides |
| ascG | -1.89 | 2.75 | 0.59 | -1.25 | 0.13 | 0.00 | ascBF operon repressor |
| asd | -0.16 | -1.52 | -0.96 | -0.30 | -1.97 | 0.05 | aspartate-semialdehyde dehydrogenase |
| aslA | 2.28 | -1.75 | 0.99 | 1.75 | 1.13 | 1.50 | arylsulfatase |
| aslB | -0.69 | 1.02 | 0.85 | 0.35 | 1.40 | 1.70 | putative arylsulfatase regulator |
| asmA | 0.09 | -1.00 | -0.85 | -0.40 | -0.33 | -0.10 | suppressor of ompF assembly mutants |
| asnA | -1.31 | -1.34 | -1.35 | -4.55 | -0.47 | -1.25 | asparagine synthetase A |
| asnB | -0.78 | -1.14 | -1.29 | -1.25 | -0.33 | -0.15 | asparagine synthetase B |
| asnC | 0.22 | -1.20 | 0.52 | -0.40 | -0.47 | 0.15 | regulator for asnA, asnC and gidA |
| asnS | -0.46 | -0.62 | 0.94 | -1.50 | -0.33 | 0.50 | asparagine tRNA synthetase |
| asnT | 0.53 | -1.91 | -0.08 | 1.55 | -1.25 | 5.30 | Asparagine tRNA |
| asnU | 0.48 | -1.69 | -0.62 | 1.50 | 6.00 | 0.10 | Asparagine tRNA |
| asnV | 0.38 | -1.76 | 0.09 | 1.45 | -1.40 | 7.40 | Asparagine tRNA |
| asnW | 0.57 | -1.74 | 0.11 | 1.70 | -1.35 | 10.90 | Asparagine tRNA |
| aspA | -1.04 | -8.94 | -1.27 | -1.35 | -2.33 | -1.65 | aspartate ammonia-lyase (aspartase) |
| aspC | -0.82 | 1.00 | -0.56 | -1.75 | 0.40 | 0.05 | aspartate aminotransferase |
| aspS | 0.07 | 1.50 | 0.85 | 0.05 | 2.00 | 0.10 | 1948546.00 |
| aspT | 0.71 | -1.57 | 0.26 | 1.00 | 27.80 | 10.80 | Aspartate tRNA1 triplicated gene |
| aspU | 0.55 | -3.96 | 1.29 | 0.35 | 330.77 | 13.10 | Aspartate tRNA1 triplicated gene, in rrnH operon |
| aspV | 0.59 | -2.30 | 0.71 | 0.60 | 422.40 | 22.90 | Aspartate tRNA1 triplicated gene |
| asr | 1.94 | 1.52 | -1.49 | 1.90 | 1.67 | -1.15 | acid shock protein |
| atoA | -0.31 | -0.66 | -0.66 | -0.40 | 0.63 | 0.00 | acetyl-CoA:acetoacetyl-CoA transferase beta subunit |
| atoB | 3.38 | -0.73 | 1.24 | 0.45 | -0.10 | 1.40 | acetyl-CoA acetyltransferase |
| atoC | -0.23 | 0.72 | 0.69 | 0.40 | 0.57 | 0.45 | response regulator of ato, ornithine decarboxylase antizyme (sensor ATOS) |
| atoD | 0.47 | 0.69 | -0.79 | 0.20 | 0.53 | 0.00 | acetyl-CoA:acetoacetyl-CoA transferase alpha subunit |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| atoE | 0.89 | -1.37 | -1.29 | 0.65 | -1.10 | -0.10 | short chain fatty acid transporter |
| atoS | 0.54 | 0.19 | -1.42 | 1.70 | 0.27 | -1.40 | sensor protein AtoS for response regulator AtoC |
| atpA | 0.21 | 0.48 | 1.01 | 0.30 | -1.30 | 1.05 | membrane-bound ATP synthase, F1 sector, alpha-subunit |
| atpB | 0.38 | 1.29 | 0.11 | 1.85 | 1.10 | 0.10 | membrane-bound ATP synthase, F0 sector, subunit a |
| atpC | 0.88 | -2.65 | -0.47 | 1.10 | -2.53 | 0.30 | membrane-bound ATP synthase, F1 sector, epsilon-subunit |
| atpD | -0.08 | -0.62 | -0.77 | 0.15 | -1.90 | -1.30 | membrane-bound ATP synthase, F1 sector, beta-subunit |
| atpE | 0.14 | 1.29 | -0.55 | 1.25 | 1.50 | -1.55 | membrane-bound ATP synthase, F0 sector, subunit c |
| atpF | 0.24 | 0.06 | -0.14 | 1.70 | -1.57 | -0.05 | membrane-bound ATP synthase, F0 sector, subunit b |
| atpG | -0.37 | 0.68 | 1.07 | 0.10 | 0.33 | 0.50 | membrane-bound ATP synthase, F1 sector, gamma-subunit |
| atpH | 0.45 | 0.52 | -0.13 | 1.60 | -1.37 | -1.35 | membrane-bound ATP synthase, F1 sector, delta-subunit |
| atpI | 1.56 | 0.58 | 1.37 | 1.45 | -0.27 | 1.15 | membrane-bound ATP synthase, dispensable protein, affects expression of atpB |
| avtA | 0.39 | -0.88 | 0.70 | 2.00 | -0.07 | 1.50 | alanine-alpha-ketoisovalerate (or valine-pyruvate) transaminase, transaminase C |
| b0005 | 3.11 | -1.06 | -1.18 | 1.25 | -0.53 | -0.35 | orf, hypothetical protein |
| b0011 | 0.06 | -1.56 | -1.33 | 0.10 | -1.33 | -0.45 | putative oxidoreductase |
| b0024 | 0.54 | -1.34 | -1.32 | 0.35 | -1.10 | -2.25 | orf, hypothetical protein |
| b0100 | 1.18 | -0.89 | -1.21 | 6.10 | -0.53 | -1.75 | orf, hypothetical protein |
| b0105 | 0.74 | 0.83 | -0.61 | 0.15 | 1.50 | 0.05 | orf, hypothetical protein |
| b0165 | -0.95 | -1.44 | -0.86 | -2.45 | -0.60 | -0.05 | orf, hypothetical protein |
| b0235 | 0.35 | -1.50 | -1.33 | 1.60 | -1.17 | -0.45 | orf, hypothetical protein |
| b0245 | 1.18 | -1.29 | 0.77 | 1.65 | -0.43 | 0.00 | orf, hypothetical protein |
| b0257 | 0.58 | -1.32 | -1.31 | 0.35 | -1.33 | -1.45 | putative transposase |
| b0263 | 0.71 | 0.40 | -1.30 | 1.85 | 1.23 | -1.80 | putative transport system permease protein |
| b0302 | -0.44 | -1.17 | -0.89 | 0.00 | -0.10 | 0.00 | orf, hypothetical protein |
| b0309 | 1.38 | 1.32 | 1.42 | 2.05 | -0.30 | 0.05 | orf, hypothetical protein |
| b0332 | 0.22 | -1.18 | -1.03 | 1.75 | -0.17 | -0.05 | orf, hypothetical protein |
| b0359 | -1.51 | -0.40 | 0.85 | -1.35 | 0.43 | -0.05 | putative transferase |
| b0362 | -0.14 | -1.51 | -1.34 | 0.05 | -1.10 | -1.85 | orf, hypothetical protein |
| b0370 | 0.07 | -1.49 | -1.32 | -0.40 | -1.23 | -1.40 | orf, hypothetical protein |
| b0373 | 0.42 | 1.91 | -1.00 | 1.20 | 1.93 | -0.05 | putative factor |
| b0379 | -0.38 | 1.97 | 0.73 | 0.25 | 2.03 | 1.70 | orf, hypothetical protein |
| b0380 | -0.41 | -2.66 | -1.36 | 0.15 | -1.37 | -1.95 | orf, hypothetical protein |
| b0392 | 0.03 | -2.41 | 0.62 | 1.30 | -1.60 | 0.20 | orf, hypothetical protein |
| b0395 | -0.98 | -1.29 | -1.33 | -2.95 | -1.57 | -1.30 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b0499 | 2.74 | -1.48 | -0.11 | 1.30 | -1.63 | 0.00 | orf, hypothetical protein |
| b0501 | 1.34 | 0.26 | 0.83 | 1.60 | 1.10 | 1.40 | orf, hypothetical protein |
| b0502 | 0.00 | 0.00 | -1.33 | -2.90 | -1.63 | -1.15 | orf, hypothetical protein |
| b0538 | -0.55 | -0.58 | 0.79 | -0.20 | -0.03 | 1.40 | putative sensory transduction regulator |
| b0539 | 1.46 | -0.88 | -1.44 | 2.35 | -0.30 | -1.35 | putative exonuclease (EC 3.1.11.3) similar to lambda |
| b0542 | 0.20 | 0.19 | -1.36 | -0.05 | 0.53 | -2.55 | orf, hypothetical protein |
| b0609 | 0.12 | -1.56 | -1.20 | -0.40 | -1.50 | -1.45 | orf, hypothetical protein |
| b0663 | 0.10 | -1.53 | -1.29 | -0.65 | -2.03 | -1.60 | putative RNA |
| b0667 | 0.35 | -1.85 | -1.33 | 1.45 | -1.40 | -1.70 | putative RNA |
| b0669 | -1.24 | -1.38 | -1.38 | -0.80 | -1.50 | -1.60 | putative RNA |
| b0671 | 0.35 | -2.35 | -0.47 | -0.10 | -1.17 | 0.20 | putative RNA |
| b0703 | 0.34 | -1.33 | 0.63 | -0.55 | 0.27 | 0.05 | orf, hypothetical protein |
| b0725 | -0.47 | -0.37 | -1.08 | -2.00 | 0.20 | -0.05 | orf, hypothetical protein |
| b0753 | -0.80 | -1.54 | 0.60 | -0.45 | -1.40 | -0.10 | putative homeobox protein |
| b0762 | -0.31 | 0.44 | 1.12 | -0.40 | 1.00 | 1.80 | orf, hypothetical protein |
| b0795 | -2.75 | 0.58 | -0.32 | -1.30 | 0.57 | 0.10 | putative membrane protein |
| b0805 | -1.26 | -1.86 | 0.47 | -2.10 | -1.37 | 0.20 | putative outer membrane receptor for iron transport |
| b0816 | 0.00 | -1.33 | 0.96 | -0.60 | -0.30 | 1.30 | orf, hypothetical protein |
| b0817 | -0.72 | -1.84 | -1.12 | 0.00 | -1.67 | 0.10 | putative toxin |
| b0822 | -0.87 | 0.56 | -1.38 | -0.25 | 0.40 | -1.50 | orf, hypothetical protein |
| b0829 | -2.38 | -1.03 | -1.39 | -2.85 | -0.13 | -1.50 | putative ATP-binding component of a transport system |
| b0830 | -0.93 | -1.34 | -1.34 | -13.25 | -1.93 | -1.20 | putative transport protein |
| b0831 | -3.37 | -1.54 | 0.82 | -2.60 | -1.67 | 1.25 | putative transport system permease protein |
| b0832 | -47.09 | -1.92 | -1.40 | -2.55 | -1.43 | -1.30 | putative transport system permease protein |
| b0833 | -1.23 | -0.47 | 0.81 | -3.15 | 0.13 | 1.40 | orf, hypothetical protein |
| b0834 | -0.90 | 0.07 | -0.06 | -2.40 | 1.50 | 0.25 | orf, hypothetical protein |
| b0836 | -1.09 | -1.34 | -1.37 | -8.35 | -3.07 | -1.85 | putative receptor |
| b0844 | 0.13 | -0.91 | -0.92 | 0.85 | 0.30 | -0.05 | orf, hypothetical protein |
| b0845 | 0.07 | -0.93 | -0.13 | 1.25 | -0.30 | -0.35 | putative DEOR-type transcriptional regulator |
| b0846 | 0.00 | -1.34 | 0.77 | -2.45 | -2.10 | -0.10 | putative DEOR-type transcriptional regulator |
| b0847 | 1.57 | 1.45 | 0.76 | 1.40 | -1.07 | -0.10 | putative transport protein |
| b0866 | -1.20 | -2.49 | 0.20 | -0.50 | -1.60 | 0.00 | orf, hypothetical protein |
| b0867 | 0.05 | 0.94 | 0.02 | -0.05 | 1.33 | 1.10 | putative regulator |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b0868 | -2.40 | -0.03 | 0.74 | -2.70 | 0.13 | 0.15 | putative nucleotide di-P-sugar epimerase or dehydratase |
| b0872 | 0.12 | -1.32 | 1.47 | 0.15 | -0.53 | 1.30 | putative enzyme |
| b0878 | 1.35 | -0.45 | -1.63 | 1.25 | -0.03 | -1.45 | putative membrane protein |
| b0899 | -0.73 | -1.12 | 0.36 | -0.15 | -0.33 | -0.05 | putative transport |
| b0919 | -3.77 | -1.93 | -0.63 | -1.55 | -1.43 | 0.05 | orf, hypothetical protein |
| b0941 | -0.33 | -1.64 | 0.67 | -0.15 | -1.13 | 0.05 | homolog of Salmonella FimH protein |
| b0942 | 0.73 | -1.34 | 0.81 | 1.45 | -0.53 | 0.10 | putative fimbrial-like protein |
| b0943 | -0.78 | -1.31 | -1.22 | -1.70 | -0.23 | -1.35 | putative fimbrial-like protein |
| b0947 | 0.16 | 0.00 | -1.25 | -0.05 | 1.63 | -0.15 | orf, hypothetical protein |
| b0955 | 0.43 | 1.50 | 1.13 | 0.35 | 1.53 | 1.35 | putative ATP-dependent protease |
| b0959 | -0.86 | -1.33 | -1.38 | -0.45 | -0.63 | -1.40 | orf, hypothetical protein |
| b0960 | 1.18 | -0.47 | 0.77 | 1.75 | 0.83 | 1.25 | orf, hypothetical protein |
| b0964 | 1.18 | -1.23 | 1.99 | 0.95 | -0.43 | 1.30 | orf, hypothetical protein |
| b0965 | -0.29 | -1.47 | -1.32 | 0.05 | -1.30 | -1.50 | orf, hypothetical protein |
| b0967 | -0.26 | -0.35 | -1.23 | -0.25 | -1.07 | -1.25 | putative oxidoreductase |
| b0968 | -0.06 | 0.00 | -0.66 | -2.00 | 0.33 | 0.10 | orf, hypothetical protein |
| b1007 | -0.07 | 4.09 | -0.86 | 0.20 | 1.47 | -1.25 | orf, hypothetical protein |
| b1008 | 0.00 | 0.00 | -0.76 | -1.25 | 0.57 | 0.00 | putative enzyme |
| b1009 | -0.96 | -1.34 | 0.00 | -1.70 | -1.40 | -0.10 | putative acetyltransferase |
| b1010 | 0.98 | -1.32 | 0.86 | -1.20 | -1.83 | 1.50 | orf, hypothetical protein |
| b1011 | -0.86 | 0.44 | -0.09 | 1.65 | -1.23 | 0.05 | putative synthetase |
| b1012 | 0.42 | -1.17 | -0.65 | 2.00 | -1.80 | 0.00 | orf, hypothetical protein |
| b1016 | 0.43 | 0.11 | -1.83 | 1.75 | 1.20 | -1.10 | orf, hypothetical protein |
| b1017 | 0.53 | 0.00 | 0.81 | 0.85 | 1.37 | 1.20 | putative cytochrome |
| b1028 | -0.31 | 6.65 | 0.50 | 1.40 | -0.13 | -0.35 | orf, hypothetical protein |
| b1044 | -0.86 | -0.28 | 0.77 | -0.45 | 0.17 | -0.05 | orf, hypothetical protein |
| b1045 | -0.32 | 1.63 | -1.41 | 0.10 | -0.17 | -1.05 | putative polyprotein |
| b1052 | 0.62 | -1.34 | 0.82 | 0.15 | 0.23 | 1.20 | orf, hypothetical protein |
| b1057 | -0.84 | -1.40 | 0.71 | 0.10 | -0.77 | 0.10 | putative cytochrome |
| b1085 | -0.29 | 1.87 | -1.14 | 0.25 | 0.60 | 0.25 | orf, hypothetical protein |
| b1121 | -1.07 | -0.10 | -1.32 | -1.25 | 1.60 | -1.20 | homolog of virulence factor |
| b1134 | 0.98 | -1.24 | 0.07 | 0.40 | -0.33 | 0.20 | putative phosphohydrolase |
| b1141 | 1.69 | 0.40 | -1.33 | 12.85 | 1.30 | -1.30 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b1145 | 0.13 | 1.60 | 1.23 | -0.05 | 1.37 | 1.40 | putative phage repressor |
| b1146 | 1.59 | -0.97 | 0.61 | 4.25 | -1.30 | 0.00 | orf, hypothetical protein |
| b1152 | 2.45 | 3.06 | -1.15 | 2.35 | 1.53 | -0.10 | orf, hypothetical protein |
| b1153 | 0.79 | 0.91 | -0.58 | 1.70 | 0.53 | 0.10 | orf, hypothetical protein |
| b1155 | 1.05 | -1.41 | -0.79 | 0.85 | -1.13 | -0.25 | orf, hypothetical protein |
| b1157 | 1.09 | -1.34 | -1.00 | 0.35 | -0.43 | -0.05 | putative tail fiber protein |
| b1163 | 1.25 | -2.75 | -1.34 | 2.80 | -1.47 | -1.40 | orf, hypothetical protein |
| b1168 | -0.83 | 0.77 | 0.33 | 0.15 | 1.40 | -0.20 | putative proteases |
| b1169 | 2.61 | 0.89 | 0.75 | 1.70 | 1.37 | 1.35 | putative ATP-binding component of a transport system |
| b1170 | 2.05 | 7.71 | 0.91 | 1.25 | 1.83 | 1.35 | putative part of putative ATP-binding component of a transport system |
| b1171 | 0.92 | 1.54 | 0.99 | 1.75 | 1.33 | -0.10 | orf, hypothetical protein |
| b1172 | 0.70 | 1.81 | 0.41 | 1.75 | 1.37 | -0.15 | orf, hypothetical protein |
| b1180 | 0.30 | -0.40 | -0.82 | 0.15 | 0.37 | -0.05 | putative isomerase |
| b1191 | -1.27 | -0.66 | 0.20 | -2.10 | 0.03 | -0.15 | orf, hypothetical protein |
| b1192 | -0.91 | 1.61 | 0.11 | -0.05 | 0.03 | 1.05 | orf, hypothetical protein |
| b1199 | 0.89 | 2.90 | -0.92 | 3.45 | 1.77 | -1.25 | putative dihydroxyacetone kinase (EC 2.7.1.2) |
| b1200 | 0.38 | 0.21 | -0.93 | 1.35 | 1.23 | -0.05 | putative dihydroxyacetone kinase (EC 2.7.1.2) |
| b1201 | -0.98 | -1.19 | 0.80 | -0.30 | -0.23 | 1.55 | putative sensor-type regulator |
| b1202 | -1.15 | -1.56 | -1.36 | -1.55 | -1.73 | -1.55 | putative adhesion and penetration protein |
| b1213 | 0.49 | 0.10 | -0.04 | 0.30 | 0.90 | 0.15 | orf, hypothetical protein |
| b1228 | -0.79 | 0.87 | 0.82 | -1.10 | 1.33 | 1.85 | orf, hypothetical protein |
| b1240 | 1.47 | 0.58 | -0.64 | 1.90 | 1.50 | 0.00 | orf, hypothetical protein |
| b1248 | -1.65 | 1.90 | -1.36 | -1.65 | 1.47 | -1.45 | orf, hypothetical protein |
| b1284 | -0.25 | -1.52 | 0.83 | -0.30 | -1.27 | 1.40 | putative DEOR-type transcriptional regulator |
| b1297 | -0.70 | 1.71 | -0.07 | -0.40 | 1.47 | -0.05 | putative glutamine synthetase (EC 6.3.1.2) |
| b1310 | -0.30 | 0.00 | -1.39 | 0.95 | 0.07 | -1.25 | putative transport periplasmic protein |
| b1314 | -0.99 | -1.33 | -0.48 | -2.30 | -0.87 | 0.05 | putative transient receptor potential locus |
| b1327 | 0.34 | -0.87 | -0.39 | 1.75 | -0.23 | -0.05 | orf, hypothetical protein |
| b1329 | 0.02 | -2.47 | 0.77 | -0.20 | -1.27 | 1.40 | putative transport periplasmic protein |
| b1330 | 0.55 | 1.43 | 1.09 | 1.55 | 1.17 | 1.35 | orf, hypothetical protein |
| b1337 | 0.78 | -1.50 | -0.97 | 2.85 | -1.67 | -1.30 | orf, hypothetical protein |
| b1341 | -0.86 | -0.18 | 0.75 | 0.05 | 0.20 | 1.60 | orf, hypothetical protein |
| b1342 | 0.22 | -1.52 | -1.37 | 1.90 | -0.70 | -1.60 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b1345 | **0.98** | **-1.34** | **0.60** | 1.45 | -0.27 | 0.20 | putative transposase |
| b1354 | **0.80** | **0.00** | **0.99** | 1.35 | 0.33 | 1.15 | orf, hypothetical protein |
| b1355 | **0.00** | **1.70** | **1.51** | -0.20 | 0.53 | 1.50 | orf, hypothetical protein |
| b1360 | **1.05** | **-1.86** | **0.83** | 2.25 | -1.27 | 1.55 | putative DNA replication factor |
| b1362 | **1.00** | **-1.51** | **0.76** | 1.40 | -1.37 | 0.00 | putative Rac prophage endopeptidase |
| b1364 | **0.10** | **-1.57** | **-1.30** | 1.40 | -1.17 | -1.75 | orf, hypothetical protein |
| b1365 | **0.00** | **-1.32** | **0.82** | -2.20 | 0.00 | 1.30 | orf, hypothetical protein |
| b1367 | **-0.86** | **0.73** | **-1.30** | -0.25 | 1.17 | -0.10 | orf, hypothetical protein |
| b1368 | **0.97** | **-1.30** | **0.76** | 1.20 | 0.10 | 1.45 | putative alpha helix protein |
| b1369 | **0.00** | **0.00** | **0.00** | -1.85 | 1.67 | 0.20 | orf, hypothetical protein |
| b1371 | **0.00** | **0.00** | **-0.63** | -2.45 | 1.47 | 0.10 | orf, hypothetical protein |
| b1372 | **0.72** | **0.81** | **-1.35** | 0.05 | 0.37 | -1.40 | putative membrane protein |
| b1374 | **-0.33** | **-1.59** | **0.50** | 0.80 | -1.17 | 0.10 | putative transposon resolvase |
| b1377 | **-0.99** | **0.83** | **0.73** | -0.65 | 1.83 | 1.55 | putative outer membrane protein |
| b1391 | **1.28** | **-1.20** | **-1.27** | 0.50 | -0.43 | -0.15 | orf, hypothetical protein |
| b1392 | **-0.02** | **-1.28** | **-0.88** | -1.50 | 1.03 | -0.45 | putative oxidoreductase |
| b1394 | **0.54** | **1.66** | **-1.30** | 0.05 | 1.17 | -1.45 | putative enzyme |
| b1396 | **1.15** | **-1.25** | **0.81** | 1.60 | -0.27 | 1.05 | orf, hypothetical protein |
| b1397 | **2.25** | **0.63** | **-1.07** | 1.30 | 1.37 | -0.10 | putative acyltransferase |
| b1398 | **1.53** | **-1.20** | **-0.63** | 1.75 | -0.23 | 0.05 | orf, hypothetical protein |
| b1399 | **1.02** | **-1.43** | **-0.66** | 0.10 | -1.23 | 0.05 | orf, hypothetical protein |
| b1400 | **-0.29** | **0.23** | **-1.34** | 1.00 | 1.07 | -1.25 | putative transferase |
| b1408 | **1.25** | **-1.27** | **-0.39** | 3.45 | -0.47 | -1.15 | probable enzyme |
| b1409 | **-0.97** | **0.23** | **-0.75** | 0.05 | 0.40 | 0.00 | putative phosphatidate cytidiltransferase |
| b1410 | **1.00** | **-0.24** | **-1.34** | -1.20 | -0.30 | -0.05 | orf, hypothetical protein |
| b1420 | **-0.68** | **-2.11** | **-11.41** | -2.65 | -2.03 | -1.20 | orf, hypothetical protein |
| b1422 | **0.36** | **1.45** | **-1.20** | 1.10 | 2.10 | -1.15 | putative transcriptional regulator LYSR-type |
| b1423 | **-0.31** | **-1.20** | **-1.95** | 2.65 | 0.40 | -1.25 | orf, hypothetical protein |
| b1425 | **0.64** | **-0.31** | **0.45** | 1.45 | -0.40 | -0.15 | orf, hypothetical protein |
| b1428 | **-1.14** | **-1.34** | **1.50** | -0.65 | -1.77 | 1.70 | orf, hypothetical protein |
| b1431 | **-1.46** | **-0.12** | **0.85** | -1.70 | -0.03 | 0.05 | orf, hypothetical protein |
| b1432 | **1.63** | **-13.14** | **-1.33** | 1.85 | -3.27 | -1.30 | putative virulence protein |
| b1433 | **-0.35** | **-2.09** | **0.82** | 0.05 | -0.33 | 1.20 | putative membrane transport protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b1436 | -1.53 | -0.71 | 1.24 | -2.80 | 0.03 | 1.35 | orf, hypothetical protein |
| b1437 | -0.21 | -0.28 | -0.08 | 0.60 | 0.63 | 0.30 | orf, hypothetical protein |
| b1438 | -1.21 | -1.13 | -1.30 | -0.25 | 0.00 | -1.45 | orf, hypothetical protein |
| b1439 | 0.92 | -1.43 | -1.23 | 1.25 | -1.60 | -1.45 | multi modular; putative transcriptional regulator; also putative ATP-binding component |
| b1440 | -0.99 | -1.54 | -1.05 | -1.80 | -1.23 | -0.05 | putative transport protein |
| b1441 | 0.18 | -0.45 | -0.43 | 0.05 | -0.03 | -0.40 | putative ATP-binding component of a transport system |
| b1442 | -0.94 | 0.12 | 0.77 | 0.20 | 0.50 | 1.50 | putative transport system permease protein |
| b1443 | 0.05 | -1.31 | -1.23 | -0.50 | -0.37 | -1.15 | putative transport system permease protein |
| b1444 | -0.04 | 6.09 | -0.80 | 0.00 | 1.63 | -0.10 | putative aldehyde dehydrogenase |
| b1445 | 0.98 | 0.76 | 0.00 | 1.50 | 1.47 | 0.15 | orf, hypothetical protein |
| b1446 | 0.13 | -5.18 | -0.70 | 0.10 | -1.77 | -1.20 | orf, hypothetical protein |
| b1447 | 0.04 | 1.17 | -1.24 | 0.40 | 1.57 | -0.30 | orf, hypothetical protein |
| b1448 | 0.57 | -1.38 | -1.21 | 1.40 | -0.93 | -1.30 | putative resistance protein |
| b1450 | 0.00 | -1.34 | 0.77 | 0.65 | -1.27 | 1.55 | orf, hypothetical protein |
| b1451 | 0.31 | -1.39 | 1.01 | 0.30 | -1.07 | 0.05 | putative outer membrane receptor for iron transport |
| b1452 | -0.09 | 1.54 | -0.05 | 0.45 | 0.13 | -0.15 | putative receptor |
| b1454 | -0.03 | 0.25 | -1.38 | -1.15 | 1.37 | -1.15 | putative transferase |
| b1455 | -0.79 | 3.02 | 0.77 | 0.10 | 1.47 | -0.10 | orf, hypothetical protein |
| b1458 | 0.07 | -1.46 | -1.20 | 0.05 | -1.50 | -1.15 | orf, hypothetical protein |
| b1459 | 2.11 | -0.47 | -0.93 | 1.80 | 1.67 | -0.05 | orf, hypothetical protein |
| b1462 | 0.83 | -1.23 | 0.11 | 2.55 | -0.40 | 1.45 | orf, hypothetical protein |
| b1463 | 2.13 | -1.46 | -0.79 | 1.80 | -1.27 | -1.35 | putative N-hydroxyarylamine O-acetyltransferase |
| b1470 | -0.37 | 0.06 | -0.83 | -1.15 | 0.43 | 0.15 | orf, hypothetical protein |
| b1471 | 0.98 | -1.12 | 0.00 | 0.35 | 0.57 | 0.10 | putative glycoportein |
| b1472 | 0.37 | -1.48 | -1.31 | 0.45 | -1.47 | -0.25 | putative outer membrane porin protein |
| b1481 | -1.31 | -0.18 | -1.38 | -0.55 | 1.07 | -1.15 | orf, hypothetical protein |
| b1483 | 0.47 | -3.01 | 0.77 | 1.10 | 0.07 | -1.45 | putative ATP-binding component of a transport system |
| b1484 | 0.72 | 0.00 | 0.77 | -0.05 | 1.17 | 0.20 | putative ATP-binding component of a transport system |
| b1485 | 0.91 | -1.34 | 0.64 | 1.85 | -0.90 | 1.10 | putative transport protein |
| b1486 | -1.02 | -1.21 | 0.68 | -0.25 | -0.40 | -0.05 | putative transport system permease protein |
| b1487 | -1.20 | 0.60 | 1.82 | -2.05 | 0.37 | 1.25 | putative hemin-binding lipoprotein |
| b1488 | 0.31 | -1.64 | -0.28 | 0.70 | 1.17 | -0.10 | orf, hypothetical protein |
| b1489 | 1.28 | -1.28 | 0.74 | 1.25 | -0.43 | 1.25 | putative enzyme |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b1490 | 1.57 | 0.62 | 0.63 | 1.35 | 0.57 | 0.00 | orf, hypothetical protein |
| b1491 | 0.84 | 0.56 | 0.84 | 1.65 | 2.57 | 0.25 | orf, hypothetical protein |
| b1497 | 0.43 | 0.60 | 0.91 | 1.55 | 1.13 | 0.00 | putative enzyme |
| b1498 | 0.38 | 4.05 | 0.44 | -0.60 | -0.20 | 0.15 | putative sulfatase |
| b1499 | 0.15 | 0.00 | 0.22 | -0.25 | 1.40 | 0.30 | putative ARAC-type regulatory protein |
| b1500 | 0.41 | 2.38 | 1.16 | 1.55 | 1.40 | 1.00 | orf, hypothetical protein |
| b1501 | -0.99 | 1.20 | -1.34 | -0.35 | 1.30 | -1.15 | putative oxidoreductase, major subunit |
| b1502 | 0.48 | -1.38 | 0.78 | 0.35 | -2.00 | 1.65 | putative adhesin; similar to FimH protein |
| b1503 | 0.24 | -1.34 | -1.35 | 0.10 | -1.17 | -1.35 | putative fimbrial-like protein |
| b1504 | 0.09 | 0.18 | 0.81 | 1.50 | -0.73 | 1.20 | putative fimbrial-like protein |
| b1505 | 0.98 | 1.01 | 0.62 | 2.50 | 1.37 | 0.00 | putative outer membrane protein |
| b1506 | -0.98 | -1.52 | -1.31 | -0.35 | -1.70 | -1.20 | orf, hypothetical protein |
| b1509 | 0.15 | 0.00 | -0.48 | -0.35 | 0.10 | 0.05 | putative ATP-binding component of a transport system and adhesin protein |
| b1513 | 1.41 | -2.07 | -0.60 | 1.70 | -1.17 | 0.00 | putative ATP-binding component of a transport system |
| b1516 | 0.71 | -1.28 | 1.12 | 0.20 | -1.17 | 1.35 | putative LACI-type transcriptional regulator |
| b1518 | -0.99 | 2.34 | -0.22 | -0.15 | 1.57 | -0.10 | orf, hypothetical protein |
| b1519 | 0.38 | 1.03 | 0.71 | 1.40 | -0.73 | 1.35 | putative enzyme |
| b1520 | -0.45 | 2.63 | -0.56 | 0.10 | 1.33 | -0.25 | orf, hypothetical protein |
| b1522 | 2.57 | 0.33 | -0.58 | 1.65 | 0.53 | 0.10 | orf, hypothetical protein |
| b1523 | 1.18 | 0.09 | -0.91 | 2.15 | 0.37 | -0.05 | orf, hypothetical protein |
| b1525 | 0.00 | -1.34 | -1.34 | -1.95 | -1.30 | -1.25 | putative aldehyde dehydrogenase |
| b1527 | -0.41 | 0.92 | 0.00 | -1.25 | 1.07 | -0.15 | orf, hypothetical protein |
| b1541 | 0.93 | 0.49 | 1.26 | 2.45 | -0.03 | 0.15 | orf, hypothetical protein |
| b1543 | 0.97 | 0.44 | 1.07 | 0.10 | 1.17 | 1.35 | putative transport protein |
| b1547 | 0.35 | 1.71 | 1.29 | 2.75 | 1.50 | 1.25 | orf, hypothetical protein |
| b1550 | 0.84 | -4.14 | -0.21 | 0.80 | -1.43 | 0.15 | orf, hypothetical protein |
| b1551 | 0.87 | -1.34 | 0.76 | -0.10 | -0.27 | -0.05 | orf, hypothetical protein |
| b1553 | -0.76 | -1.43 | 0.73 | 0.10 | -0.53 | 0.25 | orf, hypothetical protein |
| b1554 | 2.79 | -0.46 | -1.33 | 2.25 | 0.23 | -0.20 | putative lysozyme |
| b1555 | 1.02 | -1.27 | 1.38 | 1.40 | -0.37 | 1.35 | orf, hypothetical protein |
| b1556 | -1.17 | -0.35 | 0.32 | -0.25 | 0.27 | -0.10 | orf, hypothetical protein |
| b1559 | 0.29 | 0.00 | -0.51 | -0.05 | 2.00 | 0.20 | orf, hypothetical protein |
| b1560 | 0.26 | 0.09 | 0.18 | 1.45 | 1.10 | -0.20 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b1565 | 0.47 | 0.76 | -1.36 | 0.20 | 1.47 | -1.40 | orf, hypothetical protein |
| b1567 | 0.00 | -1.33 | -0.85 | 1.40 | -1.17 | -0.05 | orf, hypothetical protein |
| b1568 | 0.11 | 0.46 | -1.31 | 1.45 | -0.73 | -1.45 | orf, hypothetical protein |
| b1579 | 1.01 | -1.93 | -1.32 | 0.05 | -1.20 | -1.65 | putative transposase |
| b1582 | -1.42 | 0.78 | 1.61 | -1.65 | 0.67 | 1.25 | orf, hypothetical protein |
| b1583 | -0.21 | 1.67 | 0.83 | -0.40 | 1.43 | 0.30 | orf, hypothetical protein |
| b1586 | 1.00 | -2.61 | 0.78 | 0.35 | -1.17 | 1.60 | orf, hypothetical protein |
| b1587 | 0.43 | -1.03 | 0.73 | 1.00 | 0.27 | 1.20 | putative oxidoreductase, major subunit |
| b1588 | -0.71 | -4.18 | -1.34 | 0.35 | -1.30 | -1.20 | putative oxidoreductase, major subunit |
| b1589 | -1.57 | -1.57 | 0.40 | -2.05 | -1.40 | 0.25 | putative oxidoreductase, Fe-S subunit |
| b1590 | -0.09 | -1.85 | 1.30 | -0.65 | -1.40 | 1.30 | putative DMSO reductase anchor subunit |
| b1591 | 0.24 | 2.51 | -0.73 | 0.15 | 1.30 | 0.05 | putative oxidoreductase component |
| b1592 | 0.05 | 0.70 | 0.30 | 1.45 | 0.93 | -0.05 | putative chloride channel |
| b1593 | -6.36 | 0.24 | 0.04 | -1.85 | -0.60 | 0.05 | orf, hypothetical protein |
| b1598 | 0.62 | -1.40 | 1.43 | 2.65 | -1.00 | 0.10 | orf, hypothetical protein |
| b1599 | -0.87 | -2.31 | -1.47 | -1.50 | -1.37 | -1.20 | possible chaperone |
| b1600 | -5.56 | -2.71 | 0.69 | -1.90 | -1.37 | 0.00 | possible chaperone |
| b1601 | -0.30 | -1.08 | -1.08 | -1.30 | -0.40 | -1.25 | putative transport protein |
| b1604 | 1.13 | -1.47 | 0.05 | 0.85 | 0.13 | -0.30 | orf, hypothetical protein |
| b1605 | 0.69 | 0.66 | 0.30 | 2.55 | 0.53 | -0.10 | putative arginine |
| b1624 | 1.59 | -0.58 | 0.73 | 1.40 | -0.17 | 0.05 | orf, hypothetical protein |
| b1625 | 0.46 | -1.44 | -0.25 | -0.15 | -1.67 | -1.20 | orf, hypothetical protein |
| b1626 | 0.41 | 2.69 | 0.63 | 1.20 | 1.60 | -0.10 | orf, hypothetical protein |
| b1627 | 6.81 | -1.48 | 1.26 | 1.45 | -0.80 | 1.15 | orf, hypothetical protein |
| b1628 | -0.01 | -0.32 | 1.61 | 0.25 | 0.00 | 1.55 | orf, hypothetical protein |
| b1629 | -0.70 | 1.07 | -0.63 | -1.40 | 0.47 | 0.00 | putative membrane protein |
| b1631 | -0.43 | -1.25 | 0.00 | -0.20 | 1.00 | 0.15 | orf, hypothetical protein |
| b1640 | 0.29 | 0.69 | -0.53 | 0.20 | 0.87 | 0.00 | orf, hypothetical protein |
| b1643 | 0.60 | 2.07 | -0.67 | 0.55 | 1.40 | 0.10 | orf, hypothetical protein |
| b1644 | -1.24 | 1.04 | 0.52 | -0.60 | 1.07 | 1.10 | putative membrane protein |
| b1645 | 1.57 | -1.15 | 0.69 | 1.40 | -0.20 | 0.10 | orf, hypothetical protein |
| b1647 | 1.30 | -1.45 | -1.52 | 1.45 | -0.73 | -1.25 | orf, hypothetical protein |
| b1648 | -0.34 | -0.09 | 0.72 | 2.50 | 0.73 | 0.05 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b1649 | 2.27 | 1.48 | 0.77 | 1.70 | 1.33 | 1.30 | orf, hypothetical protein |
| b1657 | 0.15 | 1.48 | -0.15 | 0.00 | 1.67 | 0.15 | putative transport protein |
| b1664 | 0.19 | -1.67 | -0.07 | -0.05 | -1.83 | 0.25 | possible enzyme |
| b1667 | -0.10 | -0.51 | -1.42 | -0.25 | -0.73 | -1.40 | orf, hypothetical protein |
| b1668 | -0.62 | -1.28 | 0.82 | 0.30 | -1.27 | 1.20 | orf, hypothetical protein |
| b1669 | -1.09 | -1.22 | -0.82 | -0.40 | 0.10 | -0.05 | orf, hypothetical protein |
| b1671 | 1.08 | -1.39 | -1.33 | 1.55 | -1.43 | -1.60 | putative oxidoreductase, Fe-S subunit |
| b1672 | -1.24 | -0.13 | 0.13 | -1.70 | 1.50 | -0.30 | orf, hypothetical protein |
| b1673 | -0.64 | -1.37 | 0.78 | 0.00 | -1.53 | 0.05 | orf, hypothetical protein |
| b1674 | 0.57 | -1.34 | -1.33 | -0.15 | -1.73 | -1.45 | putative oxidoreductase, Fe-S subunit |
| b1675 | -1.20 | -1.29 | -0.50 | -1.90 | 0.50 | 0.15 | orf, hypothetical protein |
| b1680 | 0.13 | -0.02 | -0.39 | 1.40 | 0.50 | 0.00 | orf, hypothetical protein |
| b1685 | -0.52 | -1.22 | -0.23 | -0.15 | -0.27 | -0.45 | orf, hypothetical protein |
| b1686 | -5.05 | 0.19 | -1.47 | -1.80 | 1.13 | -1.40 | orf, hypothetical protein |
| b1688 | 0.80 | -0.90 | 0.00 | 0.25 | 0.07 | 0.20 | orf, hypothetical protein |
| b1689 | 0.03 | -1.84 | -1.33 | -0.05 | -0.80 | -1.45 | orf, hypothetical protein |
| b1690 | 0.16 | 0.43 | 0.98 | 1.25 | 0.57 | 1.55 | putative transport system permease protein |
| b1691 | -0.53 | -0.39 | -1.31 | 0.05 | -0.03 | 0.10 | putative amino acid |
| b1695 | 0.00 | 0.00 | -1.34 | -0.05 | 1.53 | -1.60 | putative oxidoreductase |
| b1696 | 1.55 | -2.23 | 0.73 | 1.95 | -0.37 | -0.25 | putative ARAC-type regulatory protein |
| b1706 | 0.07 | 0.00 | 0.38 | -0.05 | 1.53 | 0.10 | orf, hypothetical protein |
| b1707 | 2.00 | -0.22 | 0.56 | 1.90 | 0.47 | 1.20 | orf, hypothetical protein |
| b1720 | -0.77 | 2.33 | 1.21 | 0.15 | -0.20 | -0.05 | orf, hypothetical protein |
| b1721 | -0.73 | -0.36 | 1.16 | 0.05 | 0.40 | 0.05 | orf, hypothetical protein |
| b1722 | 0.07 | 2.16 | 1.01 | 0.50 | 0.67 | 1.20 | orf, hypothetical protein |
| b1724 | 0.58 | -0.15 | -1.35 | 1.55 | 0.43 | -1.55 | orf, hypothetical protein |
| b1725 | 0.67 | -2.30 | -0.48 | 1.35 | 0.80 | 0.05 | orf, hypothetical protein |
| b1726 | -1.17 | -1.85 | -1.15 | -1.30 | -1.47 | -1.40 | orf, hypothetical protein |
| b1728 | -0.50 | -1.28 | -1.37 | 0.65 | -0.80 | -1.15 | orf, hypothetical protein |
| b1729 | -89.15 | 1.38 | 1.20 | -2.30 | 1.97 | 1.50 | part of a kinase |
| b1730 | 0.00 | -1.29 | 1.39 | -1.35 | -1.27 | 0.05 | orf, hypothetical protein |
| b1731 | -0.94 | -1.53 | 0.43 | 1.10 | -1.30 | 0.00 | orf, hypothetical protein |
| b1741 | 0.91 | -1.16 | 0.13 | 1.20 | -0.93 | 0.20 | putative excinuclease subunit |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b1742 | 0.17 | -1.40 | -1.34 | -0.50 | -1.23 | -1.65 | orf, hypothetical protein |
| b1745 | -0.72 | -1.26 | -0.66 | 0.00 | -0.27 | 0.05 | orf, hypothetical protein |
| b1746 | 0.79 | 1.02 | -1.40 | 1.70 | 1.00 | -1.20 | putative aldehyde dehydrogenase |
| b1747 | -0.95 | 1.47 | 0.78 | -0.15 | 1.87 | 1.20 | orf, hypothetical protein |
| b1754 | -0.94 | -9.01 | 0.31 | 0.00 | -1.50 | 0.20 | orf, hypothetical protein |
| b1755 | 1.24 | -1.42 | -1.22 | 1.95 | -1.53 | -1.70 | putative transport system permease protein |
| b1756 | -0.88 | -1.92 | 0.73 | 0.10 | -0.73 | -0.15 | putative ATP-binding component of a transport system |
| b1757 | -1.09 | -1.30 | 0.76 | -0.40 | 0.53 | 1.40 | putative thiosulfate sulfur transferase |
| b1758 | -0.26 | 0.24 | -1.31 | 0.45 | 0.80 | -1.30 | putative cytochrome oxidase |
| b1759 | 1.02 | -0.64 | -1.38 | 2.00 | 0.67 | -1.30 | orf, hypothetical protein |
| b1760 | -0.69 | 1.11 | 0.56 | -1.70 | 1.80 | 0.25 | orf, hypothetical protein |
| b1762 | 0.34 | 1.47 | 4.77 | 2.05 | 0.43 | 1.20 | orf, hypothetical protein |
| b1770 | -0.62 | 0.46 | 0.72 | -1.35 | 1.33 | 1.25 | putative DEOR-type transcriptional regulator |
| b1771 | 0.45 | -1.30 | -0.93 | -0.55 | -0.33 | -0.10 | orf, hypothetical protein |
| b1772 | 0.26 | -0.36 | 0.84 | 0.25 | 0.93 | 0.00 | putative kinase |
| b1773 | 1.87 | 2.45 | 0.82 | 1.60 | 1.07 | 1.25 | putative aldolase |
| b1775 | 0.36 | 0.75 | 1.43 | 0.40 | 1.13 | 1.10 | putative transport protein |
| b1776 | -0.99 | -4.96 | -1.35 | -2.10 | -1.57 | -1.40 | putative oxidoreductase |
| b1777 | -0.65 | 2.01 | -0.29 | -1.75 | 0.80 | -0.05 | orf, hypothetical protein |
| b1781 | -1.04 | 1.15 | 0.67 | -0.25 | 0.33 | 0.05 | putative an aldehyde reductase |
| b1788 | -0.80 | -0.15 | -1.27 | 0.90 | 1.73 | -0.10 | orf, hypothetical protein |
| b1806 | 0.28 | 1.11 | 1.53 | -0.80 | -0.23 | 1.30 | putative outer membrane protein |
| b1808 | 0.33 | -1.38 | -0.91 | -1.05 | -0.33 | -0.10 | putative enzyme |
| b1809 | 0.98 | 1.05 | 0.14 | 1.35 | 0.73 | -0.15 | orf, hypothetical protein |
| b1810 | 0.00 | -1.34 | -0.70 | -3.80 | -2.20 | 0.10 | orf, hypothetical protein |
| b1811 | -0.38 | -0.55 | -0.82 | -0.15 | -0.13 | -0.10 | orf, hypothetical protein |
| b1815 | -0.03 | 0.81 | 0.74 | 0.65 | 1.60 | 1.40 | orf, hypothetical protein |
| b1820 | -1.14 | 1.29 | -1.09 | -0.55 | 1.30 | -0.10 | orf, hypothetical protein |
| b1821 | -0.99 | 1.36 | 0.75 | 0.10 | 1.43 | 1.30 | orf, hypothetical protein |
| b1824 | 1.08 | -10.49 | -0.37 | 1.20 | -1.87 | 0.30 | orf, hypothetical protein |
| b1825 | 1.09 | 0.77 | 2.10 | 1.30 | 1.80 | 1.15 | orf, hypothetical protein |
| b1826 | -2.30 | 0.68 | -1.53 | -1.30 | 1.47 | -1.65 | orf, hypothetical protein |
| b1827 | -1.57 | 1.13 | 0.86 | -1.70 | 0.60 | 1.80 | putative regulator |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b1828 | -0.14 | -1.34 | -0.85 | 1.40 | 0.33 | -0.05 | putative transport protein |
| b1832 | 0.10 | -0.37 | 0.76 | 0.50 | -1.57 | 1.60 | orf, hypothetical protein |
| b1833 | 1.57 | 0.75 | 0.39 | 1.60 | 1.33 | -0.25 | orf, hypothetical protein |
| b1834 | -0.47 | 0.76 | 0.61 | -2.00 | 1.50 | 1.20 | orf, hypothetical protein |
| b1836 | -1.73 | -0.13 | -1.29 | -2.50 | 0.33 | -0.10 | orf, hypothetical protein |
| b1837 | -1.06 | -0.34 | -1.33 | -1.95 | -0.20 | -1.05 | orf, hypothetical protein |
| b1839 | 0.70 | 2.00 | -0.62 | 1.25 | 1.43 | -0.15 | orf, hypothetical protein |
| b1840 | 0.44 | -1.29 | 1.16 | 0.15 | -0.93 | 1.30 | putative resistance protein |
| b1841 | 0.16 | -0.18 | 0.42 | 0.25 | 1.00 | 0.30 | orf, hypothetical protein |
| b1843 | 0.49 | 0.38 | -1.32 | -0.05 | 0.30 | -1.15 | orf, hypothetical protein |
| b1844 | -0.65 | -1.70 | 0.66 | 0.25 | -1.20 | 0.20 | orf, hypothetical protein |
| b1903 | 16.73 | -1.73 | -0.50 | 1.75 | 1.13 | 0.15 | orf, hypothetical protein |
| b1904 | -1.95 | -5.82 | -1.10 | -1.85 | -1.47 | -0.15 | orf, hypothetical protein |
| b1933 | -0.19 | -1.36 | -1.36 | 1.60 | -1.43 | -1.20 | orf, hypothetical protein |
| b1936 | -0.30 | 2.74 | -0.18 | -0.20 | 1.17 | 0.15 | orf, hypothetical protein |
| b1953 | -1.02 | -9.07 | 0.52 | -4.75 | -1.77 | 0.00 | orf, hypothetical protein |
| b1955 | -0.19 | -0.93 | 1.00 | 0.00 | -1.17 | 1.30 | orf, hypothetical protein |
| b1956 | 0.00 | 1.39 | 0.67 | -2.05 | 0.73 | 0.30 | orf, hypothetical protein |
| b1957 | -0.90 | -1.44 | 0.81 | -0.40 | -0.93 | 1.50 | orf, hypothetical protein |
| b1963 | 0.98 | -1.41 | -0.70 | 1.70 | -0.33 | 0.00 | orf, hypothetical protein |
| b1964 | -0.52 | -1.24 | -1.32 | -1.65 | -0.30 | -0.25 | putative outer membrane protein |
| b1965 | -0.61 | 0.77 | 0.85 | -0.05 | 1.57 | -0.10 | orf, hypothetical protein |
| b1966 | -0.95 | -1.52 | 0.26 | 0.00 | -0.40 | 0.00 | putative outer membrane protein |
| b1970 | 0.52 | -0.91 | 1.11 | 3.50 | 0.07 | 1.45 | orf, hypothetical protein |
| b1971 | 0.38 | 0.74 | 0.26 | -0.25 | -0.37 | 0.10 | putative reductase |
| b1972 | 1.90 | 9.22 | -1.36 | 1.70 | 1.83 | -1.65 | orf, hypothetical protein |
| b1973 | 0.05 | -1.26 | 1.42 | -0.25 | -0.60 | 1.25 | orf, hypothetical protein |
| b1976 | 0.35 | -1.44 | 0.35 | 0.05 | -0.50 | 0.05 | orf, hypothetical protein |
| b1978 | -1.37 | 0.00 | 0.77 | -1.35 | 1.80 | 0.60 | putative factor |
| b1979 | -0.77 | -0.42 | -0.20 | -0.05 | 0.87 | 0.00 | orf, hypothetical protein |
| b1980 | 1.09 | -1.45 | -1.15 | 0.60 | -1.57 | -0.10 | orf, hypothetical protein |
| b1983 | 1.70 | 4.85 | 1.17 | 2.35 | 2.47 | 1.20 | orf, hypothetical protein |
| b1995 | 0.51 | -0.27 | -0.89 | -0.10 | 0.27 | -1.15 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b1998 | 0.13 | -1.13 | 0.85 | 1.25 | -0.10 | 1.35 | orf, hypothetical protein |
| b2001 | 0.00 | -0.09 | 0.80 | -1.85 | -0.23 | -0.40 | orf, hypothetical protein |
| b2016 | -0.46 | -1.27 | -0.46 | -0.05 | -0.17 | 0.05 | putative enzyme of sugar metabolism |
| b2060 | 0.00 | 0.76 | 0.88 | -0.15 | 0.80 | 1.40 | orf, hypothetical protein |
| b2070 | -1.17 | -1.59 | 0.77 | -0.55 | -0.73 | 0.00 | putative chaperonin |
| b2071 | 0.46 | -1.21 | 0.73 | 1.30 | -0.23 | 1.30 | orf, hypothetical protein |
| b2072 | 0.65 | -1.64 | -1.06 | 2.25 | -1.20 | 0.05 | orf, hypothetical protein |
| b2073 | 0.37 | 0.26 | -1.33 | 1.45 | 0.87 | -0.15 | orf, hypothetical protein |
| b2074 | 0.97 | 0.00 | 0.78 | 0.35 | 1.50 | 1.40 | putative membrane protein |
| b2080 | -1.08 | -0.12 | -2.35 | -3.60 | -0.03 | -1.00 | orf, hypothetical protein |
| b2083 | 0.14 | -1.28 | 0.77 | -0.70 | 0.07 | 1.30 | orf, hypothetical protein |
| b2084 | 0.95 | -1.22 | -1.53 | 1.60 | -0.93 | -1.20 | orf, hypothetical protein |
| b2085 | 0.95 | -1.36 | 0.82 | 0.30 | -0.73 | 1.30 | orf, hypothetical protein |
| b2086 | -1.23 | 1.34 | -0.76 | -0.25 | 1.53 | 0.05 | orf, hypothetical protein |
| b2097 | -1.27 | -3.05 | -1.01 | -3.75 | -2.33 | -0.05 | orf, hypothetical protein |
| b2099 | -1.56 | -1.18 | -1.24 | -1.30 | -0.20 | -1.10 | orf, hypothetical protein |
| b2100 | 0.70 | -3.39 | -0.08 | 1.75 | 0.67 | -0.30 | putative kinase |
| b2107 | -1.46 | -1.21 | 1.21 | -1.95 | -1.37 | 1.35 | orf, hypothetical protein |
| b2145 | -0.53 | -1.45 | -1.39 | -0.30 | -0.80 | -1.30 | orf, hypothetical protein |
| b2146 | -0.03 | 3.14 | -0.26 | 0.00 | 1.70 | 0.00 | putative oxidoreductase |
| b2174 | 0.52 | -1.18 | -0.89 | 1.45 | -0.33 | -0.05 | orf, hypothetical protein |
| b2225 | 1.04 | -0.22 | -1.60 | 0.20 | -0.20 | -1.10 | orf, hypothetical protein |
| b2226 | -0.35 | -1.17 | -1.24 | 0.10 | -0.80 | -0.15 | orf, hypothetical protein |
| b2227 | 0.55 | 0.00 | 0.84 | 1.65 | -0.30 | 1.60 | orf, hypothetical protein |
| b2228 | 1.29 | -1.33 | 0.77 | 1.30 | -0.13 | 0.55 | putative membrane protein |
| b2229 | 1.36 | -1.32 | -1.33 | 2.60 | -0.80 | -0.45 | orf, hypothetical protein |
| b2245 | 0.89 | -0.30 | -1.33 | 2.35 | 0.80 | -0.05 | orf, hypothetical protein |
| b2246 | -0.43 | 0.62 | -1.33 | 0.20 | 1.23 | -0.05 | putative transport protein |
| b2247 | -1.02 | -1.01 | -0.81 | -0.20 | -0.17 | -1.30 | putative racemase |
| b2248 | -1.10 | 0.76 | 1.37 | -0.55 | 0.00 | 1.50 | putative regulator |
| b2249 | 0.22 | -0.56 | 0.93 | -0.15 | 1.03 | 1.35 | orf, hypothetical protein |
| b2250 | 0.45 | 0.15 | 1.54 | 0.65 | 0.53 | 0.25 | orf, hypothetical protein |
| b2253 | -0.07 | -0.12 | -0.98 | -1.55 | 0.37 | -1.10 | putative enzyme |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b2254 | **-0.67** | **0.15** | **-1.19** | -0.40 | 1.07 | -0.25 | putative sugar transferase |
| b2255 | **-1.58** | **-1.12** | **0.47** | -1.60 | -0.47 | -1.05 | putative transformylase |
| b2256 | **1.56** | **-1.09** | **-1.06** | 1.25 | -0.37 | -0.05 | orf, hypothetical protein |
| b2257 | **-0.01** | **0.60** | **-1.40** | -0.10 | 0.93 | -1.55 | orf, hypothetical protein |
| b2258 | **0.32** | **-1.30** | **0.87** | -0.20 | 0.40 | 1.20 | putative transport |
| b2274 | **-1.14** | **-0.42** | **-1.37** | -0.05 | 1.23 | -1.25 | orf, hypothetical protein |
| b2275 | **1.02** | **-1.26** | **-1.31** | 1.50 | -0.53 | -1.70 | orf, hypothetical protein |
| b2290 | **0.85** | **-1.20** | **0.74** | 0.15 | -0.33 | 1.20 | putative aminotransferase |
| b2291 | **1.63** | **-0.37** | **-1.24** | 2.10 | 0.73 | -1.05 | putative alpha helix protein |
| b2294 | **0.07** | **-1.41** | **0.75** | -0.15 | -1.53 | 1.35 | orf, hypothetical protein |
| b2295 | **0.64** | **0.07** | **1.11** | 0.10 | 0.93 | 1.20 | orf, hypothetical protein |
| b2299 | **-0.17** | **1.56** | **2.25** | 0.05 | 1.33 | 1.55 | putative regulator |
| b2304 | **-0.08** | **-0.66** | **-0.60** | 0.00 | 1.53 | 0.25 | putative sugar nucleotide epimerase |
| b2322 | **-0.26** | **-1.41** | **0.07** | -1.15 | -0.37 | 0.15 | putative transport protein |
| b2324 | **1.21** | **-1.11** | **0.84** | 0.15 | -0.50 | 1.60 | putative peptidase |
| b2325 | **-0.67** | **0.10** | **-1.38** | -1.60 | 0.60 | -1.40 | orf, hypothetical protein |
| b2326 | **1.03** | **2.31** | **0.02** | -1.20 | 1.23 | -0.15 | putative transporting ATPase |
| b2331 | **-0.35** | **1.39** | **-0.16** | -0.30 | 1.57 | -0.25 | orf, hypothetical protein |
| b2332 | **1.34** | **-1.35** | **-1.36** | -0.15 | -0.33 | -1.15 | orf, hypothetical protein |
| b2333 | **1.11** | **1.76** | **-1.86** | 1.35 | 0.30 | -1.35 | putative fimbrial-like protein |
| b2334 | **0.13** | **2.84** | **0.59** | 0.20 | 1.83 | 0.20 | orf, hypothetical protein |
| b2335 | **-0.23** | **-1.90** | **0.00** | 0.05 | -1.30 | -0.50 | putative fimbrial protein |
| b2337 | **0.70** | **-0.29** | **-1.14** | 1.90 | 0.23 | -1.15 | putative outer membrane protein |
| b2339 | **0.67** | **-5.04** | **0.62** | 1.50 | -0.33 | -0.10 | putative fimbrial-like protein |
| b2340 | **-0.62** | **-1.06** | **0.04** | -0.50 | -0.67 | 0.25 | orf, hypothetical protein |
| b2341 | **-2.39** | **0.00** | **-0.43** | -1.65 | 0.30 | 0.05 | putative enzyme |
| b2342 | **-0.76** | **1.34** | **-1.37** | -0.15 | 1.47 | -1.45 | putative acyltransferase |
| b2343 | **0.44** | **-3.05** | **-1.06** | 0.00 | -1.13 | -0.15 | orf, hypothetical protein |
| b2345 | **-0.20** | **-1.32** | **-1.10** | 0.00 | -0.40 | -1.15 | orf, hypothetical protein |
| b2350 | **0.96** | **1.77** | **-1.36** | 1.70 | 0.73 | -1.45 | orf, hypothetical protein |
| b2351 | **0.21** | **-1.40** | **1.87** | 0.25 | -2.00 | 1.40 | putative glycan biosynthesis enzyme |
| b2352 | **-0.88** | **-1.44** | **0.99** | -1.60 | -1.67 | 1.50 | putative ligase |
| b2353 | **-1.15** | **-0.69** | **1.32** | -0.75 | 0.30 | 1.50 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b2354 | 1.02 | 1.38 | -0.85 | 2.25 | 1.60 | 0.00 | orf, hypothetical protein |
| b2359 | -0.99 | -2.22 | 0.53 | -4.05 | -1.63 | 0.05 | orf, hypothetical protein |
| b2360 | 0.07 | -1.28 | 0.73 | -0.55 | -0.50 | 0.15 | orf, hypothetical protein |
| b2361 | 0.41 | 1.93 | 0.91 | 1.35 | 1.13 | 1.45 | orf, hypothetical protein |
| b2362 | 0.43 | -1.25 | -0.27 | 0.35 | -0.67 | -0.55 | orf, hypothetical protein |
| b2363 | 0.16 | 0.64 | 0.33 | 0.00 | 1.27 | 0.15 | orf, hypothetical protein |
| b2372 | 0.41 | 1.97 | 0.77 | -1.55 | 1.47 | 0.45 | putative receptor protein |
| b2373 | 1.00 | 1.26 | 0.41 | 1.55 | 1.60 | -0.25 | putative enzyme |
| b2374 | -0.75 | -1.05 | -0.75 | 0.35 | -0.20 | 0.05 | putative enzyme |
| b2375 | -1.38 | -0.59 | 0.18 | -1.10 | 0.10 | -0.05 | orf, hypothetical protein |
| b2376 | 1.35 | -1.43 | 0.00 | 1.10 | -1.63 | 0.00 | orf, hypothetical protein |
| b2377 | -0.82 | 0.98 | 0.66 | -1.55 | 1.27 | -0.15 | orf, hypothetical protein |
| b2379 | -0.23 | 0.42 | -0.98 | 0.30 | 1.13 | -0.10 | putative aminotransferase |
| b2380 | 0.37 | 0.08 | 1.01 | 1.45 | 1.23 | 1.45 | putative sensor protein |
| b2381 | -1.34 | 0.38 | 0.76 | -1.70 | 1.67 | 0.30 | putative 2-component transcriptional regulator |
| b2382 | 0.53 | 0.83 | 0.73 | 2.00 | 1.53 | 0.25 | putative ARAC-type regulatory protein |
| b2383 | -1.02 | 0.96 | -1.27 | -0.15 | 2.23 | -1.25 | putative PTS system enzyme IIA component, enzyme I |
| b2384 | -0.60 | -2.50 | -1.33 | 0.05 | 1.23 | -0.25 | orf, hypothetical protein |
| b2385 | -1.57 | 0.00 | 1.00 | -0.15 | -1.40 | 1.50 | putative peptidase |
| b2386 | -1.06 | 1.38 | -1.33 | -0.10 | 1.30 | -1.35 | putative transport protein |
| b2387 | 0.32 | 0.53 | -1.34 | 0.05 | 1.53 | -1.10 | putative PTS system enzyme IIB component |
| b2389 | 1.63 | -1.75 | -1.22 | 2.50 | -1.27 | -0.25 | orf, hypothetical protein |
| b2390 | 0.00 | 0.00 | 0.77 | -1.70 | 0.03 | 1.35 | orf, hypothetical protein |
| b2392 | 10.31 | -0.28 | -0.18 | 1.35 | 0.43 | 0.20 | putative transport system permease |
| b2420 | -1.17 | -1.32 | -0.82 | -1.25 | -0.67 | -0.10 | orf, hypothetical protein |
| b2429 | 1.12 | -1.35 | -1.33 | 1.80 | -0.77 | -0.15 | putative PTS enzyme II |
| b2430 | 0.27 | -0.60 | 0.89 | -2.95 | 0.03 | 0.00 | putative beta-lactamase |
| b2431 | -0.01 | -0.48 | 1.32 | 0.95 | -1.67 | 1.20 | orf, hypothetical protein |
| b2432 | -0.64 | 0.10 | -0.30 | 0.10 | -0.07 | -1.20 | orf, hypothetical protein |
| b2433 | 0.70 | 1.01 | -0.13 | 1.15 | 1.53 | -0.10 | orf, hypothetical protein |
| b2434 | -0.37 | -0.64 | -1.41 | 0.00 | 0.40 | -1.20 | orf, hypothetical protein |
| b2438 | 0.76 | 1.33 | 1.05 | 1.75 | 1.87 | 1.30 | orf, hypothetical protein |
| b2439 | -1.13 | -1.50 | -0.36 | 0.00 | -1.17 | -0.05 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b2442 | 0.57 | -0.23 | 1.74 | 1.45 | 1.17 | 1.20 | putative prophage integrase |
| b2443 | 1.03 | -1.31 | -1.39 | 0.05 | -0.67 | -1.60 | orf, hypothetical protein |
| b2444 | -1.09 | -0.19 | 0.77 | -1.55 | 0.37 | 1.30 | orf, hypothetical protein |
| b2445 | -0.01 | -1.31 | -1.38 | 0.00 | -1.30 | -0.10 | orf, hypothetical protein |
| b2446 | 0.00 | -1.34 | -1.14 | -0.05 | -1.47 | -0.10 | orf, hypothetical protein |
| b2447 | 1.10 | 0.01 | 0.76 | 1.80 | -1.07 | 1.35 | orf, hypothetical protein |
| b2448 | 0.00 | -0.75 | 0.14 | -0.50 | -0.23 | 0.20 | orf, hypothetical protein |
| b2449 | 0.00 | 0.00 | 0.68 | 0.00 | 1.10 | 1.10 | orf, hypothetical protein |
| b2450 | 0.46 | -0.24 | 2.50 | 1.70 | -0.20 | 1.15 | orf, hypothetical protein |
| b2451 | -0.98 | 0.43 | -1.15 | -2.00 | 1.27 | -0.70 | orf, hypothetical protein |
| b2459 | 0.24 | -1.39 | 0.17 | 1.65 | -0.50 | 0.20 | orf, hypothetical protein |
| b2460 | 0.30 | -1.42 | 1.12 | 1.60 | -0.70 | 1.50 | orf, hypothetical protein |
| b2461 | 0.00 | -1.34 | -1.34 | -2.50 | -1.50 | -1.15 | orf, hypothetical protein |
| b2462 | -1.34 | 0.24 | 1.39 | -1.30 | 0.63 | 1.15 | orf, hypothetical protein |
| b2463 | -2.45 | -2.36 | -0.96 | -3.25 | 0.23 | -0.05 | putative multimodular enzyme |
| b2466 | 0.91 | 0.22 | -0.64 | 0.25 | -0.47 | 0.00 | orf, hypothetical protein |
| b2475 | 0.02 | -1.15 | 1.09 | 0.30 | -1.27 | 1.20 | orf, hypothetical protein |
| b2490 | 0.51 | -1.12 | -1.58 | 1.40 | 0.00 | -1.35 | putative protein processing element |
| b2494 | 0.37 | -0.45 | 0.93 | 0.15 | -1.17 | 1.10 | orf, hypothetical protein |
| b2495 | 0.38 | 0.19 | -1.42 | 0.15 | 0.20 | -1.80 | putative oxidoreductase |
| b2496 | -1.11 | 0.86 | 0.70 | -1.45 | 0.67 | 1.35 | putative DNA replication factor |
| b2503 | 1.03 | -1.72 | -0.90 | 0.60 | -1.20 | 0.00 | putative cytochrome C-type biogenesis protein |
| b2504 | -3.30 | -0.24 | -1.42 | -2.30 | 0.23 | -1.55 | orf, hypothetical protein |
| b2505 | -0.03 | -1.64 | 0.65 | 1.30 | -1.10 | 0.05 | putative outer membrane lipoprotein |
| b2506 | -0.33 | -0.13 | 1.22 | -0.45 | 0.37 | -0.40 | putative membrane protein |
| b2510 | -1.03 | -1.16 | -1.20 | -0.30 | -0.30 | -0.25 | orf, hypothetical protein |
| b2511 | -1.37 | 2.63 | -1.11 | -1.30 | 1.63 | -1.05 | putative GTP-binding factor |
| b2512 | -0.42 | -1.61 | -0.49 | -1.30 | -2.03 | 0.05 | putative dehydrogenase |
| b2513 | 1.21 | 1.34 | 0.37 | 2.10 | 1.33 | 0.20 | orf, hypothetical protein |
| b2520 | 0.56 | 0.53 | -1.44 | 1.35 | 1.13 | -1.40 | orf, hypothetical protein |
| b2529 | 0.39 | 3.91 | -1.13 | 0.35 | 1.77 | -1.35 | orf, hypothetical protein |
| b2531 | 0.14 | 10.47 | 0.50 | 0.25 | 2.90 | 0.20 | orf, hypothetical protein |
| b2532 | -0.99 | 0.00 | 0.97 | -5.25 | 0.30 | 0.10 | putative ATP synthase beta subunit |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b2534 | **0.96** | **0.62** | **0.32** | 1.65 | 1.73 | -0.20 | putative enzyme (3.4.-) |
| b2595 | **0.13** | **0.28** | **-1.16** | 1.20 | -2.13 | -1.15 | orf, hypothetical protein |
| b2596 | **0.52** | **0.51** | **-0.39** | 1.15 | -0.20 | 0.00 | orf, hypothetical protein |
| b2603 | **-3.88** | **0.59** | **-1.33** | -1.85 | 1.50 | -0.10 | orf, hypothetical protein |
| b2611 | **-0.70** | **-1.27** | **0.66** | -1.60 | -0.37 | -0.20 | orf, hypothetical protein |
| b2618 | **0.07** | **-1.37** | **-1.41** | -0.10 | -1.40 | -1.45 | orf, hypothetical protein |
| b2619 | **-0.40** | **-1.17** | **-1.12** | -0.45 | -0.37 | -0.10 | orf, hypothetical protein |
| b2636 | **0.12** | **0.59** | **1.02** | 0.30 | 1.47 | 0.10 | orf, hypothetical protein |
| b2638 | **0.16** | **0.84** | **0.71** | 0.35 | 1.83 | 1.30 | orf, hypothetical protein |
| b2639 | **0.27** | **-1.33** | **1.16** | -0.70 | -0.07 | 1.35 | putative pump protein |
| b2640 | **-1.05** | **-1.07** | **-0.66** | -0.25 | -0.13 | 0.05 | orf, hypothetical protein |
| b2641 | **-0.70** | **0.76** | **0.77** | -2.05 | 1.57 | 0.00 | orf, hypothetical protein |
| b2648 | **2.40** | **-1.34** | **-1.17** | 2.10 | -0.93 | -0.15 | orf, hypothetical protein |
| b2649 | **0.17** | **-1.31** | **-1.32** | 1.20 | -0.63 | 0.10 | orf, hypothetical protein |
| b2650 | **-0.81** | **-0.82** | **-0.60** | -1.30 | 1.73 | 0.05 | orf, hypothetical protein |
| b2651 | **3.65** | **1.14** | **0.95** | 1.65 | 1.70 | 1.35 | orf, hypothetical protein |
| b2653 | **0.18** | **-1.26** | **-1.21** | 0.25 | -0.73 | -1.25 | orf, hypothetical protein |
| b2654 | **-0.36** | **-1.33** | **0.79** | -0.20 | -0.70 | 0.25 | orf, hypothetical protein |
| b2655 | **4.84** | **-1.13** | **0.77** | 1.75 | -0.17 | -0.25 | orf, hypothetical protein |
| b2656 | **1.48** | **0.48** | **1.43** | 2.15 | 0.60 | 1.30 | orf, hypothetical protein |
| b2657 | **-0.71** | **-1.17** | **-0.82** | 0.00 | -0.20 | 0.00 | putative enzyme |
| b2658 | **-0.99** | **-1.24** | **0.78** | -1.35 | -0.10 | 1.50 | orf, hypothetical protein |
| b2659 | **1.09** | **1.13** | **-0.19** | 1.80 | 1.43 | -0.35 | orf, hypothetical protein |
| b2666 | **-0.02** | **2.24** | **-0.53** | 0.00 | 1.87 | 0.10 | orf, hypothetical protein |
| b2667 | **-0.79** | **-0.12** | **0.72** | -0.40 | 0.50 | -0.20 | orf, hypothetical protein |
| b2670 | **-0.17** | **3.10** | **-2.59** | -0.20 | 1.37 | -1.10 | orf, hypothetical protein |
| b2680 | **-0.91** | **-1.44** | **-1.48** | -0.20 | -1.27 | -1.30 | orf, hypothetical protein |
| b2681 | **-0.62** | **-1.34** | **0.85** | 0.55 | -0.47 | 1.10 | putative transport protein |
| b2682 | **0.91** | **0.17** | **0.79** | 1.05 | 0.63 | 1.45 | orf, hypothetical protein |
| b2689 | **1.29** | **2.54** | **-0.12** | 2.40 | 1.53 | -1.20 | orf, hypothetical protein |
| b2710 | **1.10** | **-1.30** | **0.45** | 2.60 | -0.30 | 1.00 | putative flavodoxin |
| b2736 | **-0.13** | **0.91** | **0.78** | -1.40 | 1.50 | 1.40 | putative dehydrogenase |
| b2737 | **3.77** | **-2.28** | **-0.50** | 0.30 | -0.53 | -1.35 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b2740 | 1.41 | -1.16 | -0.43 | 2.30 | 0.43 | -1.10 | putative transport protein |
| b2748 | -0.03 | -0.24 | 1.05 | 0.00 | -0.17 | 1.35 | orf, hypothetical protein |
| b2755 | 0.20 | 0.79 | 0.94 | -0.25 | 1.13 | 1.20 | orf, hypothetical protein |
| b2756 | 1.16 | 1.66 | 0.74 | 1.80 | -0.17 | 1.55 | orf, hypothetical protein |
| b2757 | 0.45 | 1.20 | -1.40 | 2.20 | 1.47 | -1.40 | orf, hypothetical protein |
| b2758 | 0.88 | 1.04 | 0.66 | 2.00 | 1.27 | -0.15 | orf, hypothetical protein |
| b2760 | -1.00 | 1.78 | -1.28 | -0.10 | 1.37 | -1.35 | orf, hypothetical protein |
| b2772 | 0.44 | 1.76 | -0.76 | 0.25 | 1.23 | -1.00 | orf, hypothetical protein |
| b2789 | -0.50 | 1.88 | -0.37 | -1.35 | 1.97 | 0.10 | putative transport protein |
| b2790 | -0.46 | 1.10 | 0.15 | -0.20 | 1.83 | -0.10 | orf, hypothetical protein |
| b2792 | 0.86 | -1.14 | -1.20 | 1.50 | -0.13 | -1.50 | orf, hypothetical protein |
| b2809 | -0.98 | -0.47 | -0.36 | -2.35 | -0.20 | -0.10 | orf, hypothetical protein |
| b2810 | 1.63 | 0.33 | 1.07 | 1.25 | -0.33 | 1.15 | orf, hypothetical protein |
| b2817 | 0.47 | 2.05 | 0.80 | 1.25 | 1.60 | 1.40 | putative amidase |
| b2832 | 0.32 | -1.14 | -0.50 | 1.30 | -0.23 | 0.00 | putative transport protein |
| b2833 | 0.04 | 0.56 | -1.71 | -0.05 | 0.70 | -1.45 | orf, hypothetical protein |
| b2834 | -0.14 | 1.78 | -0.84 | 0.20 | 1.70 | 0.00 | orf, hypothetical protein |
| b2845 | 1.32 | -1.20 | 0.62 | 1.30 | -0.30 | 0.40 | putative transporter protein |
| b2853 | 1.22 | -0.95 | 0.76 | 1.50 | 0.03 | -0.20 | orf, hypothetical protein |
| b2854 | 0.98 | 1.00 | -1.34 | 0.25 | 1.20 | -1.20 | orf, hypothetical protein |
| b2856 | 1.76 | -1.32 | 0.79 | 1.80 | -0.60 | 1.30 | orf, hypothetical protein |
| b2857 | 0.71 | 0.75 | 0.70 | -0.40 | 1.40 | 0.30 | orf, hypothetical protein |
| b2858 | 1.01 | 0.04 | -1.34 | 0.45 | 1.23 | -1.30 | orf, hypothetical protein |
| b2859 | -0.55 | 0.94 | -1.40 | 0.05 | 1.30 | -1.00 | orf, hypothetical protein |
| b2862 | -0.79 | -1.28 | -0.11 | -0.25 | -0.37 | 0.15 | orf, hypothetical protein |
| b2863 | -1.25 | 0.54 | 0.21 | -0.55 | 1.13 | 0.10 | orf, hypothetical protein |
| b2865 | 1.41 | 0.13 | -0.72 | 1.90 | 1.60 | 0.00 | putative lipoprotein |
| b2866 | -0.12 | -0.92 | -0.03 | -1.35 | 0.10 | -0.05 | orf, hypothetical protein |
| b2868 | 2.27 | -1.40 | 0.70 | 1.85 | -0.50 | 1.35 | putative dehydrogenase |
| b2873 | 0.12 | 1.26 | -1.52 | 0.95 | 1.70 | -1.30 | orf, hypothetical protein |
| b2875 | -0.11 | -1.22 | 0.72 | 1.25 | -0.17 | 1.40 | putative synthases |
| b2876 | -1.17 | -0.96 | 0.64 | -1.45 | -0.63 | 0.00 | orf, hypothetical protein |
| b2878 | 1.46 | 4.58 | -0.29 | 0.55 | 1.17 | -0.15 | putative oxidoreductase, Fe-S subunit |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b2879 | -0.05 | 0.77 | -1.37 | -0.10 | 1.53 | -1.35 | putative proteoglycan |
| b2880 | -0.97 | 0.00 | -1.80 | 0.00 | 1.43 | -1.05 | orf, hypothetical protein |
| b2881 | -1.07 | -1.54 | -1.43 | -0.20 | -1.30 | -1.15 | putative dehydrogenase |
| b2889 | -1.27 | -0.06 | 1.00 | -2.40 | -0.30 | 1.15 | putative enzyme |
| b2896 | 0.30 | 2.12 | -1.08 | 0.05 | 1.30 | -0.20 | orf, hypothetical protein |
| b2899 | 0.67 | -1.35 | -0.05 | 0.05 | -1.60 | 0.25 | putative oxidoreductase |
| b2931 | 0.35 | 0.00 | 0.80 | -0.60 | 1.90 | 1.80 | putative oxidoreductase |
| b2970 | -0.86 | -1.74 | 0.77 | -1.55 | -1.47 | 1.70 | putative general secretion pathway for protein export (GSP) |
| b2971 | 0.97 | 0.00 | 0.77 | 0.25 | 0.27 | 1.45 | orf, hypothetical protein |
| b2972 | -0.05 | -0.26 | 0.81 | -1.85 | 0.17 | -0.05 | putative peptidase |
| b2973 | 0.41 | -1.44 | -1.37 | 0.25 | -1.30 | -1.70 | orf, hypothetical protein |
| b2974 | 0.02 | -1.50 | 1.00 | -0.05 | -0.33 | 1.20 | putative endoglucanase |
| b2981 | -1.14 | 0.93 | -1.33 | -0.55 | 1.13 | -1.20 | orf, hypothetical protein |
| b2989 | 0.48 | -0.03 | -1.28 | 1.30 | 0.10 | -1.50 | orf, hypothetical protein |
| b2997 | -0.67 | -1.31 | -1.38 | -1.05 | -1.63 | -1.25 | putative hydrogenase subunit |
| b2998 | -0.65 | -0.60 | -0.56 | -0.25 | 0.37 | 0.10 | orf, hypothetical protein |
| b2999 | 0.17 | 1.18 | 0.55 | 0.25 | 0.40 | 0.35 | orf, hypothetical protein |
| b3000 | -0.69 | -1.35 | 0.72 | 0.05 | -0.87 | 0.10 | orf, hypothetical protein |
| b3001 | 0.93 | -1.34 | -1.24 | -0.50 | -2.07 | -1.35 | putative reductase |
| b3004 | 0.18 | -1.91 | 1.44 | -0.15 | 0.27 | 1.35 | orf, hypothetical protein |
| b3007 | 0.64 | -0.48 | 0.89 | 1.10 | 0.27 | 1.65 | orf, hypothetical protein |
| b3015 | -0.63 | -1.12 | 0.75 | 0.05 | -0.13 | 0.10 | orf, hypothetical protein |
| b3020 | -0.08 | 1.33 | -1.34 | 0.05 | 1.43 | -1.25 | putative transport periplasmic protein |
| b3021 | -0.15 | 1.06 | 0.59 | 0.15 | 1.33 | 0.05 | orf, hypothetical protein |
| b3022 | 0.36 | -1.29 | -0.18 | 1.40 | -0.50 | 0.15 | orf, hypothetical protein |
| b3023 | 2.22 | 0.90 | -1.40 | 2.40 | 1.03 | -1.20 | orf, hypothetical protein |
| b3027 | -0.01 | -1.12 | 0.76 | 0.40 | -0.33 | 0.10 | orf, hypothetical protein |
| b3042 | 0.34 | -1.04 | 0.43 | 1.35 | -0.53 | 0.20 | orf, hypothetical protein |
| b3050 | 0.78 | -0.58 | 0.49 | 1.55 | 0.30 | 0.30 | putative oxidoreductase |
| b3051 | -0.06 | 1.69 | -1.54 | 0.10 | 1.17 | -1.50 | putative membrane protein |
| b3052 | -0.43 | 0.74 | 0.83 | -1.20 | 1.23 | 1.40 | putative kinase |
| b3100 | -0.92 | -4.74 | 0.81 | -1.60 | -2.20 | 1.15 | orf, hypothetical protein |
| b3122 | 0.73 | 0.85 | 0.95 | 1.25 | 1.33 | 1.35 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| b3254 | 0.70 | -1.33 | -0.21 | 0.55 | -0.23 | 0.20 | orf, hypothetical protein |
| b3472 | 0.34 | 2.00 | -0.20 | 0.25 | 1.37 | 0.15 | orf, hypothetical protein |
| b3694 | 0.54 | 0.08 | -1.62 | 1.75 | 0.17 | -1.10 | putative FADA-type transcriptional regulator |
| b3776 | -0.05 | -0.30 | 1.06 | 0.15 | -1.20 | 1.45 | orf, hypothetical protein |
| b3808 | 0.80 | -0.21 | 0.34 | 2.90 | 0.67 | -0.05 | orf, hypothetical protein |
| b3814 | 0.25 | -1.33 | 1.11 | 1.40 | -0.17 | 1.35 | orf, hypothetical protein |
| b3836 | 0.07 | -1.07 | 0.67 | 0.10 | -0.20 | -0.10 | orf, hypothetical protein |
| b3837 | 0.21 | 0.48 | 1.14 | -0.65 | -0.37 | 1.55 | putative histone |
| b3838 | 0.26 | 1.88 | 0.90 | 1.10 | 1.17 | -0.05 | orf, hypothetical protein |
| b3913 | -2.50 | 0.67 | 0.40 | -1.80 | 1.33 | 0.20 | orf, hypothetical protein |
| b3914 | -12.05 | 1.57 | -0.25 | -1.80 | 2.40 | 0.00 | orf, hypothetical protein |
| b3975 | 1.00 | -1.28 | -0.34 | 0.80 | -0.37 | 0.05 | orf, hypothetical protein |
| b4103 | 2.18 | 0.29 | -1.12 | 2.00 | -0.37 | -1.20 | orf, hypothetical protein |
| b4140 | -0.67 | -0.59 | 0.04 | -1.95 | -0.37 | 0.20 | orf, hypothetical protein |
| b4250 | 0.21 | 1.12 | -1.34 | 0.00 | 1.50 | -1.10 | orf, hypothetical protein |
| b4256 | 1.66 | -1.40 | 0.17 | 1.70 | -0.67 | 0.20 | orf, hypothetical protein |
| b4285 | -0.13 | -1.37 | 0.67 | 0.20 | -0.10 | -0.10 | putative transposase |
| b4286 | -2.04 | -0.13 | 1.05 | -1.65 | 0.60 | 1.25 | orf, hypothetical protein |
| bacA | 0.37 | 1.63 | -1.34 | 0.35 | 2.03 | 0.25 | bacitracin resistance; possibly phosphorylates undecaprenol |
| baeR | 0.58 | -1.34 | 0.08 | 0.10 | -1.17 | 0.25 | transcriptional response regulatory protein (sensor BaeS) |
| baeS | 0.15 | -1.38 | 1.04 | 1.45 | -1.37 | 1.30 | sensor protein (for BaeR) |
| barA | 0.15 | -4.25 | 0.89 | 1.10 | -1.13 | 0.05 | sensor-regulator, activates OmpR by phophorylation |
| basR | 0.12 | -1.38 | -1.07 | -0.45 | -1.37 | -0.10 | transcriptional regulatory protein, member of 2-component regulatory system |
| basS | 0.18 | -0.81 | -0.64 | 0.10 | 0.63 | -0.05 | sensor protein for basR |
| bax | -1.02 | -1.31 | 0.45 | -1.40 | -0.57 | -0.05 | putative ATP-binding protein |
| bcp | 0.47 | -0.02 | 1.01 | 1.65 | 0.33 | 1.35 | bacterioferritin comigratory protein |
| bcr | 0.40 | -0.57 | 0.73 | 1.90 | -0.10 | 0.20 | bicyclomycin resistance protein; transmembrane protein |
| betA | 1.63 | -0.92 | -1.33 | 0.30 | -0.33 | 0.15 | choline dehydrogenase, a flavoprotein |
| betB | 0.08 | 0.17 | -1.46 | -0.40 | 1.27 | -1.35 | NAD+-dependent betaine aldehyde dehydrogenase |
| betI | 0.86 | 2.19 | 0.55 | 0.30 | 0.60 | -0.10 | probably transcriptional repressor of bet genes |
| betT | 1.55 | -1.22 | -1.20 | 1.65 | -1.23 | -0.20 | high-affinity choline transport |
| bfr | -1.18 | -3.35 | 0.57 | -6.80 | -3.03 | 1.05 | bacterioferrin, an iron storage homoprotein |
| bglA | -0.12 | -2.07 | -0.80 | -0.60 | -1.83 | -0.05 | 6-phospho-beta-glucosidase A; cryptic |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| bglB | 0.46 | -0.90 | -1.35 | 1.30 | -0.13 | -1.30 | phospho-beta-glucosidase B; cryptic |
| bglF | -0.26 | 1.59 | 0.88 | 1.10 | 2.07 | 1.40 | PTS system beta-glucosides, enzyme II, cryptic |
| bglG | 0.37 | -0.08 | 0.63 | 0.85 | 1.00 | 0.25 | positive regulation of bgl operon |
| bglJ | -0.18 | -1.62 | -0.78 | 0.30 | -1.10 | 0.00 | 2-component transcriptional regulator |
| bglX | -0.25 | -0.18 | -0.90 | 0.35 | 1.03 | -0.20 | beta-D-glucoside glucohydrolase, periplasmic |
| bioA | 0.00 | 0.31 | 0.77 | -1.10 | 0.07 | 1.25 | 7,8-diaminopelargonic acid synthetase |
| bioB | 0.16 | -1.19 | 1.28 | 2.45 | -0.03 | 1.25 | biotin synthesis, sulfur insertion? |
| bioC | -0.02 | -1.27 | 0.77 | 0.65 | 0.33 | 1.30 | biotin biosynthesis; reaction prior to pimeloyl CoA |
| bioD | 2.31 | 0.04 | -1.28 | 2.35 | -0.03 | -1.05 | dethiobiotin synthetase |
| bioF | 0.66 | 0.08 | 0.92 | 2.35 | 0.03 | 0.25 | 8-amino-7-oxononanoate synthase |
| bioH | -0.13 | -0.89 | 0.64 | 0.30 | -0.27 | 1.45 | biotin biosynthesis; reaction prior to pimeloyl CoA |
| birA | 0.51 | -0.70 | -0.90 | 1.75 | -0.37 | -0.05 | biotin-[acetylCoA carboxylase] holoenzyme synthetase and biotin operon repressor |
| bisC | -0.79 | -0.19 | -1.18 | 0.00 | 0.13 | -0.30 | biotin sulfoxide reductase |
| bisZ | -1.33 | 2.80 | 0.12 | -1.70 | 3.80 | 0.15 | biotin sulfoxide reductase 2 |
| blc | 1.37 | -1.56 | 0.74 | 1.70 | -1.17 | 0.05 | outer membrane lipoprotein (lipocalin) |
| bolA | -0.68 | -2.16 | -1.20 | -0.65 | -1.87 | -0.30 | possible regulator of murein genes |
| brnQ | -0.23 | -1.58 | -1.06 | -0.05 | -1.60 | -1.90 | branched chain amino acid transport system II carrier protein |
| btuB | 1.33 | -1.46 | -1.32 | 1.40 | -1.20 | -1.10 | outer membrane receptor for transport of vitamin B12, E colicins, and bacteriophage BF23 |
| btuC | 0.06 | 0.47 | -0.93 | 1.85 | 1.70 | -0.05 | vitamin B12 transport permease protein |
| btuD | 0.75 | -1.33 | 0.77 | 0.05 | -0.30 | 0.30 | ATP-binding component of vitamin B12 transport system |
| btuE | 0.89 | -1.34 | -0.14 | 1.35 | -1.33 | -0.10 | vitamin B12 transport |
| btuR | -0.27 | 0.91 | -0.79 | -1.25 | 1.23 | -1.70 | cob(I)alamin adenolsyltransferase |
| cadA | -0.39 | -1.45 | -0.30 | 0.25 | -1.50 | 0.05 | lysine decarboxylase 1 |
| cadB | -0.18 | 0.48 | 0.79 | 0.60 | 0.57 | 1.45 | transport of lysine |
| cadC | -0.15 | -0.94 | 1.22 | 0.10 | 1.20 | 1.15 | transcriptional activator of cad operon |
| cafA | -1.55 | -1.16 | 0.39 | -1.10 | -0.03 | 1.30 | bundles of cytoplasmic filaments |
| caiA | 0.78 | -0.21 | -1.30 | 1.60 | 0.40 | -1.60 | probable carnitine operon oxidoreductase |
| caiB | 1.88 | -1.33 | -1.34 | 1.60 | -1.40 | -1.40 | l-carnitine dehydratase |
| caiC | -0.44 | -1.80 | 0.82 | -0.60 | -1.67 | 1.40 | probable crotonobetaine |
| caiD | -0.63 | -1.37 | -1.23 | -0.25 | -1.73 | -1.45 | carnitine racemase |
| caiE | -0.34 | -1.37 | -1.09 | 0.30 | -1.63 | -0.20 | possible synthesis of cofactor for carnitine racemase and dehydratase |
| caiF | -0.76 | -0.99 | -1.37 | -0.80 | -1.53 | -2.05 | transcriptional regulator of cai operon |
| caiT | -0.67 | -1.48 | -1.13 | 1.15 | -0.40 | -1.25 | probable carnitine transporter |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| carA | 1.40 | -0.90 | 0.45 | 1.50 | -0.83 | 7.10 | carbamoyl-phosphate synthetase, glutamine (small) subunit |
| carB | 0.45 | -1.14 | -1.24 | 1.40 | -1.43 | -3.10 | carbamoyl-phosphate synthase large subunit |
| cbl | -0.01 | 1.34 | 0.82 | -0.55 | 1.63 | 0.35 | transcriptional regulator cys regulon; accessory regulatory circuit affecting cysM |
| cbpA | 0.46 | 1.27 | -1.34 | 0.50 | 1.53 | -0.35 | curved DNA-binding protein; functions closely related to DnaJ |
| cca | -0.14 | -0.90 | 0.17 | 0.05 | 0.13 | 0.10 | tRNA nucleotidyl transferase |
| cchA | -0.71 | -1.35 | -0.16 | -0.10 | -0.77 | -0.05 | detox protein |
| cchB | 0.56 | -1.79 | 0.80 | 1.10 | -0.33 | 1.20 | detox protein |
| ccmA | -3.21 | -1.20 | 0.66 | -1.65 | -0.27 | -0.15 | ATP binding protein of heme exporter A |
| ccmB | 0.21 | 0.02 | 0.04 | 1.10 | 0.63 | 0.25 | heme exporter protein B, cytochrome c-type biogenesis protein |
| ccmC | 0.23 | -1.80 | 1.58 | -0.60 | -1.80 | 1.40 | heme exporter protein C |
| ccmD | -1.31 | 0.79 | 0.86 | -0.35 | 1.40 | 1.40 | heme exporter protein C |
| ccmE | -1.58 | -0.90 | 0.60 | -2.25 | 0.63 | 0.00 | cytochrome c biogenesis, possible subunit of a heme lyase |
| ccmF | -0.78 | -0.39 | 0.67 | -0.15 | 0.33 | 0.00 | cytochrome c-type biogenesis protein |
| ccmH | -1.54 | -0.27 | 0.76 | -1.35 | 0.07 | -0.15 | possible subunit of heme lyase |
| cdd | -1.85 | -5.21 | 0.97 | -2.35 | -3.27 | 1.20 | cytidine |
| cdh | 0.27 | 6.93 | 0.56 | 1.20 | 1.50 | 0.05 | CDP-diacylglycerol phosphotidylhydrolase |
| cdsA | -0.20 | 0.09 | 0.39 | -0.60 | 0.27 | 0.00 | CDP-diglyceride synthetase |
| celA | -1.54 | -0.44 | -0.70 | -1.85 | 0.33 | 0.10 | PEP-dependent phosphotransferase enzyme IV for cellobiose, arbutin, and salicin |
| celB | 0.35 | -1.57 | -1.32 | 1.95 | -1.13 | -1.35 | PEP-dependent phosphotransferase enzyme II for cellobiose, arbutin, and salicin |
| celC | -1.05 | -0.95 | -0.78 | -2.60 | 0.10 | -0.10 | PEP-dependent phosphotransferase enzyme III for cellobiose, arbutin, and salicin |
| celD | 1.28 | -0.98 | 0.17 | 2.00 | 0.07 | 0.20 | negative transcriptional regulator of cel operon |
| celF | -1.00 | -1.16 | 0.83 | 0.15 | -0.40 | 1.45 | phospho-beta-glucosidase; cryptic |
| cfa | -0.03 | 0.53 | -1.31 | -0.10 | -1.10 | -1.35 | cyclopropane fatty acyl phospholipid synthase |
| chaA | 0.01 | -0.85 | 0.83 | -0.55 | 0.00 | 1.35 | sodium-calcium |
| chaB | 2.15 | -1.29 | 0.54 | 1.80 | -1.40 | 0.00 | cation transport regulator |
| chaC | 0.39 | -0.06 | 0.41 | -0.25 | 0.33 | -0.10 | cation transport regulator |
| cheA | -3.74 | -2.25 | 0.75 | -3.35 | -2.03 | 0.40 | sensory transducer kinase between chemo- signal receptors and CheB and CheY |
| cheB | -0.74 | -0.08 | 1.51 | -1.65 | 0.40 | 1.30 | response regulator for chemotaxis (cheA sensor); protein methylesterase |
| cheR | -1.02 | 4.45 | -1.31 | -1.25 | 1.33 | -1.10 | response regulator for chemotaxis; protein glutamate methyltransferase |
| cheW | -1.43 | -5.55 | -0.79 | -4.65 | -2.73 | -0.05 | positive regulator of CheA protein activity |
| cheY | -1.67 | -3.04 | 0.53 | -2.90 | -1.27 | 0.30 | chemotaxis regulator transmits chemoreceptor signals to flagelllar motor components |
| cheZ | -1.39 | -0.28 | -0.17 | -4.15 | 0.20 | -0.05 | chemotactic response; CheY protein phophatase; antagonist of CheY as switch regulator |
| chpA | -0.26 | 0.91 | 1.02 | 0.35 | -0.07 | 1.35 | probable growth inhibitor, PemK-like, autoregulated |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| chpB | -0.66 | 0.85 | 0.60 | -0.20 | 1.93 | 1.25 | probable growth inhibitor, PemK-like, autoregulated |
| chpR | -1.03 | -2.37 | -1.42 | -1.15 | -1.13 | -1.40 | suppressor of inhibitory function of ChpA, PemI-like, autoregulated |
| chpS | -0.80 | -1.00 | 0.72 | -0.70 | -0.17 | 1.20 | suppressor of inhibitory function of ChpB, PemI-like, autoregulated |
| cirA | 0.13 | 2.19 | -1.36 | -0.35 | 1.43 | -1.60 | outer membrane receptor for iron-regulated colicin I receptor; porin; requires tonB gene product |
| citA | -0.30 | 1.78 | 0.92 | -1.30 | 1.40 | 1.55 | putative sensor-type protein |
| citB | -0.76 | -1.27 | -1.33 | -0.05 | -0.30 | -0.15 | sequence similarity to Shigella regulator |
| citC | -0.99 | 0.56 | 0.88 | -0.10 | 1.70 | 1.50 | citrate lyase synthetase (citrate (pro-3S)-lyase ligase |
| citD | -1.33 | 2.01 | 1.12 | -2.50 | 1.67 | 1.15 | citrate lyase acyl carrier protein (gamma chain) |
| citE | -1.46 | -1.34 | -0.83 | -2.10 | -1.27 | -1.15 | citrate lyase beta chain (acyl lyase subunit) |
| citF | 0.45 | 0.00 | 0.85 | -0.50 | 0.37 | 1.35 | citrate lyase alpha chain |
| citG | -0.99 | 0.76 | -1.33 | -1.75 | -1.07 | -1.60 | orf, hypothetical protein |
| clpA | 2.60 | -2.58 | -0.50 | 1.25 | -1.67 | 0.10 | ATP-binding component of serine protease |
| clpB | -0.05 | -0.66 | 0.90 | -0.15 | -0.53 | 1.35 | heat shock protein |
| clpP | 0.27 | -0.05 | 0.04 | 1.25 | 0.33 | 1.15 | ATP-dependent proteolytic subunit of clpA-clpP serine protease, heat shock protein F21.5 |
| clpX | -1.83 | -3.06 | 2.27 | -1.15 | -0.03 | 1.50 | ATP-dependent specificity component of clpP serine protease, chaperone |
| cls | 0.90 | -1.59 | -1.38 | 2.00 | -1.70 | -1.80 | cardiolipin synthase, a major membrane phospholipid; novobiocin sensitivity |
| cmk | 0.49 | -0.36 | 1.16 | 0.15 | -0.37 | 1.15 | cytidylate kinase |
| cmr | -1.24 | 0.61 | 0.42 | -0.15 | 0.50 | 1.50 | proton motive force efflux pump |
| cmtA | 0.73 | 2.79 | -1.01 | 1.90 | 3.73 | -1.10 | PTS system, mannitol-specific enzyme II component, cryptic |
| cmtB | 0.71 | -1.74 | -1.27 | 1.45 | -0.40 | -1.30 | PTS system, mannitol-specific enzyme II component, cryptic |
| coaA | 0.22 | 0.04 | -0.48 | 0.00 | 0.23 | 0.05 | pantothenate kinase |
| cobB | 2.31 | 1.26 | 0.56 | 1.15 | 1.17 | 0.05 | putative nicotinic acid mononucleotide:5,6-dimethylbenzimidazole (DMB) phosphoribosyltransferase |
| cobS | 0.01 | 1.48 | 0.58 | 0.90 | -0.03 | 0.35 | cobalamin 5 -phosphate synthase |
| cobT | -0.29 | 1.03 | 0.82 | -0.10 | 0.60 | -0.10 | nicotinate-nucleotide dimethylbenzimidazole-P phophoribosyl transferase |
| cobU | -0.99 | -1.99 | 0.67 | -0.55 | -1.70 | 0.10 | cobinamide kinase |
| codA | 0.64 | -1.45 | 0.72 | 1.50 | -1.37 | 1.55 | cytosine deaminase |
| codB | 0.26 | -1.96 | -0.80 | -0.30 | -1.23 | -1.35 | cytosine permease |
| cof | -0.17 | 0.59 | -0.16 | -0.95 | 2.03 | 0.20 | orf, hypothetical protein |
| corA | 2.05 | 2.78 | 0.49 | 3.00 | 1.63 | 0.10 | Mg2+ transport, system I |
| cpdB | -1.31 | -1.62 | 1.17 | -1.20 | -1.10 | 1.25 | 2 :3 -cyclic-nucleotide 2 -phosphodiesterase |
| cpsB | -0.10 | 5.43 | -1.35 | 0.00 | 1.30 | -1.20 | mannose-1-phosphate guanyltransferase |
| cpsG | 0.00 | 3.63 | 0.77 | -0.55 | 1.87 | 0.00 | phosphomannomutase |
| cpxA | -0.28 | -1.18 | -1.33 | -0.40 | 0.10 | -1.05 | probable sensor protein (histidine protein kinase), acting on arcA |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| cpxR | -1.05 | -0.67 | 0.77 | -0.55 | -0.23 | 0.25 | transcriptional regulator in 2-component system |
| crcA | -0.16 | -1.85 | -1.29 | -0.10 | -1.30 | -0.05 | orf, hypothetical protein |
| crcB | -0.02 | 1.53 | -1.15 | 0.10 | 2.00 | -1.05 | orf, hypothetical protein |
| creA | 0.08 | -1.24 | -0.24 | -0.55 | -1.63 | 0.00 | orf, hypothetical protein |
| creB | -0.75 | 0.47 | 0.83 | -0.05 | -0.33 | 1.25 | catabolic regulation response regulator |
| creC | -0.27 | -1.34 | 1.09 | 0.00 | -0.23 | -0.05 | catabolite repression sensor kinase for PhoB; alternative sensor for pho regulon |
| creD | -1.27 | 1.14 | -1.36 | -0.35 | 1.37 | -1.25 | tolerance to colicin E2 |
| crl | 0.99 | -0.70 | 0.42 | -1.10 | -0.07 | -0.25 | transcriptional regulator of cryptic csgA gene for curli surface fibers |
| crp | 0.22 | -3.11 | 1.31 | 1.15 | -1.80 | 1.25 | cyclic AMP receptor protein |
| crr | -1.60 | -0.49 | 0.94 | -1.25 | 0.30 | 1.65 | PTS system, glucose-specific IIA component |
| csgA | -0.92 | -1.44 | 0.58 | -2.20 | -1.27 | 0.00 | curlin major subunit, coiled surface structures; cryptic |
| csgB | 0.50 | -1.21 | 1.03 | 0.05 | -0.43 | 1.40 | minor curlin subunit precursor, similar ro CsgA |
| csgC | -0.16 | -1.34 | 0.77 | -1.30 | -1.30 | 1.15 | putative curli production protein |
| csgD | 1.98 | 1.52 | -0.90 | 1.50 | 1.37 | -1.20 | putative 2-component transcriptional regulator for 2nd curli operon |
| csgE | 0.11 | -1.30 | 0.77 | 0.10 | 0.03 | 0.15 | curli production assembly |
| csgF | 2.11 | 1.44 | -1.44 | 1.80 | 1.33 | -1.25 | curli production assembly |
| csgG | 0.96 | 0.46 | -0.28 | 2.30 | 1.33 | -0.25 | curli production assembly |
| csiE | -0.84 | -1.32 | 0.78 | -0.25 | -1.53 | 1.40 | orf, hypothetical protein |
| cspA | 0.01 | -5.76 | 0.03 | 0.00 | -2.35 | 0.10 | cold shock protein 7.4, transcriptional activator of hns |
| cspB | 0.06 | -2.43 | -1.35 | 0.00 | -3.73 | -0.80 | cold shock protein; may affect transcription |
| cspC | 0.59 | -1.43 | 0.69 | 0.50 | -0.80 | 2.20 | cold shock protein |
| cspD | -1.18 | -4.44 | 0.31 | -3.25 | -3.10 | 1.10 | cold shock protein |
| cspE | -2.18 | -0.87 | 0.20 | -1.35 | -0.15 | 1.15 | cold shock protein |
| cspF | -0.44 | 0.01 | 0.33 | -0.30 | 0.43 | 0.05 | cold shock protein |
| cspG | -1.14 | -1.71 | 2.58 | -0.45 | -5.10 | 1.45 | homolog of Salmonella cold shock protein |
| cspH | 0.39 | -0.77 | 1.01 | 0.10 | -0.37 | -0.20 | cold shock-like protein |
| cspI | -0.97 | -4.33 | 0.63 | -2.10 | -2.43 | 0.20 | cold shock-like protein |
| csrA | -1.63 | -5.09 | 0.85 | -1.75 | -1.43 | 1.45 | carbon storage regulator; controls glycogen synthesis, gluconeogenesis, cell size and surface |
| cstA | -1.62 | -1.08 | 0.73 | -3.05 | -1.10 | 0.40 | carbon starvation protein |
| cstC | 0.35 | -0.32 | 0.42 | 0.20 | 0.10 | 0.30 | acetylornithine delta-aminotransferase |
| cutA | 2.69 | -0.23 | -1.42 | 1.65 | -1.50 | -1.50 | divalent cation tolerance protein; cytochrome c biogenesis |
| cutC | -0.91 | -0.86 | -1.07 | -2.40 | 0.30 | -0.05 | copper homeostasis protein |
| cutF | -1.32 | 1.20 | -0.02 | -1.00 | 1.23 | 1.00 | copper homeostasis protein (lipoprotein) |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| cvpA | -0.27 | 0.03 | -0.91 | -1.15 | -0.07 | -0.05 | membrane protein required for colicin V production |
| cyaA | 0.19 | -1.61 | 0.74 | 1.20 | -1.30 | 1.35 | adenylate cyclase |
| cyaY | 2.86 | 1.33 | 0.03 | 1.95 | 1.13 | -1.05 | orf, hypothetical protein |
| cybB | -0.88 | -1.73 | 0.06 | -0.30 | -1.17 | 1.05 | cytochrome b(561) |
| cybC | 2.35 | -1.14 | 0.81 | 1.45 | -0.60 | 1.55 | cytochrome b(562) |
| cycA | 0.23 | 0.78 | 1.05 | -0.15 | 1.30 | 1.60 | transport of D-alanine, D-serine, and glycine |
| cydA | -1.02 | -0.58 | -0.84 | -0.60 | -0.47 | 0.00 | cytochrome d terminal oxidase, polypeptide subunit I |
| cydB | -1.03 | -12.21 | -0.50 | -2.40 | -2.17 | -1.45 | cytochrome d terminal oxidase polypeptide subunit II |
| cydC | -0.52 | -1.21 | 0.81 | -2.00 | -1.40 | 2.00 | ATP-binding component of cytochrome-related transport |
| cydD | -0.33 | -0.48 | 0.71 | -0.25 | 0.30 | 1.45 | ATP-binding component of cytochrome-related transport, Zn sensitive |
| cynR | 0.58 | -2.21 | -1.30 | 0.50 | -1.60 | -1.20 | cyn operon positive regulator |
| cynS | -0.20 | 0.79 | 1.49 | 0.85 | 1.37 | 1.40 | cyanate aminohydrolase, cyanase |
| cynT | 1.20 | 1.27 | 0.20 | 2.20 | 1.50 | 0.40 | carbonic anhydrase |
| cynX | -0.06 | 0.71 | 1.92 | 0.15 | 0.60 | 1.25 | cyanate transport |
| cyoA | -0.09 | 1.47 | 0.46 | -1.25 | 1.43 | 0.00 | cytochrome o ubiquinol oxidase subunit II |
| cyoB | -0.65 | -0.82 | -1.30 | -1.80 | -1.13 | -1.55 | cytochrome o ubiquinol oxidase subunit I |
| cyoC | -3.09 | 1.01 | -0.44 | -2.10 | 0.37 | 0.10 | cytochrome o ubiquinol oxidase subunit III |
| cyoD | -2.70 | -0.25 | 1.13 | -3.30 | -1.20 | -0.05 | cytochrome o ubiquinol oxidase subunit IV |
| cyoE | -2.66 | 2.56 | -1.46 | -1.80 | 2.23 | -1.40 | protoheme IX farnesyltransferase (haeme O biosynthesis) |
| cysA | -0.74 | -1.81 | -0.16 | -22.25 | -2.77 | 0.00 | ATP-binding component of sulfate permease A protein; chromate resistance |
| cysB | 0.29 | -0.49 | 1.49 | 0.25 | 0.33 | 1.30 | positive transcriptional regulator for cysteine regulon |
| cysC | -0.65 | 0.10 | -0.29 | -4.75 | -0.07 | 0.35 | adenosine 5 -phosphosulfate kinase |
| cysD | -0.99 | 0.97 | -0.82 | -5.60 | 0.17 | -1.10 | ATP:sulfurylase (ATP:sulfate adenylyltransferase), subunit 2 |
| cysE | 0.50 | 1.01 | -0.52 | 0.50 | 0.30 | 0.15 | serine acetyltransferase |
| cysG | 0.68 | 0.71 | -1.58 | 1.75 | 1.23 | -1.20 | uroporphyrinogen III methylase; sirohaeme biosynthesis |
| cysH | -0.57 | -1.32 | -0.97 | -6.20 | -1.40 | -1.35 | 3 -phosphoadenosine 5 -phosphosulfate reductase |
| cysI | -0.39 | -2.19 | -0.46 | -4.25 | -1.70 | -1.10 | sulfite reductase, alpha subunit |
| cysJ | 0.13 | 1.48 | 0.28 | -1.20 | 0.50 | 0.15 | sulfite reductase (NADPH), flavoprotein beta subunit |
| cysK | -0.93 | 0.88 | 3.33 | -1.55 | 0.20 | 1.75 | cysteine synthase A, O-acetylserine sulfhydrolase A |
| cysM | -0.79 | -0.06 | -1.07 | -8.40 | 0.60 | -0.20 | cysteine synthase B, O-acetylserine sulfhydrolase B |
| cysN | -0.99 | -0.55 | 0.73 | -10.15 | -2.70 | -0.15 | ATP-sulfurylase (ATP:sulfate adenylyltransferase), subunit 1, probably a GTPase |
| cysP | 0.04 | 0.95 | 2.91 | -0.60 | 0.23 | 1.10 | thiosulfate binding protein |
| cysQ | -0.10 | -1.86 | -1.18 | 0.95 | -1.53 | -1.65 | affects pool of 3 -phosphoadenosine-5 -phosphosulfate in pathway of sulfite synthesis |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| cysS | 1.05 | -0.99 | 2.02 | 1.35 | -1.07 | 1.50 | cysteine tRNA synthetase |
| cysT | 0.15 | 0.25 | 0.67 | 0.00 | 1.50 | 2.55 | Cysteine tRNA |
| cysU | -0.99 | 0.14 | -1.19 | -5.30 | 0.33 | -1.15 | sulfate, thiosulfate transport system permease T protein |
| cysW | -0.24 | 3.11 | 0.87 | -4.50 | 1.07 | 0.20 | sulfate transport system permease W protein |
| cysZ | 0.26 | 4.40 | -0.79 | 1.15 | 1.30 | -0.05 | required for sulfate transport |
| cytR | -0.17 | -0.49 | -0.70 | -0.40 | 0.37 | -0.05 | regulator for deo operon, udp, cdd, tsx, nupC, and nupG |
| dacA | 0.80 | 9.67 | 1.13 | 0.25 | 2.17 | 0.20 | D-alanyl-D-alanine carboxypeptidase, fraction A; penicillin-binding protein 5 |
| dacB | 3.08 | 0.17 | 0.56 | 3.70 | 0.33 | 0.45 | D-alanyl-D-alanine carboxypeptidase, fraction B; penicillin-binding protein 4 |
| dacC | -0.40 | -1.12 | -0.50 | -1.30 | -0.30 | 0.25 | D-alanyl-D-alanine carboxypeptidase; penicillin-binding protein 6 |
| dacD | 0.08 | -0.10 | 0.89 | -0.35 | 0.47 | 0.25 | penicillin binding protein 6b |
| dadA | -0.25 | 1.52 | -6.22 | -0.65 | 1.33 | -1.10 | D-amino acid dehydrogenase subunit |
| dadX | -0.81 | -1.41 | -0.51 | -0.30 | -1.20 | 0.10 | alanine racemase 2, catabolic |
| dam | -0.43 | 1.12 | -0.46 | -0.50 | 0.37 | 0.15 | DNA adenine methylase |
| damX | -1.60 | 0.73 | -0.46 | -2.05 | 0.50 | -1.10 | putative membrane protein; interferes with cell division |
| dapA | 0.07 | 0.44 | 0.23 | -2.65 | 0.23 | 1.00 | dihydrodipicolinate synthase |
| dapB | 0.15 | -1.41 | -1.22 | 0.05 | -2.20 | -1.90 | dihydrodipicolinate reductase |
| dapD | 0.36 | -0.20 | -1.43 | 1.20 | 0.17 | -2.00 | 2,3,4,5-tetrahydropyridine-2-carboxylate N-succinyltransferase |
| dapE | 1.65 | -1.51 | 0.89 | 1.20 | -1.63 | 1.20 | N-succinyl-diaminopimelate deacylase |
| dapF | 1.40 | -1.30 | -1.01 | 1.35 | -0.43 | -1.15 | diaminopimelate epimerase |
| dbpA | -0.90 | -1.15 | -1.17 | -0.10 | -0.47 | -0.15 | ATP-dependent RNA helicase |
| dcd | 0.19 | -1.34 | 1.17 | -1.65 | -1.77 | 1.30 | 2 -deoxycytidine 5 -triphosphate deaminase |
| dcm | -0.27 | -0.20 | 1.06 | -0.55 | 0.37 | 1.15 | DNA cytosine methylase |
| dcp | -0.27 | 0.90 | 0.32 | -0.10 | 0.47 | 0.05 | dipeptidyl carboxypeptidase II |
| dctA | -0.86 | -4.08 | 0.00 | -3.30 | -2.00 | 0.20 | uptake of C4-dicarboxylic acids |
| dcuA | -2.03 | -2.98 | -0.60 | -2.30 | -1.43 | 0.10 | anaerobic dicarboxylate transport |
| dcuB | 0.52 | 0.98 | 0.64 | 0.05 | 1.50 | -0.30 | anaerobic dicarboxylate transport |
| dcuC | 0.05 | -1.98 | -1.34 | -0.05 | -1.30 | 0.10 | transport of dicarboxylates |
| ddg | -1.55 | -1.26 | 1.72 | -1.60 | 1.17 | 1.10 | putative heat shock protein |
| ddlA | 0.63 | 2.17 | 0.77 | 1.25 | 1.80 | 0.30 | D-alanine-D-alanine ligase A |
| ddlB | -0.13 | -1.26 | 0.96 | -1.90 | -2.03 | 1.50 | D-alanine-D-alanine ligase B, affects cell division |
| deaD | 1.19 | 2.29 | -1.49 | 2.65 | 3.50 | -1.55 | inducible ATP-independent RNA helicase |
| dedA | -0.18 | -1.27 | 0.15 | 0.10 | -1.33 | -0.25 | orf, hypothetical protein |
| dedD | -0.21 | -1.35 | -0.94 | -1.20 | -0.10 | -1.40 | putative lipoprotein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| def | 0.10 | 2.45 | 0.76 | -0.25 | 1.40 | 0.10 | peptide deformylase |
| degQ | 0.45 | 0.61 | -1.36 | 0.00 | 1.30 | -1.10 | serine endoprotease |
| degS | 1.40 | -0.18 | 0.81 | 1.85 | 0.37 | 0.10 | protease |
| deoA | -1.23 | -7.40 | 1.13 | -2.65 | -3.10 | 1.20 | thymidine phosphorylase |
| deoB | -1.27 | -0.53 | 1.31 | -1.05 | -1.57 | 1.25 | phosphopentomutase |
| deoC | -1.11 | -1.16 | 0.53 | -3.30 | -1.10 | 1.10 | 2-deoxyribose-5-phosphate aldolase |
| deoD | -2.43 | -0.01 | -0.97 | -2.80 | -0.27 | -0.15 | purine-nucleoside phosphorylase |
| deoR | 1.41 | -1.10 | -1.34 | 1.45 | -0.30 | -1.45 | transcriptional repressor for deo operon, tsx, nupG |
| dfp | 0.21 | 2.79 | 0.94 | -0.05 | 1.47 | 1.30 | flavoprotein affecting synthesis of DNA and pantothenate metabolism |
| dgkA | 0.27 | -1.44 | 0.65 | 0.35 | -0.47 | -0.25 | diacylglycerol kinase |
| dgoA | 1.79 | 0.91 | 1.82 | 1.45 | -1.20 | 1.40 | 2-oxo-3-deoxygalactonate 6-phosphate aldolase and galactonate dehydratase |
| dgoK | 0.60 | -1.40 | 0.28 | 1.85 | -1.13 | -0.10 | 2-oxo-3-deoxygalactonate kinase |
| dgoT | 0.36 | -1.45 | 0.48 | 1.45 | -1.53 | -0.10 | D-galactonate transport |
| dgt | -0.74 | -1.34 | 1.03 | -0.25 | -0.57 | 1.05 | deoxyguanosine triphosphate triphosphohydrolase |
| dicA | -3.49 | -1.34 | 0.95 | -1.75 | -1.93 | 1.05 | regulator of dicB |
| dicB | -1.05 | -1.42 | 0.15 | -0.05 | -1.23 | 0.15 | inhibition of cell division |
| dicC | 0.67 | 1.54 | -0.15 | 2.95 | 1.33 | 0.20 | regulator of dicB |
| dicF | -1.08 | -2.05 | 1.05 | -0.10 | -1.23 | 1.40 | DicF antisense RNA; inhibits ftsZ |
| dinD | 4.01 | 0.85 | 1.04 | 2.75 | 0.37 | 1.20 | DNA-damage-inducible protein |
| dinF | 0.63 | -0.97 | 0.06 | 4.60 | -0.27 | 0.20 | DNA-damage-inducible protein F |
| dinG | 2.61 | -1.11 | 1.37 | 3.05 | -0.40 | 1.35 | probably ATP-dependent helicase |
| dinI | 1.36 | 9.20 | 1.23 | 17.65 | 2.83 | 1.70 | damage-inducible protein I |
| dinJ | -1.64 | -1.39 | 0.24 | -2.30 | -1.57 | -1.15 | damage-inducible protein J |
| dinP | 1.89 | -0.96 | -1.39 | -0.05 | -0.07 | -1.35 | damage-inducible protein P; putative tRNA synthetase |
| div | -0.15 | -1.33 | 0.59 | -1.35 | -0.40 | 0.35 | cell division protein |
| dksA | 0.72 | -2.29 | 0.70 | 1.20 | -1.77 | 0.15 | dnaK suppressor protein |
| dld | -1.58 | -1.67 | 0.77 | -2.15 | -2.13 | 0.25 | D-lactate dehydrogenase, FAD protein, NADH independent |
| dmsA | -1.37 | -2.18 | 1.08 | -0.60 | -1.63 | 1.40 | anaerobic dimethyl sulfoxide reductase subunit A |
| dmsB | -0.62 | -0.58 | -1.12 | -0.65 | 0.13 | -1.20 | anaerobic dimethyl sulfoxide reductase subunit B |
| dmsC | 0.27 | -1.85 | 1.37 | 0.05 | -1.77 | 1.35 | anaerobic dimethyl sulfoxide reductase subunit C |
| dnaA | 0.23 | 1.47 | 0.86 | -0.05 | 1.93 | 1.10 | DNA biosynthesis; initiation of chromosome replication; can be transcription regulator |
| dnaB | 0.27 | 0.74 | 2.08 | -0.10 | 0.50 | 1.25 | replicative DNA helicase; part of primosome |
| dnaC | -0.03 | 0.71 | -1.24 | -0.60 | 1.07 | -1.15 | chromosome replication; initiation and chain elongation |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| dnaE | 0.61 | -0.69 | -0.95 | 0.55 | -1.17 | -1.15 | DNA polymerase III, alpha subunit |
| dnaG | 0.59 | 5.72 | -1.64 | 0.10 | 1.93 | -1.15 | DNA biosynthesis; DNA primase |
| dnaJ | 1.87 | -1.25 | -0.36 | 1.55 | -1.17 | -1.50 | chaperone with DnaK; heat shock protein |
| dnaK | -0.06 | -2.48 | 0.40 | 0.00 | -2.27 | 3.85 | chaperone Hsp70; DNA biosynthesis; autoregulated heat shock proteins |
| dnaN | 1.04 | -0.92 | 1.35 | 1.45 | -0.17 | 1.40 | DNA polymerase III, beta-subunit |
| dnaQ | -1.39 | 1.63 | 0.87 | -0.95 | 1.50 | 1.30 | DNA polymerase III, epsilon subunit |
| dnaT | -0.63 | -1.10 | -0.16 | -1.15 | -0.13 | -0.20 | DNA biosynthesis; primosomal protein i |
| dnaX | 0.25 | 0.91 | -0.49 | 0.40 | 2.13 | -1.40 | DNA polymerase III, tau and gamma subunits; DNA elongation factor III |
| dniR | -0.60 | -3.22 | -0.20 | -0.65 | -1.37 | 0.15 | transcriptional regulator for nitrite reductase (cytochrome c552) |
| dppA | 1.98 | -1.07 | 0.70 | 3.45 | -0.27 | 1.15 | dipeptide transport protein |
| dppB | -0.48 | 0.10 | 0.76 | 1.25 | 0.47 | 1.70 | dipeptide transport system permease protein 1 |
| dppC | -0.07 | -1.82 | -0.94 | 1.50 | -1.40 | -1.35 | dipeptide transport system permease protein 2 |
| dppD | 2.06 | -1.88 | -0.38 | 2.55 | -1.27 | 0.15 | putative ATP-binding component of dipeptide transport system |
| dppF | -0.51 | -1.59 | 0.25 | 0.25 | -1.17 | -0.10 | putative ATP-binding component of dipeptide transport system |
| dps | -1.46 | -4.80 | -1.23 | -13.55 | -3.47 | -1.80 | global regulator, starvation conditions |
| dsbA | 0.25 | 4.02 | 0.79 | 0.55 | 2.03 | 1.65 | protein disulfide isomerase I, essential for cytochrome c synthesis |
| dsbB | 0.12 | 0.59 | 0.81 | -0.05 | 0.47 | 1.20 | reoxidizes DsbA protein following formation of disulfide bond in P-ring of flagella. |
| dsbC | 0.60 | 0.44 | 0.85 | 1.20 | 0.27 | 1.50 | protein disulfide isomerase II |
| dsbD | -0.44 | -1.77 | 0.76 | -0.10 | 1.03 | 0.05 | thiol:disulfide interchange protein; copper tolerance |
| dsbE | -1.09 | -1.49 | 0.97 | -1.40 | -1.27 | 1.10 | disulfide oxidoreductase (in biogenesis of cytochrome c? |
| dsbG | 0.38 | -1.30 | -0.51 | 1.25 | -0.40 | 0.05 | thiol:disulfide interchange protein |
| dsdA | -0.88 | 0.76 | -1.31 | 0.40 | 1.40 | -1.00 | D-serine dehydratase (deaminase) |
| dsdC | 1.26 | 1.54 | 0.75 | 0.30 | 1.37 | 1.55 | D-serine dehydratase (deaminase) transcriptional activator |
| dsdX | -0.08 | -1.72 | 0.78 | 0.50 | -1.43 | 1.65 | transport system permease (serine?) |
| dsrA | -4.56 | -0.65 | 1.10 | -1.90 | 0.33 | 0.20 | Regulatory RNA; positive regulation of promoters sensitive to HNS negative regulation |
| dsrB | 1.18 | -1.07 | 0.43 | 1.80 | 0.37 | 0.00 | orf, hypothetical protein |
| dut | 0.74 | -0.72 | 1.09 | 1.40 | -1.20 | 0.25 | deoxyuridinetriphosphatase |
| dxs | 1.02 | -1.24 | 0.88 | 0.00 | -0.37 | 1.30 | 1-deoxyxylulose-5-phosphate synthase; flavoprotein |
| eaeH | 0.16 | 1.65 | 0.25 | 1.95 | 1.27 | 0.10 | attaching and effacing protein, pathogenesis factor |
| ebgA | -0.51 | -0.17 | -2.74 | 0.00 | 1.13 | -1.40 | evolved beta-D-galactosidase, alpha subunit; cryptic gene |
| ebgC | 1.60 | -1.12 | -0.68 | 0.30 | -0.23 | -0.15 | evolved beta-D-galactosidase, beta subunit; cryptic gene |
| ebgR | 0.27 | -2.02 | 0.78 | -0.25 | -1.40 | 0.00 | regulator of ebg operon |
| eco | -0.31 | -2.70 | 1.09 | -1.55 | -1.80 | 1.40 | ecotin, a serine protease inhibitor |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ecpD | -0.37 | 0.17 | -1.35 | -1.65 | 1.20 | -1.30 | probable pilin chaperone similar to PapD |
| eda | 0.85 | 1.05 | 0.29 | 0.10 | -1.30 | -0.05 | 2-keto-3-deoxygluconate 6-phosphate aldolase and 2-keto-4-hydroxyglutarate aldolase |
| edd | 1.79 | -0.36 | 1.07 | 1.35 | -0.40 | 0.00 | 6-phosphogluconate dehydratase |
| efp | 0.42 | -0.17 | -0.55 | 1.70 | -0.20 | 0.00 | elongation factor P (EF-P) |
| elaA | -0.64 | -1.13 | -0.03 | 0.00 | -0.20 | -1.20 | orf, hypothetical protein |
| elaB | -1.40 | -2.19 | -1.52 | -5.35 | -2.37 | -1.85 | orf, hypothetical protein |
| elaC | -1.21 | -1.44 | -1.37 | -0.70 | -1.57 | -1.40 | orf, hypothetical protein |
| elaD | -0.22 | 1.49 | 0.06 | 0.35 | 1.27 | 0.20 | putative sulfatase |
| emrA | 0.00 | -1.30 | -1.27 | 0.60 | -0.63 | -1.25 | multidrug resistance secretion protein |
| emrB | 0.22 | -1.28 | 0.79 | 1.50 | -0.37 | 1.35 | multidrug resistance; probably membrane translocase |
| emrD | 0.87 | -1.36 | -1.58 | 1.35 | -0.37 | -1.30 | 2-module integral membrane pump; multidrug resistance |
| emrE | -1.52 | -1.78 | -1.34 | -1.55 | -0.47 | -1.40 | methylviologen resistance |
| emrK | 2.05 | -1.09 | -1.01 | 1.45 | 0.27 | -1.60 | multidrug resistance protein K |
| emrR | 0.17 | 2.00 | 1.10 | 0.05 | 1.50 | 1.65 | regulator of plasmid mcrB operon (microcin B17 synthesis) |
| emrY | 1.27 | 0.58 | -0.19 | 0.10 | 1.33 | 0.10 | multidrug resistance protein Y |
| endA | -1.07 | -0.14 | -1.25 | -0.20 | -1.13 | -1.35 | DNA-specific endonuclease I |
| eno | -0.66 | 0.23 | -0.97 | -1.20 | -1.30 | -1.35 | enolase |
| entA | 0.00 | 0.00 | 0.27 | -2.50 | 1.17 | 0.30 | 2,3-dihydro-2,3-dihydroxybenzoate dehydrogenase, enterochelin biosynthesis |
| entB | -0.98 | -1.31 | 0.82 | -2.20 | -0.67 | 1.80 | 2,3-dihydro-2,3-dihydroxybenzoate synthetase, isochroismatase |
| entC | 0.31 | -1.47 | -1.45 | -1.35 | -1.63 | -1.55 | isochorismate hydroxymutase 2, enterochelin biosynthesis |
| entD | -1.11 | 1.69 | -0.78 | -0.30 | 1.77 | 0.00 | enterochelin synthetase, component D |
| entE | 0.31 | 0.50 | -0.86 | -0.95 | -1.10 | -1.50 | 2,3-dihydroxybenzoate-AMP ligase |
| entF | -0.03 | -1.04 | -1.43 | -0.35 | -0.20 | -1.30 | ATP-dependent serine activating enzyme (may be part of enterobactin synthase as component F) |
| envR | -0.24 | -1.48 | 0.54 | 0.25 | -1.20 | 0.30 | putative transcriptional regulator |
| envY | -0.18 | -1.56 | -1.21 | 0.00 | -1.30 | -0.10 | envelope protein; thermoregulation of porin biosynthesis |
| envZ | 1.39 | -0.18 | -1.32 | 1.60 | 0.33 | -1.60 | protein histidine kinase |
| epd | -1.16 | -2.29 | -1.43 | -0.60 | -0.20 | -1.50 | D-erythrose 4-phosphate dehydrogenase |
| era | 1.36 | 2.66 | 0.69 | 1.55 | 1.20 | -0.35 | GTP-binding protein |
| erfK | -1.42 | -1.38 | 1.38 | -2.60 | -1.67 | 1.40 | orf, hypothetical protein |
| eutB | 1.65 | -1.54 | 0.33 | 1.30 | -0.43 | -0.05 | ethanolamine ammonia-lyase, heavy chain |
| eutC | -0.57 | 2.38 | 0.36 | 0.90 | 1.43 | -0.15 | ethanolamine ammonia-lyase, light chain |
| eutE | 0.19 | 0.18 | 0.76 | -1.00 | 0.53 | 1.20 | ethanolamine utilization; similar to acetaldehyde dehydrogenase |
| eutG | 0.75 | -1.48 | 1.39 | 2.20 | -0.47 | 1.45 | ethanolamine utilization; homolog of Salmonella enzyme |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| eutH | -0.71 | 2.09 | -1.74 | -0.05 | 1.87 | -1.30 | ethanolamine utilization; homolog of Salmonella putative transport protein |
| eutI | -0.87 | -1.33 | 0.00 | -1.95 | -0.63 | -1.05 | ethanolamine utilization; homolog of Salmonella acetyl |
| eutJ | 0.53 | 0.14 | -1.31 | 1.40 | -1.43 | -0.30 | ethanolamine utilization; homolog of Salmonella gene |
| evgA | -0.03 | 0.01 | -1.38 | -0.10 | 0.43 | -1.25 | putative positive transcription regulator (sensor EvgS) |
| evgS | 0.66 | -0.74 | -0.56 | 1.60 | 0.43 | 0.10 | putative sensor for regulator EvgA |
| exbB | -0.10 | 3.26 | -1.09 | -1.35 | 1.70 | -0.05 | uptake of enterochelin; tonB-dependent uptake of B colicins |
| exbD | 0.35 | -0.18 | 0.31 | 1.75 | 0.73 | 0.40 | uptake of enterochelin; tonB-dependent uptake of B colicins |
| exo | 0.51 | -1.14 | -1.56 | 1.15 | -0.30 | -1.70 | 5 -3 exonuclease |
| exuR | -0.70 | -1.36 | 1.35 | -1.75 | -0.53 | 1.20 | negative regulator of exu regulon, exuT, uxaAC, and uxuB |
| exuT | 0.88 | -1.46 | -1.20 | 0.15 | -1.33 | -1.15 | transport of hexuronates |
| fabA | 0.82 | 0.00 | -0.99 | 1.30 | -0.53 | -1.50 | beta-hydroxydecanoyl thioester dehydrase, trans-2-decenoyl-ACP isomerase |
| fabB | 0.13 | -1.30 | 1.39 | -0.15 | -2.57 | 1.45 | 3-oxoacyl-[acyl-carrier-protein] synthase I |
| fabD | 0.04 | 1.21 | 1.35 | -0.25 | 2.27 | 0.25 | malonyl-CoA-[acyl-carrier-protein] transacylase |
| fabF | 1.91 | 3.84 | 0.28 | 3.90 | 1.90 | 0.25 | 3-oxoacyl-[acyl-carrier-protein] synthase II |
| fabG | 0.27 | 0.52 | -0.02 | 0.50 | 0.17 | -0.10 | 3-oxoacyl-[acyl-carrier-protein] reductase |
| fabH | 0.12 | 1.08 | -0.72 | -0.30 | 1.47 | 0.00 | 3-oxoacyl-[acyl-carrier-protein] synthase III; acetylCoA ACP transacylase |
| fabI | -0.35 | 1.31 | 0.49 | -2.70 | 2.13 | 0.30 | enoyl-[acyl-carrier-protein] reductase (NADH) |
| fabZ | 1.01 | -1.45 | 1.13 | 0.55 | -1.80 | 1.30 | (3R)-hydroxymyristol acyl carrier protein dehydratase |
| fadA | -0.62 | 1.16 | -0.25 | -0.75 | 1.33 | -0.05 | thiolase I; 3-ketoacyl-CoA thiolase; acetyl-CoA transferase |
| fadB | 0.26 | -1.33 | 0.77 | -0.25 | -0.10 | 0.05 | 4-enzyme protein: 3-hydroxyacyl-CoA dehydrogenase; 3-hydroxybutyryl-CoA epimerase |
| fadD | -0.04 | 4.33 | 0.65 | 0.00 | 1.40 | -0.30 | acyl-CoA synthetase, long-chain-fatty-acid--CoA ligase |
| fadL | -0.94 | -1.11 | 0.71 | -1.80 | -0.47 | -0.05 | transport of long-chain fatty acids; sensitivity to phage T2 |
| fadR | -1.38 | 0.78 | 2.29 | -1.80 | 0.10 | 1.20 | negative regulator for fad regulon, and positive activator of fabA |
| farR | 0.58 | 1.24 | -0.48 | 1.40 | 1.20 | -1.30 | transcriptional regulator of succinylCoA synthetase operon |
| fba | -0.25 | -1.88 | 0.43 | -1.10 | -2.07 | -0.15 | fructose-bisphosphate aldolase, class II |
| fbp | 0.19 | -1.75 | -1.37 | -0.75 | -2.03 | -1.45 | fructose-bisphosphatase |
| fdhD | 2.02 | -1.14 | 0.34 | 1.85 | 0.03 | -0.40 | affects formate dehydrogenase-N |
| fdhE | 0.64 | -1.31 | 0.67 | -0.20 | 0.00 | 1.10 | affects formate dehydrogenase-N |
| fdhF | -0.94 | -0.04 | -0.06 | -0.45 | 0.43 | -0.30 | selenopolypeptide subunit of formate dehydrogenase H |
| fdnG | 0.03 | -1.21 | 1.06 | -0.25 | -1.47 | 0.00 | formate dehydrogenase-N, nitrate-inducible, alpha subunit |
| fdnH | -0.04 | 0.77 | -1.08 | 0.05 | 1.47 | -1.15 | formate dehydrogenase-N, nitrate-inducible, iron-sulfur beta subunit |
| fdnI | 0.64 | -0.53 | -1.11 | 1.80 | -0.43 | -1.35 | formate dehydrogenase-N, nitrate-inducible, cytochrome B556(Fdn) gamma subunit |
| fdoG | 0.27 | 1.04 | 0.24 | 1.20 | 0.23 | -1.05 | formate dehydrogenase-O, major subunit |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| fdoH | 0.39 | 1.15 | 1.04 | 1.35 | 0.40 | 1.35 | formate dehydrogenase-O, iron-sulfur subunit |
| fdoI | -0.66 | -3.71 | -0.25 | -0.15 | -1.23 | 0.05 | formate dehydrogenase, cytochrome B556 (FDO) subunit |
| fdrA | 0.22 | 1.49 | -1.37 | -0.20 | -0.20 | -1.30 | involved in protein transport; multicopy suppressor of dominant negative ftsH mutants |
| fdx | -0.26 | -0.75 | 1.48 | -0.90 | -0.10 | 1.35 | [2FE-2S] ferredoxin, electron carrer protein |
| feaB | -1.09 | -1.52 | -1.33 | 1.50 | -0.67 | 0.10 | phenylacetaldehyde dehydrogenase |
| feaR | 1.29 | -1.35 | -0.81 | 2.55 | -1.37 | 0.00 | regulatory protein for 2-phenylethylamine catabolism |
| fecA | 1.17 | 0.42 | 0.86 | 1.85 | 1.57 | 1.05 | outer membrane receptor; citrate-dependent iron transport, outer membrane receptor |
| fecB | 1.06 | 2.32 | 0.75 | 1.65 | 1.27 | 1.25 | citrate-dependent iron transport, periplasmic protein |
| fecC | 0.31 | -1.68 | 0.29 | 0.30 | -1.20 | 0.30 | citrate-dependent iron(III) transport protein, cytosolic |
| fecD | -0.14 | 0.83 | 0.69 | 1.20 | 1.27 | 1.10 | citrate-dependent iron transport, membrane-bound protein |
| fecE | 0.30 | -0.07 | 0.13 | 1.45 | 0.30 | 0.00 | ATP-binding component of citrate-dependent iron(III) transport protein |
| fecI | 0.10 | -1.01 | 0.78 | 0.10 | 0.20 | 1.55 | probable RNA polymerase sigma factor |
| fecR | -0.88 | -1.25 | -1.16 | 0.45 | -0.50 | -0.25 | regulator for fec operon, periplasmic |
| feoA | -2.00 | -0.26 | 0.61 | -2.35 | 0.43 | 1.20 | ferrous iron transport protein A |
| feoB | -1.54 | 0.99 | -2.34 | -2.90 | 1.10 | -1.10 | ferrous iron transport protein B |
| fepA | -6.71 | -1.27 | -1.26 | -2.70 | -1.47 | -1.60 | outer membrane receptor for ferric enterobactin (enterochelin) and colicins B and D |
| fepB | 2.92 | -1.55 | -1.03 | 1.60 | -1.97 | -0.20 | ferric enterobactin (enterochelin) binding protein; periplasmic component |
| fepC | -1.45 | 0.79 | 0.71 | -1.25 | 1.87 | -0.05 | ATP-binding component of ferric enterobactin transport |
| fepD | -0.38 | -1.47 | -1.14 | -0.30 | -0.40 | -1.05 | ferric enterobactin (enterochelin) transport |
| fepE | -0.16 | -1.01 | -0.73 | 0.50 | -0.13 | -1.55 | ferric enterobactin (enterochelin) transport |
| fepG | -0.53 | -1.37 | -1.32 | -0.25 | -1.37 | -1.60 | ferric enterobactin transport protein |
| fes | -1.47 | 0.36 | -0.26 | -1.80 | 0.80 | 0.05 | enterochelin esterase |
| ffh | 0.78 | -0.58 | 0.90 | 0.25 | -0.20 | 0.20 | GTP-binding export factor binds to signal sequence, GTP and RNA |
| ffs | 0.53 | -0.31 | 0.45 | 0.55 | -0.05 | 42.80 | 4.5S rRNA; mammalian counterpart, SRP, includes 4.5S RNA; cotranslational integration of proteins |
| fhiA | 0.00 | 0.51 | -1.35 | -2.35 | 0.40 | -1.85 | flagellar biosynthesis |
| fhlA | 0.28 | 0.98 | 0.14 | 1.45 | 1.33 | 0.05 | formate hydrogen-lyase transcriptional activator for fdhF, hyc and hyp operons |
| fhuA | -0.71 | -1.82 | -1.47 | -1.50 | -0.53 | -1.55 | outer membrane protein receptor for ferrichrome, colicin M, and phages T1, T5, and phi80 |
| fhuB | -1.13 | 1.70 | -0.35 | -1.25 | 0.23 | 0.00 | hydroxamate-dependent iron uptake, cytoplasmic membrane component |
| fhuC | 0.31 | -0.92 | -0.27 | -0.10 | 1.10 | 0.25 | ATP-binding component of hydroxymate-dependent iron transport |
| fhuD | -0.16 | -0.08 | -1.34 | -0.10 | -0.07 | -1.20 | hydroxamate-dependent iron uptake, cytoplasmic membrane component |
| fhuE | 0.46 | -1.35 | 0.72 | -0.35 | -1.53 | -0.10 | outer membrane receptor for ferric iron uptake |
| fhuF | 0.38 | 1.21 | 0.86 | 1.80 | 1.07 | 1.05 | orf, hypothetical protein |
| fic | 0.50 | -1.24 | 0.42 | 0.10 | -0.37 | 0.20 | induced in stationary phase, recognized by rpoS, affects cell division |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| fimA | -0.27 | -3.60 | 2.11 | -0.25 | -1.90 | 1.25 | major type 1 subunit fimbrin (pilin) |
| fimB | 0.34 | -1.37 | 1.49 | 1.15 | -0.47 | 1.35 | recombinase involved in phase variation; regulator for fimA |
| fimC | 0.18 | 0.46 | 0.82 | 0.00 | -0.43 | 1.60 | periplasmic chaperone, required for type 1 fimbriae |
| fimD | -5.65 | 8.74 | -0.26 | -2.20 | 1.53 | -0.20 | outer membrane protein; export and assembly of type 1 fimbriae, interrupted |
| fimE | 0.40 | -0.75 | 0.27 | 0.25 | 0.23 | 0.05 | recombinase involved in phase variation; regulator for fimA |
| fimF | -0.82 | 0.37 | 0.38 | -1.55 | 0.53 | 0.35 | fimbrial morphology |
| fimG | -0.71 | -1.46 | -1.18 | -2.00 | -1.30 | -1.25 | fimbrial morphology |
| fimH | -7.07 | -0.07 | -0.11 | -2.05 | 0.20 | 0.05 | minor fimbrial subunit, D-mannose specific adhesin |
| fimI | 0.04 | -1.97 | 1.11 | -0.70 | -1.57 | 1.80 | fimbrial protein |
| fimZ | -0.25 | -0.94 | 0.72 | -1.10 | 0.83 | 1.20 | fimbrial Z protein; probable signal transducer |
| fis | -0.09 | 1.69 | 0.73 | 1.15 | 2.20 | 0.00 | site-specific DNA inversion stimulation factor; DNA-binding protein |
| fixA | -0.54 | -1.33 | 0.77 | 0.30 | 0.27 | 1.40 | probable flavoprotein subunit, carnitine metabolism |
| fixB | -0.17 | -0.01 | 1.12 | -1.40 | 0.50 | 0.00 | probable flavoprotein subunit, carnitine metabolism |
| fixC | 1.12 | -0.95 | -1.30 | 1.40 | 0.07 | -1.15 | flavoprotein; electron transport |
| fixX | 1.75 | -2.03 | -0.12 | 2.20 | 1.03 | 0.50 | putative ferredoxin |
| fklB | 0.00 | -0.13 | -0.62 | -0.20 | -0.20 | 0.05 | FKBP-type 22KD peptidyl-prolyl cis-trans isomerase (rotamase) |
| fkpA | 0.37 | 0.55 | 1.44 | 1.40 | -5.10 | 1.30 | FKBP-type peptidyl-prolyl cis-trans isomerase (rotamase) |
| fldA | 0.61 | 1.45 | -0.74 | 1.40 | 1.83 | -0.10 | flavodoxin 1 |
| fldB | -1.03 | 0.69 | 0.21 | -1.55 | 0.63 | 0.05 | flavodoxin 2 |
| flgA | -5.03 | -1.11 | 0.58 | -2.85 | -1.43 | 1.05 | flagellar biosynthesis; assembly of basal-body periplasmic P ring |
| flgB | -1.27 | -3.64 | -1.29 | -1.75 | -3.80 | -0.25 | flagellar biosynthesis, cell-proximal portion of basal-body rod |
| flgC | -0.76 | -1.27 | -0.29 | -2.45 | -1.97 | 0.10 | flagellar biosynthesis, cell-proximal portion of basal-body rod |
| flgD | -5.90 | -4.27 | 0.51 | -2.95 | -4.07 | 1.10 | flagellar biosynthesis, initiation of hook assembly |
| flgE | -1.09 | -5.37 | -0.71 | -2.85 | -2.67 | 0.05 | flagellar biosynthesis, hook protein |
| flgF | -1.34 | -5.59 | -1.11 | -3.65 | -4.10 | -0.05 | flagellar biosynthesis, cell-proximal portion of basal-body rod |
| flgG | -4.23 | -1.18 | -1.32 | -3.25 | -1.70 | -0.30 | flagellar biosynthesis, cell-distal portion of basal-body rod |
| flgH | -2.14 | -1.09 | -1.31 | -1.75 | -1.50 | -0.05 | flagellar biosynthesis, basal-body outer-membrane L (lipopolysaccharide layer) ring protein |
| flgI | -112.98 | -1.33 | 0.77 | -3.25 | 0.03 | 1.40 | homolog of Salmonella P-ring of flagella basal body |
| flgJ | -0.74 | -1.60 | 0.27 | -0.30 | -1.47 | 0.25 | flagellar biosynthesis |
| flgK | -2.27 | -0.20 | 0.72 | -2.20 | 0.07 | 1.40 | flagellar biosynthesis, hook-filament junction protein 1 |
| flgL | -2.76 | -3.34 | -1.33 | -5.45 | -3.70 | -1.35 | flagellar biosynthesis; hook-filament junction protein |
| flgM | -22.09 | -1.03 | 0.80 | -2.95 | -0.37 | 1.75 | anti-FliA (anti-sigma) factor; also known as RflB protein |
| flgN | -4.68 | -5.20 | -1.30 | -3.85 | -2.70 | -0.20 | protein of flagellar biosynthesis |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| flhA | -1.49 | -1.47 | -1.38 | -1.85 | -1.80 | -1.40 | flagellar biosynthesis; possible export of flagellar proteins |
| flhB | -35.99 | -0.58 | -0.85 | -2.20 | 0.30 | 0.00 | putative part of export apparatus for flagellar proteins |
| flhC | -0.16 | 1.80 | 0.51 | -1.15 | 1.73 | 0.25 | regulator of flagellar biosynthesis acting on class 2 operons; transcription initiation factor |
| flhD | 0.44 | -4.49 | -1.36 | 0.80 | -1.33 | -0.15 | regulator of flagellar biosynthesis, acting on class 2 operons; transcriptional initiation factor |
| flhE | -1.65 | -0.38 | 0.83 | -1.65 | 0.23 | 1.70 | flagellar protein |
| fliA | -2.80 | -15.73 | -3.33 | -2.20 | -2.83 | -1.45 | flagellar biosynthesis; alternative sigma factor 28; regulation of flagellar operons |
| fliC | -1.16 | -3.59 | -1.09 | -9.15 | -7.10 | -0.35 | flagellar biosynthesis; flagellin, filament structural protein |
| fliD | -4.29 | -0.84 | 0.77 | -1.90 | 0.13 | 1.20 | flagellar biosynthesis; filament capping protein; enables filament assembly |
| fliE | -0.03 | -1.76 | -1.26 | 0.25 | -1.30 | -1.50 | flagellar biosynthesis; basal-body component, possibly at (MS-ring)-rod junction |
| fliF | -0.35 | 1.03 | -0.95 | -1.50 | 0.20 | -1.20 | flagellar biosynthesis; basal-body MS(membrane and supramembrane)-ring and collar protein |
| fliG | -1.36 | -0.75 | 0.83 | -1.95 | -1.00 | 0.25 | flagellar biosynthesis, component of motor switching and energizing, enabling rotation |
| fliH | -0.06 | -4.76 | 0.47 | -1.25 | -1.57 | -0.05 | flagellar biosynthesis; export of flagellar proteins? |
| fliI | -0.70 | -1.48 | 0.76 | -1.55 | -1.50 | 1.15 | flagellum-specific ATP synthase |
| fliJ | -3.67 | -1.19 | -1.34 | -2.15 | -0.53 | -0.05 | flagellar fliJ protein |
| fliK | -1.95 | -4.67 | -1.33 | -1.60 | -1.87 | -0.10 | flagellar hook-length control protein |
| fliL | -1.61 | -9.30 | -0.31 | -2.45 | -4.00 | -0.10 | flagellar biosynthesis |
| fliM | -1.69 | -1.53 | -0.27 | -1.75 | -2.47 | 0.20 | flagellar biosynthesis, component of motor switch and energizing, enabling rotation |
| fliN | -1.28 | -2.34 | 1.28 | -3.05 | -2.83 | 1.40 | flagellar biosynthesis, component of motor switch and energizing, enabling rotation |
| fliO | -0.12 | -1.45 | 0.24 | 0.00 | -2.50 | -0.10 | flagellar biosynthesis |
| fliP | -0.09 | -1.33 | 0.76 | -1.35 | -0.30 | 1.50 | flagellar biosynthesis |
| fliQ | 0.57 | -0.61 | 0.72 | 1.20 | 0.27 | 1.10 | flagellar biosynthesis |
| fliR | 0.87 | -1.34 | 0.11 | 1.15 | -0.60 | -0.05 | flagellar biosynthesis |
| fliS | -1.49 | -29.21 | 1.11 | -3.25 | -2.10 | 1.05 | flagellar biosynthesis; repressor of class 3a and 3b operons (RflA activity) |
| fliT | -3.71 | -6.98 | 0.90 | -2.60 | -1.93 | 1.30 | flagellar biosynthesis; repressor of class 3a and 3b operons (RflA activity) |
| fliY | -0.72 | -0.18 | 1.19 | -2.00 | -1.70 | 1.25 | putative periplasmic binding transport protein |
| fliZ | -1.91 | -0.82 | 0.54 | -1.85 | 0.17 | 0.35 | orf, hypothetical protein |
| flu | -1.16 | -0.88 | -0.26 | -0.50 | 0.17 | 0.05 | outer membrane fluffing protein, similar to adhesin |
| flxA | 0.66 | -0.36 | 0.97 | -1.00 | 0.13 | 1.25 | orf, hypothetical protein |
| fmt | 0.08 | -0.93 | 0.03 | -0.20 | -0.23 | 0.15 | 10-formyltetrahydrofolate:L-methionyl-tRNA(fMet) N-formyltransferase |
| fnr | 0.14 | 3.36 | -1.32 | 0.00 | 1.53 | -1.35 | transcriptional regulation of aerobic, anaerobic respiration, osmotic balance |
| focA | -0.29 | -0.73 | -0.81 | -0.60 | -2.07 | -0.25 | probable formate transporter (formate channel 1) |
| focB | -0.24 | 0.30 | 0.41 | 0.25 | 1.70 | -0.10 | probable formate transporter (formate channel 2) |
| folA | 0.19 | 0.56 | 0.12 | 0.00 | 0.37 | -0.35 | dihydrofolate reductase type I; trimethoprim resistance |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| folC | -1.42 | 3.61 | -1.67 | -2.45 | 1.13 | -1.55 | dihydrofolate:folylpolyglutamate synthetase; dihydrofolate synthetase |
| folD | -0.19 | 2.47 | 1.00 | -1.40 | 1.63 | 1.30 | 5,10-methylene-tetrahydrofolate dehydrogenase; 5,10-methylene-tetrahydrofolate cyclohydrolase |
| folE | -0.10 | -0.76 | -0.36 | 0.00 | -0.27 | 0.20 | GTP cyclohydrolase I |
| folK | 0.41 | -1.23 | -1.22 | 1.20 | -0.23 | -1.30 | 7,8-dihydro-6-hydroxymethylpterin- pyrophosphokinase |
| folP | -0.51 | -1.00 | -0.33 | -0.20 | -1.13 | 0.05 | 7,8-dihydropteroate synthase |
| folX | 1.06 | -1.10 | -1.19 | 1.35 | -0.27 | -0.40 | D-erythro-7,8-dihydroneopterin tri P epimerase |
| FPLMCG | 1.08 | 0.67 | -1.34 | 0.30 | -0.03 | 0.10 | |
| FPLMCG | 0.83 | -1.20 | 0.67 | 0.20 | 0.00 | 1.00 | |
| FPLMCG | 0.76 | 0.00 | 0.76 | 1.40 | -1.30 | 1.30 | |
| FPLMCG | 0.92 | 0.00 | 0.89 | -1.65 | 0.33 | 1.30 | |
| FPLMCG | -0.07 | -1.34 | 0.92 | -0.45 | -1.43 | 1.05 | |
| FPLMCG | 1.67 | -1.29 | 1.29 | 1.20 | -0.60 | -0.15 | |
| FPLMCG | -0.45 | -0.79 | 1.49 | 1.80 | -0.37 | 1.10 | |
| FPLTRAII | 1.04 | -2.48 | -1.23 | 0.30 | -1.27 | -0.10 | |
| FPLTRAII | -0.48 | -1.29 | 0.77 | 2.25 | -0.50 | 0.00 | |
| FPLTRAII | 0.00 | -1.34 | 0.98 | -0.90 | -2.00 | 1.30 | |
| fpr | 0.33 | 0.83 | -1.22 | 0.35 | 0.53 | -1.40 | ferredoxin-NADP reductase |
| frdA | -0.87 | -2.52 | -0.57 | -0.30 | -3.60 | 0.05 | fumarate reductase, anaerobic, flavoprotein subunit |
| frdB | -0.68 | -4.78 | -1.05 | -1.20 | -3.53 | -1.10 | fumarate reductase, anaerobic, iron-sulfur protein subunit |
| frdC | -1.36 | -1.31 | -1.26 | -1.15 | -0.23 | -1.25 | fumarate reductase, anaerobic, membrane anchor polypeptide |
| frdD | -0.99 | -2.93 | 0.84 | -0.45 | -2.07 | 2.05 | fumarate reductase, anaerobic, membrane anchor polypeptide |
| frr | -0.01 | -0.25 | 0.69 | -0.25 | -1.13 | 0.00 | ribosome releasing factor |
| fruA | 0.15 | 0.00 | 0.00 | -0.80 | -0.03 | 0.05 | PTS system, fructose-specific transport protein |
| fruB | -3.51 | 0.51 | 0.13 | -1.65 | 0.37 | -0.20 | PTS system, fructose-specific IIA |
| fruK | -0.56 | 0.63 | 1.36 | -1.25 | -1.07 | 1.75 | fructose-1-phosphate kinase |
| fruL | 0.57 | -1.34 | -1.26 | 1.25 | -0.37 | -0.45 | fruR leader peptide |
| fruR | -2.89 | -1.58 | -1.33 | -2.35 | -2.53 | -1.75 | transcriptional repressor of fru operon and others |
| frvA | -0.96 | 1.30 | -1.27 | 0.05 | 2.03 | -1.30 | PTS system, fructose-specific IIA component |
| frvB | 0.46 | 1.23 | -1.38 | 1.30 | 2.03 | -0.25 | PTS system, fructose-like enzyme IIBC component |
| frvR | 0.00 | -1.29 | 0.98 | -0.65 | 2.77 | 1.60 | putative frv operon regulatory protein |
| frvX | -0.32 | 1.45 | -0.51 | 0.15 | 2.03 | -0.10 | frv operon protein |
| frwB | 0.20 | -1.02 | -0.69 | 0.05 | 0.07 | 0.10 | PTS system fructose-like IIB component 1 |
| frwC | -0.94 | -0.24 | -0.27 | -0.20 | 0.70 | 0.00 | PTS system, fructose-like enzyme II component |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| frwD | -0.97 | 0.75 | -0.12 | -0.40 | 0.33 | 0.20 | PTS system fructose-like IIB component 2 |
| fsr | -0.88 | 2.32 | -0.62 | -0.25 | 1.57 | 0.00 | fosmidomycin resistance protein |
| ftn | -1.26 | -1.34 | -1.10 | -1.45 | 0.00 | -1.20 | cytoplasmic ferritin (an iron storage protein) |
| ftsA | -4.14 | -1.70 | 0.48 | -1.90 | -2.13 | 1.15 | ATP-binding cell division protein, complexes with FtsZ, associated with junctions of inner and outer |
| ftsE | -0.67 | -0.69 | 0.87 | 0.10 | 0.10 | 1.25 | ATP-binding component of a membrane-associated complex involved in cell division |
| ftsI | -2.33 | -1.46 | -0.16 | -1.75 | -2.17 | -1.05 | septum formation; penicillin-binding protein 3; peptidoglycan synthetase |
| ftsJ | 0.25 | -0.86 | 0.74 | 1.25 | -0.53 | 0.15 | cell division protein |
| ftsK | -0.85 | 0.23 | 1.58 | -1.05 | 0.27 | 1.15 | cell division protein |
| ftsL | -0.44 | -2.14 | -0.14 | -0.10 | -1.73 | 0.20 | cell division protein; ingrowth of wall at septum |
| ftsN | 0.26 | -1.34 | 0.54 | -0.30 | -2.73 | 0.10 | essential cell division protein |
| ftsQ | -0.58 | -1.86 | -0.16 | -2.20 | -2.83 | -0.60 | cell division protein; ingrowth of wall at septum |
| ftsW | 0.34 | -0.15 | -0.80 | 1.15 | 0.40 | -1.30 | cell division; membrane protein involved in shape determination |
| ftsX | -0.02 | -2.18 | 0.77 | -0.90 | -1.80 | 1.70 | cell division membrane protein |
| ftsY | 2.56 | 2.96 | -1.45 | 1.60 | -0.13 | -1.40 | cell division membrane protein |
| ftsZ | -0.71 | -1.78 | -1.05 | -2.25 | -2.27 | -0.25 | cell division; forms circumferential ring; tubulin-like GTP-binding protein and GTPase |
| fucA | 6.61 | 1.76 | -1.14 | 0.65 | 1.63 | -0.15 | L-fuculose-1-phosphate aldolase |
| fucI | 0.73 | -1.00 | -0.56 | 0.15 | -0.10 | 0.00 | L-fucose isomerase |
| fucK | -1.37 | 1.09 | -3.20 | -1.65 | 1.23 | -1.05 | L-fuculokinase |
| fucO | -0.83 | 0.35 | 0.33 | -0.05 | 1.43 | 0.00 | L-1,2-propanediol oxidoreductase |
| fucP | 0.80 | 0.46 | -0.57 | 1.40 | 1.60 | 0.00 | fucose permease |
| fucR | -0.14 | 0.79 | -0.68 | 0.00 | 1.33 | 0.15 | positive regulator of the fuc operon |
| fucU | 0.70 | -1.88 | -1.26 | 0.80 | -1.37 | -0.25 | protein of fucose operon |
| fumA | -0.51 | -1.39 | 0.66 | -1.15 | -1.13 | 0.05 | fumarase A |
| fumB | 0.34 | -1.34 | 0.77 | 0.00 | -0.10 | 1.55 | fumarase B |
| fumC | -1.15 | -1.18 | -0.66 | -0.45 | -0.33 | 0.05 | fumarase C |
| fur | 0.30 | 5.68 | 1.73 | -0.10 | 1.60 | 1.20 | negative regulator |
| fusA | 0.32 | 2.32 | 0.55 | 0.85 | 1.87 | 0.00 | GTP-binding protein chain elongation factor EF-G |
| gabD | 0.54 | 0.77 | -1.10 | -1.90 | -0.27 | -1.15 | succinate-semialdehyde dehydrogenase, NADP-dependent activity |
| gabP | 1.17 | 1.70 | 1.35 | 1.65 | 0.70 | 1.25 | transport permease protein of gamma-aminobutyrate |
| gabT | 0.51 | 0.34 | 0.58 | 0.25 | 0.30 | 0.15 | 4-aminobutyrate aminotransferase activity |
| gadA | -0.86 | -1.49 | -1.27 | 0.45 | -1.63 | -1.30 | glutamate decarboxylase isozyme |
| gadB | 0.18 | -0.65 | 0.87 | 0.30 | 0.20 | 1.15 | glutamate decarboxylase isozyme |
| galE | -2.56 | -0.83 | 1.19 | -4.95 | -4.93 | -0.05 | UDP-galactose-4-epimerase |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| galF | 0.51 | 2.12 | 1.13 | 1.45 | 1.83 | 1.40 | homolog of Salmonella UTP--glucose-1-P uridyltransferase, probably a UDP-gal transferase |
| galK | -2.06 | -3.43 | -0.95 | -1.70 | -3.70 | -1.55 | galactokinase |
| galM | -1.07 | -2.76 | 0.53 | -1.65 | -2.60 | 0.00 | galactose-1-epimerase (mutarotase) |
| galP | -0.76 | -1.95 | -1.38 | -0.80 | 0.43 | -1.45 | galactose-proton symport of transport system |
| galR | -0.93 | -1.32 | 0.03 | -0.15 | -0.27 | -0.15 | repressor of galETK operon |
| galS | 0.49 | 1.07 | -1.07 | 0.65 | 1.27 | -0.20 | mgl repressor, galactose operon inducer |
| galT | -2.25 | -2.09 | -0.44 | -1.80 | -2.80 | 0.10 | galactose-1-phosphate uridylyltransferase |
| galU | -1.08 | 0.07 | -0.84 | -1.25 | -0.27 | -0.10 | glucose-1-phosphate uridylyltransferase |
| gapA | -0.81 | -0.92 | 1.18 | -1.20 | -2.27 | 1.55 | glyceraldehyde-3-phosphate dehydrogenase A |
| gapC | 0.39 | -1.81 | 0.75 | 1.15 | -1.17 | 1.75 | glyceraldehyde-3-phosphate dehydrogenase (second fragment) |
| gapC | -1.08 | -1.57 | 1.65 | -0.70 | -2.30 | 1.30 | glyceraldehyde 3-phosphate dehydrogenase C, interrupted |
| gatA | -0.14 | -0.02 | -1.36 | -0.25 | 0.40 | -1.60 | galactitol-specific enzyme IIA of phosphotransferase system |
| gatB | -1.84 | -1.33 | 0.78 | -3.20 | -1.70 | 1.55 | galactitol-specific enzyme IIB of phosphotransferase system |
| gatC | -1.63 | -1.02 | 0.56 | -5.00 | -1.23 | 0.10 | PTS system galactitol-specific enzyme IIC |
| gatD | -0.57 | -1.32 | 1.11 | -1.55 | 0.13 | 1.30 | galactitol-1-phosphate dehydrogenase |
| gatR | -0.32 | -0.82 | -1.10 | 1.80 | 2.23 | -0.05 | split galactitol utilization operon repressor, fragment 2 |
| gatR | 0.66 | 3.05 | -1.00 | 1.20 | 0.50 | -1.05 | split galactitol utilization operon repressor, interrupted |
| gatY | -1.60 | -0.92 | -0.22 | -3.15 | -1.10 | 0.20 | tagatose-bisphosphate aldolase 1 |
| gatZ | -0.47 | -1.71 | -0.83 | -2.25 | -2.13 | -1.10 | putative tagatose 6-phosphate kinase 1 |
| gcd | 1.68 | -1.16 | -1.05 | 2.20 | -0.37 | -0.20 | glucose dehydrogenase |
| gcl | -1.98 | 0.76 | 0.00 | -4.10 | 1.63 | 0.10 | glyoxylate carboligase |
| gcpE | -0.98 | -1.42 | 1.19 | -1.05 | -0.47 | 1.30 | orf, hypothetical protein |
| gcvA | 0.27 | -1.43 | 0.79 | 0.50 | -1.23 | 1.05 | positive regulator of gcv operon |
| gcvH | -2.67 | -6.77 | -1.40 | -1.75 | -3.53 | -1.35 | in glycine cleavage complex, carrier of aminomethyl moiety via covalently bound lipoyl cofactor |
| gcvP | -4.72 | -1.70 | 1.03 | -2.00 | -1.60 | 1.30 | glycine decarboxylase, P protein of glycine cleavage system |
| gcvR | 3.64 | -1.07 | 0.44 | 1.40 | -0.33 | 0.30 | transcriptional regulation of gcv operon |
| gcvT | -6.72 | -1.41 | -1.34 | -1.35 | -1.70 | -1.85 | aminomethyltransferase (T protein; tetrahydrofolate-dependent) of glycine cleavage system |
| gdhA | -1.48 | 0.78 | 0.45 | 0.10 | 1.43 | -0.05 | NADP-specific glutamate dehydrogenase |
| gef | 0.47 | -1.36 | 0.66 | 0.30 | -1.70 | 3.60 | Gef protein interferes with membrane function when in excess |
| ggt | -0.81 | -1.34 | -0.06 | 0.35 | -0.63 | 0.00 | gamma-glutamyltranspeptidase |
| gidA | 0.18 | 2.84 | -1.25 | 1.25 | 2.00 | -1.35 | glucose-inhibited division; chromosome replication? |
| gidB | 1.17 | 3.17 | 0.55 | 1.85 | 1.50 | -0.05 | glucose-inhibited division; chromosome replication? |
| gip | -6.75 | -1.20 | 2.77 | -4.10 | -0.60 | 1.05 | glyoxylate-induced protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| glcB | -1.61 | -1.52 | -1.34 | -15.55 | -1.33 | -0.30 | malate synthase G |
| glcC | 0.02 | -1.22 | 0.81 | 0.95 | -0.23 | 1.55 | transcriptional activator for glc operon |
| glcD | -1.25 | -1.79 | 0.57 | -9.15 | -1.10 | 1.25 | glycolate oxidase subunit D |
| glcF | -0.64 | -1.12 | -0.77 | -7.10 | -0.23 | -0.05 | glycolate oxidase iron-sulfur subunit |
| glcG | -1.25 | -1.55 | -0.08 | -12.20 | -2.07 | 0.05 | orf, hypothetical protein |
| gldA | -1.84 | -2.13 | -0.11 | -2.60 | -1.57 | 0.15 | glycerol dehydrogenase, (NAD) |
| glf | -0.33 | 1.98 | 1.22 | -0.10 | 1.30 | 1.25 | UDP-galactopyranose mutase |
| glgA | -0.49 | -1.37 | -1.96 | -0.70 | -0.53 | -1.25 | glycogen synthase |
| glgB | -0.76 | -0.70 | -0.01 | -0.20 | 0.27 | -0.05 | 1,4-alpha-glucan branching enzyme |
| glgC | -0.82 | -0.08 | -0.10 | -0.35 | 0.40 | 0.10 | glucose-1-phosphate adenylyltransferase |
| glgP | -0.59 | -2.57 | 0.30 | -1.30 | -3.30 | -0.25 | glycogen phosphorylase |
| glgS | -0.91 | -11.18 | 0.76 | -3.10 | -4.63 | 1.30 | glycogen biosynthesis, rpoS dependent |
| glgX | -1.12 | -1.56 | -1.42 | -0.70 | -1.67 | -1.30 | part of glycogen operon, a glycosyl hydrolase, debranching enzyme |
| glk | -0.02 | -0.26 | 0.66 | -1.20 | -1.13 | -0.05 | glucokinase |
| glmS | -0.01 | -1.03 | 1.25 | 0.00 | -1.80 | 0.10 | L-glutamine:D-fructose-6-phosphate aminotransferase |
| glmU | 1.03 | 0.40 | 0.86 | 2.00 | -1.27 | 0.30 | N-acetyl glucosamine-1-phosphate uridyltransferase |
| glnA | -0.08 | -1.61 | 1.22 | -1.65 | -1.20 | 1.55 | glutamine synthetase |
| glnB | -2.01 | -1.27 | 0.71 | -2.25 | -0.70 | 1.10 | regulatory protein P-II for glutamine synthetase |
| glnD | 0.00 | -0.02 | -1.04 | 1.20 | 1.17 | -1.45 | protein PII; uridylyltransferase acts on regulator of glnA |
| glnE | 1.81 | 1.07 | 0.72 | 1.50 | 1.20 | 1.30 | adenylylating enzyme for glutamine synthetase |
| glnG | 0.32 | 0.00 | 0.00 | -0.60 | -1.33 | -0.05 | response regulator for gln (sensor glnL) (nitrogen regulator I, NRI) |
| glnH | -1.41 | 0.49 | 0.09 | -3.75 | 0.27 | -0.15 | periplasmic glutamine-binding protein; permease |
| glnK | 1.89 | 1.12 | -1.38 | 2.25 | 0.43 | -1.40 | nitrogen regulatory protein P-II 2 |
| glnL | 0.91 | -0.71 | -1.19 | 1.45 | 1.17 | -1.35 | histidine protein kinase sensor for GlnG regulator (nitrogen regulator II, NRII) |
| glnP | -2.07 | -1.15 | 0.55 | -1.85 | -0.33 | 0.00 | glutamine high-affinity transport system; membrane component |
| glnQ | -1.66 | -1.26 | 0.41 | -2.85 | -0.43 | -0.05 | ATP-binding component of glutamine high-affinity transport system |
| glnS | 0.89 | 2.29 | 2.53 | 0.90 | 1.67 | 1.35 | glutamine tRNA synthetase |
| glnV | 0.41 | -1.95 | 0.90 | 0.25 | -1.25 | 2.10 | Glutamine tRNA2 |
| glnW | 0.35 | -0.54 | 0.65 | 0.35 | -1.00 | 3.20 | Glutamine tRNA1 |
| glnX | 0.60 | -2.02 | 0.51 | 0.55 | 0.00 | 2.35 | Glutamine tRNA2 |
| gloA | -1.07 | 0.58 | -1.38 | -0.20 | -0.33 | -1.10 | lactoylglutathione lyase |
| gloB | -0.98 | -1.47 | -1.39 | -0.35 | -0.33 | -1.30 | probable hydroxyacylglutathione hydrolase |
| glpA | -1.34 | -0.60 | 1.73 | -2.35 | -1.13 | 1.30 | sn-glycerol-3-phosphate dehydrogenase (anaerobic), large subunit |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| glpB | -2.24 | -3.38 | -1.10 | -2.80 | -5.80 | -1.25 | sn-glycerol-3-phosphate dehydrogenase (anaerobic), membrane anchor subunit |
| glpC | -1.86 | -3.29 | -1.15 | -3.55 | -3.00 | -0.15 | sn-glycerol-3-phosphate dehydrogenase (anaerobic), K-small subunit |
| glpD | -0.98 | -0.45 | 2.42 | -1.15 | -0.33 | 1.25 | sn-glycerol-3-phosphate dehydrogenase (aerobic) |
| glpE | 0.30 | 2.71 | 1.79 | 0.15 | 1.63 | 1.20 | protein of glp regulon |
| glpF | -0.93 | -14.06 | -1.08 | -3.50 | -2.87 | -1.30 | facilitated diffusion of glycerol |
| glpG | 0.38 | 0.64 | -1.33 | -0.05 | 1.87 | -0.35 | protein of glp regulon |
| glpK | -1.92 | -21.68 | -1.24 | -11.75 | -6.87 | -1.25 | glycerol kinase |
| glpQ | -1.14 | -6.52 | -1.44 | -2.70 | -1.57 | -1.35 | glycerophosphodiester phosphodiesterase, periplasmic |
| glpR | -0.26 | -1.30 | -0.17 | -0.40 | -1.10 | 0.05 | repressor of the glp operon |
| glpT | -6.31 | -2.12 | 0.06 | -2.85 | -2.23 | 1.15 | sn-glycerol-3-phosphate permease |
| glpX | -0.28 | -1.41 | -0.29 | -0.50 | -1.63 | -1.00 | unknown function in glycerol metabolism |
| gltA | -0.59 | -0.76 | 0.83 | -4.30 | -0.23 | 1.25 | citrate synthase |
| gltB | 0.20 | 0.00 | 1.38 | -0.75 | 1.47 | 1.55 | glutamate synthase, large subunit |
| gltD | -0.32 | 0.77 | -0.22 | -0.85 | 0.30 | 0.30 | glutamate synthase, small subunit |
| gltF | 0.86 | 2.36 | 0.85 | 0.90 | 1.57 | 0.25 | regulator of gltBDF operon, induction of Ntr enzymes |
| gltJ | -0.52 | -0.78 | -1.00 | -0.05 | -0.03 | -0.15 | glutamate |
| gltK | 2.32 | 0.18 | -1.73 | 0.70 | 1.60 | -1.10 | glutamate |
| gltL | -1.83 | 14.47 | 1.51 | -1.65 | 2.00 | 1.25 | ATP-binding protein of glutamate |
| gltP | 0.23 | 1.01 | 0.94 | 0.20 | 1.40 | 1.65 | glutamate-aspartate symport protein |
| gltS | 0.79 | -1.33 | 0.91 | 1.40 | 0.23 | 1.50 | glutamate transport |
| gltT | 0.50 | -0.20 | 0.06 | 0.40 | 6.33 | 31.90 | Glutamate tRNA2 |
| gltU | 0.54 | -0.13 | 0.30 | 0.50 | 51.90 | 43.00 | Glutamate tRNA2 |
| gltV | 0.52 | -0.12 | -0.13 | 0.50 | 39.77 | 47.70 | Glutamate tRNA2 |
| gltW | 0.53 | -0.16 | 0.13 | 0.45 | 19.43 | 32.20 | Glutamate tRNA2 |
| gltX | 1.31 | 1.40 | 1.32 | 1.60 | 0.77 | 1.40 | glutamate tRNA synthetase, catalytic subunit |
| glvB | 1.11 | -1.25 | -1.31 | 1.80 | -0.30 | -1.15 | PTS system, arbutin-like IIB component |
| glvC | -0.06 | 0.99 | -1.04 | 0.55 | 0.50 | -1.10 | PTS system, arbutin-like IIC component |
| glvG | 6.10 | -0.93 | -1.30 | 2.65 | -0.20 | -0.15 | probable 6-phospho-beta-glucosidase |
| glyA | -0.11 | 0.89 | 1.10 | -1.25 | 0.27 | 1.85 | serine hydroxymethyltransferase |
| glyQ | 0.33 | -1.21 | -0.83 | 0.05 | -1.37 | 0.00 | glycine tRNA synthetase, alpha subunit |
| glyS | 0.22 | 2.17 | 1.00 | 1.20 | 1.30 | 0.15 | glycine tRNA synthetase, beta subunit |
| glyT | 0.44 | -0.06 | 0.34 | 0.40 | 0.25 | 8.50 | Glycine tRNA2, UGA suppression |
| glyU | -0.01 | 0.12 | -0.21 | 0.25 | 0.50 | 0.70 | Glycine tRNA1 |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| glyV | 0.48 | -0.15 | 0.70 | 0.40 | -4.00 | 17.40 | Glycine tRNA3 |
| glyW | 0.48 | -0.20 | 1.27 | 0.40 | -1.65 | 15.75 | Glycine tRNA3 |
| glyX | 0.50 | -3.11 | 0.76 | 0.50 | -1.75 | 20.35 | Glycine tRNA3 |
| glyY | 0.50 | -2.28 | 0.54 | 0.35 | 18.37 | 21.85 | Glycine tRNA3 |
| gmd | -0.71 | 1.36 | 0.77 | -0.35 | 2.00 | 1.60 | GDP-D-mannose dehydratase |
| gmhA | -0.05 | -1.65 | -1.61 | 0.00 | -1.70 | -1.45 | phosphoheptose isomerase |
| gmk | 0.09 | 2.06 | 2.25 | -0.10 | 1.37 | 1.40 | guanylate kinase |
| gnd | -0.16 | -0.92 | -0.54 | -1.30 | -2.37 | -0.05 | gluconate-6-phosphate dehydrogenase, decarboxylating |
| gntK | 0.37 | 0.00 | 0.86 | 1.35 | 0.47 | 1.15 | gluconokinase 2, thermoresistant |
| gntP | 0.03 | -1.30 | -0.02 | 0.30 | -0.37 | 0.05 | gluconate transport system permease 3 |
| gntR | 0.18 | 0.00 | 0.77 | -0.60 | 0.60 | 0.15 | regulator of gluconate (gnt) operon |
| gntT | -0.49 | -1.49 | 1.24 | -0.70 | -0.73 | 1.40 | high-affinity transport of gluconate |
| gntU | 0.37 | -1.17 | -1.45 | 0.00 | -0.03 | -1.50 | low-affinity gluconate transport permease protein, interrupted |
| gntU | 0.84 | -0.66 | -0.07 | 1.90 | 0.37 | 0.05 | low-affinity gluconate transport permease protein, fragment 2 |
| goaG | -1.14 | 2.80 | 0.64 | -0.65 | 1.77 | 0.10 | 4-aminobutyrate aminotransferase |
| gor | 1.85 | -0.47 | 0.87 | 1.75 | -0.23 | -0.05 | glutathione oxidoreductase |
| gph | -0.03 | -1.82 | -1.25 | -0.50 | -0.33 | -1.30 | phosphoglycolate phosphatase |
| gpmA | -0.50 | -0.95 | -0.31 | -0.15 | -1.57 | 0.35 | phosphoglyceromutase 1 |
| gpmB | -0.72 | -1.49 | 0.14 | -0.35 | -1.47 | -0.10 | phosphoglyceromutase 2 |
| gppA | -0.41 | -1.33 | -1.18 | 0.05 | 1.20 | -1.10 | guanosine pentaphosphatase; exopolyphosphatase |
| gpsA | 0.39 | -3.14 | 1.01 | 1.40 | -1.33 | 1.50 | glycerol-3-phosphate dehydrogenase (NAD+) |
| gpt | 0.40 | 2.19 | 1.10 | 0.50 | 1.27 | 1.30 | guanine-hypoxanthine phosphoribosyltransferase |
| greA | 1.35 | 1.18 | -0.40 | 2.10 | 1.37 | -1.05 | transcription elongation factor: cleaves 3 nucleotide of paused mRNA |
| greB | 0.14 | 0.35 | -0.61 | 0.30 | -0.33 | -0.30 | transcription elongation factor and transcript cleavage |
| grpE | 0.75 | -0.95 | -0.36 | 2.30 | -1.20 | 0.05 | phage lambda replication; host DNA synthesis; heat shock protein; protein repair |
| grxA | -0.34 | 1.40 | 2.94 | 0.05 | 1.40 | 1.50 | glutaredoxin1 redox coenzyme for glutathione-dependent ribonucleotide reductase |
| grxB | -1.54 | -0.10 | 0.72 | -2.05 | -1.57 | 1.30 | glutaredoxin 2 |
| grxC | 0.47 | 0.97 | 0.12 | 1.80 | 0.17 | 0.05 | glutaredoxin 3 |
| gshA | 0.87 | -1.84 | -2.05 | 0.30 | -1.43 | -1.25 | gamma-glutamate-cysteine ligase |
| gshB | 0.13 | 1.82 | 0.62 | 0.20 | 1.13 | 0.40 | glutathione synthetase |
| gsk | -0.90 | -1.19 | -1.19 | -2.50 | -0.27 | -0.20 | inosine-guanosine kinase |
| gsp | 0.02 | 1.06 | -0.57 | 0.30 | 1.30 | -1.05 | glutathionylspermidine synthetase |
| gst | -1.28 | -1.39 | -0.17 | -1.75 | -0.63 | 0.10 | glutathionine S-transferase |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| guaA | -0.17 | 0.71 | -1.10 | -1.80 | 0.27 | -1.55 | GMP synthetase (glutamine-hydrolyzing) |
| guaB | -0.62 | 0.81 | 0.72 | -0.10 | 0.57 | 0.10 | IMP dehydrogenase |
| guaC | -1.86 | 1.22 | 1.41 | -1.70 | 1.37 | 1.85 | GMP reductase |
| gutM | 1.59 | -1.26 | 1.01 | 1.50 | -0.37 | 1.30 | glucitol operon activator |
| gutQ | -0.19 | -1.34 | 0.78 | -1.35 | -1.67 | 1.70 | orf, hypothetical protein |
| gyrA | 1.14 | 9.21 | -0.74 | 0.85 | 2.30 | -0.05 | DNA gyrase, subunit A, type II topoisomerase |
| gyrB | 1.31 | 5.62 | -0.66 | 1.15 | 1.93 | -0.05 | DNA gyrase subunit B, type II topoisomerase, ATPase activity |
| hcaA1 | -0.21 | -1.38 | 0.77 | -1.20 | -1.53 | 1.20 | large terminal subunit of phenylpropionate dioxygenase |
| hcaA2 | -1.29 | -1.55 | -1.24 | -1.65 | -1.83 | -1.35 | small terminal subunit of phenylpropionate dioxygenase |
| hcaB | -0.18 | -1.11 | -1.48 | -0.25 | 1.43 | -1.10 | 2,3-dihydroxy-2,3-dihydrophenylpropionate dehydrogenase |
| hcaC | 0.05 | -0.58 | -0.53 | 1.80 | -1.23 | 0.10 | ferredoxin subunit of phenylpropionate dioxygenase |
| hcaD | -0.96 | 1.54 | -1.38 | -0.35 | 1.53 | -0.10 | ferredoxin reductase subunit of phenylpropionate dioxygenase |
| hcaR | -0.56 | -1.22 | 0.79 | 0.10 | -0.43 | 0.00 | transcriptional activator of hca cluster |
| hcaT | 0.52 | -1.19 | 0.08 | 0.15 | -0.27 | -0.25 | MFS (major facilitator superfamily) transporter |
| hdeA | -0.87 | -0.96 | -1.37 | -2.10 | -1.73 | -1.20 | orf, hypothetical protein |
| hdeB | -0.83 | -1.24 | 0.59 | -1.10 | -0.30 | -0.15 | orf, hypothetical protein |
| hdeD | -0.02 | -1.05 | 0.85 | 0.35 | -1.03 | 1.25 | orf, hypothetical protein |
| hdhA | -1.24 | -2.00 | -0.84 | -0.45 | -1.83 | -1.15 | NAD-dependent 7alpha-hydroxysteroid dehydrogenase, dehydroxylation of bile acids |
| helD | -1.88 | -1.18 | -1.33 | -0.10 | -0.33 | 0.15 | DNA helicase IV |
| hemA | 1.00 | 0.77 | 0.58 | 0.55 | 1.33 | 1.05 | enzyme in alternate path of synthesis of 5-aminolevulinate |
| hemB | 0.80 | 0.81 | -0.83 | 1.50 | 1.03 | -0.15 | 5-aminolevulinate dehydratase |
| hemC | 5.72 | -0.06 | -1.21 | 1.55 | -0.23 | -1.55 | porphobilinogen deaminase |
| hemD | 1.20 | -1.89 | -1.55 | 1.40 | -1.47 | -2.05 | uroporphyrinogen III synthase |
| hemE | -0.67 | -1.80 | 0.79 | -0.35 | -1.40 | 0.40 | uroporphyrinogen decarboxylase |
| hemF | 0.89 | -1.37 | -1.38 | 1.35 | -0.60 | -1.45 | coproporphyrinogen III oxidase |
| hemG | 0.04 | -0.80 | 0.44 | -0.45 | -1.07 | 0.05 | protoporphyrin oxidase |
| hemH | -1.35 | -1.23 | -1.33 | -2.00 | 0.13 | -1.40 | ferrochelatase: final enzyme of heme biosynthesis |
| hemK | -1.03 | 0.76 | 1.31 | -0.20 | 0.53 | 1.10 | possible protoporphyrinogen oxidase |
| hemL | 0.29 | -1.43 | -0.75 | 0.50 | -1.93 | 0.05 | glutamate-1-semialdehyde aminotransferase (aminomutase) |
| hemM | 1.63 | 1.38 | 0.74 | 1.10 | 1.37 | 1.45 | an enzyme in main pathway of synthesis of 5-aminolevulinate, possibly glutamyl-tRNA [illegible] |
| hemN | 0.28 | -1.08 | 0.93 | 0.65 | -0.30 | 1.20 | O2-independent coproporphyrinogen III oxidase |
| hemX | 1.41 | -1.33 | 1.03 | 1.70 | -0.73 | 1.30 | uroporphyrinogen III methylase |
| hemY | 0.75 | -1.32 | 1.05 | 0.15 | -0.43 | 1.55 | a late step of protoheme IX synthesis |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| hepA | -0.27 | 1.75 | 0.92 | -1.40 | 1.57 | 0.10 | probable ATP-dependent RNA helicase |
| hflB | 0.43 | 2.47 | -0.42 | 1.85 | 1.47 | 0.10 | degrades sigma32, integral membrane peptidase, cell division protein |
| hflC | -0.38 | 1.36 | 0.75 | -1.10 | 1.20 | 1.40 | protease specific for phage lambda cII repressor |
| hflK | 0.55 | 2.25 | -1.02 | 1.30 | 1.30 | -1.10 | protease specific for phage lambda cII repressor |
| hflX | 0.06 | -1.11 | -0.86 | 0.05 | -1.53 | -1.20 | GTP - binding subunit of protease specific for phage lambda cII repressor |
| hfq | 0.95 | -4.21 | -1.65 | 0.30 | -1.50 | -0.10 | host factor I for bacteriophage Q beta replication, a growth-related protein |
| hha | -3.34 | 1.38 | -1.26 | -2.05 | 1.33 | -1.30 | haemolysin expression modulating protein |
| himA | -0.92 | -1.70 | -0.54 | -1.35 | -1.73 | 0.00 | integration host factor (IHF), alpha subunit; site specific recombination |
| himD | -0.82 | -1.20 | 1.41 | -0.55 | -1.03 | 1.30 | integration host factor (IHF), beta subunit; site-specific recombination |
| hipA | -0.75 | 0.09 | -1.09 | 0.25 | 0.23 | -0.25 | persistence to inhibition of murein or DNA biosynthesis, DNA-binding regulator |
| hipB | -0.28 | -0.87 | 0.04 | -1.10 | -0.17 | 0.20 | persistence to inhibition of murein or DNA biosynthesis; regulatory protein |
| hisA | -0.07 | 0.10 | 0.82 | 0.55 | -0.40 | -0.15 | N-(5 -phospho-L-ribosyl-formimino)-5-amino-1-(5 - phosphoribosyl)-4-imidazolecarboxamide |
| hisB | 0.91 | -0.36 | 0.72 | 0.25 | 0.47 | 1.40 | imidazoleglycerolphosphate dehydratase and histidinol-phosphate phosphatase |
| hisC | 0.55 | -0.30 | 0.77 | 1.30 | 0.33 | 1.55 | histidinol-phosphate aminotransferase |
| hisD | 1.67 | 0.00 | -1.16 | 1.60 | 0.37 | -0.10 | L-histidinal:NAD+ oxidoreductase; L-histidinol:NAD+ oxidoreductase |
| hisF | 0.05 | -1.38 | -1.27 | -0.10 | -0.47 | -1.80 | imidazole glycerol phosphate synthase subunit in heterodimer with HisH |
| hisG | -1.19 | 0.76 | -1.33 | -1.30 | 1.20 | 0.05 | ATP phosphoribosyltransferase |
| hisH | 0.00 | -0.27 | -0.28 | -4.05 | 0.47 | 0.10 | glutamine amidotransferase subunit of heterodimer with HisF |
| hisI | -0.99 | -3.73 | 0.76 | -1.75 | -1.80 | 2.15 | phosphoribosyl-amp cyclohydrolase; phosphoribosyl-ATP pyrophosphatase |
| hisJ | 0.90 | -0.90 | -0.19 | -0.05 | -0.17 | 0.00 | histidine-binding periplasmic protein of high-affinity histidine transport system |
| hisL | 0.31 | -1.63 | 0.27 | -0.25 | -0.40 | 0.25 | his operon leader peptide |
| hisM | 0.74 | 1.86 | -0.30 | 1.05 | 2.30 | 0.10 | histidine transport, membrane protein M |
| hisP | 0.85 | 2.35 | 1.05 | 1.75 | 1.30 | 1.40 | ATP-binding component of histidine transport |
| hisQ | -0.94 | -1.09 | -0.60 | -0.20 | 0.17 | -1.45 | histidine transport system permease protein |
| hisR | 0.53 | 0.45 | 0.21 | 0.60 | 1.70 | 3.15 | Histidine tRNA |
| hisS | -0.04 | -0.09 | 0.97 | -1.10 | -1.10 | 0.00 | histidine tRNA synthetase |
| hlpA | 0.03 | 0.10 | -1.12 | 1.10 | -0.37 | -0.25 | histone-like protein, located in outer membrane or nucleoid |
| hlyE | 1.16 | 0.16 | 0.79 | 2.40 | 0.20 | 0.25 | hemolysin E |
| hmpA | 1.06 | -1.45 | -1.65 | 1.40 | -1.00 | -1.65 | dihydropteridine reductase, ferrisiderophore reductase activity |
| hnr | -0.62 | 1.20 | 0.45 | -0.10 | 1.50 | 0.40 | Hnr protein |
| hns | -1.73 | -1.46 | 1.25 | -2.45 | -2.43 | 1.10 | DNA-binding protein HLP-II (HU, BH2, HD, NS); pleiotropic regulator |
| hofB | 0.35 | -1.45 | 0.94 | 1.10 | -0.27 | 1.40 | putative integral membrane protein involved in biogenesis of fimbriae, protein transport |
| hofC | -0.25 | -0.85 | -1.33 | 0.20 | -0.10 | -0.55 | putative integral membrane protein involved in biogenesis of fimbriae, protein transport |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| hofD | -0.11 | 0.31 | 0.45 | 0.30 | 1.30 | 0.10 | leader peptidase, integral membrane protein |
| hofF | 1.22 | 0.50 | -1.35 | 0.55 | 1.50 | -1.30 | putative general protein secretion protein |
| hofG | 1.99 | -0.66 | -0.91 | 2.05 | 0.13 | 0.25 | putative general protein secretion protein |
| hofH | 0.00 | -1.34 | 0.14 | -0.20 | -1.47 | -0.10 | putative general protein secretion protein |
| hofQ | -0.64 | -2.09 | 0.77 | 0.45 | 1.10 | 1.20 | putative transport portein |
| holA | -0.02 | 1.23 | 0.25 | -0.05 | 1.27 | -1.25 | DNA polymerase III, delta subunit |
| holB | 0.05 | -1.48 | -1.36 | -0.15 | -1.20 | -1.30 | DNA polymerase III, delta prime subunit |
| holC | -1.53 | -1.21 | 0.44 | -1.50 | -0.47 | 1.20 | DNA polymerase III, chi subunit |
| holD | -1.60 | 0.28 | -1.33 | -1.20 | 1.60 | -1.35 | DNA polymerase III, psi subunit |
| holE | -1.41 | -1.51 | -3.83 | -1.40 | -1.30 | -1.10 | DNA polymerase III, theta subunit |
| hpt | 0.26 | -0.34 | -0.91 | -0.05 | 0.13 | -1.20 | hypoxanthine phosphoribosyltransferase |
| hrpA | 0.45 | -0.99 | 0.60 | 1.10 | -0.37 | -0.10 | helicase, ATP-dependent |
| hrpB | -0.50 | -2.52 | -0.90 | -0.10 | -1.13 | -1.15 | helicase, ATP-dependent |
| hrsA | -0.33 | -0.22 | -0.25 | -0.35 | 1.13 | 0.20 | protein modification enzyme, induction of ompC |
| hscA | 0.41 | 2.46 | -1.56 | 1.30 | 1.97 | -1.90 | heat shock protein, chaperone, member of Hsp70 protein family |
| hsdM | 0.23 | 0.37 | -0.32 | 0.10 | 1.17 | 0.00 | host modification; DNA methylase M |
| hsdR | -0.20 | 0.84 | 0.26 | -0.45 | 0.43 | 0.05 | host restriction; endonuclease R |
| hsdS | -0.06 | 0.04 | -1.14 | 0.05 | 0.87 | -1.15 | specificity determinant for hsdM and hsdR |
| hslJ | 0.71 | 1.73 | 0.77 | 1.50 | 1.30 | 1.25 | heat shock protein hslJ |
| hslU | 0.38 | 0.59 | -0.91 | 1.85 | 0.13 | -1.05 | heat shock protein hslVU, ATPase subunit, homologous to chaperones |
| hslV | 0.45 | -2.29 | -0.17 | 1.90 | -2.00 | 0.00 | heat shock protein hslVU, proteasome-related peptidase subunit |
| htgA | 0.50 | -1.36 | -1.26 | 0.25 | -0.63 | -2.30 | positive regulator for sigma 32 heat shock promoters |
| htpG | 0.03 | 0.01 | 1.25 | -0.25 | -0.80 | 1.80 | chaperone Hsp90, heat shock protein C 62.5 |
| htpX | -1.48 | -0.94 | -1.40 | -1.65 | -0.43 | -1.35 | heat shock protein, integral membrane protein |
| htrA | -0.65 | -1.96 | -0.12 | -1.15 | -1.87 | 0.25 | periplasmic serine protease Do; heat shock protein HtrA |
| htrB | -0.26 | -1.43 | -1.03 | 0.05 | -1.27 | -1.20 | heat shock protein |
| htrC | 1.03 | 2.89 | -0.82 | 1.45 | 1.40 | 0.00 | heat shock protein htrC |
| htrE | 0.60 | -0.23 | 0.34 | 1.35 | 1.80 | 0.35 | probable outer membrane porin protein involved in fimbrial assembly |
| htrL | 1.79 | -0.09 | -1.16 | 1.80 | 0.27 | -0.15 | involved in lipopolysaccharide biosynthesis |
| hupA | 0.03 | -1.13 | -0.35 | -0.70 | -2.20 | -0.10 | DNA-binding protein HU-alpha (HU-2) |
| hupB | -0.81 | -2.37 | -1.47 | -0.15 | -4.47 | -1.60 | DNA-binding protein HU-beta, NS1 (HU-1) |
| hyaA | -1.31 | -1.34 | 0.70 | -1.80 | -1.63 | 0.05 | hydrogenase-1 small subunit |
| hyaB | -0.07 | -1.43 | 0.73 | 0.45 | -1.40 | 1.60 | hydrogenase-1 large subunit |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| hyaC | 1.03 | -1.33 | 1.33 | 0.30 | -0.67 | 1.15 | probable Ni |
| hyaD | 0.17 | -1.24 | -0.72 | 1.10 | 0.17 | -0.25 | processing of HyaA and HyaB proteins |
| hyaE | 1.07 | -1.34 | 0.75 | 0.50 | -0.23 | 1.45 | processing of HyaA and HyaB proteins |
| hyaF | -1.05 | -1.34 | 0.76 | -0.40 | -1.47 | 1.20 | nickel incorporation into hydrogenase-1 proteins |
| hybA | 2.92 | 1.93 | 0.66 | 1.60 | 1.30 | 0.15 | hydrogenase-2 small subunit |
| hybB | 0.47 | -1.89 | 0.85 | 0.45 | -1.27 | 1.50 | probable cytochrome Ni |
| hybC | -1.27 | -0.37 | -1.21 | -0.35 | 0.77 | -1.45 | probable large subunit, hydrogenase-2 |
| hybD | 0.23 | -1.33 | 0.77 | 1.80 | -1.33 | 1.75 | probable processing element for hydrogenase-2 |
| hybE | 0.23 | -1.34 | -0.91 | 0.70 | -0.63 | 0.15 | member of hyb operon |
| hybF | 0.36 | -1.34 | 0.77 | -0.35 | -1.67 | -0.10 | may modulate levels of hydrogenease-2 |
| hybG | 0.21 | -1.66 | 0.92 | 1.65 | -1.47 | 1.20 | hydrogenase-2 operon protein: may effect maturation of large subunit of hydrogenase-2 |
| hycA | 0.23 | -1.32 | 0.07 | -0.20 | -1.13 | 0.15 | transcriptional repression of hyc and hyp operons |
| hycB | 0.93 | 0.62 | -0.53 | 0.10 | 1.30 | 0.10 | probable small subunit of hydrogenase-3, iron-sulfur protein (part of formate hydrogenlyase (FHL) |
| hycC | 0.40 | 0.65 | -1.62 | 0.30 | 1.20 | -1.20 | membrane-spanning protein of hydrogenase 3 (part of FHL complex) |
| hycD | -0.18 | 1.09 | 0.71 | -0.05 | 2.27 | 1.70 | membrane-spanning protein of hydrogenase 3 (part of FHL complex) |
| hycE | -0.92 | -1.13 | 0.19 | 0.50 | 0.40 | 0.20 | large subunit of hydrogenase 3 (part of FHL complex) |
| hycF | -0.30 | -1.41 | 0.72 | 0.05 | -0.40 | 1.15 | probable iron-sulfur protein of hydrogenase 3 (part of FHL complex) |
| hycG | -0.99 | 0.00 | -0.81 | -1.95 | 1.70 | 0.00 | hydrogenase activity |
| hycH | 0.54 | 2.54 | 0.87 | 0.65 | 1.70 | 1.15 | processing of large subunit (HycE) of hydrogenase 3 (part of the FHL complex) |
| hycI | 1.04 | 0.77 | 0.76 | 1.75 | -1.27 | 1.05 | protease involved in processing C-terminal end of the large subunit of hydrogenase 3 |
| hydG | 0.74 | -0.42 | -0.42 | -1.05 | 0.07 | 0.05 | response regulator of hydrogenase 3 activity (sensor HydH) |
| hydH | 0.28 | 0.00 | 0.77 | 0.05 | 0.43 | -0.30 | sensor kinase for HydG, hydrogenase 3 activity |
| hydN | 0.20 | -1.34 | -1.35 | 0.10 | -1.60 | -0.35 | involved in electron transport from formate to hydrogen, Fe-S centers |
| hyfA | -0.08 | 1.38 | 0.73 | 0.80 | 1.53 | 1.50 | hydrogenase 4 Fe-S subunit |
| hyfB | -2.87 | -1.44 | -0.17 | -1.80 | -1.20 | 0.25 | hydrogenase 4 membrane subunit |
| hyfC | 0.48 | -1.42 | 1.22 | -0.40 | -0.20 | 1.60 | hydrogenase 4 membrane subunit |
| hyfD | 0.23 | 0.77 | -1.18 | 0.45 | -0.13 | -0.20 | hydrogenase 4 membrane subunit |
| hyfE | -1.12 | 5.16 | -0.52 | -1.60 | 1.87 | -1.10 | hydrogenase 4 membrane subunit |
| hyfF | 0.61 | -1.37 | -1.28 | -0.05 | -1.07 | -1.15 | hydrogenase 4 membrane subunit |
| hyfG | -0.90 | 0.76 | 0.70 | -0.25 | 1.13 | -0.25 | hydrogenase 4 subunit |
| hyfH | -1.07 | 1.40 | -1.17 | -0.30 | 1.33 | -1.50 | hydrogenase 4 Fe-S subunit |
| hyfI | 0.05 | 0.24 | 0.82 | 0.40 | -1.40 | 0.50 | hydrogenase 4 Fe-S subunit |
| hyfR | -0.24 | -1.28 | -0.48 | 0.10 | -0.23 | -1.25 | putative 2-component regulator, interaction with sigma 54 |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| hypA | -0.29 | 2.02 | 0.79 | -0.15 | 1.57 | 0.15 | pleiotrophic effects on 3 hydrogenase isozymes |
| hypB | -0.60 | -0.15 | 0.85 | -0.15 | 1.17 | 1.30 | guanine-nucleotide binding protein, functions as nickel donor for large subunit of hydrogenase 3 |
| hypC | -0.52 | -1.49 | 0.49 | -0.15 | -1.93 | 0.05 | pleiotrophic effects on 3 hydrogenase isozymes |
| hypD | 1.44 | -1.54 | 0.80 | 1.85 | -1.23 | 1.25 | pleiotrophic effects on 3 hydrogenase isozymes |
| hypE | 1.60 | -1.37 | -1.09 | 2.25 | -0.37 | -0.10 | plays structural role in maturation of all 3 hydrogenases |
| hypF | 1.93 | -1.86 | -0.63 | 3.00 | -1.07 | 0.00 | transcriptional regulatory protein |
| iadA | 0.11 | -1.15 | -1.38 | -0.15 | -0.50 | -1.55 | isoaspartyl dipeptidase |
| iap | -0.08 | 1.44 | 1.28 | 0.05 | 1.23 | 1.50 | alkaline phosphatase isozyme conversion, aminopeptidase |
| ibpA | 0.08 | -1.16 | 0.41 | 1.05 | -0.33 | 0.30 | heat shock protein |
| ibpB | 0.07 | 1.73 | 1.24 | 1.25 | 1.43 | 1.25 | heat shock protein |
| icc | 0.59 | -1.33 | -1.34 | 1.50 | -0.87 | -1.55 | regulator of lacZ |
| icdA | -0.24 | -1.05 | -1.03 | -3.90 | -1.57 | -0.05 | isocitrate dehydrogenase, specific for NADP+ |
| iciA | -0.91 | 1.26 | -1.24 | -0.55 | 0.13 | -1.20 | replication initiation inhibitor, binds to 13-mers at oriC |
| iclR | -0.11 | 1.31 | -1.10 | 0.05 | 1.23 | -1.40 | repressor of aceBA operon |
| idnD | -0.85 | -1.09 | -0.06 | -0.15 | -0.17 | -0.10 | L-idonate dehydrogenase |
| idnK | 0.22 | -1.77 | 0.46 | 0.20 | -0.40 | 0.05 | gluconate kinase, thermosensitive glucokinase |
| idnO | 0.76 | -1.32 | -1.60 | 2.00 | -0.33 | -1.60 | 5-keto-D-gluconate 5-reductase |
| idnR | 4.30 | -1.36 | 0.76 | 0.40 | -1.23 | 1.10 | L-idonate transcriptional regulator |
| idnT | -0.87 | -1.64 | -1.61 | -0.50 | -1.13 | -1.15 | L-idonate transporter |
| ileS | 1.06 | -1.14 | -1.17 | 0.10 | -1.83 | -2.70 | isoleucine tRNA synthetase |
| ileT | 0.63 | -1.57 | 0.43 | 1.85 | -1.25 | 13.90 | Isoleucine tRNA1, triplicate |
| ileU | 0.62 | -1.54 | 0.59 | 1.75 | -1.30 | 16.30 | Isoleucine tRNA1, triplicate |
| ileX | 0.43 | 0.43 | 0.08 | 1.85 | 1.50 | -2.95 | Isoleucine tRNA2 |
| ileY | 0.34 | 1.60 | 0.33 | 2.55 | 3.03 | -3.00 | Isoleucine tRNA2 variant |
| ilvA | 0.25 | 0.00 | 0.77 | -0.55 | -1.47 | -0.10 | threonine deaminase (dehydratase) |
| ilvB | -0.60 | -0.11 | 0.81 | -1.20 | 0.27 | 1.20 | acetolactate synthase I,valine-sensitive, large subunit |
| ilvC | 2.18 | 0.74 | -0.38 | 1.95 | 1.60 | 0.05 | ketol-acid reductoisomerase |
| ilvD | 0.18 | -1.18 | 0.00 | 1.50 | -0.27 | 0.20 | dihydroxyacid dehydratase |
| ilvE | 1.25 | 0.14 | -1.00 | 2.50 | 0.23 | -1.25 | branched-chain amino-acid aminotransferase |
| ilvG | -0.37 | 0.82 | -0.35 | -0.25 | 1.40 | 0.10 | acetolactate synthase II, large subunit, cryptic, interrupted |
| ilvH | -0.49 | -0.89 | -1.49 | -1.45 | -0.23 | -1.15 | acetolactate synthase III, valine sensitive, small subunit |
| ilvI | 0.45 | -1.52 | -1.34 | 1.85 | -1.83 | -1.25 | acetolactate synthase III, valine sensitive, large subunit |
| ilvL | -0.50 | -1.95 | -0.65 | -1.20 | -3.10 | 0.15 | ilvGEDA operon leader peptide |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ilvM | -0.05 | -1.36 | -1.44 | 0.35 | -0.53 | -1.55 | acetolactate synthase II, valine insensitive, small subunit |
| ilvN | -0.30 | -1.82 | -0.35 | -0.15 | -1.50 | -0.05 | acetolactate synthase I, valine sensitive, small subunit |
| ilvY | 0.26 | -1.40 | -0.92 | -0.25 | -1.17 | 0.00 | positive regulator for ilvC |
| imp | -0.06 | 2.05 | -1.33 | -1.25 | 0.63 | -1.35 | organic solvent tolerance |
| inaA | -1.09 | 3.20 | -0.02 | -0.10 | 1.63 | 0.00 | pH-inducible protein involved in stress response |
| infA | 0.92 | 5.61 | 1.23 | 0.55 | 1.90 | 1.45 | protein chain initiation factor IF-1 |
| infB | 0.99 | 3.52 | 0.81 | 0.30 | 2.67 | 0.00 | protein chain initiation factor IF-2 |
| infC | 0.39 | 0.49 | -0.22 | 0.45 | 0.00 | 0.35 | protein chain initiation factor IF-3 |
| INM13X | -0.99 | 1.01 | -1.38 | 2.00 | -0.30 | 1.35 | |
| INM13X | -0.71 | -0.41 | -1.34 | 1.40 | -0.30 | 1.05 | |
| INM13X | 1.03 | -1.32 | -1.32 | -1.60 | 0.33 | -1.35 | |
| INM13X | 0.00 | -1.39 | -1.20 | 0.00 | -0.20 | 0.25 | |
| INM13X | 0.43 | 0.13 | 0.76 | -1.50 | -1.73 | -2.15 | |
| INM13X | 0.00 | 0.00 | 0.77 | -1.30 | 1.13 | 1.35 | |
| INM13X | 0.00 | -1.32 | 0.78 | 1.45 | 0.40 | -1.20 | |
| INM13X | 1.20 | -1.25 | 0.81 | -1.10 | 1.27 | -1.75 | |
| INM13X | 0.01 | -0.54 | 0.82 | -2.40 | -1.07 | 1.55 | |
| INM13X | 1.16 | -0.96 | 0.86 | -0.10 | -0.33 | 1.30 | |
| insA | -2.54 | 1.49 | -1.16 | -0.20 | -0.27 | 0.00 | IS1 protein InsA |
| insA | -0.39 | -0.92 | -1.13 | -1.55 | -0.20 | -0.15 | IS1 protein InsA |
| insA | -0.19 | -0.92 | -1.04 | 0.10 | 1.70 | 1.50 | IS1 protein InsA |
| insA | 0.21 | 0.91 | 0.64 | -1.40 | 1.47 | -0.15 | IS1 protein InsA |
| intA | 0.97 | -1.35 | 0.81 | 1.80 | -0.37 | 0.05 | prophage CP4-57 integrase |
| intB | 0.70 | -1.36 | -0.09 | 0.40 | -0.83 | 0.25 | prophage P4 integrase |
| intC | -0.98 | -1.34 | 1.48 | -0.15 | -1.23 | 1.30 | putative prophage Sf6-like integrase |
| intD | 0.09 | 0.11 | -0.30 | 0.00 | 0.20 | -0.05 | prophage DLP12 integrase |
| intE | 1.66 | -0.57 | 0.52 | 4.25 | -0.20 | 0.25 | prophage e14 integrase |
| intF | -0.82 | -1.21 | 0.80 | -0.20 | -0.17 | -0.05 | putative phage integrase |
| ispA | -1.09 | -1.38 | -1.28 | -1.20 | -1.67 | -0.30 | geranyltranstransferase (farnesyldiphosphate synthase) |
| ispB | 0.31 | -1.38 | 0.13 | 0.25 | -0.67 | 0.05 | octaprenyl diphosphate synthase |
| ivbL | -1.96 | -2.01 | -1.52 | -2.50 | -2.00 | -1.50 | ilvB operon leader peptide |
| katE | -1.09 | -0.52 | 0.85 | -0.60 | 0.40 | 1.30 | catalase; hydroperoxidase HPII(III) |
| katG | -0.72 | -2.38 | -0.79 | -1.30 | -1.83 | -0.05 | catalase; hydroperoxidase HPI(I) |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| kbl | 0.46 | -1.19 | -1.30 | 0.30 | -1.37 | -1.35 | 2-amino-3-ketobutyrate CoA ligase (glycine acetyltransferase) |
| kch | 1.07 | -0.10 | 0.68 | 1.20 | 0.37 | 0.35 | putative potassium channel protein |
| kdgK | -0.74 | -0.76 | 1.25 | -0.80 | -1.37 | 1.20 | ketodeoxygluconokinase |
| kdgT | 1.66 | 2.26 | 0.46 | 1.65 | -0.10 | 0.00 | 2-keto-3-deoxy-D-gluconate transport system |
| kdpA | -1.05 | 1.42 | 0.54 | -0.40 | 1.47 | 0.10 | ATPase of high-affinity potassium transport system, A chain |
| kdpB | -1.01 | -0.41 | 0.67 | -0.15 | 0.43 | -0.25 | ATPase of high-affinity potassium transport system, B chain |
| kdpC | 0.03 | 1.94 | -0.70 | -0.10 | 1.20 | 0.00 | high-affinity potassium transport system |
| kdpD | -0.40 | 0.86 | 0.90 | -0.25 | 1.40 | 1.45 | sensor for high-affinity potassium transport system |
| kdpE | -0.63 | -1.55 | 0.96 | 0.10 | -1.40 | 1.10 | regulator of kdp operon (transcriptional effector) |
| kdsA | -0.93 | 1.97 | -1.00 | -2.45 | 1.37 | -1.40 | 2-dehydro-3-deoxyphosphooctulonate aldolase |
| kdsB | 0.04 | 1.42 | -1.08 | 1.20 | 1.37 | -0.20 | CTP:CMP-3-deoxy-D-manno-octulosonate transferase |
| kdtA | -1.09 | -1.37 | -1.13 | -0.45 | -0.50 | -0.15 | 3-deoxy-D-manno-octulosonic-acid transferase (KDO transferase) |
| kdtB | -0.03 | 1.55 | -0.24 | 0.10 | 1.33 | 0.05 | putative enzyme of lipopolysaccharide synthesis |
| kduD | 1.17 | -1.45 | 0.61 | 0.05 | -1.67 | 1.45 | 2-deoxy-D-gluconate 3-dehydrogenase |
| kduI | -0.80 | -0.08 | 0.62 | -0.20 | 0.47 | 1.30 | homolog of pectin degrading enzyme 5-keto 4-deoxyuronate isomerase |
| kefB | -0.16 | -1.27 | 0.83 | 2.35 | -0.43 | 0.20 | K+ efflux; NEM-activable K+ |
| kefC | -0.26 | 0.56 | 0.15 | -0.05 | 0.07 | -1.75 | K+ efflux antiporter, glutathione-regulated |
| kgtP | 1.07 | 0.94 | -0.05 | 1.30 | 2.07 | -0.70 | alpha-ketoglutarate permease |
| ksgA | -0.20 | -0.76 | -1.08 | -1.10 | -1.23 | -1.35 | S-adenosylmethionine-6-N ,N -adenosyl (rRNA) dimethyltransferase |
| kup | -0.69 | 0.59 | -1.17 | -0.45 | 1.20 | -0.10 | low affinity potassium transport system |
| lacA | -0.16 | -1.35 | -0.74 | 0.70 | -1.30 | 0.00 | thiogalactoside acetyltransferase |
| lacI | 0.16 | 1.31 | 0.75 | -0.20 | 1.57 | 1.55 | transcriptional repressor of the lac operon |
| lacY | 0.43 | 0.77 | -1.26 | 2.10 | 1.43 | -0.50 | galactoside permease (M protein) |
| lacZ | -0.23 | 0.87 | 1.32 | -0.55 | 1.50 | 1.25 | beta-D-galactosidase |
| lamB | -0.40 | -1.48 | 0.67 | -1.80 | -5.63 | 0.05 | phage lambda receptor protein; maltose high-affinity receptor |
| lar | 1.00 | -0.87 | -1.16 | 1.50 | 0.23 | -0.25 | restriction alleviation and modification enhancement |
| lasT | 0.19 | 2.15 | -0.37 | 0.30 | 1.23 | -0.10 | orf, hypothetical protein |
| ldcC | -0.27 | -1.33 | -1.33 | -1.15 | -0.90 | 0.05 | lysine decarboxylase 2, constitutive |
| ldhA | -0.21 | 2.51 | 2.52 | -0.05 | 1.40 | 1.20 | fermentative D-lactate dehydrogenase, NAD-dependent |
| lepA | 1.06 | -0.71 | 0.52 | 0.30 | -0.23 | 0.10 | GTP-binding elongation factor, may be inner membrane protein |
| lepB | -2.80 | -1.37 | -0.44 | -2.70 | -1.77 | -1.20 | leader peptidase (signal peptidase I) |
| leuA | 0.13 | 1.36 | -0.42 | 2.00 | 1.77 | 0.05 | 2-isopropylmalate synthase |
| leuB | -0.04 | 1.60 | -1.27 | 1.75 | 1.17 | -1.20 | 3-isopropylmalate dehydrogenase |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| leuC | -3.27 | -1.26 | -1.17 | -2.15 | -0.27 | -0.10 | 3-isopropylmalate isomerase (dehydratase) subunit |
| leuD | -0.97 | -2.53 | -0.21 | -0.10 | -1.27 | 0.20 | isopropylmalate isomerase subunit |
| leuL | -0.54 | -1.35 | -0.10 | -0.70 | -1.37 | -0.15 | leu operon leader peptide |
| leuO | 0.30 | -0.22 | 0.15 | 0.25 | 0.37 | 0.15 | probable transcriptional activator for leuABCD operon |
| leuP | 0.57 | 0.61 | 0.85 | 0.65 | 1.80 | 3.15 | Leucine tRNA1; tandemly triplicate leuVPQ, duplicate with leuT |
| leuQ | 0.51 | 0.52 | 0.80 | 0.45 | 1.70 | 2.60 | Leucine tRNA1; tandemly triplicate, and duplicate with leuT |
| leuS | 0.35 | 1.22 | 0.73 | 0.15 | 1.30 | 1.50 | leucine tRNA synthetase |
| leuT | 0.70 | -0.82 | 0.64 | 2.05 | -0.05 | 3.05 | Leucine tRNA1, duplicate with leuVPQ |
| leuU | -0.12 | 0.78 | 0.46 | -1.10 | 2.33 | 2.10 | Leucine tRNA2 |
| leuV | 0.60 | 0.15 | 1.34 | 1.70 | 1.35 | 4.95 | Leucine tRNA1, tandemly triplicate leuVPQ, duplicate with leuT |
| leuW | 0.35 | -2.81 | 0.39 | 1.40 | -1.45 | 3.40 | Leucine tRNA3 |
| leuX | 0.39 | 0.35 | 0.15 | 1.65 | 0.80 | 1.40 | Leucine tRNA5 (amber [UAG] suppressor) |
| leuZ | 0.44 | -1.74 | -1.10 | -2.00 | -1.55 | 0.10 | Leucine tRNA4 |
| lexA | 0.72 | 1.63 | 1.49 | 3.70 | 1.53 | 1.45 | regulator for SOS(lexA) regulon |
| lgt | 0.04 | -2.49 | -1.13 | -0.10 | -1.40 | -1.40 | phosphatidylglycerol-prolipoprotein diacylglyceryl transferase; a major membrane phospholipid |
| lhr | 0.27 | 0.90 | -1.16 | 0.00 | 1.37 | -0.85 | member of ATP-dependent helicase superfamily II |
| lig | 1.05 | 1.21 | -0.87 | 2.20 | 1.13 | 0.00 | DNA ligase |
| lipA | -0.14 | 4.24 | 1.39 | -1.80 | 1.03 | 0.15 | lipoate synthesis, sulfur insertion? |
| lipB | 0.97 | 1.16 | 0.81 | 1.65 | 0.33 | 1.30 | protein of lipoate biosynthesis |
| lit | -1.49 | -0.71 | 0.73 | -2.25 | 1.27 | 0.10 | phage T4 late gene expression; at locus of e14 element |
| livF | -0.29 | 0.17 | -1.30 | -0.30 | 0.33 | -0.30 | ATP-binding component of leucine transport |
| livG | 0.00 | -1.30 | -0.05 | -1.85 | 0.13 | 0.10 | ATP-binding component of high-affinity branched-chain amino acid transport system |
| livH | -0.10 | 1.03 | 0.23 | 1.65 | 1.20 | -0.35 | high-affinity branched-chain amino acid transport system; membrane component |
| livJ | -0.14 | 0.73 | -0.43 | 0.40 | 1.43 | 0.10 | high-affinity amino acid transport system; periplasmic binding protein |
| livK | 0.26 | 0.77 | 0.49 | 0.05 | 2.10 | 0.25 | high-affinity leucine-specific transport system; periplasmic binding protein |
| livM | -0.51 | -0.01 | 0.34 | 0.20 | -1.13 | 0.20 | high-affinity branched-chain amino acid transport |
| lldD | 0.33 | -1.79 | -0.46 | 14.60 | -1.57 | -1.05 | L-lactate dehydrogenase |
| lldP | 0.27 | 0.09 | -1.32 | 2.45 | 0.27 | -1.35 | L-lactate permease |
| lldR | 0.40 | -2.15 | -0.59 | 9.40 | -1.37 | 0.00 | transcriptional regulator |
| lnt | -1.53 | 0.74 | -0.90 | -1.20 | 0.53 | -1.30 | apolipoprotein N-acyltransferase, copper homeostasis protein, inner membrane |
| lolA | 0.41 | 0.07 | -1.22 | 0.05 | -0.40 | -0.10 | periplasmic protein effects translocation of lipoproteins from inner membrane to outer |
| lon | -0.44 | 0.58 | 0.95 | -0.10 | 0.23 | 0.00 | DNA-binding, ATP-dependent protease La; heat shock K-protein |
| lpdA | -0.23 | 1.49 | 0.84 | -1.10 | 1.37 | -0.20 | lipoamide dehydrogenase (NADH); component of 2-oxodehydrogenase and pyruvate complexes |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| lplA | 1.46 | -0.12 | -0.07 | 1.50 | 0.10 | 0.05 | lipoate-protein ligase A |
| lpp | 0.55 | -2.00 | -0.09 | 0.50 | 5.53 | 7.20 | 1755681.00 |
| lpxA | 0.92 | 1.28 | 1.74 | 0.40 | 1.53 | 1.40 | UDP-N-acetylglucosamine acetyltransferase; lipid A biosynthesis |
| lpxB | 0.27 | -2.21 | -1.10 | -0.65 | -1.47 | -0.20 | tetraacyldisaccharide-1-P; lipid A biosynthesis, penultimate step |
| lpxC | 4.37 | 1.78 | -1.03 | 1.25 | 1.47 | -1.45 | UDP-3-O-acyl N-acetylglucosamine deacetylase; lipid A biosynthesis |
| lpxD | -0.31 | -0.60 | -0.72 | -0.05 | -1.43 | -1.25 | UDP-3-O-(3-hydroxymyristoyl)-glucosamine N-acyltransferase; third step of endotoxin (lipidA) synth. |
| lrhA | 0.51 | -1.30 | -1.04 | 0.20 | -0.40 | -1.30 | NADH dehydrogenase transcriptional regulator, LysR family |
| lrp | -0.09 | 0.55 | 0.69 | -0.05 | 0.50 | 1.30 | regulator for leucine (or lrp) regulon and high-affinity branched-chain amino acid transport system |
| lspA | -0.05 | -1.04 | -1.29 | -0.05 | -1.27 | -2.35 | prolipoprotein signal peptidase (SPase II) |
| lysA | 0.10 | -2.83 | -0.92 | 1.65 | 0.30 | -1.15 | diaminopimelate decarboxylase |
| lysC | -0.21 | -0.20 | -1.44 | -0.30 | -1.07 | -1.40 | aspartokinase III, lysine sensitive |
| lysP | 0.23 | 7.01 | -1.15 | 1.15 | 1.93 | -1.45 | lysine-specific permease |
| lysQ | 0.51 | -1.64 | -0.04 | 0.40 | 9.37 | 3.00 | Lysine tRNA |
| lysR | -0.19 | -2.64 | -0.39 | -0.10 | -1.20 | -0.05 | positive regulator for lys |
| lysS | 0.54 | 1.20 | -0.33 | 0.40 | 1.20 | 0.15 | lysine tRNA synthetase, constitutive; suppressor of ColE1 mutation in primer RNA |
| lysT | 0.55 | -2.56 | -0.02 | 0.50 | -1.25 | 3.50 | Lysine tRNA |
| lysU | 0.23 | -1.75 | -1.00 | 0.15 | -2.33 | -0.25 | lysine tRNA synthetase, inducible; heat shock protein |
| lysW | 0.60 | -0.45 | -0.46 | 0.70 | 0.10 | 0.10 | Lysine tRNA |
| lysY | 0.58 | -0.26 | -0.71 | 0.65 | 0.15 | -1.70 | Lysine tRNA |
| lysZ | 0.60 | -3.01 | 0.64 | 0.65 | -1.70 | 4.60 | Lysine tRNA |
| lytB | 0.96 | -0.88 | -1.34 | 1.55 | -1.97 | -2.45 | control of stringent response; involved in penicillin tolerance |
| lyxK | 0.56 | -1.66 | 0.85 | 2.10 | -0.40 | 0.00 | L-xylulose kinase, cryptic |
| malE | -2.46 | -1.50 | 0.72 | -3.20 | -7.93 | 1.15 | periplasmic maltose-binding protein; substrate recognition for transport and chemotaxis |
| malF | 1.42 | -1.73 | 0.82 | 1.10 | -1.90 | 0.05 | part of maltose permease, periplasmic |
| malG | -0.56 | -2.38 | -1.05 | -0.40 | -1.57 | -0.20 | part of maltose permease, inner membrane |
| malI | 0.59 | -0.97 | -0.21 | 1.50 | 1.27 | 0.10 | repressor of malX and Y genes |
| malK | -0.02 | -1.22 | 0.76 | 0.15 | -1.83 | 2.10 | ATP-binding component of transport system for maltose |
| malM | -3.60 | -2.40 | 0.76 | -1.75 | -2.10 | 1.10 | periplasmic protein of mal regulon |
| malP | -0.33 | -0.97 | 0.62 | -1.30 | -0.20 | -0.05 | maltodextrin phosphorylase |
| malQ | 1.57 | -1.83 | 0.77 | 1.65 | -1.53 | 1.45 | 4-alpha-glucanotransferase (amylomaltase) |
| malS | -0.51 | -1.39 | -0.85 | -0.25 | -1.20 | 0.00 | alpha-amylase |
| malT | -0.47 | -5.76 | -0.24 | -0.50 | -2.23 | 0.05 | positive regulator of mal regulon |
| malX | 0.02 | -1.12 | -1.36 | 1.35 | -0.30 | -1.45 | PTS system, maltose and glucose-specific II ABC |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| malY | -0.86 | 2.15 | 0.04 | -0.15 | 1.47 | -0.45 | enzyme that may degrade or block biosynthesis of endogenous mal inducer |
| malZ | 0.35 | -1.67 | -1.14 | 1.40 | -1.37 | -1.35 | maltodextrin glucosidase |
| manA | -0.33 | -1.38 | 0.81 | -0.35 | -2.00 | 1.25 | mannose-6-phosphate isomerase |
| manX | -2.96 | -1.90 | 0.34 | -3.70 | -2.10 | 0.00 | PTS enzyme IIAB, mannose-specific |
| manY | -3.72 | -0.98 | -1.47 | -3.30 | -0.13 | -1.30 | PTS enzyme IIC, mannose-specific |
| manZ | -2.01 | -1.05 | 0.26 | -2.60 | -0.40 | 0.00 | PTS enzyme IID, mannose-specific |
| maoC | -1.14 | -1.30 | 0.64 | -0.35 | -0.47 | 1.40 | putative aldehyde dehydrogenase |
| map | 0.12 | 1.12 | 0.15 | 0.00 | 0.43 | -0.05 | methionine aminopeptidase |
| marA | 0.91 | -0.80 | 1.11 | 0.70 | -1.47 | 1.05 | multiple antibiotic resistance; transcriptional activator of defense systems |
| marB | -0.22 | 3.52 | 1.03 | 0.10 | 1.63 | 1.55 | multiple antibiotic resistance protein |
| marR | -2.08 | 0.22 | 1.25 | -2.00 | 0.20 | 1.40 | multiple antibiotic resistance protein; repressor of mar operon |
| mazG | 5.99 | -1.35 | 2.02 | 1.15 | -1.43 | 1.15 | orf, hypothetical protein |
| mbhA | -0.47 | 1.24 | 0.46 | -0.20 | 1.83 | -0.30 | putative motility protein |
| mcrA | -0.09 | -1.28 | 0.86 | 0.05 | -0.40 | 1.35 | restriction of DNA at 5-methylcytosine residues; at locus of e14 element |
| mcrB | 0.83 | 0.43 | 0.58 | 1.40 | 0.43 | 0.05 | component of McrBC 5-methylcytosine restriction system |
| mcrC | -0.91 | 3.32 | 0.41 | 0.05 | 1.60 | -0.05 | component of McrBC 5-methylcytosine restriction system, expands range of sequences restricted |
| mcrD | 0.00 | 0.00 | -0.49 | -1.75 | 1.60 | 0.05 | inhibits McrE 5-methylcytosine restriction system |
| mdaA | -0.94 | 1.15 | 0.78 | -0.50 | 0.70 | -0.15 | modulator of drug activity A |
| mdaB | 0.59 | 0.77 | 0.77 | 0.50 | 1.27 | 0.15 | modulator of drug activity B |
| mdh | -4.51 | -11.51 | -1.20 | -3.05 | -4.70 | -0.15 | malate dehydrogenase |
| mdlA | -0.23 | 1.98 | 0.41 | -0.30 | 2.00 | -0.55 | ATP-binding component of a transport system |
| mdlB | 1.02 | 1.88 | -1.31 | 2.15 | 2.60 | -0.10 | putative ATP-binding component of a transport system |
| mdoB | 0.49 | -0.53 | -1.33 | 1.65 | -0.03 | -1.35 | phosphoglycerol transferase I |
| mdoG | -2.87 | -0.69 | -1.02 | -1.50 | -0.30 | -1.05 | periplasmic glucans biosynthesis protein |
| mdoH | -0.99 | -1.20 | 0.67 | -1.65 | -0.17 | 1.35 | membrane glycosyltransferase; synthesis of membrane-derived oligosaccharide (MDO) |
| melA | -0.58 | -7.07 | -1.32 | -1.35 | -1.40 | -1.50 | alpha-galactosidase |
| melB | -1.02 | 0.73 | 0.78 | -0.35 | 1.27 | 1.20 | melibiose permease II |
| melR | 0.31 | 0.00 | 0.75 | 0.10 | 1.27 | 1.55 | regulator of melibiose operon |
| menA | 0.05 | -1.17 | -0.67 | 0.15 | -0.47 | -0.05 | 1,4-dihydroxy-2-naphthoate --> dimethylmenaquinone |
| menB | 0.42 | -1.50 | -0.11 | 0.35 | -1.87 | 0.00 | dihydroxynaphtoic acid synthetase |
| menC | -0.97 | -1.56 | 0.83 | -4.15 | -0.40 | 1.50 | o-succinylbenzoyl-CoA synthase; conversion of chorismate to 2-o-succinylbenzoyl-CoA |
| menD | -0.30 | 2.08 | -1.37 | 1.25 | 1.17 | -1.40 | 2-oxoglutarate decarboxylase; SHCHC synthase |
| menE | 0.15 | -0.72 | 0.15 | 1.10 | -0.20 | 0.00 | o-succinylbenzoate-CoA ligase |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| menF | -1.11 | 0.86 | -0.94 | -0.40 | 1.23 | -1.25 | isochorismate hydroxymutase 2, menaquinone biosynthesis |
| menG | -1.66 | -1.67 | -0.21 | -1.60 | -2.33 | -0.05 | menaquinone biosynthesis, unknown |
| mepA | 1.11 | -1.32 | 0.58 | 1.20 | -0.33 | 0.30 | murein DD-endopeptidase, penicillin-insensitive |
| mesJ | -1.05 | 0.47 | 1.21 | -0.10 | 0.00 | 1.25 | cell cycle protein |
| metA | 0.41 | 0.00 | -1.26 | 1.00 | 1.03 | 0.00 | homoserine transsuccinylase |
| metB | 0.42 | -1.40 | -1.38 | 0.30 | -1.40 | -1.35 | cystathionine gamma-synthase |
| metC | 3.25 | 0.45 | 0.61 | 1.95 | 0.63 | -0.20 | cystathionine beta-lyase (beta-cystathionase) |
| metE | -3.60 | 0.89 | -0.02 | -1.85 | 1.27 | -1.20 | tetrahydropteroyltriglutamate methyltransferase |
| metF | -1.07 | -1.20 | 0.91 | -0.65 | -1.13 | 0.05 | 5,10-methylenetetrahydrofolate reductase |
| metG | -0.02 | -0.54 | -0.28 | -1.10 | -1.57 | 0.00 | methionine tRNA synthetase |
| metH | 0.06 | -0.92 | -1.58 | 0.00 | -0.17 | -1.50 | B12-dependent homocysteine-N5-methyltetrahydrofolate transmethylase, repressor of metE |
| metJ | -0.72 | 1.09 | -0.47 | -2.75 | 0.73 | 0.10 | repressor of all met genes but metF |
| metK | 3.15 | -1.02 | 1.60 | 1.80 | -1.50 | 1.10 | methionine adenosyltransferase 1 (AdoMet synthetase); methyl and propylamine donor, corepressor |
| metL | -0.86 | 2.21 | 0.81 | -0.55 | 1.43 | 1.50 | aspartokinase II and homoserine dehydrogenase II |
| metR | 0.73 | -1.34 | 0.78 | 0.45 | -0.10 | 1.45 | regulator for metE and metH |
| metT | 0.66 | -1.74 | 0.62 | 1.80 | -1.85 | 7.45 | Methionine tRNAm; duplicate gene |
| metU | 0.64 | -1.82 | 0.64 | 0.70 | -1.90 | 11.60 | Methionine tRNAm; duplicate gene |
| metV | 0.43 | 1.39 | 0.92 | 0.25 | 2.97 | 3.55 | Initiator methionine tRNAf1; triplicate gene |
| metW | 0.36 | 0.99 | 0.53 | 0.20 | 2.95 | 6.10 | Initiator methionine tRNAf1; triplicate gene |
| metY | -0.09 | 1.90 | 1.71 | 0.05 | 3.93 | 2.10 | Initiator methionine tRNAf2 |
| metZ | 0.38 | 1.36 | 0.24 | 0.15 | 4.10 | 0.85 | Initiator methionine tRNAf1; triplicate gene |
| mfd | 0.34 | 0.44 | 0.99 | 0.05 | 0.33 | 1.35 | transcription-repair coupling factor; mutation frequency decline |
| mglA | -1.46 | 2.77 | 1.57 | -1.35 | 0.10 | 1.05 | ATP-binding component of methyl-galactoside transport and galactose taxis |
| mglB | -2.35 | -0.78 | 0.09 | -6.40 | -1.50 | -0.10 | galactose-binding transport protein; receptor for galactose taxis |
| mglC | -2.01 | -1.69 | -1.44 | -1.65 | -1.03 | -1.45 | methyl-galactoside transport and galactose taxis |
| mgsA | -3.53 | -0.83 | 1.01 | -1.50 | -0.47 | 1.10 | methylglyoxal synthase |
| mgtA | 1.40 | 2.62 | 0.74 | 1.65 | 2.20 | 0.05 | Mg2+ transport ATPase, P-type 1 |
| mhpA | 0.13 | -2.65 | 1.22 | 0.05 | -2.30 | 1.40 | 3-(3-hydroxyphenyl)propionate hydroxylase |
| mhpB | -0.91 | -1.34 | 0.50 | 0.15 | -0.87 | -0.50 | 2,3-dihydroxyphenylpropionate 1,2-dioxygenase |
| mhpC | -0.07 | -1.34 | -1.61 | -0.45 | -0.43 | -1.30 | 2-hydroxy-6-ketonona-2,4-dienedioic acid hydrolase |
| mhpD | -0.76 | -1.31 | 0.78 | -1.95 | -0.23 | 1.20 | 2-keto-4-pentenoate hydratase |
| mhpE | -0.78 | 16.22 | -1.16 | -1.40 | 1.37 | 0.20 | 4-hydroxy-2-ketovalerate aldolase |
| mhpF | -0.11 | -0.83 | -0.89 | 0.05 | 0.27 | -1.35 | acetaldehyde dehydrogenase |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| mhpR | 1.95 | -1.30 | -4.25 | 1.80 | -0.37 | -1.25 | transcriptional regulator for mhp operon |
| mhpT | -0.41 | -0.17 | -0.23 | 0.10 | 0.30 | 0.30 | putative transport protein |
| miaA | 1.65 | 0.46 | 0.01 | 1.30 | 0.50 | -0.05 | delta(2)-isopentenylpyrophosphate tRNA-adenosine transferase |
| minC | -2.20 | -1.66 | -0.87 | -2.15 | -2.20 | -1.30 | cell division inhibitor, inhibits ftsZ ring formation |
| minD | -0.05 | -1.64 | -0.38 | 0.05 | -1.63 | 0.00 | cell division inhibitor, a membrane ATPase, activates minC |
| minE | -4.99 | 0.23 | -1.30 | -1.90 | 0.10 | -1.60 | cell division topological specificity factor, reverses MinC inhibition of ftsZ ring formation |
| mioC | 0.93 | 3.00 | 1.33 | 1.45 | 1.57 | 1.35 | initiation of chromosome replication |
| mipB | 0.00 | 0.00 | 0.77 | -1.90 | 0.77 | 1.20 | putative transaldolase |
| mlc | -0.16 | 1.42 | -0.81 | 0.30 | 1.50 | -1.30 | putative NAGC-like transcriptional regulator |
| mltA | -0.26 | 1.30 | -0.74 | -0.35 | 1.53 | -1.20 | membrane-bound lytic murein transglycosylase A |
| mltB | 0.98 | -1.13 | 0.71 | -0.35 | -1.23 | -0.05 | membrane-bound lytic murein transglycosylase B |
| mltC | -0.18 | -1.31 | 0.56 | -0.05 | -0.47 | 0.10 | membrane-bound lytic murein transglycosylase C |
| mltE | 0.83 | 1.62 | 0.55 | 1.50 | 0.33 | 0.20 | murein transglycosylase E |
| moaA | 0.23 | -2.05 | 0.68 | 1.45 | -1.37 | -0.10 | molybdopterin biosynthesis, protein A |
| moaB | 0.14 | -1.36 | 0.30 | -1.15 | -1.43 | 0.05 | molybdopterin biosynthesis, protein B |
| moaC | 2.28 | -2.33 | 0.36 | 1.35 | -1.77 | -0.30 | molybdopterin biosynthesis, protein C |
| moaD | 0.84 | 0.46 | 1.06 | 0.20 | 0.37 | 1.20 | molybdopterin biosynthesis |
| moaE | 0.67 | 1.74 | -1.31 | 0.55 | 1.23 | -1.40 | molybdopterin converting factor, subunit 2 |
| mobA | 0.54 | -1.69 | -1.38 | 1.70 | -1.07 | -1.15 | molybdopterin ---> molybdopterin-guanine dinucleotide, protein Ar |
| mobB | 1.69 | -1.32 | -0.77 | 0.30 | 0.30 | -1.20 | molybdopterin-guanine dinucleotide biosynthesis protein B |
| modA | -0.56 | 0.57 | -1.33 | -1.50 | 0.67 | -0.45 | molybdate-binding periplasmic protein; permease |
| modB | -0.90 | -1.25 | 1.37 | 0.05 | -0.40 | 1.40 | molybdate transport permease protein |
| modC | 0.00 | 1.34 | 0.75 | -3.45 | 1.17 | 1.35 | ATP-binding component of molybdate transport |
| modE | -0.38 | -1.34 | 0.74 | -0.45 | -1.80 | 0.15 | molybdate uptake regulatory protein |
| modF | 0.01 | 0.41 | -3.11 | -0.10 | 1.37 | -1.40 | ATP-binding component of molybdate transport system |
| moeA | 0.47 | -1.34 | 0.77 | 0.15 | -1.40 | -0.40 | molybdopterin biosynthesis |
| moeB | -0.77 | -0.86 | -1.11 | -0.80 | -0.10 | -1.60 | molybdopterin biosynthesis |
| mog | 0.93 | 1.68 | -1.37 | 1.40 | 1.30 | -1.50 | required for the efficient incorporation of molybdate into molybdoproteins |
| molR | 0.59 | 0.00 | -0.60 | 0.95 | 1.17 | -1.25 | molybdate metabolism regulator, second fragment 2 |
| molR | -1.06 | 1.23 | -0.26 | -0.10 | 1.30 | 0.10 | molybdate metabolism regulator, first fragment |
| molR | 1.00 | 0.65 | 0.85 | 2.75 | 0.40 | -0.05 | molybdate metabolism regulator, third fragment |
| mopA | 0.50 | -1.68 | 0.31 | 0.25 | -0.03 | 0.45 | GroEL, chaperone Hsp60, peptide-dependent ATPase, heat shock protein |
| mopB | 0.30 | -4.43 | 0.50 | 0.30 | -1.67 | -1.55 | GroES, 10 Kd chaperone binds to Hsp60 in pres. Mg-ATP, suppressing its ATPase activity |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| motA | 0.15 | 0.80 | 0.79 | 0.00 | 2.47 | 1.30 | proton conductor component of motor; no effect on switching |
| motB | -0.98 | 0.25 | 0.69 | -2.20 | 1.63 | 1.45 | enables flagellar motor rotation, linking torque machinery to cell wall |
| mraY | -0.69 | -0.08 | 1.30 | -1.25 | 0.37 | 1.50 | phospho-N-acetylmuramoyl-pentapeptide transferase? |
| mrcA | -0.99 | -1.35 | 0.81 | -0.25 | -0.37 | 1.30 | peptidoglycan synthetase; penicillin-binding protein 1A |
| mrcB | 0.91 | -1.08 | -1.02 | 2.05 | -0.33 | -1.45 | peptidoglycan synthetase; penicillin-binding protein 1B |
| mrdA | 0.16 | 1.57 | 0.87 | 0.05 | 1.33 | 0.10 | cell elongation, e phase; peptidoglycan synthetase; penicillin-binding protein 2 |
| mrdB | 1.06 | 0.42 | -0.69 | 0.75 | 0.23 | -0.05 | rod shape-determining membrane protein; sensitivity to radiation and drugs |
| mreB | 0.64 | -0.84 | -1.22 | 1.55 | -0.33 | -1.60 | regulator of ftsI, penicillin binding protein 3, septation function |
| mreC | 0.11 | 1.61 | -0.93 | 1.25 | 1.30 | -1.05 | rod shape-determining protein |
| mreD | 0.34 | 2.33 | -1.35 | 0.35 | 1.93 | -1.25 | rod shape-determining protein |
| mrp | -0.10 | -0.87 | 1.06 | -0.45 | -1.57 | 1.30 | putative ATPase |
| mrr | -1.18 | -1.55 | -1.24 | -1.10 | -0.43 | -0.10 | restriction of methylated adenine |
| mrsA | -0.31 | 0.73 | -1.31 | 1.20 | 0.10 | -1.15 | similar to phosphoglucomutases and phosphomannomutases |
| msbA | -0.65 | -1.01 | -1.26 | -1.90 | -1.37 | -1.40 | ATP-binding transport protein; multicopy suppressor of htrB |
| msbB | 0.29 | 1.51 | 0.85 | -0.20 | 1.80 | 0.20 | suppressor of htrB, heat shock protein |
| mscL | 0.49 | 1.39 | -1.48 | 1.35 | 1.47 | -1.35 | mechanosensitive channel |
| msrA | 1.31 | -1.35 | -1.39 | 1.50 | -1.07 | -1.50 | peptide methionine sulfoxide reductase |
| msyB | -0.14 | 0.43 | -1.22 | 0.15 | 0.50 | -0.40 | acidic protein suppresses mutants lacking function of protein export |
| mtgA | 1.02 | 1.26 | 0.96 | -0.10 | 1.93 | 1.60 | putative peptidoglycan enzyme |
| mtlA | -0.35 | -4.54 | 0.10 | -2.80 | -5.10 | 0.10 | PTS system, mannitol-specific enzyme IIABC components |
| mtlD | -0.11 | -1.00 | -0.78 | -0.90 | -1.00 | -1.30 | mannitol-1-phosphate dehydrogenase |
| mtlR | 0.19 | 0.11 | 0.65 | 0.05 | 0.63 | 0.15 | repressor for mtl |
| mtr | -0.88 | -1.70 | -1.36 | -2.50 | -1.57 | -1.25 | tryptophan-specific transport protein |
| mukB | -0.31 | -1.79 | 0.78 | -1.25 | -2.10 | 0.10 | kinesin-like cell division protein involved in chromosome partitioning |
| mukE | 0.23 | 0.69 | -0.94 | -0.85 | 1.23 | -1.10 | orf, hypothetical protein |
| mukF | 0.05 | 1.14 | 0.66 | 0.05 | 1.33 | -1.60 | mukF protein (killing factor KICB) |
| murA | 0.16 | -0.17 | 1.09 | 0.00 | 1.10 | 1.30 | first step in murein biosynthesis;UDP-N-glucosamine 1-carboxyvinyltransferase |
| murB | 1.55 | 4.73 | 0.35 | 1.90 | 1.33 | 0.00 | UDP-N-acetylenolpyruvoylglucosamine reductase |
| murC | -0.89 | -1.32 | -1.38 | -1.55 | -1.80 | -1.60 | L-alanine adding enzyme, UDP-N-acetyl-muramate:alanine ligase |
| murD | -0.31 | -1.37 | 0.16 | -0.20 | -2.03 | -0.05 | UDP-N-acetylmuramoylalanine-D-glutamate ligase |
| murE | -0.33 | -1.55 | 0.43 | -1.25 | -1.83 | 0.25 | meso-diaminopimelate-adding enzyme |
| murF | -2.61 | 1.28 | -1.31 | -1.65 | 0.47 | -1.30 | D-alanine:D-alanine-adding enzyme |
| murG | -3.13 | -1.56 | -1.12 | -2.10 | -1.93 | -5.20 | UDP-N-acetylglucosamine:N-acetylmuramyl- (pentapeptide) pyrophosphoryl-undecaprenol |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| murI | 0.69 | 2.47 | 0.51 | 1.70 | 1.60 | -0.20 | glutamate racemase, required for biosynthesis of D-glutamate and peptidoglycan |
| mutH | 0.00 | 0.00 | 0.14 | -1.85 | 0.37 | 0.20 | methyl-directed mismatch repair |
| mutL | -5.27 | -1.28 | 0.59 | -1.60 | -0.50 | 0.05 | enzyme in methyl-directed mismatch repair |
| mutM | 0.09 | 2.39 | 0.46 | 0.75 | 1.33 | 1.30 | formamidopyrimidine DNA glycosylase |
| mutS | 0.34 | -1.45 | -1.19 | -0.05 | -1.80 | -0.20 | methyl-directed mismatch repair |
| mutT | 0.98 | -1.17 | -0.82 | 2.65 | -1.20 | -0.10 | 7,8-dihydro-8-oxoguanine-triphosphatase, prefers dGTP, causes AT-GC transversions |
| mutY | 0.80 | -0.34 | 0.73 | 0.40 | 0.20 | 1.45 | adenine glycosylase; G.C --> T.A transversions |
| mviM | -0.03 | 0.61 | 0.26 | -1.65 | 1.00 | 0.05 | putative virulence factor |
| mviN | 0.23 | 0.00 | 0.39 | -2.65 | 2.20 | 0.40 | putative virulence factor |
| MYP1CRI | 0.00 | -1.29 | -0.88 | 1.60 | 0.47 | 0.05 | |
| MYP1CRI | 0.96 | 0.78 | -0.59 | 1.10 | -1.07 | -0.10 | |
| nac | 0.54 | -0.26 | 0.31 | 0.55 | -1.10 | -0.10 | nitrogen assimilation control protein |
| nadA | -0.05 | 2.89 | -1.29 | -1.05 | 1.67 | -1.35 | quinolinate synthetase, A protein |
| nadB | 0.44 | 1.26 | -1.39 | 1.55 | 1.10 | -1.75 | quinolinate synthetase, B protein |
| nadC | -0.46 | 1.29 | -1.38 | -0.20 | 1.40 | -1.20 | quinolinate phosphoribosyltransferase |
| nadE | 0.50 | 2.62 | -1.07 | 1.75 | 1.20 | -0.10 | NAD synthetase, prefers NH3 over glutamine |
| nadR | -0.95 | -0.95 | 1.45 | -0.75 | 0.23 | 1.40 | probable nadAB transcriptional regulator |
| nagA | -0.10 | 0.61 | 0.78 | -0.10 | -1.13 | -0.10 | N-acetylglucosamine-6-phosphate deacetylase |
| nagB | -0.58 | -1.19 | 0.84 | -1.55 | -0.53 | 1.30 | glucosamine-6-phosphate deaminase |
| nagC | -0.06 | -1.07 | -1.21 | 1.05 | -0.20 | -0.20 | transcriptional repressor of nag (N-acetylglucosamine) operon |
| nagD | 0.01 | -1.76 | 0.43 | -0.35 | -1.10 | -0.10 | N-acetylglucosamine metabolism |
| nagE | -2.05 | -1.76 | -3.07 | -1.70 | -2.83 | -1.20 | PTS system, N-acetylglucosamine-specific enzyme IIABC |
| nanA | -0.40 | -0.56 | -0.40 | -0.25 | -0.03 | 0.15 | N-acetylneuraminate lyase (aldolase); catabolism of sialic acid; not K-12? |
| nanT | -0.05 | 0.00 | 0.94 | 0.15 | 0.80 | 1.10 | sialic acid transporter |
| napA | -1.71 | -1.44 | 1.09 | -2.10 | -1.97 | 1.40 | probable nitrate reductase 3 |
| napB | 2.00 | -0.98 | 0.81 | 1.80 | -0.30 | 0.00 | cytochrome c-type protein |
| napC | -0.29 | -0.23 | -1.34 | -0.25 | -0.13 | -1.40 | cytochrome c-type protein |
| napD | 0.58 | -0.84 | 0.91 | -0.80 | -0.43 | -0.20 | orf, hypothetical protein |
| napF | -0.83 | 1.24 | 0.64 | -1.55 | 1.47 | 0.25 | ferredoxin-type protein: electron transfer |
| napG | 1.02 | 1.44 | 0.05 | 1.80 | 1.17 | 0.15 | ferredoxin-type protein: electron transfer |
| napH | -0.33 | 0.00 | -1.18 | -1.20 | 1.13 | -1.30 | ferredoxin-type protein: electron transfer |
| narG | 0.72 | -1.75 | -1.28 | 1.65 | 0.50 | -1.50 | nitrate reductase 1, alpha subunit |
| narH | 1.63 | -2.26 | 0.58 | 1.45 | -2.47 | -0.25 | nitrate reductase 1, beta subunit |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| narI | -0.11 | -1.06 | -1.27 | -1.00 | -2.17 | -1.60 | nitrate reductase 1, cytochrome b(NR), gamma subunit |
| narJ | 0.82 | -2.17 | 1.72 | 2.00 | -2.10 | 1.25 | nitrate reductase 1, delta subunit, assembly function |
| narK | 2.84 | 1.01 | 1.35 | 1.40 | 1.43 | 1.30 | nitrite extrusion protein |
| narL | -0.92 | -0.06 | -1.39 | -1.05 | 0.30 | -1.65 | pleiotrophic regulation of anaerobic respiration: response regulator for nar, frd, dms and tor genes |
| narP | -0.49 | -2.47 | -0.81 | -2.10 | -1.60 | 0.15 | nitrate |
| narQ | -0.99 | -2.33 | 0.18 | 0.00 | 0.33 | 0.10 | sensor for nitrate reductase system, protein histidine kinase (acts on NarP and narL) |
| narU | -0.53 | -1.27 | -2.04 | 0.95 | -0.43 | -1.10 | nitrite extrusion protein 2 |
| narV | -1.07 | -1.59 | 0.83 | -0.35 | -0.53 | 1.15 | cryptic nitrate reductase 2, gamma subunit |
| narW | -0.21 | -1.12 | 0.94 | -1.90 | -1.53 | 1.05 | cryptic nitrate reductase 2, delta subunit, assembly function |
| narX | 0.16 | 1.06 | 1.05 | -0.15 | 1.50 | 1.40 | nitrate |
| narY | 1.43 | -1.14 | 0.85 | 2.50 | -1.13 | 1.40 | cryptic nitrate reductase 2, beta subunit |
| narZ | 0.48 | -1.27 | 0.98 | 1.60 | -1.40 | 1.05 | cryptic nitrate reductase 2, alpha subunit |
| ndh | 0.17 | 5.66 | 0.98 | 0.10 | 2.57 | 1.50 | respiratory NADH dehydrogenase |
| ndk | -1.07 | 0.69 | 0.38 | -1.55 | 0.10 | 0.15 | nucleoside diphosphate kinase |
| nei | 0.13 | -0.77 | -0.15 | 1.05 | 0.03 | -1.20 | endonuclease VIII and DNA N-glycosylase with an AP lyase activity |
| nemA | 0.53 | -1.38 | 0.87 | 1.55 | -1.37 | 1.65 | N-ethylmaleimide reductase |
| nfi | 0.15 | -1.34 | 0.87 | 0.15 | -1.17 | 1.45 | endonuclease V (deoxyinosine 3 endoduclease) |
| nfnB | -0.75 | -1.29 | 0.59 | -1.50 | -1.53 | -0.05 | oxygen-insensitive NAD(P)H nitroreductase |
| nfo | 0.64 | -0.63 | -0.78 | 0.05 | 0.13 | 0.05 | endonuclease IV |
| nfrA | -0.92 | 1.42 | -0.66 | 0.05 | 1.63 | -0.05 | bacteriophage N4 receptor, outer membrane protein |
| nfrB | -0.85 | -1.40 | -0.63 | -1.70 | -1.20 | 0.10 | bacteriophage N4 receptor, outer membrane protein |
| nhaA | 2.12 | -0.93 | -0.02 | 1.30 | -0.27 | 0.20 | Na+ |
| nhaB | -1.62 | 0.39 | 0.74 | -1.55 | 0.43 | 1.45 | Na+ |
| nhaR | 1.31 | -0.74 | -1.22 | 1.90 | 0.13 | -1.90 | transcriptional activator of nhaA |
| nikA | 0.29 | -0.96 | -1.34 | 0.15 | 0.27 | -1.30 | periplasmic binding protein for nickel |
| nikB | 1.33 | -1.70 | 0.23 | 2.30 | -1.23 | -0.05 | transport of nickel, membrane protein |
| nikC | -0.08 | -1.22 | 0.76 | 0.80 | -0.27 | 1.10 | transport of nickel, membrane protein |
| nikD | -0.36 | -1.28 | -0.32 | 0.20 | -0.40 | 0.40 | ATP-binding protein of nickel transport system |
| nikE | 0.32 | -1.20 | 0.03 | 0.65 | -0.40 | 0.25 | ATP-binding protein of nickel transport system |
| ninE | 0.03 | -1.36 | 0.71 | 0.20 | -1.67 | 0.05 | similar to phage 82 and lambda proteins |
| nirB | -0.29 | -1.74 | 2.97 | -0.10 | -1.07 | 1.55 | nitrite reductase (NAD(P)H) subunit |
| nirC | -0.34 | -1.30 | 0.81 | 0.45 | -0.33 | 1.25 | nitrite reductase activity |
| nirD | -1.79 | 0.81 | -0.33 | -1.30 | 0.17 | -1.30 | nitrite reductase (NAD(P)H) subunit |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| nlp | 0.24 | 0.68 | 0.77 | 2.05 | 0.60 | 0.40 | regulatory factor of maltose metabolism; similar to Ner repressor protein of phage Mu |
| nlpA | -1.22 | -1.16 | -0.14 | -0.70 | -1.20 | -0.30 | lipoprotein-28 |
| nlpB | 0.17 | 0.40 | 0.47 | 0.00 | 0.43 | 0.30 | lipoprotein-34 |
| nlpC | 0.86 | 1.08 | 0.71 | 1.30 | 1.13 | 1.40 | lipoprotein |
| nlpD | -2.10 | -0.12 | -1.20 | -2.60 | 0.67 | -0.05 | lipoprotein |
| nmpC | -1.14 | -1.24 | -1.30 | -1.20 | -0.53 | -1.25 | outer membrane porin protein; locus of qsr prophage |
| nohA | 0.63 | 2.39 | 0.78 | 0.90 | 1.70 | 0.40 | homolog of Qin prophage packaging protein NU1 |
| nrdA | 2.20 | 2.19 | 0.06 | 2.60 | 1.93 | -0.35 | ribonucleoside diphosphate reductase 1, alpha subunit, B1 |
| nrdB | 1.90 | 1.51 | 0.53 | 2.85 | 1.43 | 0.20 | ribonucleoside-diphosphate reductase 1, beta subunit, B2 |
| nrdD | 1.33 | -1.24 | 1.38 | 1.55 | -1.43 | 1.50 | anaerobic ribonucleoside-triphosphate reductase |
| nrdE | 0.87 | 0.76 | -0.84 | 1.40 | 0.03 | -1.15 | ribonucleoside-diphosphate reductase 2, alpha subunit |
| nrdF | 0.07 | -1.39 | -1.32 | 1.25 | -0.57 | -0.05 | ribonucleoside-diphosphate reductase 2, beta chain, frag |
| nrdG | -0.86 | 1.44 | 1.07 | -0.15 | 1.30 | -0.10 | anaerobic ribonucleotide reductase activating protein |
| nrdH | -0.32 | 1.27 | 0.23 | 0.20 | 1.17 | 0.05 | glutaredoxin-like protein; hydrogen donor |
| nrdI | 0.14 | -1.22 | 0.78 | 0.15 | -0.37 | 1.25 | orf, hypothetical protein |
| nrfA | 2.83 | -2.07 | -0.23 | 1.20 | -1.10 | -0.05 | periplasmic cytochrome c(552): plays a role in nitrite reduction |
| nrfB | 0.99 | 1.47 | 0.01 | 1.35 | 1.47 | 0.30 | formate-dependent nitrite reductase; a penta-haeme cytochrome c |
| nrfC | -0.41 | -1.27 | 0.98 | -0.90 | -1.17 | 1.55 | formate-dependent nitrite reductase; Fe-S centers |
| nrfD | -0.15 | -0.69 | 0.64 | 0.00 | 0.20 | 1.25 | formate-dependent nitrate reductase complex; transmembrane protein |
| nrfE | -0.92 | -1.53 | 0.87 | 0.25 | -1.47 | 1.30 | formate-dependent nitrite reductase; possible assembly function |
| nrfF | 0.44 | -1.30 | 1.38 | 1.70 | 0.30 | 1.20 | part of formate-dependent nitrite reductase complex |
| nrfG | -1.09 | -2.13 | 1.26 | -0.40 | -1.20 | 1.30 | part of formate-dependent nitrite reductase complex |
| nth | 0.29 | 0.74 | -1.07 | 0.15 | 0.40 | 0.00 | endonuclease III; specific for apurinic and |
| ntpA | 0.87 | 0.36 | 5.83 | 0.50 | 0.07 | 1.25 | dATP pyrophosphohydrolase |
| nuoA | 0.02 | -1.30 | -1.13 | -0.05 | -1.23 | -0.10 | NADH dehydrogenase I chain A |
| nuoB | 0.38 | 1.42 | 0.40 | 1.15 | 0.43 | 0.25 | NADH dehydrogenase I chain B |
| nuoC | 0.79 | 1.46 | -0.16 | 1.20 | 1.47 | 0.10 | NADH dehydrogenase I chain C, D |
| nuoE | -1.34 | 0.43 | 0.53 | -2.35 | 0.37 | -0.10 | NADH dehydrogenase I chain E |
| nuoF | -0.86 | -1.54 | 1.19 | -0.15 | -1.73 | 1.70 | NADH dehydrogenase I chain F |
| nuoG | -0.70 | 0.75 | 0.94 | -1.75 | -1.20 | -0.15 | NADH dehydrogenase I chain G |
| nuoH | -1.84 | -0.63 | 0.73 | -1.45 | 0.33 | 1.20 | NADH dehydrogenase I chain H |
| nuoI | -0.13 | 1.66 | -1.33 | -1.50 | 1.37 | -1.15 | NADH dehydrogenase I chain I |
| nuoJ | -3.86 | -0.62 | 0.58 | -1.70 | 0.20 | 1.10 | NADH dehydrogenase I chain J |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| nuoK | **-1.51** | **0.87** | **-0.63** | -1.60 | 0.47 | 0.00 | NADH dehydrogenase I chain K |
| nuoL | **-3.05** | **-2.42** | **-1.16** | -2.00 | -1.30 | -1.40 | NADH dehydrogenase I chain L |
| nuoM | **-1.75** | **-1.71** | **0.94** | -1.75 | 0.13 | 0.05 | NADH dehydrogenase I chain M |
| nuoN | **-0.83** | **-1.67** | **0.81** | -1.35 | -1.33 | 1.30 | NADH dehydrogenase I chain N |
| nupC | **-4.12** | **-0.40** | **-1.52** | -1.35 | -0.03 | -1.10 | permease of transport system for 3 nucleosides |
| nupG | **-1.17** | **-16.79** | **-0.80** | -1.25 | -1.67 | 0.00 | transport of nucleosides, permease protein |
| nusA | **1.96** | **3.91** | **1.12** | 1.75 | 2.33 | 1.45 | transcription pausing; L factor |
| nusB | **0.01** | **0.78** | **2.23** | -0.30 | 1.57 | 1.75 | transcription termination; L factor |
| nusG | **2.00** | **3.25** | **-0.35** | 2.00 | 2.10 | -0.10 | component in transcription antitermination |
| ogrK | **1.03** | **-1.25** | **-1.33** | 1.50 | -0.57 | -0.45 | prophage P2 ogr protein |
| ogt | **1.64** | **0.27** | **0.10** | 1.35 | 0.23 | -0.10 | O-6-alkylguanine-DNA |
| ompA | **0.12** | **2.17** | **1.04** | 0.20 | 2.23 | 0.40 | outer membrane protein 3a (II*;G;d) |
| ompC | **-2.46** | **-4.30** | **-1.11** | -1.80 | -4.50 | -0.40 | outer membrane protein 1b (Ib;c) |
| ompF | **-2.50** | **-8.76** | **-1.40** | -3.00 | -1.73 | -1.60 | outer membrane protein 1a (Ia;b;F) |
| ompG | **-0.01** | **-1.04** | **0.34** | 0.05 | -0.47 | -0.10 | outer membrane protein |
| ompR | **-0.02** | **0.49** | **-0.17** | -0.15 | 0.60 | 0.15 | response regulator (sensor, EnvZ) affecting transcription of ompC and ompF: outer membrane |
| ompT | **-1.46** | **-2.06** | **0.94** | -3.35 | -2.73 | 1.25 | outer membrane protein 3b (a), protease VII |
| ompX | **0.61** | **2.34** | **1.88** | 1.90 | 2.27 | 1.60 | outer membrane protein X |
| oppA | **-2.22** | **2.81** | **1.04** | -3.35 | 1.63 | 0.00 | oligopeptide transport; periplasmic binding protein |
| oppB | **-1.15** | **-1.46** | **1.03** | -1.70 | -1.40 | 1.40 | oligopeptide transport permease protein |
| oppC | **-1.69** | **0.55** | **1.97** | -1.90 | 0.37 | 1.30 | homolog of Salmonella oligopeptide transport permease protein |
| oppD | **-0.96** | **-1.26** | **-1.19** | -2.35 | -1.43 | -0.35 | homolog of Salmonella ATP-binding protein of oligopeptide ABC transport system |
| oppF | **-0.59** | **-0.27** | **-1.45** | -1.30 | 0.23 | -1.75 | homolog of Salmonella ATP-binding protein of oligopeptide ABC transport system |
| oraA | **2.06** | **3.40** | **1.01** | 3.50 | 3.20 | 1.80 | regulator, OraA protein |
| ordL | **0.12** | **0.45** | **0.00** | -0.30 | 0.17 | 0.30 | probable oxidoreductase |
| osmB | **-1.89** | **-0.90** | **-0.69** | -2.70 | -1.17 | 0.20 | osmotically inducible lipoprotein |
| osmC | **-1.83** | **-4.16** | **-3.08** | -1.70 | -2.17 | -1.30 | osmotically inducible protein |
| osmE | **-1.14** | **-4.38** | **0.21** | -5.05 | -3.20 | -0.25 | activator of ntrL gene |
| osmY | **-1.06** | **-0.97** | **-0.63** | -6.40 | -0.87 | 0.10 | hyperosmotically inducible periplasmic protein |
| otsA | **-0.93** | **0.00** | **-0.39** | -2.20 | 0.87 | 0.10 | trehalose-6-phosphate synthase |
| otsB | **-0.69** | **9.46** | **-0.54** | 0.25 | 2.07 | 0.05 | trehalose-6-phosphate phophatase, biosynthetic |
| oxyR | **0.21** | **-0.96** | **-0.95** | -0.70 | 0.17 | -0.10 | activator, hydrogen peroxide-inducible genes |
| pabA | **1.36** | **-1.16** | **-0.86** | 0.10 | -0.07 | -1.35 | p-aminobenzoate synthetase, component II |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| pabB | -0.50 | 1.31 | 0.78 | -1.10 | 1.17 | 0.05 | p-aminobenzoate synthetase, component I |
| pabC | 0.16 | -1.52 | -1.07 | 0.20 | -1.10 | -1.20 | 4-amino-4-deoxychorismate lyase |
| pal | -0.13 | -0.02 | 0.90 | 0.00 | -1.23 | -0.30 | peptidoglycan-associated lipoprotein |
| panB | 62.80 | -1.65 | 1.09 | 1.35 | -1.80 | 1.65 | 3-methyl-2-oxobutanoate hydroxymethyltransferase |
| panC | -0.55 | -2.15 | -0.95 | -1.00 | -1.47 | -0.10 | pantothenate synthetase |
| panD | 0.18 | -1.16 | 0.97 | 1.25 | -0.50 | 1.35 | aspartate 1-decarboxylase |
| panF | -0.20 | -0.56 | 0.68 | 1.80 | 0.27 | 0.30 | sodium |
| parC | -1.21 | 0.65 | 0.73 | -0.20 | 1.33 | 0.20 | DNA topoisomerase IV subunit A |
| parE | 0.11 | 1.60 | 0.50 | 0.00 | 0.43 | 0.30 | DNA topoisomerase IV subunit B |
| pbpC | -1.00 | -0.06 | 0.17 | -3.35 | -0.30 | 0.10 | putative peptidoglycan enzyme |
| pbpG | -0.54 | -0.15 | -0.96 | -0.25 | 0.17 | -1.20 | penicillin-binding protein 7 |
| pckA | 0.14 | -1.81 | -0.11 | -0.40 | -2.20 | -0.10 | phosphoenolpyruvate carboxykinase |
| pcm | -0.59 | 0.55 | 1.12 | -2.15 | -0.10 | 1.15 | L-isoaspartate protein carboxylmethyltransferase type II |
| pcnB | 1.22 | -1.27 | -1.18 | 1.45 | -1.77 | -1.30 | poly(A) polymerase I |
| pdhR | -0.85 | -1.33 | -1.33 | 0.05 | -1.40 | -1.30 | transcriptional regulator for pyruvate dehydrogenase complex |
| pdxA | 1.55 | 0.09 | -1.23 | 1.75 | 1.07 | -0.45 | pyridoxine biosynthesis |
| pdxB | -0.47 | 0.49 | 0.32 | -0.30 | -0.27 | -0.10 | erythronate-4-phosphate dehyrogenase |
| pdxH | 3.18 | -1.27 | 1.27 | 1.65 | -1.53 | 1.40 | pyridoxinephosphate oxidase |
| pdxJ | -0.15 | -0.96 | 0.67 | 0.00 | -0.23 | 1.25 | pyridoxine biosynthesis |
| pdxK | -1.09 | -1.30 | 0.87 | -1.65 | 0.13 | 1.45 | pyridoxal |
| pdxY | 0.88 | -1.51 | -1.17 | 1.50 | -1.40 | -0.25 | pyridoxal kinase 2 |
| pepA | -0.19 | -1.61 | -1.40 | -0.70 | -1.53 | -1.60 | aminopeptidase A |
| pepB | -0.87 | -0.79 | 0.74 | -1.55 | -1.10 | -0.10 | putative peptidase |
| pepD | 0.10 | -2.05 | 0.23 | 0.05 | -1.57 | -0.15 | aminoacyl-histidine dipeptidase (peptidase D) |
| pepE | 0.47 | -0.31 | 1.67 | -0.05 | 0.80 | 1.25 | peptidase E, a dipeptidase where amino-terminal residue is aspartate |
| pepN | -1.46 | -0.02 | 0.84 | -1.15 | 0.00 | 2.05 | aminopeptidase N |
| pepP | 0.47 | 0.79 | -1.34 | -0.05 | 0.30 | -1.10 | proline aminopeptidase P II |
| pepQ | 0.11 | 19.69 | 0.75 | -0.10 | 1.30 | 0:00 | proline dipeptidase |
| pepT | -0.12 | -1.75 | 0.56 | -0.45 | -4.33 | 0.55 | putative peptidase T |
| perM | -1.12 | -0.45 | 0.62 | -0.15 | -1.07 | 1.15 | putative permease |
| perR | 1.62 | -1.50 | 0.79 | 1.45 | -1.60 | 1.30 | putative transcriptional regulator LYSR-type |
| pfkA | 0.30 | -1.31 | -0.25 | 0.45 | -1.20 | 0.15 | 6-phosphofructokinase I |
| pfkB | 0.85 | 0.89 | 0.86 | 0.35 | -1.10 | 1.15 | 6-phosphofructokinase II; suppressor of pfkA |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| pflA | 0.17 | 1.80 | 1.03 | 0.00 | 1.10 | 0.30 | pyruvate formate lyase activating enzyme 1 |
| pflB | -0.61 | -1.91 | 0.92 | -0.10 | -5.27 | 0.55 | formate acetyltransferase 1 |
| pflC | -0.01 | -1.68 | -0.89 | 1.50 | -1.20 | -1.40 | probable pyruvate formate lyase activating enzyme 2 |
| pflD | 0.58 | 1.41 | 0.60 | 1.85 | 1.30 | 0.25 | formate acetyltransferase 2 |
| pfs | 0.01 | 0.89 | 0.74 | -0.30 | 1.47 | -0.30 | orf, hypothetical protein |
| pgi | 0.18 | 0.31 | 0.84 | -0.25 | 0.63 | 1.15 | glucosephosphate isomerase |
| pgk | -0.24 | 0.31 | -1.22 | -0.15 | -1.43 | -1.15 | phosphoglycerate kinase |
| pgm | 0.28 | 0.74 | 1.03 | 1.25 | 0.47 | 1.25 | phosphoglucomutase |
| pgpA | -0.67 | -4.76 | 0.91 | -1.10 | -1.27 | 1.20 | phosphatidylglycerophosphatase |
| pgpB | 1.25 | 0.28 | -0.58 | 1.90 | 0.53 | 0.05 | non-essential phosphatidylglycerophosphate phosphatase, membrane bound |
| pgsA | -1.68 | -1.16 | 0.47 | -1.90 | 1.10 | 0.00 | phosphatidylglycerophosphate synthetase |
| pheA | -0.94 | -1.51 | 0.54 | -0.50 | -1.80 | 0.05 | chorismate mutase-P and prephenate dehydratase |
| pheL | 0.65 | 0.05 | -0.43 | 0.05 | 1.23 | 0.05 | leader peptide of chorismate mutase-P-prephenate dehydratase |
| pheM | 0.57 | -1.19 | -1.02 | 1.25 | -0.23 | -0.05 | phenylalanyl-tRNA synthetase (pheST) operon leader peptide |
| pheP | -1.31 | -1.30 | 0.68 | -1.75 | 0.07 | 0.05 | phenylalanine-specific transport system |
| pheS | 0.04 | -0.60 | -1.04 | 0.00 | 0.07 | -1.15 | phenylalanine tRNA synthetase, alpha-subunit |
| pheT | -0.82 | -0.68 | -1.23 | -1.55 | -1.70 | -0.35 | phenylalanine tRNA synthetase, beta-subunit |
| pheU | 0.43 | -2.49 | 0.67 | 0.05 | -1.65 | 8.90 | Phenylalanine tRNA |
| pheV | 0.46 | -2.25 | 0.86 | 0.40 | -2.25 | 14.90 | Phenylalanine tRNA |
| phnA | 0.38 | 0.17 | -0.40 | 0.20 | 0.27 | 0.00 | orf, hypothetical protein |
| phnB | 0.37 | -1.33 | 1.52 | 0.45 | 0.23 | 1.30 | orf, hypothetical protein |
| phnC | 1.83 | 1.41 | 0.46 | 1.60 | 1.43 | 0.15 | ATP-binding component of phosphonate transport |
| phnD | -0.78 | -0.84 | -1.38 | -0.35 | -0.13 | -1.40 | periplasmic binding protein component of Pn transporter |
| phnE | 0.15 | -1.44 | -0.79 | 1.15 | -0.57 | -1.35 | membrane channel protein component of Pn transporter |
| phnF | 1.24 | -1.36 | 0.70 | 1.50 | -0.37 | 0.10 | putative transcriptional regulator |
| phnG | -0.11 | 1.49 | -0.64 | 0.40 | 1.10 | -0.20 | phosphonate metabolism |
| phnH | 0.64 | -1.33 | 0.78 | 0.50 | -0.10 | 1.20 | phosphonate metabolism |
| phnI | 0.31 | 1.41 | -0.82 | 2.05 | 1.30 | 0.00 | phosphonate metabolism |
| phnJ | -0.19 | -1.33 | -1.42 | 1.55 | -0.37 | -1.35 | phosphonate metabolism |
| phnK | -0.99 | 0.48 | 0.80 | -2.50 | 0.23 | 1.55 | ATP-binding component of phosphonate transport |
| phnL | -0.82 | 1.07 | 0.39 | 0.20 | 1.37 | 0.15 | ATP-binding component of phosphonate transport |
| phnM | -0.03 | -1.25 | 0.93 | 0.05 | -0.33 | 1.25 | phosphonate metabolism |
| phnN | 0.15 | 4.59 | 0.88 | -0.05 | 2.27 | 1.45 | ATP-binding component of phosphonate transport |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| phnO | -0.71 | -0.33 | -0.15 | -0.20 | -0.30 | -0.25 | putative regulator, phn operon |
| phnP | -0.31 | -0.73 | 0.44 | 0.40 | 0.37 | 0.60 | phosphonate metabolism |
| phnQ | 1.39 | -1.35 | 0.60 | 2.15 | -0.37 | 0.30 | orf, hypothetical protein |
| phoA | 0.52 | -1.23 | 1.25 | -1.15 | -1.23 | 1.05 | alkaline phosphatase |
| phoB | 1.01 | 1.24 | -1.08 | 0.65 | 1.33 | -1.20 | positive response regulator for pho regulon, sensor is PhoR (or CreC) |
| phoE | 1.35 | 0.00 | 0.77 | 2.25 | 1.03 | 1.25 | outer membrane pore protein E (E,Ic,NmpAB) |
| phoH | 0.21 | -1.29 | -0.96 | 0.85 | -0.70 | -1.05 | PhoB-dependent, ATP-binding pho regulon component; may be helicase; induced by P starvation |
| phoP | -0.14 | -1.32 | -1.21 | 0.00 | -1.57 | -1.50 | transcriptional regulatory protein |
| phoQ | -0.05 | 1.15 | -1.21 | -0.05 | 1.10 | -1.70 | sensor protein PhoQ |
| phoR | 0.72 | 0.99 | 1.23 | 1.70 | 1.27 | 1.20 | positive and negative sensor protein for pho regulon |
| phoU | -0.33 | 1.64 | 0.73 | -0.30 | 1.53 | -0.30 | negative regulator for pho regulon and putative enzyme in phosphate metabolism |
| phpB | 0.11 | -1.26 | -1.38 | 0.15 | -0.70 | -1.70 | homolog of Salmonella cobC, a phosphohistidine protein |
| phrB | 0.44 | 1.10 | 0.88 | 0.60 | 1.33 | 1.60 | deoxyribodipyrimidine photolyase (photoreactivation) |
| pin | -0.52 | -1.14 | -0.52 | -0.05 | -0.27 | 0.05 | inversion of adjacent DNA; at locus of e14 element |
| pinO | 0.35 | 1.21 | 0.67 | 0.40 | 1.63 | 0.05 | calcium-binding protein required for initiation of chromosome replication |
| pitA | 0.09 | -0.94 | -0.71 | 0.10 | -0.53 | 0.00 | low-affinity phosphate transport |
| pitB | -0.94 | 0.87 | 0.52 | 0.05 | 1.83 | 0.05 | low-affinity phosphate transport |
| pldA | 1.53 | 5.25 | -1.30 | 1.65 | 1.60 | -0.15 | outer membrane phospholipase A |
| pldB | 0.32 | 0.00 | -0.58 | 0.50 | 0.60 | 0.05 | lysophospholipase L(2) |
| plsB | -0.73 | -1.22 | 0.81 | -0.55 | -1.47 | 0.05 | glycerol-3-phosphate acyltransferase |
| plsC | 1.13 | -1.27 | 0.75 | 1.75 | -0.40 | -0.30 | 1-acyl-sn-glycerol-3-phosphate acyltransferase |
| plsX | 0.46 | 1.23 | -1.15 | 0.85 | 1.43 | -1.60 | glycerolphosphate auxotrophy in plsB background |
| pmbA | -0.35 | -0.29 | -0.40 | 0.05 | 0.13 | 0.05 | maturation of antibiotic MccB17, see tld genes |
| pmrD | 0.21 | 1.27 | 0.67 | -0.15 | 0.33 | 0.10 | polymyxin resistance protein B |
| pncB | 1.72 | -1.33 | 1.33 | 2.10 | 1.20 | 1.25 | nicotinate phosphoribosyltransferase |
| pnp | 0.61 | 2.83 | 0.87 | -0.20 | 1.60 | 0.15 | polynucleotide phosphorylase; cytidylate kinase activity |
| pntA | 0.31 | -1.59 | -0.78 | 0.10 | -1.20 | 0.00 | pyridine nucleotide transhydrogenase, alpha subunit |
| pntB | -1.50 | -0.75 | -0.76 | -2.40 | -0.50 | -1.35 | pyridine nucleotide transhydrogenase, beta subunit |
| pnuC | 0.29 | -1.32 | 0.86 | 0.50 | -0.87 | 1.40 | required for NMN transport |
| polA | 2.18 | 0.34 | 1.78 | 1.95 | -0.20 | 1.25 | DNA polymerase I, 3 --> 5 polymerase, 5 --> 3 and 3 --> 5 exonuclease |
| polB | -0.66 | -0.83 | -1.32 | 0.05 | -0.37 | -1.35 | DNA polymerase II |
| potA | 1.15 | 1.17 | -0.46 | 1.10 | -0.10 | 0.05 | ATP-binding component of spermidine |
| potB | 0.04 | -1.16 | -1.08 | 1.10 | -1.20 | -0.15 | spermidine |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| potC | -0.81 | -1.30 | -0.57 | -1.25 | -1.37 | 0.05 | spermidine |
| potD | -3.42 | 0.75 | 9.71 | -1.50 | 0.10 | 1.55 | spermidine |
| potE | 0.18 | -1.31 | 1.28 | -0.10 | -0.63 | 1.60 | putrescine transport protein |
| potF | 0.70 | 0.52 | -1.00 | 1.60 | 1.23 | -0.05 | periplasmic putrescine-binding protein; permease protein |
| potG | 0.36 | -1.34 | 0.65 | 0.35 | -1.93 | 0.00 | ATP-binding component of putrescine transport system |
| potH | -0.61 | 0.04 | -1.05 | 0.10 | 1.30 | -0.10 | putrescine transport protein; permease |
| potI | -0.56 | 0.23 | 1.00 | 0.10 | 1.53 | 1.30 | putrescine transport protein; permease |
| poxB | 0.30 | 0.82 | -1.16 | -0.15 | 1.57 | -0.20 | pyruvate oxidase |
| ppa | 0.21 | 1.10 | 1.19 | 1.40 | 0.50 | -0.10 | inorganic pyrophosphatase |
| ppc | -0.47 | -102.25 | -1.85 | -1.25 | 0.07 | -1.40 | phosphoenolpyruvate carboxylase |
| ppdA | 1.25 | -19.65 | 0.72 | 2.05 | -0.33 | 0.20 | prepilin peptidase dependent protein A |
| ppdB | 0.34 | 0.55 | -1.39 | 1.50 | 0.43 | -1.20 | prepilin peptidase dependent protein B |
| ppdC | -0.09 | 0.00 | -1.30 | -1.60 | -1.20 | -0.10 | prepilin peptidase dependent protein C |
| ppdD | 0.61 | -1.33 | -1.37 | 0.50 | 0.57 | -1.30 | prelipin peptidase dependent protein |
| pphA | 0.08 | 0.08 | 0.86 | 1.20 | 1.30 | 0.20 | protein phosphatase 1 modulates phosphoproteins, signals protein misfolding |
| pphB | -0.77 | -1.74 | -1.36 | -0.05 | -1.30 | -1.50 | protein phosphatase 2 |
| ppiA | 0.02 | -1.45 | 0.71 | 0.10 | -1.40 | 0.05 | peptidyl-prolyl cis-trans isomerase A (rotamase A) |
| ppiB | 0.36 | 1.79 | 2.36 | 0.15 | 0.57 | 1.20 | peptidyl-prolyl cis-trans isomerase B (rotamase B) |
| ppiC | 0.23 | -0.20 | -0.55 | -0.20 | -0.30 | 0.00 | peptidyl-prolyl cis-trans isomerase C (rotamase C) |
| ppk | -1.10 | -0.98 | -0.47 | -0.10 | 0.03 | 0.10 | polyphosphate kinase |
| ppsA | -0.73 | -2.20 | 0.64 | -1.25 | -1.87 | 0.10 | phosphoenolpyruvate synthase |
| ppx | -1.59 | 1.06 | -1.00 | -1.50 | 0.60 | -0.30 | exopolyphosphatase |
| pqiA | 0.82 | -0.72 | 1.61 | 1.25 | -0.30 | 1.30 | paraquat-inducible protein A |
| pqiB | -1.84 | -1.34 | 0.37 | -1.50 | -1.57 | 0.15 | paraquat-inducible protein B |
| pqqL | -3.68 | 1.97 | 0.21 | -2.15 | -0.17 | 0.05 | putative peptidase |
| prc | -0.81 | -0.79 | -0.02 | -1.25 | -1.23 | -1.10 | carboxy-terminal protease for penicillin-binding protein 3 |
| prfA | 0.95 | 0.00 | 0.87 | -1.05 | -1.40 | 1.45 | peptide chain release factor RF-1 |
| prfB | -0.05 | 2.99 | 0.89 | 0.05 | 1.40 | 0.10 | peptide chain release factor RF-2 |
| prfC | -0.37 | -1.15 | 0.65 | -1.30 | -0.60 | -1.45 | peptide chain release factor RF-3 |
| prfH | -1.03 | -1.83 | 0.72 | -0.20 | -1.20 | 0.00 | probable peptide chain release factor |
| priA | 0.75 | 0.00 | 0.94 | 1.35 | 0.40 | 1.60 | primosomal protein N ( |
| priB | 0.02 | 4.14 | 0.37 | 0.60 | 2.07 | 0.20 | primosomal replication protein N |
| priC | -0.95 | -1.90 | -1.35 | -0.35 | -0.07 | -1.55 | primosomal replication protein N |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| prkB | 0.70 | -0.56 | -1.47 | 1.25 | 1.07 | -1.25 | probable phosphoribulokinase |
| prlA | 0.35 | 4.52 | 0.97 | 0.55 | 2.27 | 0.45 | putative ATPase subunit of translocase |
| prlC | 0.62 | 1.43 | -1.55 | 2.40 | 1.47 | -1.50 | oligopeptidase A |
| prmA | -1.14 | -1.33 | -0.73 | -1.45 | -0.43 | 0.05 | methylase for 50S ribosomal subunit protein L11 |
| proA | -0.30 | -0.97 | -1.27 | -0.20 | -0.13 | -1.75 | gamma-glutamylphosphate reductase |
| proB | 0.13 | -1.31 | -0.77 | -0.35 | -1.57 | -1.15 | gamma-glutamate kinase |
| proC | -0.02 | -1.75 | -1.03 | -0.35 | -1.23 | -0.10 | pyrroline-5-carboxylate reductase |
| proK | 0.14 | 0.67 | 0.42 | 0.05 | 4.17 | 2.75 | Proline tRNA1 |
| proL | 0.19 | -0.29 | 0.01 | 1.20 | 0.20 | 4.20 | Proline tRNA2 |
| proM | 0.50 | 0.73 | 0.10 | 0.50 | 3.40 | 1.00 | Proline tRNA3 |
| proP | -0.67 | -0.71 | 0.41 | -0.95 | 1.20 | 0.05 | low-affinity transport system; proline permease II |
| proS | -0.89 | 1.48 | 1.01 | -0.15 | 1.23 | -0.10 | proline tRNA synthetase |
| proV | -0.03 | 0.24 | -1.51 | -0.20 | 0.30 | -1.10 | ATP-binding component of transport system for glycine, betaine and proline |
| proW | 0.12 | -1.34 | 1.06 | -0.15 | -1.20 | 1.55 | high-affinity transport system for glycine betaine and proline |
| proX | -0.18 | -1.33 | -0.99 | -1.70 | -2.50 | -1.15 | high-affinity transport system for glycine betaine and proline |
| proY | -1.40 | 1.68 | -1.29 | -1.30 | 1.87 | -1.10 | proline permease transport protein |
| prpB | -0.53 | 1.45 | 1.34 | -0.10 | 0.03 | 1.40 | putative phosphonomutase 2 |
| prpC | 1.03 | 0.21 | -1.34 | 0.40 | 0.63 | -0.05 | putative citrate synthase; propionate metabolism? |
| prpD | -0.44 | -1.33 | -1.12 | -1.30 | -0.03 | 0.00 | orf, hypothetical protein |
| prpE | 2.23 | -1.40 | -0.76 | 2.50 | -1.43 | 0.00 | putative propionyl-CoA synthetase |
| prpR | 0.66 | 0.96 | -0.98 | 1.85 | 1.57 | -0.10 | regulator for prp operon |
| prsA | 1.61 | 1.65 | 0.59 | 2.80 | 1.53 | 0.15 | phosphoribosylpyrophosphate synthetase |
| psd | -0.17 | 1.96 | -1.35 | -0.05 | 1.23 | -1.40 | phosphatidylserine decarboxylase; phospholipid synthesis |
| pshM | 0.29 | 0.59 | -1.41 | 1.40 | -0.30 | -1.35 | putative general secretion |
| psiF | -0.95 | 0.33 | 0.50 | -0.95 | 0.40 | 1.30 | induced by phosphate starvation |
| pspA | 0.65 | 4.91 | 0.59 | 0.20 | 2.53 | 1.15 | phage shock protein, inner membrane protein |
| pspB | 0.40 | 3.00 | 0.33 | 0.45 | 1.60 | -0.40 | phage shock protein |
| pspC | 0.87 | 2.36 | -1.41 | 0.05 | 1.57 | -1.50 | phage shock protein: activates phage shock-protein expression |
| pspD | 0.69 | -0.98 | 0.70 | 1.60 | 0.03 | -0.40 | phage shock protein |
| pspE | -0.64 | -0.87 | 1.38 | -3.25 | 0.13 | 0.10 | phage shock protein |
| pspF | 0.60 | -1.41 | 0.75 | -0.10 | -1.37 | -0.30 | psp operon transcriptional activator |
| pssA | -0.56 | 2.01 | -1.29 | -1.05 | 1.30 | -1.35 | phosphatidylserine synthase; phospholipid synthesis |
| pssR | -0.01 | -1.12 | 0.14 | 0.85 | -0.23 | 0.00 | regulator of pssA |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| pstA | -0.56 | 0.97 | 0.26 | -0.05 | 0.20 | -0.10 | high-affinity phosphate-specific transport system |
| pstB | -0.39 | 2.00 | -1.36 | -0.35 | 1.40 | -1.25 | ATP-binding component of high-affinity phosphate-specific transport system |
| pstC | -0.48 | 0.47 | -0.54 | -0.20 | 0.13 | -1.05 | high-affinity phosphate-specific transport system, cytoplasmic membrane component |
| pstS | 1.26 | 1.72 | -1.22 | 0.20 | 2.70 | -0.20 | high-affinity phosphate-specific transport system; periplasmic phosphate-binding protein |
| pta | 0.05 | 0.45 | 1.24 | -0.30 | 0.17 | -0.05 | phosphotransacetylase |
| pth | 0.24 | 0.83 | -1.31 | 0.10 | -0.37 | -1.15 | peptidyl-tRNA hydrolase |
| ptr | -0.57 | -1.97 | 0.44 | -0.20 | -1.17 | 0.00 | protease III |
| ptrB | 0.02 | 1.38 | 0.94 | 0.10 | 1.77 | 1.35 | protease II |
| ptsA | 0.69 | 0.34 | 0.59 | 1.65 | 1.37 | 0.10 | PEP-protein phosphotransferase system enzyme I |
| ptsG | -1.63 | -12.78 | -0.19 | -2.45 | -4.97 | 0.25 | PTS system, glucose-specific IIBC component |
| ptsH | -0.56 | -1.24 | -0.16 | -1.20 | -2.47 | 0.10 | PTS system protein HPr |
| ptsI | -0.31 | -0.76 | 0.99 | -0.45 | -1.63 | -0.15 | PEP-protein phosphotransferase system enzyme I |
| ptsN | -0.49 | -1.27 | -0.02 | -0.55 | -1.53 | 0.15 | phosphotransferase system enzyme IIA, regulates N metabolism |
| ptsO | 1.59 | 1.29 | 0.92 | 2.20 | 0.30 | 1.45 | phosphocarrier protein HPr-like NPr, nitrogen related, exchanges phosphate with Enzyme I, Hpr |
| ptsP | 0.23 | 0.00 | -1.26 | -0.50 | -0.27 | -1.10 | PTS system, enzyme I, transcriptional regulator (with NPR and NTR proteins) |
| ptxA | -0.11 | -1.34 | -1.71 | -0.20 | -1.70 | -1.05 | putative PTS system enzyme II A component |
| purA | -0.27 | -0.33 | -0.14 | -0.05 | -0.17 | 0.05 | adenylosuccinate synthetase |
| purB | 0.80 | -0.72 | 0.29 | 0.90 | -0.30 | 0.35 | adenylosuccinate lyase |
| purC | 0.84 | 0.56 | 1.16 | 0.40 | 0.07 | 1.20 | phosphoribosylaminoimidazole-succinocarboxamide synthetase |
| purD | 0.16 | 1.19 | 1.26 | 0.10 | 0.57 | 1.15 | phosphoribosylglycinamide synthetase |
| purE | -2.03 | 1.43 | 0.84 | -1.25 | 1.33 | 1.25 | phosphoribosylaminoimidazole carboxylase |
| purF | -0.88 | -0.95 | -1.31 | 0.00 | -0.30 | -1.35 | amidophosphoribosyltransferase |
| purH | -0.74 | 0.78 | -1.43 | 0.00 | 1.47 | -1.45 | phosphoribosylaminoimidazolecarboxamideformyltransferase |
| purK | 0.30 | -1.27 | -1.41 | 0.20 | -0.90 | -1.20 | phosphoribosylaminoimidazole carboxylase |
| purL | -1.24 | -1.06 | 0.85 | -0.30 | -0.40 | 1.35 | phosphoribosylformyl-glycineamide synthetase |
| purM | -0.82 | 1.97 | -1.60 | -1.35 | -0.33 | -1.05 | phosphoribosylaminoimidazole synthetase |
| purN | -0.69 | -1.12 | -0.53 | 1.00 | -0.27 | -1.60 | phosphoribosylglycinamide formyltransferase 1 |
| purR | -0.58 | 0.93 | 1.46 | -0.10 | 1.40 | 1.20 | transcriptional repressor for pur regulon, glyA, glnB, prsA, speA |
| purT | 0.78 | -1.33 | -1.32 | 2.70 | -0.50 | -1.65 | phosphoribosylglycinamide formyltransferase 2 |
| purU | 0.40 | -1.44 | 0.43 | 1.45 | -1.37 | 0.00 | formyltetrahydrofolate deformylase; for purT-dependent FGAR synthesis |
| putA | -3.50 | -1.52 | -0.78 | -2.95 | -2.23 | 0.05 | proline dehydrogenase, P5C dehydrogenase |
| putP | -3.76 | 0.16 | 0.40 | -2.65 | 1.67 | 0.55 | major sodium |
| pykA | -0.39 | -0.53 | 0.88 | -1.20 | -0.20 | 1.15 | pyruvate kinase II, glucose stimulated |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| pykF | -0.17 | 0.83 | -0.91 | -0.35 | 1.07 | -1.30 | pyruvate kinase I (formerly F), fructose stimulated |
| pyrB | 0.37 | 2.04 | 0.71 | 1.40 | 1.47 | 1.15 | aspartate carbamoyltransferase, catalytic subunit |
| pyrC | 0.06 | 2.28 | 1.01 | 0.25 | 1.33 | 1.30 | dihydro-orotase |
| pyrD | 0.07 | 0.76 | -1.32 | -0.70 | 0.57 | -1.40 | dihydro-orotate dehydrogenase |
| pyrE | 1.65 | -1.15 | 1.61 | 1.65 | -0.27 | 1.30 | orotate phosphoribosyltransferase |
| pyrF | 1.26 | 1.40 | 0.55 | 0.10 | 1.33 | 0.25 | orotidine-5 -phosphate decarboxylase |
| pyrG | -1.51 | 2.70 | 0.35 | -1.50 | 1.70 | -2.85 | 2907688.00 |
| pyrH | -1.10 | 1.18 | 0.09 | -1.45 | 1.33 | 0.15 | uridylate kinase |
| pyrI | 0.18 | 0.57 | -1.14 | 0.70 | 0.30 | -1.50 | aspartate carbamoyltransferase, regulatory subunit |
| pyrL | 0.19 | -1.33 | -1.28 | 1.55 | -0.27 | -0.05 | pyrBI operon leader peptide |
| qor | -0.43 | -1.66 | 0.93 | -0.45 | -1.87 | 1.30 | quinone oxidoreductase |
| queA | 0.54 | 0.77 | 0.84 | 1.70 | 0.17 | 1.30 | synthesis of queuine in tRNA; probably S-adenosylmethionine:tRNA ribosyltransferase-isomerase |
| racC | 0.99 | -1.27 | 0.81 | 0.20 | -0.13 | 1.30 | defective prophage rac; contains recE and oriJ |
| radC | 4.33 | 0.93 | 2.00 | 1.55 | 1.40 | 1.30 | DNA repair protein |
| rarD | 0.02 | 0.96 | -0.36 | 0.50 | 1.60 | -0.05 | orf, hypothetical protein |
| rbfA | 0.92 | -0.06 | 0.97 | 0.40 | -0.23 | 1.40 | ribosome-binding factor A |
| rbn | 0.06 | -2.20 | 0.98 | 0.50 | -1.27 | 1.45 | tRNA processing exoribonuclease BN |
| rbsA | 0.28 | -1.28 | -0.27 | -0.75 | 0.33 | -0.05 | ATP-binding component of D-ribose high-affinity transport system |
| rbsB | -0.44 | -6.28 | 0.61 | -0.50 | -2.77 | 1.30 | D-ribose periplasmic binding protein |
| rbsC | 0.42 | -0.12 | -1.39 | 0.05 | 0.17 | -1.25 | D-ribose high-affinity transport system |
| rbsD | 0.03 | -1.47 | 0.06 | -0.90 | -4.83 | 0.25 | D-ribose high-affinity transport system; membrane-associated protein |
| rbsK | 0.64 | -1.41 | 1.43 | 1.75 | -1.40 | 1.40 | ribokinase |
| rbsR | 0.20 | -0.12 | 1.10 | 0.10 | -1.20 | 1.45 | regulator for rbs operon |
| rcsA | 0.62 | -1.33 | -1.25 | 1.20 | -1.23 | -1.15 | positive regulator for ctr capsule biosynthesis, positive transcription factor |
| rcsB | -0.41 | -1.40 | 1.08 | -1.45 | -1.80 | 1.30 | positive response regulator for colanic capsule biosynthesis, (sensor, RcsC) |
| rcsC | -1.77 | -1.30 | 0.00 | -1.15 | -0.77 | -1.20 | sensor for ctr capsule biosynthesis, probable histidine kinase acting on RcsB |
| rcsF | 0.13 | 2.43 | -1.35 | 0.00 | 1.33 | -2.15 | regulator in colanic acid synthesis; interacts with RcsB |
| recA | 2.22 | 4.47 | 1.06 | 16.50 | 4.27 | 2.40 | DNA strand exchange and renaturation, DNA-dependent ATPase, DNA- and ATP-dependent |
| recB | -0.36 | -0.04 | -1.05 | -0.10 | -1.17 | -0.05 | DNA helicase, ATP-dependent dsDNA |
| recC | 0.69 | 1.43 | -1.39 | 1.20 | 0.57 | -1.40 | DNA helicase, ATP-dependent dsDNA |
| recD | 0.93 | 3.91 | -0.31 | 2.00 | 2.13 | 0.05 | DNA helicase, ATP-dependent dsDNA |
| recE | 0.89 | 1.24 | -1.29 | 0.30 | 1.20 | -0.35 | exonuclease VIII, ds DNA exonuclease, 5 --> 3 specific |
| recF | 1.02 | 1.51 | -0.11 | 2.00 | 1.63 | 0.70 | ssDNA and dsDNA binding, ATP binding |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| recG | 1.20 | 1.25 | 0.74 | 1.60 | 1.63 | 1.80 | DNA helicase, resolution of Holliday junctions, branch migration |
| recJ | -0.43 | -1.05 | 0.48 | -0.05 | -0.57 | -0.05 | ssDNA exonuclease, 5 --> 3 specific |
| recN | 0.99 | 3.48 | 0.51 | 5.90 | 3.23 | 0.55 | protein used in recombination and DNA repair |
| recO | 4.79 | -1.06 | 0.71 | 2.75 | 1.23 | 0.25 | protein interacts with RecR and possibly RecF proteins |
| recQ | 0.14 | 0.10 | 0.69 | 0.10 | 0.57 | 0.10 | ATP-dependent DNA helicase |
| recR | -0.45 | 0.92 | -0.50 | 0.05 | 1.43 | 0.00 | recombination and repair |
| recT | -0.69 | 1.81 | -1.34 | 0.40 | 2.33 | -1.55 | recombinase, DNA renaturation |
| relA | -1.55 | -1.59 | 0.77 | -2.05 | -1.17 | 1.65 | (p)ppGpp synthetase I (GTP pyrophosphokinase); regulation of RNA synthesis; stringent factor |
| relB | -1.32 | -0.95 | -1.31 | -2.10 | 0.07 | -1.55 | negative regulator of translation |
| relE | -1.41 | 1.62 | 0.70 | -1.40 | 1.40 | 1.10 | orf, hypothetical protein |
| relF | -0.21 | 0.43 | -1.20 | -1.25 | 0.50 | -0.15 | polypeptide destructive to membrane potential |
| rem | -1.13 | -1.16 | -0.09 | -0.45 | -0.27 | 0.20 | orf, hypothetical protein |
| rep | -1.03 | 1.44 | 1.21 | 0.10 | 0.43 | 1.35 | rep helicase, a single-stranded DNA dependent ATPase |
| rfaB | -0.39 | -1.25 | -0.47 | -0.20 | -0.33 | 0.15 | UDP-D-galactose:(glucosyl)lipopolysaccharide-1,6- D-galactosyltransferase |
| rfaC | 0.30 | -0.09 | 1.23 | 1.40 | -0.40 | 1.35 | heptosyl transferase I; lipopolysaccharide core biosynthesis |
| rfaD | 0.42 | 0.98 | 0.68 | 0.30 | 0.17 | 0.35 | ADP-L-glycero-D-mannoheptose-6-epimerase |
| rfaF | -0.08 | 5.76 | -0.07 | 0.30 | 1.53 | 0.10 | ADP-heptose--lps heptosyltransferase II; lipopolysaccharide core biosynthesis |
| rfaG | -0.30 | 4.08 | 0.62 | -0.20 | 1.33 | 0.25 | glucosyltransferase I; lipopolysaccharide core biosynthesis |
| rfaH | 3.35 | -1.35 | -1.25 | 2.05 | -0.63 | -0.25 | transcriptional activator affecting biosynthesis of lipopolysaccharide core, F pilin, and haemolysin |
| rfaI | -0.86 | -1.35 | 0.81 | -0.05 | 0.33 | 1.00 | UDP-D-galactose:(glucosyl)lipopolysaccharide- alpha-1,3-D-galactosyltransferase |
| rfaJ | 2.06 | 0.74 | 1.63 | 1.50 | 0.67 | 1.20 | UDP-D-glucose:(galactosyl)lipopolysaccharide glucosyltransferase |
| rfaK | 1.41 | -1.07 | 0.86 | 1.45 | -0.30 | 0.05 | probably hexose transferase; lipopolysaccharide core biosynthesis |
| rfaL | 7.73 | -0.91 | 0.03 | 1.40 | -0.37 | 0.05 | O-antigen ligase; lipopolysaccharide core biosynthesis |
| rfaP | 0.08 | 2.67 | 1.13 | 0.10 | 1.30 | -0.05 | lipopolysaccharide core biosynthesis; phosphorylation of core heptose |
| rfaQ | 0.06 | -0.36 | -0.11 | -0.15 | 1.70 | -1.10 | lipopolysaccharide core biosynthesis |
| rfaS | 0.81 | -1.12 | -1.23 | 1.25 | -0.13 | -1.05 | lipopolysaccharide core biosynthesis |
| rfaY | 0.20 | -1.52 | -1.23 | 1.25 | -1.30 | -0.30 | lipopolysaccharide core biosynthesis |
| rfaZ | 1.94 | 1.21 | 0.28 | 1.80 | 0.73 | 0.25 | lipopolysaccharide core biosynthesis |
| rfbA | -1.75 | -0.14 | 0.82 | -0.30 | -0.30 | -0.10 | glucose-1-phosphate thymidylyltransferase |
| rfbB | 0.51 | 0.80 | -0.48 | 0.25 | -0.20 | -0.10 | dTDP-glucose 4,6 dehydratase |
| rfbC | 0.26 | 1.38 | 1.50 | -0.20 | 1.97 | 1.45 | dTDP-6-deoxy-D-glucose-3,5 epimerase |
| rfbD | -1.64 | -0.73 | 2.74 | -0.05 | -1.33 | 1.20 | dTDP-6-deoxy-L-mannose-dehydrogenase |
| rfbX | 0.13 | 2.46 | -1.19 | -0.25 | 1.47 | -1.15 | putative O-antigen transporter |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| rfe | 1.13 | -1.42 | -1.31 | 2.20 | -1.13 | -1.15 | UDP-GlcNAc:undecaprenylphosphate GlcNAc-1-phosphate transferase; synthesis of enterobacterial |
| rffG | -0.15 | 4.41 | 0.65 | -0.05 | 1.57 | 0.00 | dTDP-glucose 4,6-dehydratase |
| rffH | 0.13 | -1.24 | 0.56 | 1.20 | -0.70 | -0.10 | glucose-1-phosphate thymidylyltransferase |
| rhaA | -0.11 | -1.26 | -0.77 | 0.75 | -0.07 | 0.00 | L-rhamnose isomerase |
| rhaB | 0.80 | 3.27 | -1.40 | 1.65 | 2.07 | -1.45 | rhamnulokinase |
| rhaD | -0.59 | -1.29 | 0.22 | 2.10 | -0.50 | 0.10 | rhamnulose-phosphate aldolase |
| rhaR | -0.30 | -1.23 | -1.29 | 0.55 | -0.40 | -0.20 | positive regulator for rhaRS operon |
| rhaS | 1.47 | -0.65 | 0.20 | 2.40 | 1.33 | 0.05 | positive regulator for rhaBAD operon |
| rhaT | 0.01 | -1.03 | -1.33 | 1.10 | 0.10 | -1.30 | rhamnose transport |
| rhlB | 0.15 | 8.40 | 1.04 | -0.25 | 1.70 | 1.25 | putative ATP-dependent RNA helicase |
| rhlE | -0.89 | -1.35 | 0.53 | 0.10 | -1.47 | 0.25 | putative ATP-dependent RNA helicase |
| rho | 0.45 | 4.95 | 0.73 | 1.80 | 1.87 | -0.15 | transcription termination factor Rho; polarity suppressor |
| rhoL | 0.08 | 3.87 | 0.79 | 0.05 | 1.70 | 0.05 | rho operon leader peptide |
| rhsA | 0.81 | 2.06 | 0.31 | 1.55 | 1.40 | 0.40 | rhsA protein in rhs element |
| rhsB | -0.54 | 0.91 | 0.76 | 0.05 | 1.50 | 1.25 | rhsB protein in rhs element |
| rhsC | -0.85 | -0.94 | 0.05 | -0.55 | -0.27 | 0.30 | rhsC protein in rhs element |
| rhsD | -0.98 | -1.53 | -0.35 | 0.10 | -1.33 | -0.10 | rhsD protein in rhs element |
| rhsE | -0.94 | -1.43 | -1.15 | 0.15 | -0.30 | -0.20 | rhsE protein in rhs element |
| ribA | -0.49 | 0.77 | -1.07 | -2.60 | -0.17 | -0.20 | GTP cyclohydrolase II |
| ribB | -0.23 | -1.12 | 0.66 | -0.25 | -0.60 | 0.10 | 3,4 dihydroxy-2-butanone-4-phosphate synthase |
| ribD | 0.04 | -0.86 | 0.96 | -0.05 | -1.23 | -0.05 | bifunctional pyrimidine deaminase |
| ribE | 1.40 | -2.57 | 1.29 | 0.55 | -2.40 | 1.25 | riboflavin synthase, alpha chain |
| ribF | 1.13 | 1.70 | -1.33 | 1.40 | 1.20 | -1.55 | putative regulator |
| ribH | 0.78 | 2.56 | 0.46 | 1.30 | 1.50 | 0.30 | riboflavin synthase, beta chain |
| rimI | 0.06 | 2.60 | 1.00 | 0.20 | 1.53 | 0.00 | acyltransferase for 30S ribosomal subunit protein S18; acetylation of N-terminal alanine |
| rimJ | -0.37 | 0.52 | 0.54 | -0.50 | 0.13 | 0.05 | acetylation of N-terminal alanine of 30S ribosomal subunit protein S5 |
| rimK | 0.00 | 0.00 | 0.92 | -2.60 | 0.00 | 1.20 | ribosomal protein S6 modification protein |
| rimL | -0.69 | 0.87 | -0.57 | -0.25 | 3.70 | 0.10 | acetylation of N-terminal serine of 30S ribosomal subunit protein L7; acetyl transferase |
| rlpA | 0.05 | 0.00 | 0.84 | -0.65 | 0.20 | 1.25 | a minor lipoprotein |
| rlpB | -0.14 | 1.37 | -1.25 | -0.15 | 0.40 | -1.50 | a minor lipoprotein |
| rmf | -0.90 | -3.82 | -0.06 | -7.45 | -4.45 | 6.50 | ribosome modulation factor |
| rna | -0.16 | -1.13 | -0.08 | -0.15 | -0.23 | 0.25 | RNase I, cleaves phosphodiester bond between any two nucleotides |
| rnb | -1.36 | -1.54 | -1.30 | -2.60 | -1.37 | -1.35 | RNase II, mRNA degradation |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| rnc | -0.38 | 2.80 | -0.55 | -0.05 | 1.40 | -1.40 | RNase III, ds RNA |
| rnd | 0.81 | -1.02 | 0.83 | 1.45 | -0.27 | 1.15 | RNase D, processes tRNA precursor |
| rne | 0.21 | -0.32 | -1.21 | 0.05 | -0.20 | -1.30 | RNase E, membrane attachment, mRNA turnover, maturation 5S RNA |
| rnhA | 2.33 | -0.65 | -1.11 | 1.60 | -0.37 | -1.35 | RNase HI, degrades RNA of DNA-RNA hybrids, participates in DNA replication |
| rnhB | -0.50 | -1.30 | -0.41 | -0.15 | -1.50 | 0.15 | RNAse HII, degrades RNA of DNA-RNA hybrids |
| rnk | -2.03 | 0.19 | -0.36 | -1.90 | -0.27 | -1.15 | regulator of nucleoside diphosphate kinase |
| rnpA | 2.92 | 3.32 | -0.93 | 1.40 | 1.57 | -0.15 | RNase P, protein component; protein C5; processes tRNA, 4.5S RNA |
| rnpB | 0.38 | -2.17 | 0.06 | 0.15 | 16.23 | 15.60 | RNase P, RNA component; involved in tRNA and 4.5S RNA-processing |
| rnt | 0.02 | -1.29 | -1.76 | -0.10 | 0.43 | -1.05 | RNase T, degrades tRNA |
| rob | -0.53 | -1.51 | -1.10 | -2.25 | -1.40 | -0.10 | right origin-binding protein |
| rpe | 0.03 | -1.32 | 0.77 | -1.10 | -0.03 | 1.45 | D-ribulose-5-phosphate 3-epimerase |
| rph | 1.19 | -1.11 | 0.38 | 0.20 | -0.43 | -1.25 | RNase PH |
| rpiA | -0.18 | -1.37 | -0.94 | -0.20 | -1.87 | -1.45 | ribosephosphate isomerase, constitutive |
| rpiB | 1.26 | -1.00 | 0.00 | 1.80 | -0.40 | -0.05 | ribose 5-phosphate isomerase B |
| rpiR | 0.01 | 1.14 | 0.99 | 0.70 | 1.40 | 1.50 | transcriptional repressor of rpiB expression |
| rplA | 0.48 | 2.76 | 0.45 | 1.50 | 3.23 | 0.60 | 50S ribosomal subunit protein L1, regulates synthesis of L1 and L11 |
| rplB | 0.25 | 2.52 | 1.78 | 1.35 | 2.63 | 1.45 | 50S ribosomal subunit protein L2 |
| rplC | -0.22 | 2.70 | 0.64 | 0.85 | 2.40 | 0.00 | 50S ribosomal subunit protein L3 |
| rplD | -0.19 | 1.37 | -0.03 | 0.65 | 1.60 | -1.20 | 50S ribosomal subunit protein L4, regulates expression of S10 operon |
| rplE | -0.28 | 2.80 | 0.81 | 0.15 | 2.07 | 1.10 | 50S ribosomal subunit protein L5 |
| rplF | -0.12 | 3.07 | 0.64 | 0.45 | 2.30 | 0.35 | 50S ribosomal subunit protein L6 |
| rplI | -0.73 | 4.05 | 2.74 | -0.05 | 2.20 | 1.40 | 50S ribosomal subunit protein L9 |
| rplJ | 0.18 | 5.38 | 0.37 | 0.35 | 2.50 | 0.30 | 50S ribosomal subunit protein L10 |
| rplK | 0.66 | 1.35 | 1.30 | 2.05 | 1.55 | 1.50 | 50S ribosomal subunit protein L11 |
| rplL | 0.07 | 9.70 | 0.08 | 0.60 | 2.97 | -0.05 | 50S ribosomal subunit protein L7 |
| rplM | 1.07 | 4.47 | -0.05 | 1.60 | 2.23 | -1.15 | 50S ribosomal subunit protein L13 |
| rplN | 0.42 | 1.85 | -0.15 | 0.70 | 1.40 | 0.05 | 50S ribosomal subunit protein L14 |
| rplO | 0.15 | 4.09 | 1.60 | 1.25 | 3.00 | 2.00 | 50S ribosomal subunit protein L15 |
| rplP | 0.32 | 2.47 | -0.08 | 1.05 | 1.83 | -1.15 | 50S ribosomal subunit protein L16 |
| rplQ | 0.42 | 4.91 | 0.66 | 2.20 | 3.40 | 0.10 | 50S ribosomal subunit protein L17 |
| rplR | 0.01 | 1.27 | 0.14 | 0.60 | 1.77 | -1.25 | 50S ribosomal subunit protein L18 |
| rplS | 0.54 | 4.33 | 0.40 | 1.60 | 2.70 | 0.40 | 50S ribosomal subunit protein L19 |
| rplT | 0.84 | 0.52 | -0.84 | 2.50 | 1.25 | 0.05 | 50S ribosomal subunit protein L20, and regulator |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| rplU | **0.08** | **1.99** | **1.37** | 0.35 | 2.93 | 2.45 | 50S ribosomal subunit protein L21 |
| rplV | **0.19** | **2.24** | **0.66** | 1.00 | 2.07 | -0.10 | 50S ribosomal subunit protein L22 |
| rplW | **-0.15** | **3.69** | **0.40** | 0.75 | 3.47 | 0.10 | 50S ribosomal subunit protein L23 |
| rplX | **-0.31** | **2.39** | **1.15** | 0.20 | 2.33 | 0.40 | 50S ribosomal subunit protein L24 |
| rplY | **0.36** | **2.43** | **1.70** | 0.25 | 1.73 | 1.35 | 50S ribosomal subunit protein L25 |
| rpmA | **0.45** | **3.48** | **0.28** | 0.95 | 2.40 | 0.20 | 50S ribosomal subunit protein L27 |
| rpmB | **0.94** | **6.43** | **0.08** | 2.70 | 2.17 | -0.15 | 50S ribosomal subunit protein L28 |
| rpmC | **0.33** | **0.57** | **-0.27** | 5.15 | 0.10 | -0.05 | 50S ribosomal subunit protein L29 |
| rpmD | **0.07** | **1.96** | **1.52** | 0.75 | 2.87 | 1.50 | 50S ribosomal subunit protein L30 |
| rpmE | **0.15** | **-1.02** | **-1.19** | 0.30 | -2.13 | -1.65 | 50S ribosomal subunit protein L31 |
| rpmF | **0.78** | **-0.83** | **0.65** | 4.00 | -1.00 | 0.10 | 50S ribosomal subunit protein L32 |
| rpmG | **1.46** | **2.21** | **0.56** | 5.65 | 3.07 | 1.75 | 50S ribosomal subunit protein L33 |
| rpmH | **1.33** | **-0.98** | **-1.31** | 2.90 | -0.60 | -1.65 | 50S ribosomal subunit protein L34 |
| rpmI | **0.45** | **-0.99** | **-0.60** | 1.80 | -0.30 | 0.05 | 50S ribosomal subunit protein A |
| rpmJ | **0.73** | **0.74** | **0.81** | 1.45 | 1.25 | 3.65 | 50S ribosomal subunit protein L36 |
| rpoA | **0.13** | **2.92** | **-0.47** | 1.60 | 2.55 | -1.50 | RNA polymerase, alpha subunit |
| rpoB | **1.06** | **5.52** | **0.59** | 1.95 | 2.23 | 2.55 | RNA polymerase, beta subunit |
| rpoC | **0.44** | **2.57** | **-0.83** | 0.50 | 1.40 | -0.05 | RNA polymerase, beta prime subunit |
| rpoD | **0.42** | **0.51** | **-1.14** | 1.70 | 1.57 | -0.25 | RNA polymerase, sigma(70) factor; regulation of proteins induced at high temperatures |
| rpoE | **-0.39** | **0.22** | **0.73** | -1.25 | -0.07 | -0.25 | RNA polymerase, sigma-E factor; heat shock and oxidative stress |
| rpoH | **0.30** | **3.99** | **-1.44** | 0.25 | 1.73 | -1.50 | RNA polymerase, sigma(32) factor; regulation of proteins induced at high temperatures |
| rpoN | **-0.07** | **-2.67** | **0.00** | -1.00 | 0.00 | -0.30 | RNA polymerase, sigma(54 or 60) factor; nitrogen and fermentation regulation |
| rpoS | **-1.35** | **-10.87** | **-0.63** | -1.85 | -1.23 | 0.10 | RNA polymerase, sigma S (sigma38) factor; synthesis of many growth phase related proteins |
| rpoZ | **0.43** | **0.18** | **1.64** | 1.45 | -0.30 | 1.65 | RNA polymerase, omega subunit |
| rpsA | **0.07** | **1.77** | **0.96** | 0.60 | 1.67 | 0.00 | 30S ribosomal subunit protein S1 |
| rpsB | **-0.15** | **0.81** | **-0.02** | 0.55 | -0.37 | 0.05 | 30S ribosomal subunit protein S2 |
| rpsC | **0.48** | **5.27** | **0.14** | 3.10 | 2.43 | 0.15 | 30S ribosomal subunit protein S3 |
| rpsD | **0.29** | **3.22** | **1.47** | 1.10 | 2.23 | 1.20 | 30S ribosomal subunit protein S4 |
| rpsE | **0.10** | **3.20** | **0.65** | 0.85 | 2.30 | 0.05 | 30S ribosomal subunit protein S5 |
| rpsF | **-0.29** | **4.95** | **-0.14** | 0.70 | 1.90 | -0.05 | 30S ribosomal subunit protein S6 |
| rpsG | **-0.31** | **1.46** | **0.48** | 0.90 | 1.53 | 0.05 | 30S ribosomal subunit protein S7, initiates assembly |
| rpsH | **-0.11** | **2.06** | **0.78** | 0.30 | 2.40 | 0.05 | 30S ribosomal subunit protein S8, and regulator |
| rpsI | **1.08** | **8.48** | **0.95** | 2.20 | 2.50 | 0.30 | 30S ribosomal subunit protein S9 |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| rpsJ | 0.44 | 3.23 | -0.08 | 1.35 | 2.17 | -1.20 | 30S ribosomal subunit protein S10 |
| rpsK | -0.28 | 2.92 | 0.80 | 0.20 | 2.20 | 0.00 | 30S ribosomal subunit protein S11 |
| rpsL | 0.89 | 2.25 | -0.94 | 2.30 | 1.33 | -1.45 | 30S ribosomal subunit protein S12 |
| rpsM | 0.12 | 4.04 | 0.99 | 0.65 | 2.30 | 0.20 | 30S ribosomal subunit protein S13 |
| rpsN | -0.27 | 2.56 | 0.80 | 0.40 | 2.17 | -0.40 | 30S ribosomal subunit protein S14 |
| rpsO | -0.19 | 4.19 | 1.11 | 0.10 | 2.33 | 0.30 | 30S ribosomal subunit protein S15 |
| rpsP | 0.08 | 8.31 | 0.68 | 0.95 | 2.70 | 0.25 | 30S ribosomal subunit protein S16 |
| rpsQ | 0.66 | 0.97 | -1.04 | 0.80 | 1.35 | -0.20 | 30S ribosomal subunit protein S17 |
| rpsR | -0.09 | 0.32 | 1.23 | 0.60 | 0.43 | 1.45 | 30S ribosomal subunit protein S18 |
| rpsS | -0.13 | 2.34 | 1.55 | 0.75 | 1.70 | 1.30 | 30S ribosomal subunit protein S19 |
| rpsT | 1.49 | 2.20 | 0.53 | 2.15 | 1.50 | 4.20 | 30S ribosomal subunit protein S20 |
| rpsU | 1.28 | 2.55 | 0.90 | 3.30 | 2.53 | 1.85 | 30S ribosomal subunit protein S21 |
| rpsV | -1.62 | -1.76 | -1.91 | -6.40 | -3.30 | -1.85 | 30S ribosomal subunit protein S22 |
| rrfA | 0.57 | -3.58 | 0.71 | -42.95 | 0.15 | 36.30 | 5S rRNA of rrnA operon |
| rrfB | 0.62 | -3.01 | -0.42 | -0.80 | -0.25 | 8.60 | 5S rRNA of rrnB operon |
| rrfC | 0.58 | -0.09 | 0.74 | -0.05 | 18.67 | 38.90 | 5S rRNA of rrnC operon |
| rrfD | 0.54 | -2.25 | 0.97 | 0.35 | 27.87 | 24.00 | 5S rRNA of rrnD operon |
| rrfE | 0.55 | -0.04 | 0.65 | 0.35 | 13.70 | 21.50 | 5S rRNA of rrnE operon |
| rrfF | 0.58 | 0.08 | 0.09 | 0.25 | 8.40 | 23.30 | 5S rRNA of rrnD operon |
| rrfG | 0.59 | -3.39 | 0.79 | 0.60 | 21.00 | 22.80 | 5S rRNA of rrnG operon |
| rrfH | 0.61 | -0.22 | 0.74 | 2.20 | -2.30 | 49.00 | 5S rRNA of rrnH operon |
| rrlA | 0.58 | -2.64 | -0.95 | 0.60 | -1.60 | 12.70 | 23S rRNA of rrnA operon |
| rrlC | 0.76 | -1.77 | 0.67 | 3.65 | 0.65 | 13.50 | 23S rRNA of rrnC operon |
| rrlD | 0.65 | -1.10 | -0.09 | 12.65 | 1.55 | 7.80 | 23S rRNA of rrnD operon |
| rrlE | 0.67 | -1.76 | 0.31 | 0.95 | 13.70 | 9.45 | 23S rRNA of rrnE operon |
| rrlG | 0.56 | -1.67 | 1.35 | 2.00 | 15.57 | 12.20 | 2727204.00 |
| rrlH | 0.69 | -1.68 | 0.24 | 3.75 | 6.47 | 10.45 | 23S rRNA of rrnH operon |
| rrsA | 0.56 | -2.39 | 0.68 | 0.20 | 14.93 | 19.30 | 16S RNA of rrnA operon |
| rrsC | 0.51 | 0.09 | 0.74 | -0.05 | 3.30 | 14.40 | 16S RNA of rrnC operon |
| rrsG | 0.64 | -1.72 | -0.08 | 2.15 | 6.30 | 11.20 | 2729178.00 |
| rrsH | 0.63 | -1.57 | -0.06 | 0.75 | 10.90 | 6.70 | 16S RNA of rrnH operon |
| rseA | 0.26 | 0.69 | 2.68 | 0.00 | 0.53 | 1.35 | sigma-E factor, negative regulatory protein |
| rseB | -0.12 | 0.75 | 0.36 | -0.50 | 0.23 | 0.15 | regulates activity of sigma-E factor |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| rseC | 1.08 | 1.19 | 0.95 | 0.30 | 1.80 | 1.35 | sigma-E factor, negative regulatory protein |
| rspA | -1.09 | -1.51 | 1.60 | 0.00 | -0.23 | 1.10 | starvation sensing protein |
| rspB | -0.85 | -1.56 | 0.77 | 1.00 | -1.73 | 1.30 | starvation sensing protein |
| rstA | 0.02 | -0.10 | 0.74 | 0.60 | -0.17 | 0.20 | response transcriptional regulatory protein (RstB sensor) |
| rstB | 4.19 | 5.74 | -1.13 | 1.90 | 1.63 | -0.20 | sensor histidine protein kinase (RstA regulator) |
| rsuA | 0.27 | -1.15 | 0.41 | 1.85 | -1.30 | 0.00 | 16S pseudouridylate 516 synthase |
| rtcA | -0.65 | -1.18 | -0.66 | -0.15 | 0.77 | -1.15 | RNA 3 -terminal phosphate cyclase |
| rtcB | -0.13 | 0.29 | 0.26 | 0.05 | -1.10 | -0.05 | orf, hypothetical protein |
| rtcR | 0.01 | 2.47 | 0.58 | 1.40 | 1.33 | 0.00 | putative 2-component regulator |
| rtn | 1.08 | 0.77 | 0.74 | 2.05 | 1.40 | 0.30 | orf, hypothetical protein |
| rus | 3.18 | -0.53 | -0.55 | 1.90 | 0.37 | 0.05 | endodeoxyribonuclease RUS (Holliday junction resolvase) |
| ruvA | 0.72 | -0.42 | -1.40 | 2.85 | -0.20 | -1.85 | Holliday junction helicase subunit B; branch migration; repair |
| ruvB | 0.75 | -0.81 | -1.36 | 2.35 | -0.23 | -1.65 | Holliday junction helicase subunit A; branch migration; repair |
| ruvC | 0.70 | 4.50 | 1.17 | 0.50 | 1.60 | 0.15 | Holliday junction nuclease; resolution of structures; repair |
| sanA | 2.62 | -1.34 | 0.52 | 1.50 | -1.37 | 0.20 | vancomycin sensitivity |
| sapA | -0.08 | 0.84 | 0.04 | -1.65 | 0.40 | 0.10 | homolog of Salmonella peptide transport periplasmic protein |
| sapB | 1.02 | 1.12 | -1.25 | 0.40 | 1.47 | -0.10 | homolog of Salmonella peptide transport permease protein |
| sapC | -1.02 | -1.26 | -0.05 | -1.60 | -0.33 | -0.30 | homolog of Salmonella peptide transport permease protein |
| sapD | 0.62 | -2.07 | -1.35 | 1.70 | -1.37 | -0.30 | putative ATP-binding protein of peptide transport system |
| sapF | 0.19 | 0.69 | -1.40 | 1.30 | 0.57 | -1.40 | putative ATP-binding protein of peptide transport system |
| sbcB | 0.69 | 1.66 | 1.02 | 1.55 | 0.50 | 1.10 | exonuclease I, 3 --> 5 specific; deoxyribophosphodiesterase |
| sbcC | -0.14 | 0.66 | 0.86 | 0.50 | 1.43 | 1.10 | ATP-dependent dsDNA exonuclease |
| sbcD | 0.85 | 1.53 | -1.26 | 1.75 | 1.27 | -0.25 | ATP-dependent dsDNA exonuclease |
| sbm | 0.98 | 0.00 | 0.77 | 0.65 | 1.03 | 1.75 | methylmalonyl-CoA mutase (MCM) |
| sbmA | -0.99 | 1.51 | 0.79 | -0.45 | 1.67 | 0.10 | sensitivity to microcin B17, possibly envelop protein |
| sbmC | 2.36 | 1.67 | 0.70 | 2.90 | 1.63 | 1.45 | SbmC protein |
| sbp | -1.78 | 1.60 | 1.25 | -2.60 | 1.47 | 1.60 | periplasmic sulfate-binding protein |
| sdaA | 0.55 | -0.84 | 0.98 | 0.15 | -0.03 | 1.60 | L-serine deaminase |
| sdaB | 0.03 | 2.31 | -2.20 | 0.05 | 1.30 | -1.10 | L-serine dehydratase (deaminase), L-SD2 |
| sdaC | -0.12 | 0.58 | 0.61 | 0.15 | 0.43 | -0.30 | probable serine transporter |
| sdhA | -0.54 | 0.90 | 1.42 | -2.75 | 0.27 | 1.60 | succinate dehydrogenase, flavoprotein subunit |
| sdhB | -0.37 | -1.41 | 0.87 | -1.95 | -1.47 | 1.75 | succinate dehydrogenase, iron sulfur protein |
| sdhC | 0.17 | 1.11 | -0.90 | -0.25 | 1.43 | -1.25 | succinate dehydrogenase, cytochrome b556 |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| sdhD | 0.14 | -0.09 | -1.07 | -0.15 | 0.33 | -0.10 | succinate dehydrogenase, hydrophobic subunit |
| sdiA | -0.17 | 0.08 | 0.71 | -1.05 | 1.20 | 1.25 | transcriptional regulator of ftsQAZ gene cluster |
| secA | 0.21 | 0.81 | -0.73 | 0.05 | 0.20 | -0.10 | preprotein translocase; secretion protein |
| secB | 0.38 | -1.37 | 1.40 | 1.40 | -1.50 | 1.60 | protein export; molecular chaperone; may bind to signel sequence |
| secD | -0.10 | 1.04 | 0.19 | -0.05 | 0.67 | 0.35 | protein secretion; membrane protein, part of the channel |
| secE | -0.15 | 2.52 | 0.74 | -0.55 | 1.33 | -0.15 | preprotein translocase |
| secF | -0.43 | -1.61 | -1.37 | -0.05 | -1.87 | -2.20 | protein secretion, membrane protein |
| secG | 1.21 | 0.68 | 1.56 | 0.50 | 0.70 | 1.65 | protein export - membrane protein |
| selA | -0.14 | -1.40 | -1.26 | -0.05 | -1.60 | -0.10 | selenocysteine synthase: L-seryl-tRNA (Ser) selenium transferase |
| selB | 0.82 | -2.90 | -1.50 | 1.30 | -1.77 | -1.10 | selenocysteinyl-tRNA-specific translation factor |
| selC | 0.11 | -0.16 | 0.88 | 1.10 | 0.20 | 3.30 | Selenocysteyl tRNAUCA (converted from serine tRNA) |
| selD | 0.30 | 0.78 | 0.91 | 0.25 | -1.37 | 0.10 | selenophosphate synthase, H(2)Se added to acrylyl-tRNA |
| seqA | -0.16 | 0.88 | 0.84 | -0.90 | 0.20 | 0.20 | negative modulator of initiation of replication |
| serA | 0.07 | -1.29 | 0.62 | -0.75 | -0.63 | 0.20 | D-3-phosphoglycerate dehydrogenase |
| serB | 0.35 | 1.43 | 1.68 | 1.40 | 2.03 | 1.40 | 3-phosphoserine phosphatase |
| serC | -0.35 | -0.28 | 0.86 | -0.65 | 0.60 | 1.90 | 3-phosphoserine aminotransferase |
| serS | 1.12 | -1.25 | 0.17 | 1.10 | -1.83 | 0.35 | serine tRNA synthetase; also charges selenocystein tRNA with serine |
| serT | 0.35 | -2.16 | 0.29 | -2.15 | -1.80 | 6.55 | Serine tRNA1 |
| serU | 0.57 | -1.37 | 0.39 | 1.90 | -1.25 | 8.00 | Serine tRNA2 |
| serV | 0.45 | -1.66 | 0.64 | 0.40 | 29.30 | 12.70 | Serine tRNA3 |
| serW | 0.45 | -0.11 | 0.42 | 1.55 | 33.10 | 25.40 | Serine tRNA5 |
| sfa | -1.38 | 0.51 | 0.88 | -1.30 | 0.50 | -0.25 | suppresses fabA and ts growth mutation |
| sfcA | 0.54 | -0.92 | 0.66 | -0.35 | -1.50 | 0.35 | NAD-linked malate dehydrogenase (malic enzyme) |
| sfhB | 0.30 | 0.00 | -1.30 | 0.00 | 0.20 | -1.35 | suppressor of ftsH mutation |
| sfmA | 0.03 | 0.76 | 0.96 | -0.15 | 1.30 | 1.35 | putative fimbrial-like protein |
| sfmC | 0.87 | -0.11 | 1.14 | 2.05 | 1.23 | 1.15 | putative chaperone |
| sfmD | -0.39 | -1.35 | 0.83 | 0.00 | -0.53 | 1.10 | putative outer membrane protein, export function |
| sfmF | 0.67 | -1.37 | 1.26 | 2.10 | -1.33 | 1.40 | putative fimbrial-like protein |
| sfmH | -0.34 | -1.31 | 0.74 | 2.10 | -1.40 | 0.00 | involved in fimbrial asembly |
| sfsA | 1.29 | -1.54 | 0.80 | -0.10 | -1.63 | -0.15 | probable regulator for maltose metabolism |
| sgaB | -0.30 | 1.09 | 0.34 | -0.25 | 1.23 | 0.25 | orf, hypothetical protein |
| sgaE | 0.41 | -1.34 | 0.00 | 1.30 | -0.43 | -1.60 | putative epimerase |
| sgaH | -1.16 | -1.32 | -0.02 | 0.05 | 0.10 | -0.05 | probable hexulose-6-phosphate synthase |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| sgaT | 0.98 | 0.90 | -0.08 | 1.95 | 1.13 | 0.05 | orf, hypothetical protein |
| sgaU | 0.04 | 1.27 | 0.60 | 0.40 | 1.20 | 0.10 | putative hexulose-6-phosphate isomerase |
| sgbE | -0.93 | -0.54 | 0.71 | -0.35 | 0.47 | 1.25 | putative epimerase |
| sgbH | 0.33 | 1.24 | 1.30 | 0.45 | 1.67 | 1.55 | probable 3-hexulose 6-phosphate synthase |
| sgbU | -0.93 | -1.32 | 0.76 | 0.10 | 0.30 | 1.35 | probable 3-hexulose-6-phosphate isomerase |
| sgcA | 0.73 | 0.33 | 0.66 | 0.45 | -0.17 | 0.10 | putative PTS system enzyme II A component |
| sgcC | 4.31 | 1.22 | 0.88 | 1.65 | 1.37 | 1.60 | putative PTS system enzyme IIC component |
| sgcE | -0.69 | 0.70 | 0.92 | -0.15 | 1.53 | 1.10 | putative epimerase |
| sgcQ | 0.99 | -1.17 | 0.74 | 0.10 | 0.47 | 1.65 | putative nucleoside triphosphatase |
| sgcR | 0.34 | -1.43 | 0.73 | 0.10 | -1.70 | 0.15 | putative DEOR-type transcriptional regulator |
| sgcX | 2.92 | 1.41 | -1.49 | 3.20 | 1.37 | -1.30 | putative lyase |
| shiA | -0.29 | -1.76 | -0.42 | 0.20 | -1.40 | 0.00 | putative transport protein, shikimate |
| sieB | 0.10 | 0.79 | 0.99 | 0.25 | 1.33 | 1.10 | phage superinfection exclusion protein |
| slp | -0.98 | -2.64 | 0.72 | -3.05 | -1.47 | 1.45 | outer membrane protein induced after carbon starvation |
| slpA | 1.40 | -1.86 | -1.31 | 2.80 | -2.67 | -1.65 | probable FKBX-type 16KD peptidyl-prolyl cis-trans isomerase (a rotamase) |
| slt | -0.39 | 2.31 | 0.60 | -1.30 | 0.53 | 0.15 | soluble lytic murein transglycosylase |
| slyA | 0.06 | -0.72 | -1.17 | -0.10 | 0.03 | -0.30 | transcriptional regulator for cryptic hemolysin |
| slyB | -0.08 | 1.13 | -0.49 | 0.05 | 1.17 | -0.15 | putative outer membrane protein |
| slyD | 0.43 | 0.21 | 2.70 | 1.40 | -0.57 | 1.75 | FKBP-type peptidyl-prolyl cis-trans isomerase (rotamase) |
| slyX | 0.03 | -1.39 | -1.41 | -0.15 | -1.70 | -1.30 | host factor for lysis of phiX174 infection |
| smf | -0.09 | -1.22 | 0.58 | 1.10 | -1.37 | 1.15 | orf, fragment 2 |
| smf | 0.16 | -1.31 | 0.79 | -0.10 | -0.17 | 0.30 | orf, fragment 1 |
| smg | -0.26 | -12.67 | -1.60 | -2.00 | -1.87 | -1.15 | orf, hypothetical protein |
| smp | -0.88 | -1.36 | -1.28 | 0.00 | -0.47 | -0.15 | orf, hypothetical protein |
| smpA | 1.72 | 3.39 | -0.90 | 2.00 | 2.57 | -0.05 | small membrane protein A |
| smpB | 0.44 | -0.97 | 1.37 | 0.10 | -1.40 | 0.15 | small protein B |
| sms | -0.22 | -1.58 | -1.30 | 0.15 | -1.47 | -0.10 | probable ATP-dependent protease |
| smtA | 1.77 | -1.34 | -0.15 | 1.60 | -1.40 | -0.05 | S-adenosylmethionine-dependent methyltransferase |
| sodA | 0.27 | 2.56 | 0.59 | 2.35 | 3.57 | 1.55 | superoxide dismutase, manganese |
| sodB | -1.52 | -0.62 | -0.79 | -1.75 | -1.70 | -0.05 | superoxide dismutase, iron |
| sodC | -1.45 | -1.41 | 0.30 | -1.80 | -1.63 | 0.10 | superoxide dismutase precursor (Cu-Zn) |
| sohA | 0.02 | 0.49 | 1.81 | 0.05 | 0.47 | 1.25 | putative protease; htrA suppressor protein |
| sohB | 0.19 | -1.41 | 0.97 | -0.10 | -0.93 | 1.95 | putative protease |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| solA | 0.33 | 0.00 | 0.00 | 1.75 | 0.03 | -0.40 | sarcosine oxidase-like protein |
| soxR | 3.63 | 1.24 | -1.36 | 2.20 | 1.10 | -1.30 | redox-sensing activator of soxS |
| soxS | -1.27 | 2.33 | -1.36 | -2.25 | 1.37 | -1.25 | regulation of superoxide response regulon |
| speA | -1.13 | 1.00 | -0.22 | -1.45 | 0.53 | 0.05 | biosynthetic arginine decarboxylase |
| speB | 1.42 | 1.74 | 0.96 | 1.10 | 1.77 | 0.05 | agmatinase |
| speC | 0.65 | -1.48 | 0.75 | 0.35 | -1.67 | 1.50 | ornithine decarboxylase isozyme |
| speD | -0.82 | -1.20 | -0.53 | -0.30 | -0.67 | -1.25 | S-adenosylmethionine decarboxylase |
| speE | -1.51 | 1.94 | 0.18 | -1.35 | 1.37 | 0.15 | spermidine synthase |
| speF | -0.38 | -43.31 | -0.81 | -0.40 | -1.23 | -1.55 | ornithine decarboxylase isozyme, inducible |
| speG | 0.68 | 0.82 | -0.90 | 1.45 | 1.13 | -1.15 | spermidine N1-acetyltransferase |
| spf | -0.40 | 3.67 | 0.37 | -0.20 | 2.80 | 0.30 | Spot 42 RNA |
| spoT | 0.08 | -1.27 | -1.09 | 0.10 | -0.77 | -1.20 | (p)ppGpp synthetase II; also guanosine-3 ,5 -bis pyrophosphate 3 -pyrophosphohydrolase |
| spoU | 1.22 | 1.46 | -0.52 | 1.45 | 1.40 | -0.15 | putative RNA methylase |
| sppA | -0.12 | 0.41 | 0.72 | -0.20 | 0.47 | 0.25 | protease IV, a signal peptide peptidase |
| spr | -6.50 | -3.88 | 1.06 | -1.35 | -2.90 | 1.45 | putative lipoprotein |
| sprT | 0.08 | -0.68 | -0.14 | 0.45 | 0.27 | 0.05 | orf, hypothetical protein |
| spy | 0.33 | 1.06 | 0.38 | 0.85 | 0.03 | -0.10 | periplasmic protein related to spheroblast formation |
| srlA | -1.65 | 0.42 | -0.92 | -1.50 | 1.27 | -0.30 | PTS system, glucitol |
| srlB | 0.18 | -1.84 | -1.22 | 0.00 | -1.57 | -1.45 | PTS system, glucitol |
| srlD | 0.50 | -0.61 | 0.79 | -0.80 | -0.53 | 1.25 | glucitol (sorbitol)-6-phosphate dehydrogenase |
| srlE | 0.03 | -1.47 | 0.25 | -0.25 | -1.47 | 1.05 | PTS system, glucitol |
| srlR | -1.04 | 0.54 | 0.25 | -0.20 | 1.67 | 0.25 | regulator for gut (srl), glucitol operon |
| srmB | 0.61 | -0.51 | 0.94 | 0.25 | -1.23 | 1.20 | ATP-dependent RNA helicase |
| ssb | 2.17 | 3.22 | 0.19 | 1.80 | 1.63 | 0.05 | ssDNA-binding protein |
| sseA | -1.46 | -0.31 | -0.38 | -1.50 | -0.10 | -0.15 | putative thiosulfate sulfurtransferase |
| sseB | 1.08 | -0.51 | 1.04 | 1.45 | -0.10 | 1.45 | enhanced serine sensitivity |
| sspA | -0.17 | 4.34 | 0.05 | -0.70 | 2.03 | 0.25 | regulator of transcription; stringent starvation protein A |
| sspB | 0.80 | -0.30 | -1.29 | 1.65 | -0.10 | -1.60 | stringent starvation protein B |
| ssrA | 0.61 | 0.17 | 0.48 | 0.65 | 17.83 | 6.90 | 10Sa RNA (nonribosomal); role in modulating DNA-binding proteins |
| ssrS | 0.52 | -0.04 | 0.30 | 0.30 | 27.83 | 13.35 | 6S RNA |
| stpA | 1.34 | 0.38 | 0.82 | 1.70 | 0.30 | 1.35 | DNA-binding protein; H-NS-like protein; chaperone activity; RNA splicing? |
| sucA | -0.44 | -0.27 | 0.86 | -1.95 | 0.13 | 1.65 | 2-oxoglutarate dehydrogenase (decarboxylase component) |
| sucB | -2.20 | -1.65 | -1.31 | -1.60 | -2.00 | -1.25 | 2-oxoglutarate dehydrogenase (dihydrolipoyltranssuccinase E2 component) |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| sucC | -2.91 | -1.33 | 0.60 | -3.30 | -1.77 | 1.40 | succinyl-CoA synthetase, beta subunit |
| sucD | -7.52 | -1.64 | -0.39 | -4.20 | -1.87 | 0.20 | succinyl-CoA synthetase, alpha subunit |
| sufI | 0.45 | 0.79 | -1.50 | 1.40 | 1.30 | -1.30 | suppressor of ftsI |
| sugE | 1.22 | 2.44 | 0.52 | 0.10 | 0.60 | 0.15 | suppresses groEL, may be chaperone |
| suhB | 0.05 | 1.87 | 0.61 | -0.10 | 2.53 | 1.25 | enhances synthesis of sigma32 in mutant; extragenic suppressor, may modulate RNAse III lethal |
| sulA | 1.96 | 1.99 | 1.25 | 12.75 | 2.17 | 1.55 | suppressor of lon; inhibits cell division and ftsZ ring formation |
| sun | 1.37 | 1.69 | 0.79 | 1.65 | 1.90 | 1.95 | orf, hypothetical protein |
| surA | -0.04 | -1.21 | 1.04 | 0.00 | -1.47 | 0.00 | survival protein |
| surE | -0.29 | -1.40 | 0.78 | -1.40 | -1.60 | 1.65 | survival protein |
| syd | 1.41 | -3.47 | -0.94 | 1.35 | -1.27 | 0.00 | interacts with secY |
| t150 | 1.89 | -1.87 | 0.72 | 2.00 | -1.13 | 0.00 | IS150 putative transposase |
| tag | 0.05 | 0.78 | -1.42 | 0.15 | 1.37 | -1.25 | 3-methyl-adenine DNA glycosylase I, constitutive |
| talA | -1.37 | -1.66 | -0.88 | -0.50 | -1.50 | 0.15 | transaldolase A |
| talB | 0.23 | -0.45 | -0.82 | 0.05 | -2.30 | -1.85 | transaldolase B |
| talC | 0.00 | -1.34 | -1.12 | 1.35 | -1.40 | -0.20 | putative transaldolase |
| tap | -0.94 | -1.33 | -1.45 | -3.85 | -0.33 | -1.10 | methyl-accepting chemotaxis protein IV, peptide sensor receptor |
| tar | -0.94 | -1.54 | 0.24 | -2.20 | -1.20 | -0.35 | methyl-accepting chemotaxis protein II, aspartate sensor receptor |
| tauA | 0.70 | -0.58 | 0.84 | 0.40 | 1.37 | 1.25 | taurine transport system periplasmic protein |
| tauB | 0.16 | -1.10 | -1.01 | 1.30 | -0.83 | -0.15 | taurine ATP-binding component of a transport system |
| tauC | -0.19 | -1.40 | -1.36 | 1.70 | -0.53 | -1.55 | taurine transport system permease protein |
| tauD | 2.43 | 1.07 | -0.50 | 2.50 | -0.10 | 0.10 | taurine dioxygenase, 2-oxoglutarate-dependent |
| tbpA | 0.21 | -0.92 | 0.61 | 1.15 | -0.17 | 0.15 | thiamin-binding periplasmic protein |
| tdcA | -0.21 | -1.31 | 0.68 | -1.25 | -1.27 | 1.10 | transcriptional activator of tdc operon |
| tdcB | 2.63 | 1.04 | 0.66 | 2.80 | 1.40 | 0.40 | threonine dehydratase, catabolic |
| tdcC | -0.26 | 0.52 | 0.89 | -0.05 | 1.63 | 1.25 | anaerobically inducible L-threonine, L-serine permease |
| tdcD | 0.27 | -2.36 | 0.84 | 1.05 | -1.27 | 1.05 | putative kinase |
| tdcE | 0.54 | -1.36 | -1.33 | 1.35 | -0.40 | -0.40 | probable formate acetyltransferase 3 |
| tdcR | 2.01 | 0.61 | -0.01 | 1.40 | 1.50 | 0.05 | threonine dehydratase operon activator protein |
| tdh | 0.09 | -1.77 | -1.92 | -0.05 | -1.73 | -1.20 | threonine dehydrogenase |
| tdk | -1.23 | -1.06 | 0.88 | -0.45 | -0.17 | 0.10 | thymidine kinase |
| tehA | 0.15 | 0.89 | 0.07 | 0.50 | 1.70 | 0.00 | tellurite resistance |
| tehB | 0.48 | 0.07 | 2.24 | 0.25 | 0.63 | 1.45 | tellurite resistance |
| tesA | 0.96 | 1.10 | 0.63 | 0.50 | 1.37 | 0.10 | acyl-CoA thioesterase I; also functions as protease I |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| tesB | 0.32 | -1.95 | 0.79 | 0.65 | -0.37 | 1.45 | acyl-CoA thioesterase II |
| tgt | 0.02 | 0.00 | 0.20 | 0.10 | -1.40 | 0.05 | tRNA-guanine transglycosylase |
| thdF | 0.16 | 1.19 | 0.83 | 0.30 | 1.30 | 0.10 | GTP-binding protein in thiophene and furan oxidation |
| thiC | 2.41 | 0.62 | 1.18 | 1.95 | -0.30 | 1.25 | thiamin biosynthesis, pyrimidine moiety |
| thiD | 0.00 | -1.24 | 0.77 | -0.30 | 1.23 | -0.20 | phosphomethylpyrimidine kinase |
| thiE | -0.93 | 1.39 | 1.28 | -1.80 | 1.23 | 1.65 | thiamin biosynthesis, thiazole moiety |
| thiF | 0.23 | -1.26 | 0.81 | 0.05 | -0.37 | 1.25 | thiamin biosynthesis, thiazole moiety |
| thiG | 0.16 | -1.62 | 0.66 | 0.35 | -1.57 | -0.35 | thiamin biosynthesis, thiazole moiety |
| thiH | 0.94 | -1.17 | 0.40 | 1.95 | -0.33 | 0.05 | thiamin biosynthesis, thiazole moiety |
| thiJ | 0.12 | -0.33 | 0.77 | 0.05 | -0.30 | 1.75 | 4-methyl-5(beta-hydroxyethyl)-thiazole monophosphate synthesis |
| thiL | -0.46 | -2.53 | 1.26 | -0.15 | -1.63 | 1.15 | thiamin-monophosphate kinase |
| thiM | -2.52 | -1.60 | 0.65 | -1.80 | -1.37 | -0.05 | hydoxyethylthiazole kinase |
| thrA | 0.14 | -1.29 | -1.28 | 0.10 | -2.03 | -1.85 | aspartokinase I, homoserine dehydrogenase I |
| thrB | -0.37 | -0.92 | -1.25 | -1.20 | -0.47 | -1.85 | homoserine kinase |
| thrC | 0.12 | -0.99 | -1.24 | 1.10 | -1.53 | -1.40 | threonine synthase |
| thrL | -0.49 | -2.42 | -1.51 | -0.05 | -1.80 | -1.75 | thr operon leader peptide |
| thrS | -0.70 | 1.36 | 1.11 | -1.25 | 0.87 | 1.35 | threonine tRNA synthetase |
| thrT | 0.47 | -2.00 | 0.50 | 1.55 | -1.95 | 14.20 | Threonine tRNA3 |
| thrU | 0.60 | 0.41 | 0.54 | 0.75 | 1.80 | 11.20 | Threonine tRNA4 |
| thrV | 0.24 | 0.21 | 0.55 | 0.20 | 1.55 | 3.10 | Threonine tRNA1 in rrnD |
| thrW | 0.98 | 0.77 | 0.75 | 2.00 | 1.70 | 1.60 | Threonine tRNA2 |
| thyA | -0.61 | -0.48 | 1.04 | -0.35 | -0.13 | 0.00 | thymidylate synthetase |
| tig | 0.41 | 2.15 | 0.60 | 0.95 | 1.67 | 0.35 | trigger factor; a molecular chaperone involved in cell division |
| tktA | -0.36 | 0.32 | 0.07 | -1.15 | -0.03 | -2.25 | transketolase 1 isozyme |
| tktB | -1.26 | -1.65 | -5.51 | -0.30 | -1.70 | -1.05 | transketolase 2 isozyme |
| tldD | 0.07 | 0.72 | -0.17 | 0.20 | 0.40 | -0.10 | suppresses inhibitory activity of CsrA |
| tmk | -1.56 | 0.59 | 1.05 | -1.55 | -1.20 | 1.15 | thymidylate kinase |
| tnaA | -0.96 | -3.74 | -1.42 | -1.50 | -3.60 | -1.65 | tryptophanase |
| tnaB | -0.25 | -0.55 | 0.38 | -0.40 | 1.07 | 0.00 | low affinity tryptophan permease |
| tnaL | -0.28 | 1.54 | 0.75 | -0.20 | 1.17 | 0.25 | tryptophanase leader peptide |
| tolA | 0.78 | -0.75 | 1.03 | 0.05 | -0.53 | 1.65 | membrane spanning protein, required for outer membrane integrity |
| tolB | -0.58 | 0.87 | -0.05 | -2.05 | 0.20 | 0.25 | periplasmic protein involved in the tonb-independent uptake of group A colicins |
| tolC | 0.18 | 0.54 | 0.15 | -0.30 | 0.17 | 0.10 | outer membrane channel; specific tolerance to colicin E1; segregation of daughter chromosomes |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| tolQ | -0.24 | -0.64 | -1.19 | -1.25 | 0.30 | 0.00 | inner membrane protein, membrane-spanning, maintains integrity of cell envelope; tolerance |
| tolR | 0.50 | -1.25 | -1.33 | -0.05 | 0.03 | -1.55 | putative inner membrane protein, involved in the tonB-independent uptake of group A colicins |
| tonB | -0.56 | 2.40 | 0.87 | 1.15 | 1.60 | 1.15 | energy transducer; uptake of iron, cyanocobalimin; sensitivity to phages, colicins |
| topA | 0.83 | 1.18 | 1.60 | 0.30 | 0.80 | 1.40 | DNA topoisomerase type I, omega protein |
| topB | 2.34 | 2.55 | 0.20 | 1.55 | 2.00 | -0.30 | DNA topoisomerase III |
| torA | 0.55 | 1.47 | -0.86 | 0.25 | 1.43 | -0.15 | trimethylamine N-oxide reductase subunit |
| torC | 0.47 | -1.34 | 0.69 | 0.80 | -0.43 | 0.10 | trimethylamine N-oxide reductase, cytochrome c-type subunit |
| torD | -0.35 | -1.94 | 0.02 | -1.15 | -1.27 | -0.35 | part of trimethylamine-N-oxide oxidoreductase |
| torR | 0.85 | -1.00 | 0.70 | 1.85 | -0.07 | 1.30 | response transcriptional regulator for torA (sensor TorS) |
| torS | 0.78 | -1.69 | -0.92 | 0.40 | -1.37 | 0.00 | sensor protein torS (regulator TorR) |
| torT | 0.03 | -1.34 | 0.77 | -0.85 | -1.60 | 1.20 | part of regulation of tor operon, periplasmic |
| tpiA | -0.06 | -2.98 | 0.30 | -0.65 | -2.13 | 0.05 | triosephosphate isomerase |
| tpr | 0.88 | 3.25 | 0.96 | 2.40 | 1.70 | 1.40 | a protaminelike protein |
| tpx | -0.29 | 0.44 | -0.79 | -1.15 | 0.53 | 0.05 | thiol peroxidase |
| tra5 | -0.72 | -1.38 | -0.19 | -0.15 | -0.60 | -0.10 | IS3 putative transposase |
| tra5 | -0.49 | 0.87 | 0.07 | -0.30 | 1.67 | 0.00 | IS3 putative transposase |
| tra8 | 2.77 | -1.57 | -1.40 | 1.60 | -1.40 | -1.30 | IS30 transposase |
| treA | -1.30 | 1.21 | 2.63 | -1.65 | 1.43 | 1.10 | trehalase, periplasmic |
| treB | -0.18 | -1.52 | 0.69 | 0.05 | -1.23 | 0.20 | PTS system enzyme II, trehalose specific |
| treC | -0.43 | -1.34 | -0.57 | -2.50 | -1.43 | 0.10 | trehalase 6-P hydrolase |
| treF | -0.63 | -3.09 | 0.62 | 0.00 | -1.17 | 1.20 | cytoplasmic trehalase |
| treR | 1.24 | 2.96 | 0.38 | 2.75 | 1.20 | -0.20 | repressor of treA,B,C |
| trg | 0.48 | -1.24 | 0.71 | 0.05 | -0.67 | 1.00 | methyl-accepting chemotaxis protein III, ribose sensor receptor |
| trkA | 1.27 | 1.00 | -1.63 | 2.25 | 1.43 | -1.15 | transport of potassium |
| trkG | 0.99 | 1.58 | 1.62 | -0.05 | 1.50 | 1.20 | trk system potassium uptake; part of Rac prophage |
| trkH | -0.66 | 1.53 | -0.74 | -0.20 | 1.70 | 0.00 | potassium uptake, requires TrkE |
| trmA | 0.61 | 0.91 | 2.62 | 1.30 | 0.33 | 1.20 | tRNA (uracil-5-)-methyltransferase |
| trmD | 0.32 | 7.65 | 0.78 | 1.70 | 2.87 | 0.40 | tRNA methyltransferase; tRNA (guanine-7-)-methyltransferase |
| trpA | -2.14 | -0.80 | -0.89 | -2.50 | -1.53 | -0.05 | tryptophan synthase, alpha protein |
| trpB | -1.65 | -0.92 | -0.61 | -1.90 | -1.57 | -1.25 | tryptophan synthase, beta protein |
| trpC | 0.55 | -2.62 | -1.32 | -1.25 | -2.37 | -1.55 | N-(5-phosphoribosyl)anthranilate isomerase and indole-3-glycerolphosphate synthetase |
| trpD | -0.21 | -7.03 | 0.00 | -0.95 | -0.50 | -0.10 | anthranilate synthase component II, glutamine amidotransferase and phosphoribosylanthranilate |
| trpE | 0.99 | 0.00 | -0.14 | -1.75 | 0.63 | 0.25 | anthranilate synthase component I |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| trpL | 0.71 | -2.52 | -0.70 | 1.10 | -1.37 | 0.05 | trp operon leader peptide |
| trpR | -0.31 | -0.63 | -0.32 | -0.20 | -0.40 | 0.10 | regulator for trp operon and aroH; trp aporepressor |
| trpS | 0.58 | -0.38 | -0.89 | 1.30 | -0.33 | 0.00 | tryptophan tRNA synthetase |
| trpT | -0.23 | 1.53 | 0.68 | -0.20 | 2.37 | 1.85 | Tryptophan tRNA |
| trs5 | -0.98 | 0.74 | 1.10 | -0.05 | 0.20 | 1.30 | IS5 transposase |
| trs5 | -0.44 | 0.57 | 1.81 | -4.95 | 0.47 | 1.15 | IS5 transposase |
| truA | -1.29 | 1.14 | -0.67 | -0.40 | 0.40 | 0.00 | pseudouridylate synthase I |
| truB | 1.74 | 2.15 | 0.90 | 1.80 | 1.43 | -0.15 | tRNA pseudouridine 5S synthase |
| trxA | 1.08 | 3.63 | -0.46 | 1.40 | 1.80 | -1.20 | thioredoxin 1 |
| trxB | 0.18 | 2.37 | -0.49 | 0.05 | 2.00 | 0.10 | thioredoxin reductase |
| trxC | -0.42 | -0.03 | -1.61 | -0.45 | 1.43 | -1.15 | putative thioredoxin-like protein |
| tsf | 0.43 | 1.43 | 1.16 | 0.45 | 1.80 | 1.55 | protein chain elongation factor EF-Ts |
| tsr | -0.56 | -1.58 | 0.54 | -1.60 | -1.43 | 0.00 | methyl-accepting chemotaxis protein I, serine sensor receptor |
| tsx | -7.72 | -2.22 | 0.21 | -1.65 | -1.83 | -0.10 | nucleoside channel; receptor of phage T6 and colicin K |
| ttdA | -0.12 | -1.64 | -0.25 | 1.70 | -0.40 | 0.05 | L-tartrate dehydratase, subunit A |
| ttdB | -0.54 | -1.18 | 0.39 | 1.05 | -0.50 | 1.10 | L-tartrate dehydratase, subunit B |
| ttk | 0.86 | 1.20 | -0.97 | 2.00 | 1.50 | -1.15 | putative transcriptional regulator |
| tufA | 0.07 | 0.63 | 0.37 | 0.25 | 0.40 | 0.20 | protein chain elongation factor EF-Tu (duplicate of tufB) |
| tufB | 0.10 | -0.50 | -0.34 | 0.30 | -1.83 | -1.95 | protein chain elongation factor EF-Tu (duplicate of tufA) |
| tus | 0.61 | -0.39 | 1.23 | 0.05 | 0.23 | 1.55 | DNA-binding protein; inhibition of replication at Ter sites |
| tynA | 1.29 | -1.37 | 1.25 | 1.60 | -0.73 | 1.25 | copper amine oxidase (tyramine oxidase) |
| tyrA | 1.92 | 0.99 | 0.83 | 1.70 | 1.57 | 1.60 | chorismate mutase-T and prephenate dehydrogenase |
| tyrB | 0.26 | 1.63 | 0.77 | 0.55 | 0.40 | 1.35 | tyrosine aminotransferase, tyrosine repressible |
| tyrP | -0.71 | -1.46 | 0.08 | 0.05 | -1.20 | 0.15 | tyrosine-specific transport system |
| tyrR | -1.41 | -1.51 | 0.79 | -1.70 | -1.10 | 1.35 | transcriptional regulation of aroF, aroG, tyrA and aromatic amino acid transport |
| tyrS | 0.12 | 2.00 | -0.67 | 0.05 | 1.60 | 0.00 | tyrosine tRNA synthetase |
| tyrT | 0.42 | 0.65 | 0.06 | 1.45 | 1.70 | 1.30 | Tyrosine tRNA1; tandemly duplicated |
| tyrU | 0.44 | -1.60 | 0.40 | 0.40 | -2.10 | 8.90 | Tyrosine tRNA2 |
| tyrV | 0.49 | -1.86 | 0.00 | 0.45 | 5.47 | 19.80 | Tyrosine tRNA1; tandemly duplicated |
| ubiA | -0.20 | 0.83 | 0.45 | -0.55 | 0.77 | 0.10 | 4-hydroxybenzoate-octaprenyltransferase |
| ubiB | 0.04 | -1.20 | 0.97 | -0.40 | -1.20 | 1.40 | ferrisiderophore reductase; flavin reductase (NADPH:flavin oxidoreductase) |
| ubiC | 0.16 | -1.28 | -0.42 | 0.35 | -0.63 | 0.15 | chorismate lyase |
| ubiE | -0.04 | -1.27 | -1.39 | -0.45 | -0.27 | -1.20 | 2-octaprenyl-6-methoxy-1,4-benzoquinone --> 2-octaprenyl-3-methyl-6-methoxy-1,4-benzoquinone |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ubiG | 0.15 | 0.76 | -1.32 | -0.05 | 0.40 | 0.00 | 3-demethylubiquinone-9 3-methyltransferase and 2-octaprenyl-6-hydroxy phenol methylase |
| ubiH | -0.04 | -0.12 | 0.73 | -0.10 | 0.43 | -0.10 | 2-octaprenyl-6-methoxyphenol--> 2-octaprenyl-6-methoxy-1, 4-benzoquinone |
| ubiX | -0.69 | 8.69 | 0.42 | -0.05 | 1.67 | 1.05 | 3-octaprenyl-4-hydroxybenzoate carboxy-lyase |
| ucpA | -0.82 | 0.33 | 0.77 | -0.10 | 0.60 | 1.30 | putative oxidoreductase |
| udhA | 0.23 | -0.62 | 0.73 | -0.10 | -1.07 | 1.35 | putative oxidoreductase |
| udk | 0.73 | -1.31 | 0.00 | 0.15 | -0.47 | 0.00 | uridine |
| udp | -1.60 | -10.29 | -1.05 | -1.60 | -10.97 | -0.10 | uridine phosphorylase |
| ugd | 0.89 | -1.23 | -1.48 | -0.05 | -0.30 | -1.25 | UDP-glucose 6-dehydrogenase |
| ugpA | -0.42 | 0.11 | 0.91 | 0.25 | 1.70 | 2.00 | sn-glycerol 3-phosphate transport system, integral membrane protein |
| ugpB | 1.66 | 1.26 | 0.10 | 2.20 | 1.20 | 0.05 | sn-glycerol 3-phosphate transport system; periplasmic binding protein |
| ugpC | 0.04 | -0.73 | 0.68 | 1.35 | -1.10 | 1.30 | ATP-binding component of sn-glycerol 3-phosphate transport system |
| ugpE | -0.31 | 1.27 | 0.96 | 0.25 | 1.50 | 1.75 | sn-glycerol 3-phosphate transport system, integral membrane protein |
| ugpQ | 0.19 | -1.42 | 1.10 | 1.45 | -0.50 | 1.05 | glycerophosphodiester phosphodiesterase, cytosolic |
| uhpA | 0.40 | 0.09 | -1.50 | -0.05 | -0.07 | -1.55 | response regulator, positive activator of uhpT transcription (sensor, uhpB) |
| uhpB | 0.21 | 0.75 | 0.77 | -0.30 | 1.07 | 0.10 | sensor histidine protein kinase phosphorylates UhpA |
| uhpC | 4.41 | 1.52 | -1.33 | 1.95 | 1.70 | -0.10 | regulator of uhpT |
| uhpT | -0.27 | 0.40 | 0.80 | -0.05 | 1.33 | 1.15 | hexose phosphate transport protein |
| uidA | 0.73 | -1.35 | 0.77 | 2.80 | -0.80 | 2.35 | beta-D-glucuronidase |
| uidB | 0.53 | -1.22 | 0.60 | -0.05 | -0.20 | -0.05 | glucuronide permease |
| uidC | 0.00 | -1.08 | 0.80 | -1.90 | 0.40 | 1.55 | membrane-associated protein |
| uidR | 0.76 | 1.11 | 0.36 | 0.05 | 1.20 | 0.10 | repressor for uid operon |
| umuC | -0.67 | -0.92 | 0.38 | 0.25 | -0.40 | -0.20 | SOS mutagenesis and repair |
| umuD | 2.52 | 2.84 | -1.37 | 4.00 | 1.60 | -1.65 | SOS mutagenesis; error-prone repair; processed to UmuD ; forms complex with UmuC |
| ung | -0.33 | -0.61 | -0.87 | -0.10 | 0.30 | 0.00 | uracil-DNA-glycosylase |
| upp | 0.65 | 0.81 | -1.31 | 1.40 | 0.47 | -1.40 | uracil phosphoribosyltransferase |
| uraA | -0.89 | 0.00 | -0.12 | -0.70 | 2.23 | 0.10 | uracil transport |
| usg | 0.72 | 1.48 | 0.82 | 0.45 | 1.37 | 1.30 | putative PTS system enzyme II A component |
| ushA | -1.59 | 1.75 | 0.70 | 0.00 | 0.50 | 1.40 | UDP-sugar hydrolase (5 -nucleotidase) |
| uspA | 0.09 | -3.84 | -2.14 | -0.15 | -1.97 | -1.20 | universal stress protein; broad regulatory function? |
| uup | 0.03 | -1.35 | -1.44 | 0.35 | -2.23 | -1.30 | putative ATP-binding component of a transport system |
| uvrA | 15.52 | 5.67 | 0.65 | 3.40 | 3.03 | -0.15 | excision nuclease subunit A |
| uvrB | 1.70 | 2.26 | -1.09 | 2.60 | 2.10 | -1.50 | DNA repair; excision nuclease subunit B |
| uvrC | 1.06 | -0.23 | -2.55 | 1.70 | -0.90 | -1.20 | excinuclease ABC, subunit C; repair of UV damage to DNA |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| uvrD | -0.22 | 3.19 | 0.84 | 1.85 | -0.03 | 1.25 | DNA-dependent ATPase I and helicase II |
| uvrY | -0.79 | 1.00 | -0.35 | 1.00 | 0.33 | 0.10 | putative 2-component transcriptional regulator |
| uxaA | 0.00 | -1.34 | 0.77 | -2.20 | -3.03 | 1.35 | altronate hydrolase |
| uxaB | 1.63 | 0.45 | 1.02 | 1.50 | 0.60 | 1.40 | altronate oxidoreductase |
| uxaC | 2.21 | -0.27 | -1.66 | 1.30 | 0.40 | -1.25 | uronate isomerase |
| uxuA | 0.38 | 2.29 | -0.43 | 1.55 | 1.93 | 0.00 | mannonate hydrolase |
| uxuB | 0.31 | -0.86 | 0.66 | 0.45 | -0.23 | 0.10 | D-mannonate oxidoreductase |
| uxuR | -0.09 | 0.69 | 1.65 | -0.30 | 1.30 | 1.10 | regulator for uxu operon |
| vacB | -0.82 | -1.59 | 1.43 | -1.65 | 0.17 | 1.30 | putative enzyme |
| vacJ | -0.41 | -1.27 | -1.31 | -1.40 | -1.10 | -1.30 | lipoprotein precursor |
| valS | -0.34 | -3.23 | -1.22 | 0.00 | -1.47 | -0.10 | valine tRNA synthetase |
| valT | 0.38 | -2.34 | 0.32 | 0.10 | -2.10 | 14.90 | Valine tRNA1; duplicate gene with triplicated valUXY |
| valV | 0.38 | -3.31 | 0.45 | 1.45 | -2.15 | 6.50 | Valine tRNA2B |
| valW | 0.40 | -2.56 | 0.50 | 1.55 | 6.13 | 8.20 | Valine tRNA2A |
| valX | 0.42 | -2.69 | 0.14 | 0.20 | -2.15 | 9.70 | Valine tRNA1; tandemly triplicate |
| valY | 0.37 | -2.34 | 0.21 | 0.05 | -2.20 | 16.40 | Valine tRNA1; tandemly triplicate |
| valZ | 0.30 | -3.29 | 0.47 | 0.10 | -1.70 | 14.60 | Valine tRNA1 |
| visC | 0.76 | 1.88 | 0.25 | 1.55 | 1.40 | -0.10 | orf, hypothetical protein |
| vsr | -0.76 | -1.18 | 0.57 | 1.00 | 0.10 | 0.00 | DNA mismatch endonuclease, patch repair protein |
| wbbH | -0.94 | 6.34 | -1.25 | -1.45 | 1.80 | -1.30 | O-antigen polymerase |
| wbbI | 0.05 | -0.39 | 1.19 | 0.10 | -0.53 | 0.15 | putative Galf transferase |
| wbbJ | 0.00 | -0.79 | -1.28 | -0.10 | -0.27 | -1.50 | putative O-acetyl transferase |
| wbbK | -0.40 | -0.72 | 0.95 | -1.35 | -1.23 | 0.15 | putative glucose transferase |
| wcaA | -0.29 | 0.56 | 0.32 | -1.25 | 0.40 | 0.15 | putative regulator |
| wcaB | 0.84 | -0.96 | -0.35 | 1.75 | -0.37 | 0.30 | putative transferase |
| wcaC | -0.87 | 0.00 | 0.54 | -0.85 | 0.37 | -0.15 | putative glycosyl transferase |
| wcaD | 0.52 | 0.89 | 0.59 | 0.20 | 1.43 | 0.05 | putative colanic acid polymerase |
| wcaE | -0.38 | 0.52 | 0.56 | 0.70 | 1.23 | 0.05 | putative colanic acid biosynthesis glycosyl transferase |
| wcaF | -0.08 | 1.42 | 0.10 | 0.35 | 2.03 | 0.10 | putative transferase |
| wcaG | 0.17 | 0.77 | 0.43 | 0.15 | -0.33 | -0.20 | putative nucleotide di-P-sugar epimerase or dehydratase |
| wcaH | 1.01 | 2.69 | -0.73 | 2.00 | 1.53 | 0.05 | GDP-mannose mannosyl hydrolase |
| wcaI | 0.00 | 1.48 | -1.38 | -1.30 | 1.53 | -1.40 | putative colanic biosynthesis glycosyl transferase |
| wcaJ | 1.04 | -0.97 | -1.54 | 0.05 | -1.20 | -1.30 | putative colanic acid biosynthsis UDP-glucose lipid carrier transferase |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| wcaK | **1.00** | **28.09** | **-1.53** | 0.50 | 1.43 | -1.10 | putative galactokinase (EC 2.7.1.6). |
| wcaL | **0.99** | **1.34** | **0.83** | 0.00 | 1.90 | 1.40 | putative colanic acid biosynthesis glycosyl transferase |
| wcaM | **1.97** | **4.08** | **0.78** | 2.10 | 1.07 | 1.55 | orf, hypothetical protein |
| wecB | **1.81** | **0.94** | **1.41** | 1.90 | 1.03 | 1.20 | UDP-N-acetyl glucosamine -2-epimerase; synthesis of enterobacterial common antigen (ECA) |
| wecC | **0.49** | **-1.57** | **-1.39** | 1.20 | -1.57 | -1.60 | UDP-N-acetyl-D-mannosaminuronic acid dehydrogenase; synthesis of enterobacterial common antig |
| wecD | **1.40** | **0.46** | **1.82** | 1.30 | 0.23 | 1.30 | orf, hypothetical protein |
| wecE | **-0.08** | **1.24** | **-1.25** | -1.25 | 1.17 | -1.40 | putative regulator |
| wecF | **0.16** | **-0.42** | **0.91** | -0.40 | 0.50 | 1.60 | TDP-Fuc4NAc:lipidII transferase; synthesis of enterobacterial common antigen (ECA) |
| wecG | **0.81** | **-1.46** | **0.80** | 1.25 | -1.43 | 1.50 | probable UDP-N-acetyl-D-mannosaminuronic acid transferase; synthesis of enterobacterial common |
| wrbA | **-1.37** | **-2.69** | **-1.16** | -6.15 | -3.60 | -0.10 | trp repressor binding protein; affects association of trp repressor and operator |
| wza | **0.28** | **0.76** | **0.78** | 0.30 | 0.40 | 1.75 | putative polysaccharide export protein |
| wzb | **-0.03** | **-1.36** | **1.32** | 0.55 | -1.73 | 1.45 | probable protein-tyrosine-phosphatase |
| wzxC | **-0.38** | **-0.61** | **-1.32** | 0.00 | 1.13 | -0.25 | probable export protein |
| wzxE | **-0.96** | **-1.31** | **0.68** | -0.35 | -0.50 | 1.20 | putative cytochrome |
| wzzB | **0.31** | **-0.91** | **-1.09** | 0.10 | -1.00 | -1.65 | regulator of length of O-antigen component of lipopolysaccharide chains |
| wzzE | **0.76** | **-1.82** | **0.10** | 0.10 | -1.20 | 0.05 | putative transport protein |
| xapA | **0.43** | **-1.34** | **0.46** | 2.05 | -0.50 | -0.05 | xanthosine phosphorylase |
| xapB | **-0.92** | **0.36** | **0.44** | 0.10 | -0.13 | 0.15 | xanthosine permease |
| xapR | **-0.29** | **-1.31** | **0.99** | -0.40 | -1.30 | 1.15 | regulator for xapA |
| xasA | **-1.02** | **-1.22** | **-1.32** | -1.25 | -0.30 | -1.25 | acid sensitivity protein, putative transporter |
| xerC | **0.50** | **0.75** | **-1.31** | 1.40 | 0.30 | -1.30 | site-specific recombinase, acts on cer sequence of ColE1, effects chromosome segregation at cell di |
| xerD | **-0.38** | **0.00** | **-1.45** | -0.10 | 1.10 | -1.55 | site-specific recombinase |
| xseA | **-0.96** | **-0.89** | **-1.21** | -0.15 | 0.53 | -0.10 | exonuclease VII, large subunit |
| xseB | **0.94** | **1.15** | **1.09** | 1.20 | 0.40 | 1.65 | exonuclease VII, small subunit |
| xthA | **0.37** | **1.27** | **-0.18** | 1.30 | 0.60 | -0.45 | exonuclease III |
| xylA | **0.00** | **0.00** | **0.76** | -1.35 | -0.07 | -0.20 | D-xylose isomerase |
| xylB | **-0.80** | **0.71** | **0.74** | 0.30 | 1.17 | 0.10 | xylulokinase |
| xylE | **-0.69** | **0.10** | **-1.15** | -0.15 | 0.47 | -1.50 | xylose-proton symport |
| xylF | **0.29** | **-1.61** | **-0.30** | -0.40 | 1.20 | 0.25 | xylose binding protein transport system |
| xylG | **1.37** | **-1.22** | **0.77** | 1.50 | -0.60 | 0.20 | putative ATP-binding protein of xylose transport system |
| xylH | **-0.16** | **-1.42** | **0.77** | -0.70 | -0.77 | 1.55 | putative xylose transport, membrane component |
| xylR | **0.29** | **-6.25** | **-0.64** | 0.10 | -1.30 | 0.05 | putative regulator of xyl operon |
| yaaA | **1.61** | **-1.30** | **-1.20** | 1.65 | -1.80 | -1.80 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yaaF | -0.07 | -0.76 | -1.38 | -0.45 | -2.03 | -1.90 | orf, hypothetical protein |
| yaaH | 0.96 | -1.63 | -1.37 | 6.30 | -1.97 | -2.05 | orf, hypothetical protein |
| yaaI | 0.47 | 0.87 | -1.35 | 0.20 | 1.07 | -2.75 | orf, hypothetical protein |
| yaaJ | -0.56 | -0.95 | -1.31 | -0.10 | -0.53 | -2.15 | inner membrane transport protein |
| yaaU | -1.02 | -1.60 | -1.75 | -0.10 | -1.70 | -1.15 | putative transport protein |
| yabB | 0.17 | -1.74 | -1.32 | 1.10 | -1.90 | -1.60 | orf, hypothetical protein |
| yabC | -1.94 | -2.36 | -0.87 | -2.30 | -2.47 | -0.05 | putative apolipoprotein |
| yabF | -1.04 | 0.02 | 1.26 | -0.20 | 0.20 | 1.80 | putative NAD(P)H oxidoreductase |
| yabH | -0.32 | -1.23 | 0.08 | -0.30 | -1.27 | 0.20 | putative DNA binding protein |
| yabI | -0.67 | -2.71 | -1.31 | -0.45 | -1.83 | -0.50 | orf, hypothetical protein |
| yabJ | 0.95 | -0.44 | -1.05 | 3.15 | -1.27 | -1.30 | putative ATP-binding component of a transport system |
| yabK | 0.12 | -1.20 | 0.41 | 0.20 | -0.53 | 1.05 | putative transport system permease protein |
| yabM | 0.29 | -1.29 | 1.06 | 1.95 | 0.60 | 1.70 | putative transport protein |
| yabN | 2.01 | -1.45 | 0.09 | 2.05 | 1.13 | 0.25 | putative transport protein |
| yabO | -0.81 | 0.46 | -0.84 | -0.20 | 0.10 | -1.20 | orf, hypothetical protein |
| yabP | -1.23 | 1.31 | -1.23 | -0.35 | 1.23 | -1.65 | orf, hypothetical protein |
| yabQ | -1.01 | -1.31 | -0.87 | -0.20 | -0.93 | 0.00 | orf, hypothetical protein |
| yacA | 1.89 | -0.56 | 1.29 | 2.00 | 0.20 | 1.20 | orf, hypothetical protein |
| yacC | -1.04 | -0.16 | -1.36 | -0.50 | 0.37 | -1.55 | orf, hypothetical protein |
| yacE | -1.06 | 1.18 | 1.38 | -1.45 | 1.27 | 1.70 | putative DNA repair protein |
| yacF | 1.82 | -1.10 | -0.59 | 1.90 | -0.33 | 0.10 | orf, hypothetical protein |
| yacG | 2.61 | -1.26 | 0.87 | 1.80 | -0.57 | 1.30 | orf, hypothetical protein |
| yacH | -1.27 | -1.38 | 0.46 | -0.35 | -0.47 | -0.15 | putative membrane protein |
| yacK | -0.06 | -1.32 | -1.25 | 0.00 | -0.70 | -0.45 | orf, hypothetical protein |
| yacL | -0.34 | -1.21 | 3.79 | -2.10 | -1.03 | 1.15 | orf, hypothetical protein |
| yadB | 0.87 | -1.31 | -1.32 | 1.60 | -0.80 | -2.10 | putative tRNA synthetase |
| yadC | -0.61 | -1.03 | 0.77 | 0.40 | -0.10 | 1.65 | putative fimbrial-like protein |
| yadD | -1.59 | -2.07 | -1.21 | -1.30 | -1.20 | -1.20 | orf, hypothetical protein |
| yadE | 0.38 | -1.30 | -0.55 | -0.30 | -0.33 | 0.10 | orf, hypothetical protein |
| yadF | 0.37 | 0.48 | -0.01 | 1.40 | 1.37 | -0.10 | putative carbonic anhdrase (EC 4.2.1.1) |
| yadG | -0.58 | -0.84 | -0.01 | -0.75 | -0.07 | 0.05 | putative ATP-binding component of a transport system |
| yadH | 0.29 | -1.35 | -1.32 | 0.45 | -0.47 | -1.35 | orf, hypothetical protein |
| yadI | 0.79 | -1.46 | 0.73 | 1.90 | -1.47 | -0.15 | putative PTS enzyme II B component |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yadK | 0.53 | -1.55 | 0.07 | 0.45 | -1.30 | 0.10 | putative fimbrial protein |
| yadL | -0.22 | -0.07 | 1.36 | 0.05 | 0.50 | 1.50 | putative fimbrial protein |
| yadM | -1.11 | 1.56 | 0.81 | -1.60 | 2.07 | -0.10 | putative fimbrial-like protein |
| yadN | 3.63 | 0.59 | -0.08 | 1.95 | -0.10 | 0.10 | putative fimbrial-like protein |
| yadP | 0.43 | -1.27 | -1.33 | 1.15 | -1.43 | -1.45 | orf, hypothetical protein |
| yadQ | 0.29 | -1.56 | 0.53 | 0.15 | -1.53 | 0.20 | putative channel transporter |
| yadR | 0.03 | 0.88 | 0.15 | -0.05 | 2.13 | 0.00 | orf, hypothetical protein |
| yadS | 0.07 | -1.34 | 0.53 | 1.15 | -0.43 | -0.25 | orf, hypothetical protein |
| yadT | -1.05 | -1.15 | 0.14 | -0.05 | -0.60 | 2.80 | orf, hypothetical protein |
| yaeB | 1.26 | -1.19 | -1.41 | 1.80 | -0.47 | -1.20 | orf, hypothetical protein |
| yaeC | 0.10 | -0.91 | -1.25 | 1.25 | -2.13 | -2.00 | putative lipoprotein |
| yaeD | -0.10 | -1.09 | 1.27 | -0.25 | -1.97 | 0.20 | putative phosphatase |
| yaeE | -0.39 | -1.10 | -1.06 | -0.20 | -1.53 | -1.85 | putative transport system permease protein |
| yaeF | -0.54 | 2.36 | 1.19 | -0.10 | 1.47 | 1.40 | orf, hypothetical protein |
| yaeG | -0.40 | -1.07 | -1.13 | -0.50 | -1.00 | -1.75 | orf, hypothetical protein |
| yaeH | 0.51 | -2.35 | -2.07 | 1.15 | -1.97 | -1.30 | putative structural protein |
| yaeI | 0.00 | 0.00 | -1.36 | -0.30 | 1.57 | -1.30 | orf, hypothetical protein |
| yaeJ | -0.59 | 1.30 | -0.71 | -0.10 | 1.33 | 0.00 | orf, hypothetical protein |
| yaeL | -1.24 | 1.16 | 0.53 | -2.15 | 0.07 | 0.05 | orf, hypothetical protein |
| yaeM | -0.92 | 1.57 | 0.71 | -0.25 | 1.03 | -0.15 | putative ATP-binding component of a transport system |
| yaeO | 0.38 | -7.17 | 0.12 | 0.30 | -0.40 | 0.10 | orf, hypothetical protein |
| yaeQ | -0.21 | -1.27 | -1.37 | -1.05 | -0.60 | -1.55 | orf, hypothetical protein |
| yaeR | -0.75 | -1.21 | 0.26 | -0.50 | -0.17 | -0.05 | orf, hypothetical protein |
| yaeS | -0.08 | -0.25 | 0.25 | -0.25 | -0.10 | 0.05 | orf, hypothetical protein |
| yaeT | -1.42 | 0.98 | 1.18 | -2.00 | -0.43 | 0.35 | orf, hypothetical protein |
| yafA | 0.00 | 0.00 | 0.80 | 0.05 | 0.70 | 1.15 | orf, hypothetical protein |
| yafB | 1.30 | -1.34 | 5.92 | 1.35 | -1.53 | 1.30 | putative aldose reductase (EC 1.1.1.21) |
| yafC | -0.95 | -1.34 | 0.00 | -2.15 | -1.27 | -0.05 | putative transcriptional regulator LYSR-type |
| yafD | -1.77 | -74.21 | -0.30 | -2.05 | -2.10 | 0.10 | orf, hypothetical protein |
| yafE | -0.48 | 0.14 | -0.29 | -0.10 | 0.40 | 0.05 | putative biotin synthesis protein |
| yafH | -0.97 | 0.00 | 1.39 | -3.15 | 0.90 | 1.65 | putative acyl-CoA dehydrogenase (EC 1.3.99.-) |
| yafJ | 0.21 | -1.33 | 0.77 | 0.05 | 0.00 | -0.55 | putative amidotransferase |
| yafK | -0.39 | 0.83 | 0.79 | -1.30 | -1.03 | 1.10 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yafL | -0.10 | 1.12 | -1.33 | 0.45 | 1.77 | -1.30 | putative lipoprotein |
| yafM | -1.04 | -1.18 | -1.09 | -0.20 | -0.33 | -1.60 | orf, hypothetical protein |
| yafN | 1.72 | -1.35 | 0.75 | 2.35 | -1.27 | 0.15 | orf, hypothetical protein |
| yafO | 1.85 | -1.85 | -0.36 | 2.15 | -0.40 | -1.30 | orf, hypothetical protein |
| yafP | 1.98 | -1.36 | -1.63 | 2.05 | -0.63 | -1.10 | orf, hypothetical protein |
| yafQ | -2.99 | 1.02 | -0.21 | -2.05 | 1.00 | 0.20 | orf, hypothetical protein |
| yafS | 1.70 | -1.04 | 0.80 | 1.65 | -0.20 | 1.65 | orf, hypothetical protein |
| yafT | -0.12 | -1.28 | -1.19 | -0.20 | -1.67 | -1.25 | putative aminopeptidase |
| yafU | 0.28 | 1.11 | 1.51 | 1.25 | 0.77 | 1.30 | orf, hypothetical protein |
| yafV | -0.99 | 1.18 | 0.80 | -1.20 | 1.93 | 1.30 | putative EC 3.5. amidase-type enzyme |
| yafW | 0.00 | -1.33 | 0.77 | -2.20 | -1.83 | 1.45 | orf, hypothetical protein |
| yafX | 0.00 | -1.34 | 0.79 | 0.25 | -1.47 | 1.20 | orf, hypothetical protein |
| yafY | 0.00 | 0.76 | 0.62 | -0.20 | 1.57 | 0.15 | orf, hypothetical protein |
| yafZ | 0.00 | -1.33 | -1.31 | 0.00 | -0.07 | -0.15 | orf, hypothetical protein |
| yagA | -0.07 | 0.76 | 0.00 | -2.75 | 1.47 | 0.20 | orf, hypothetical protein |
| yagB | -0.26 | -1.70 | -1.54 | -0.10 | -1.40 | -1.20 | orf, hypothetical protein |
| yagD | 1.02 | -0.89 | 0.80 | 2.10 | -0.10 | 0.25 | putative enzyme |
| yagE | -1.06 | -1.34 | -1.12 | -0.05 | -1.70 | -0.35 | putative lyase |
| yagF | 1.14 | -0.96 | 0.90 | 0.05 | -0.53 | -0.20 | putative dehydratase |
| yagG | 0.00 | -1.40 | 0.00 | -0.50 | -2.40 | -0.40 | putative permease |
| yagH | -0.90 | 0.00 | -1.32 | 0.35 | 0.33 | -2.00 | putative beta-xylosidase (EC 3.2.1.37) |
| yagI | -0.26 | 4.92 | -0.06 | -0.10 | 1.43 | -0.25 | putative regulator |
| yagJ | 0.59 | -1.20 | -1.37 | 0.40 | -0.30 | -1.95 | orf, hypothetical protein |
| yagK | -1.20 | -1.62 | 0.86 | -0.20 | -1.17 | 1.20 | orf, hypothetical protein |
| yagL | 0.01 | -1.35 | 0.23 | -0.35 | 1.23 | 1.15 | DNA-binding protein |
| yagM | -1.17 | -0.29 | -0.05 | -1.70 | 0.37 | -1.10 | orf, hypothetical protein |
| yagN | 0.23 | -1.53 | -0.09 | -1.10 | -1.30 | 0.05 | orf, hypothetical protein |
| yagP | -0.53 | 1.29 | -0.53 | 0.15 | 1.50 | 0.05 | putative transcriptional regulator LYSR-type |
| yagQ | -0.86 | -1.29 | 0.45 | -0.10 | 0.10 | -0.30 | orf, hypothetical protein |
| yagR | 0.30 | -1.34 | 0.00 | -0.10 | -2.33 | -0.10 | orf, hypothetical protein |
| yagS | 0.00 | 0.00 | -0.81 | -4.25 | 2.20 | 0.00 | orf, hypothetical protein |
| yagT | 0.28 | -1.40 | -1.42 | 0.25 | -1.60 | -1.40 | putative xanthine dehydrogenase (EC 1.1.1.20) |
| yagU | 0.03 | -1.45 | -0.93 | 0.70 | -1.40 | -0.05 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yagV | 1.50 | -2.23 | -1.48 | 1.60 | -1.47 | -1.35 | orf, hypothetical protein |
| yagW | 0.60 | 0.51 | 0.35 | 1.60 | 0.43 | -0.10 | putative receptor |
| yagX | 1.71 | -1.46 | 0.47 | 3.00 | -2.27 | 1.30 | putative enzyme |
| yagY | 0.75 | 1.04 | 0.67 | 1.85 | 1.70 | 0.05 | orf, hypothetical protein |
| yagZ | 0.00 | 0.00 | 0.76 | -0.35 | -0.17 | -0.30 | orf, hypothetical protein |
| yahA | 1.14 | 1.22 | 0.98 | 1.55 | 1.40 | 1.25 | orf, hypothetical protein |
| yahB | 0.81 | 0.30 | 0.74 | 0.35 | 1.60 | -0.45 | putative transcriptional regulator LYSR-type |
| yahC | 0.00 | 0.00 | 1.15 | -3.10 | 0.63 | 1.50 | orf, hypothetical protein |
| yahD | 0.76 | -1.29 | 0.14 | 1.85 | -0.67 | -0.25 | putative transcription factor |
| yahE | 0.73 | -1.35 | -0.63 | 1.80 | -0.70 | 0.15 | orf, hypothetical protein |
| yahF | -1.09 | -0.15 | -0.38 | -1.30 | 0.30 | 0.15 | putative oxidoreductase subunit |
| yahG | -0.84 | 1.12 | -0.03 | 0.10 | 1.93 | 0.15 | orf, hypothetical protein |
| yahH | 1.35 | -2.84 | -1.21 | 0.45 | 0.13 | -1.25 | orf, hypothetical protein |
| yahI | 1.04 | -1.51 | 0.21 | 0.00 | -1.40 | 0.10 | putative kinase (EC 2.7.2.2). |
| yahJ | 0.00 | -1.33 | 1.65 | 1.20 | -1.40 | 1.60 | putative deaminase |
| yahK | -0.30 | 1.49 | -1.09 | -0.35 | 1.43 | -0.15 | putative oxidoreductase |
| yahL | 0.42 | -4.60 | -0.36 | 0.65 | -1.30 | -0.10 | orf, hypothetical protein |
| yahM | 1.18 | 1.53 | -0.58 | -0.05 | 1.27 | 0.00 | orf, hypothetical protein |
| yahN | -1.20 | -0.71 | -1.14 | -0.55 | 1.27 | -1.60 | putative cytochrome subunit of dehydrogenase |
| yahO | -1.13 | -2.02 | -0.39 | -5.95 | -3.23 | -0.20 | orf, hypothetical protein |
| yaiA | -0.94 | 0.04 | -0.23 | -2.40 | 0.07 | 0.00 | orf, hypothetical protein |
| yaiB | -0.79 | -3.80 | -1.73 | -3.30 | -0.53 | -1.40 | orf, hypothetical protein |
| yaiC | 0.32 | 4.49 | 0.24 | 0.45 | 1.77 | -0.10 | orf, hypothetical protein |
| yaiD | 0.73 | 0.84 | 1.72 | -1.30 | 1.57 | 1.45 | orf, hypothetical protein |
| yaiE | 0.13 | -1.07 | -1.63 | -0.05 | 0.43 | -1.30 | orf, hypothetical protein |
| yaiH | 0.24 | -1.40 | 1.21 | 0.00 | -1.33 | 1.40 | putative enzyme |
| yaiI | -0.24 | 0.16 | 0.82 | -0.05 | 0.33 | 0.05 | orf, hypothetical protein |
| yaiL | -0.10 | -1.52 | 1.99 | -0.15 | -1.23 | 1.30 | nucleoprotein |
| yaiM | -0.11 | -0.40 | 0.79 | 0.15 | -0.10 | 0.30 | putative esterase (EC 3.1.1.1) |
| yaiN | -0.30 | -0.81 | -0.18 | -0.05 | -1.30 | 0.25 | putative alpha helix chain |
| yaiO | -0.59 | -0.72 | -0.02 | 0.15 | -0.27 | 0.20 | orf, hypothetical protein |
| yaiP | -0.04 | -1.84 | 1.34 | 0.90 | -1.17 | 1.30 | polysaccharide metabolism |
| yaiS | 1.59 | 1.00 | -1.20 | 1.25 | 0.50 | -1.35 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yaiT | **-0.91** | **-0.85** | **-1.19** | 0.20 | 0.53 | -0.35 | orf, hypothetical protein |
| yaiU | **0.93** | **-1.35** | **-1.36** | 2.10 | -1.90 | -0.20 | putative flagellin structural protein |
| yaiV | **-0.77** | **-0.19** | **-0.56** | -0.15 | -0.33 | 0.00 | orf, hypothetical protein |
| yaiW | **1.13** | **-1.18** | **0.74** | 1.15 | 1.30 | 1.40 | orf, hypothetical protein |
| yajB | **-0.01** | **1.84** | **0.76** | 1.95 | 1.43 | -1.00 | putative glycoprotein |
| yajC | **-2.66** | **-2.18** | **-1.28** | -1.40 | -2.33 | -1.35 | orf, hypothetical protein |
| yajD | **-1.93** | **1.59** | **1.08** | -1.40 | 1.37 | 1.30 | orf, hypothetical protein |
| yajF | **-0.38** | **-1.55** | **-3.34** | -0.15 | -0.47 | -1.35 | possible NAGC-like transcriptional regulator |
| yajG | **-0.27** | **2.32** | **-0.95** | -0.20 | 1.53 | -0.05 | putative polymerase |
| yajI | **0.17** | **0.75** | **1.18** | 0.20 | 2.27 | 1.20 | orf, hypothetical protein |
| yajK | **-1.23** | **1.02** | **-0.47** | -1.45 | 0.93 | -1.40 | putative oxidoreductase |
| yajO | **-1.30** | **1.48** | **-1.41** | -2.00 | 1.23 | -1.30 | putative NAD(P)H-dependent xylose reductase |
| yajQ | **0.23** | **-1.03** | **-0.75** | 0.15 | -1.77 | -1.45 | orf, hypothetical protein |
| yajR | **-0.93** | **0.77** | **-1.37** | 0.05 | -0.20 | -1.55 | putative transport protein |
| ybaA | **0.53** | **-1.79** | **0.89** | 0.60 | -1.47 | 1.40 | orf, hypothetical protein |
| ybaB | **0.27** | **1.81** | **1.33** | 0.15 | 1.07 | 1.25 | orf, hypothetical protein |
| ybaC | **-0.94** | **1.22** | **-0.96** | -0.10 | 1.10 | -0.10 | putative lipase (EC 3.1.1.-) |
| ybaD | **-1.26** | **1.52** | **-1.20** | -1.15 | 0.43 | -0.30 | orf, hypothetical protein |
| ybaE | **-0.74** | **1.72** | **-0.93** | -1.20 | 1.27 | -1.20 | orf, hypothetical protein |
| ybaJ | **-0.75** | **0.27** | **0.80** | -1.95 | 0.57 | 1.50 | orf, hypothetical protein |
| ybaK | **-0.35** | **1.70** | **-1.26** | -0.15 | 0.63 | -0.15 | orf, hypothetical protein |
| ybaL | **-0.64** | **-1.38** | **0.64** | -0.25 | -0.47 | 0.45 | putative transport protein |
| ybaM | **0.00** | **-0.45** | **0.17** | -0.65 | 0.30 | 0.10 | orf, hypothetical protein |
| ybaN | **0.24** | **1.01** | **-1.87** | -0.65 | 1.73 | -1.25 | putative gene 58 |
| ybaO | **0.99** | **-1.26** | **-1.33** | 0.10 | 0.43 | -1.75 | putative LRP-like transcriptional regulator |
| ybaP | **1.16** | **-0.99** | **-1.29** | 3.45 | -1.13 | -1.15 | putative ligase |
| ybaQ | **-0.21** | **2.09** | **0.86** | -0.30 | 1.77 | 1.60 | orf, hypothetical protein |
| ybaR | **0.06** | **-1.34** | **0.78** | -0.60 | -0.50 | 0.05 | putative ATPase |
| ybaS | **-0.32** | **-1.51** | **0.42** | -0.05 | -1.67 | 0.05 | putative glutaminase |
| ybaT | **0.72** | **-1.34** | **-1.08** | 1.75 | -12.30 | -0.15 | putative amino acid |
| ybaU | **-0.55** | **1.88** | **1.18** | -1.25 | 1.43 | 0.40 | putative protease maturation protein |
| ybaV | **-2.59** | **1.16** | **-1.08** | -2.55 | 1.50 | -0.15 | orf, hypothetical protein |
| ybaW | **0.16** | **-1.54** | **-1.32** | 1.25 | -1.50 | -0.15 | orf, hypothetical protein |

| GENE | FC | | | $d(i)$ | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ybaX | **2.57** | **-1.66** | **0.25** | 1.20 | -1.17 | 0.10 | orf, hypothetical protein |
| ybaY | **-1.14** | **-1.31** | **-0.53** | -1.70 | -1.33 | 0.05 | glycoprotein |
| ybaZ | **-1.05** | **-0.25** | **0.12** | -0.45 | 0.70 | 0.00 | orf, hypothetical protein |
| ybbA | **-1.29** | **3.73** | **-0.69** | -0.65 | 1.23 | 0.00 | putative ATP-binding component of a transport system |
| ybbB | **0.69** | **-1.38** | **-0.53** | 0.45 | -0.60 | -1.20 | putative capsule anchoring protein |
| ybbC | **0.81** | **0.62** | **0.60** | 2.45 | 0.30 | 1.10 | orf, hypothetical protein |
| ybbD | **-1.13** | **-1.26** | **-1.25** | -0.65 | -0.63 | -0.20 | orf, hypothetical protein |
| ybbF | **-0.68** | **-0.01** | **0.79** | -0.15 | -0.07 | 1.25 | orf, hypothetical protein |
| ybbI | **-0.48** | **-1.57** | **1.67** | -1.65 | -2.03 | 1.15 | putative transcriptional regulator |
| ybbJ | **0.48** | **-0.62** | **0.66** | -1.30 | -1.27 | 1.25 | orf, hypothetical protein |
| ybbK | **-1.04** | **-1.66** | **0.74** | -3.85 | -1.37 | -0.05 | putative protease |
| ybbL | **0.60** | **0.45** | **1.23** | -0.10 | 1.37 | 1.75 | putative ATP-binding component of a transport system |
| ybbM | **0.05** | **-1.64** | **-1.29** | -0.90 | -1.40 | -1.50 | putative metal resistance protein |
| ybbN | **0.13** | **-1.64** | **-1.46** | 0.05 | -1.97 | -1.65 | putative thioredoxin-like protein |
| ybbO | **0.41** | **-1.13** | **-1.33** | 2.85 | 0.40 | -3.30 | putative oxidoreductase |
| ybbP | **-0.46** | **-0.83** | **-1.26** | -1.10 | -0.57 | -1.50 | putative oxidoreductase |
| ybbQ | **-0.16** | **4.01** | **0.64** | -0.95 | 1.87 | 0.20 | putative oxidoreductase |
| ybbS | **0.78** | **1.54** | **-1.35** | -0.05 | 1.07 | -1.25 | putative transcriptional regulator LYSR-type |
| ybbT | **-1.06** | **4.60** | **1.62** | -2.05 | 1.50 | 1.20 | orf, hypothetical protein |
| ybbU | **-1.63** | **-0.60** | **-1.13** | -2.25 | -0.20 | -1.45 | putative regulator |
| ybbV | **-1.06** | **-1.29** | **-0.67** | -1.60 | -0.77 | 0.05 | orf, hypothetical protein |
| ybbW | **-0.32** | **-1.37** | **-1.15** | 0.00 | -0.60 | -0.20 | putative transport protein |
| ybbX | **-2.11** | **0.72** | **0.77** | -2.75 | 1.20 | 1.40 | putative hydrolase |
| ybbY | **0.25** | **-1.38** | **1.33** | 1.40 | -1.63 | 1.60 | putative transport |
| ybbZ | **0.40** | **-1.19** | **0.36** | 0.55 | -0.13 | 0.20 | orf, hypothetical protein |
| ybcH | **0.91** | **0.51** | **0.54** | -0.25 | 0.50 | 0.35 | orf, hypothetical protein |
| ybcI | **0.44** | **0.99** | **-0.01** | 0.50 | 1.83 | 0.10 | orf, hypothetical protein |
| ybcJ | **-0.22** | **-1.30** | **0.80** | -1.40 | -1.10 | 1.35 | orf, hypothetical protein |
| ybcK | **1.25** | **-1.28** | **-1.21** | 1.50 | -0.53 | -0.10 | orf, hypothetical protein |
| ybcL | **-0.01** | **1.34** | **-1.22** | -0.25 | 1.17 | -1.25 | orf, hypothetical protein |
| ybcM | **-1.07** | **-1.35** | **0.81** | -1.55 | -1.07 | 1.40 | putative ARAC-type regulatory protein |
| ybcN | **0.34** | **-1.29** | **-1.43** | 1.35 | -0.63 | -1.55 | orf, hypothetical protein |
| ybcO | **-1.52** | **-0.85** | **0.41** | -1.90 | -0.20 | 0.15 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ybcQ | 0.60 | -9.68 | 0.52 | 0.95 | -1.23 | -0.20 | orf, hypothetical protein |
| ybcR | 0.98 | -1.34 | 0.81 | 1.50 | -0.27 | 1.50 | orf, hypothetical protein |
| ybcS | 0.96 | -0.92 | 1.19 | 0.20 | -0.43 | 1.30 | bacteriophage lambda lysozyme homolog |
| ybcT | 0.00 | -1.34 | -0.10 | -1.35 | -1.17 | 0.15 | bacteriophage lambda endopeptidase homolog |
| ybcU | 0.98 | -1.16 | 1.96 | 0.20 | -1.37 | 1.25 | bacteriophage lambda Bor protein homolog |
| ybcV | 0.72 | 2.14 | 0.90 | 0.45 | 1.40 | 1.20 | putative an envelop protein |
| ybcW | -0.25 | -2.86 | 1.46 | -1.30 | -0.33 | 1.20 | orf, hypothetical protein |
| ybcX | -0.67 | 1.05 | 0.75 | -0.35 | 1.63 | 1.45 | orf, hypothetical protein |
| ybcY | 0.21 | -1.25 | -1.00 | -0.55 | -0.17 | -0.10 | orf, hypothetical protein |
| ybcZ | 1.80 | -1.18 | -1.34 | 2.25 | 0.13 | -1.20 | putative 2-component sensor protein |
| ybdA | -0.35 | 1.11 | -1.41 | -0.15 | 2.17 | -0.20 | putative transport |
| ybdB | -0.49 | -1.23 | -0.20 | -2.50 | -0.40 | 0.30 | orf, hypothetical protein |
| ybdE | 0.00 | 0.00 | 0.77 | -2.20 | -1.77 | 0.60 | putative inner membrane component for iron transport |
| ybdF | -0.15 | -1.34 | -1.18 | -2.10 | -1.27 | 0.25 | orf, hypothetical protein |
| ybdG | -1.02 | -1.23 | 0.37 | -0.25 | -0.57 | 0.10 | putative transport |
| ybdH | -0.30 | -1.44 | 0.59 | 0.70 | -1.47 | 1.05 | putative oxidoreductase |
| ybdJ | -0.06 | 0.39 | 0.82 | -1.20 | 1.83 | 1.55 | orf, hypothetical protein |
| ybdK | 1.33 | -1.27 | -1.30 | 0.45 | -1.33 | -1.55 | orf, hypothetical protein |
| ybdL | -0.97 | -1.30 | 0.89 | 0.05 | -0.50 | 1.30 | putative aminotransferase |
| ybdM | -1.78 | -1.46 | 0.62 | -1.70 | -1.67 | 0.00 | orf, hypothetical protein |
| ybdN | 0.09 | -1.30 | 1.06 | 0.50 | -0.47 | 1.40 | orf, hypothetical protein |
| ybdO | 0.05 | 1.34 | -0.14 | -1.25 | 1.40 | 0.05 | putative transcriptional regulator LYSR-type |
| ybdQ | -1.42 | -1.56 | 0.65 | -3.45 | -1.70 | 0.00 | orf, hypothetical protein |
| ybdR | 6.54 | -1.48 | -0.83 | 2.75 | -1.83 | -1.50 | putative oxidoreductase |
| ybdS | -0.69 | -0.88 | 0.92 | 0.05 | 0.03 | 1.35 | putative a membrane protein |
| ybdU | -0.22 | 1.11 | 0.77 | -1.40 | 1.03 | 0.45 | orf, hypothetical protein |
| ybeA | -0.71 | 0.05 | -0.04 | -0.40 | -0.23 | 0.20 | orf, hypothetical protein |
| ybeB | 0.99 | 2.07 | 1.31 | 1.40 | 2.50 | 1.60 | orf, hypothetical protein |
| ybeC | -0.17 | -1.36 | -0.14 | -2.55 | -1.63 | 0.15 | orf, hypothetical protein |
| ybeD | 0.63 | 2.20 | 0.34 | 0.20 | 1.37 | 0.35 | orf, hypothetical protein |
| ybeF | 0.70 | 4.81 | 0.79 | 1.80 | 1.63 | 1.40 | putative transcriptional regulator LYSR-type |
| ybeH | -0.72 | 3.03 | 0.18 | 0.75 | 1.53 | 0.10 | orf, hypothetical protein |
| ybeJ | -0.81 | 0.58 | -0.46 | -1.05 | 0.40 | 0.00 | putative periplasmic binding transport protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ybeK | **-0.18** | **-1.73** | **0.35** | -0.80 | -1.53 | 0.15 | putative tRNA synthetase |
| ybeL | **-1.14** | **-2.52** | **0.82** | -4.50 | -2.27 | 1.45 | putative alpha helical protein |
| ybeM | **0.34** | **-0.44** | **-1.31** | 2.00 | 1.10 | -3.00 | putative amidase |
| ybeN | **-0.45** | **-1.48** | **-1.25** | -1.05 | -1.10 | 0.00 | orf, hypothetical protein |
| ybeQ | **-0.99** | **2.01** | **0.74** | -0.05 | 1.30 | -0.05 | orf, hypothetical protein |
| ybeR | **-0.03** | **-1.24** | **-0.46** | 0.25 | -0.37 | -0.20 | orf, hypothetical protein |
| ybeS | **0.31** | **0.16** | **-0.76** | 0.10 | 0.27 | -1.35 | putative enzyme of polynucleotide modification |
| ybeT | **0.56** | **-0.96** | **-1.42** | 1.45 | -0.07 | -1.60 | orf, hypothetical protein |
| ybeU | **3.42** | **-1.33** | **-0.02** | 1.75 | -0.60 | 0.10 | putative tRNA ligase |
| ybeV | **-0.91** | **0.76** | **-1.36** | -1.80 | 1.67 | -1.50 | orf, hypothetical protein |
| ybeW | **0.21** | **0.85** | **0.21** | 1.15 | 1.57 | 0.05 | putative dnaK protein |
| ybeX | **-1.58** | **0.89** | **1.03** | -1.75 | 0.33 | 1.45 | putative transport protein |
| ybeY | **0.04** | **-1.42** | **0.77** | -0.95 | -2.70 | 0.00 | orf, hypothetical protein |
| ybeZ | **-0.45** | **-2.57** | **-0.47** | -0.35 | -1.33 | 0.00 | putative ATP-binding protein in pho regulon |
| ybfA | **-0.08** | **-5.46** | **-0.72** | -1.50 | -1.77 | 0.00 | orf, hypothetical protein |
| ybfB | **0.77** | **0.96** | **1.09** | 1.55 | 0.50 | 1.15 | orf, hypothetical protein |
| ybfC | **1.42** | **-1.20** | **0.55** | 1.15 | -0.33 | 0.25 | orf, hypothetical protein |
| ybfD | **0.71** | **-1.23** | **-1.17** | 1.90 | -0.33 | -0.30 | putative DNA ligase |
| ybfE | **-0.99** | **-0.87** | **0.61** | -3.35 | 0.10 | 0.00 | orf, hypothetical protein |
| ybfF | **-0.18** | **0.90** | **-1.57** | 1.05 | 1.83 | -1.15 | orf, hypothetical protein |
| ybfG | **0.93** | **2.71** | **1.06** | 1.70 | 1.33 | 1.70 | orf, hypothetical protein |
| ybfH | **1.44** | **-1.29** | **-0.59** | 1.65 | -0.33 | 0.00 | orf, hypothetical protein |
| ybfL | **-0.43** | **0.87** | **1.24** | 0.70 | 1.47 | 1.20 | putative receptor protein |
| ybfM | **-0.99** | **-1.37** | **1.16** | -0.40 | -1.47 | -0.10 | orf, hypothetical protein |
| ybfN | **-0.48** | **1.10** | **1.25** | -1.70 | 1.10 | 1.40 | orf, hypothetical protein |
| ybfP | **0.72** | **-1.38** | **-0.79** | 1.05 | -1.60 | 0.00 | putative pectinase |
| ybgA | **-1.24** | **0.47** | **-1.01** | -0.65 | 1.40 | -1.05 | orf, hypothetical protein |
| ybgC | **0.48** | **-1.31** | **-1.22** | -0.10 | -1.37 | -1.20 | orf, hypothetical protein |
| ybgD | **0.26** | **1.85** | **-0.80** | 0.15 | 1.37 | 0.00 | putative fimbrial-like protein |
| ybgE | **-1.83** | **-0.42** | **1.22** | -1.60 | -0.23 | 1.40 | orf, hypothetical protein |
| ybgF | **-0.47** | **1.20** | **0.91** | 0.00 | 0.27 | 1.75 | orf, hypothetical protein |
| ybgG | **-0.11** | **-1.33** | **0.91** | -1.35 | -0.63 | 1.45 | putative sugar hydrolase |
| ybgH | **-0.29** | **5.21** | **0.57** | -1.25 | 1.77 | -0.05 | putative transport protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ybgI | -1.28 | 1.50 | 0.82 | -1.25 | 2.23 | 3.20 | orf, hypothetical protein |
| ybgJ | -0.04 | -1.25 | 0.42 | -1.95 | 0.27 | 0.55 | putative carboxylase |
| ybgK | -0.36 | -1.31 | 0.78 | -0.45 | -0.03 | 1.40 | putative carboxylase |
| ybgL | 0.36 | 0.00 | -0.70 | 0.05 | 0.50 | 0.00 | putative lactam utilization protein |
| ybgO | -1.12 | -1.49 | 0.45 | 0.10 | -1.43 | 0.15 | orf, hypothetical protein |
| ybgP | -1.15 | -1.36 | -1.05 | -0.30 | -0.87 | -0.25 | putative chaperone |
| ybgQ | 0.07 | -1.30 | -0.95 | 1.20 | -0.90 | -0.10 | putative outer membrane protein |
| ybgR | 0.68 | -1.45 | -0.47 | 2.35 | -1.23 | 0.10 | putative transport system permease protein |
| ybhA | -0.04 | -1.10 | -0.97 | 0.05 | -0.27 | -0.10 | putative phosphatase |
| ybhB | 0.25 | 0.19 | -0.47 | 0.15 | 1.10 | 0.05 | orf, hypothetical protein |
| ybhC | 0.58 | -1.21 | -0.79 | 0.50 | -0.40 | 0.00 | putative pectinesterase |
| ybhD | 0.00 | -1.26 | 0.58 | -0.20 | 0.93 | 0.35 | putative transcriptional regulator LYSR-type |
| ybhE | 0.00 | -1.49 | 1.11 | -0.05 | -1.53 | 1.50 | putative isomerase |
| ybhF | -1.36 | -1.30 | -1.20 | -0.45 | -0.80 | 0.05 | putative ATP-binding component of a transport system |
| ybhH | -0.97 | 0.56 | 1.16 | -0.15 | 1.10 | 1.50 | orf, hypothetical protein |
| ybhI | 0.35 | -1.46 | 0.76 | 0.40 | -1.30 | 0.25 | putative membrane pump protein |
| ybhJ | 0.00 | 0.75 | 0.58 | -1.85 | 1.53 | 0.10 | putative enzyme |
| ybhK | -1.01 | 0.76 | 0.68 | -0.35 | 0.37 | -0.20 | putative structural protein |
| ybhL | -2.18 | -0.67 | -1.41 | -1.60 | -1.07 | -1.35 | orf, hypothetical protein |
| ybhM | -1.12 | 1.34 | -0.46 | -0.10 | 1.33 | 0.10 | orf, hypothetical protein |
| ybhN | -1.18 | -0.57 | 0.28 | -0.25 | -0.17 | -0.20 | orf, hypothetical protein |
| ybhO | -0.99 | 1.53 | 0.79 | -1.65 | 1.70 | 0.00 | putative synthetase |
| ybhP | 0.66 | 0.77 | 1.48 | 1.85 | 0.47 | 1.65 | orf, hypothetical protein |
| ybhQ | -2.18 | -1.43 | -0.50 | -1.80 | -0.47 | -1.00 | orf, hypothetical protein |
| ybhR | 1.53 | 0.67 | 0.70 | 1.65 | 1.43 | 1.35 | orf, hypothetical protein |
| ybhS | 0.12 | -1.34 | 0.65 | 0.25 | -0.27 | 1.40 | orf, hypothetical protein |
| ybiA | -0.28 | -1.30 | -0.69 | -1.50 | -0.73 | -1.25 | orf, hypothetical protein |
| ybiB | -0.19 | 1.57 | 1.27 | 0.20 | 0.83 | 0.10 | putative enzyme |
| ybiC | -3.80 | -1.26 | -0.86 | -2.25 | -0.70 | -0.05 | putative dehydrogenase |
| ybiF | 1.56 | 0.82 | -1.43 | 1.95 | 1.60 | -1.35 | putative transmembrane subunit |
| ybiH | 0.30 | 0.84 | 0.12 | 0.10 | 1.23 | -0.10 | putative transcriptional regulator |
| ybiI | -1.11 | -0.47 | 1.09 | -1.30 | 0.33 | -0.10 | orf, hypothetical protein |
| ybiJ | -0.28 | -0.88 | 0.93 | -0.05 | -1.13 | 1.45 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ybiK | -0.98 | 0.00 | -1.34 | -4.05 | 0.03 | -1.20 | putative asparaginase |
| ybiM | 0.53 | 1.55 | 0.90 | 0.20 | 1.47 | 1.20 | orf, hypothetical protein |
| ybiN | 0.00 | -0.80 | -0.96 | -0.15 | -0.10 | -1.50 | orf, hypothetical protein |
| ybiO | -0.75 | 1.37 | -1.19 | 0.15 | 1.53 | -0.15 | putative transport protein |
| ybiP | 0.80 | 0.00 | -0.16 | -0.10 | 1.47 | -0.15 | putative enzyme |
| ybiR | -0.25 | -1.26 | 0.24 | 1.45 | -0.30 | -0.15 | orf, hypothetical protein |
| ybiS | 1.11 | 2.95 | 0.15 | 0.35 | 1.87 | -1.30 | orf, hypothetical protein |
| ybiT | -0.99 | 0.77 | 0.00 | -0.25 | 2.33 | -0.10 | putative ATP-binding component of a transport system |
| ybiU | 0.91 | -0.61 | 0.82 | 1.80 | 1.10 | 1.15 | orf, hypothetical protein |
| ybiW | -0.01 | 3.17 | 1.18 | -1.15 | 2.60 | 1.55 | putative formate acetyltransferase |
| ybiX | -2.04 | -1.38 | -0.03 | -1.55 | -1.50 | 0.05 | putative enzyme |
| ybiY | -0.53 | 0.00 | 1.50 | 0.25 | 1.23 | 1.55 | putative pyruvate formate-lyase 2 activating enzyme |
| ybjC | -0.15 | -1.07 | -0.57 | 1.25 | -0.53 | -1.25 | orf, hypothetical protein |
| ybjD | 2.22 | -1.34 | -0.19 | 1.55 | -0.13 | 0.20 | orf, hypothetical protein |
| ybjE | -0.44 | -1.30 | -0.56 | 0.20 | -0.40 | 0.05 | putative surface protein |
| ybjF | 0.00 | 0.76 | -1.37 | -1.75 | 1.27 | -1.35 | putative enzyme |
| ybjG | 0.49 | 1.57 | 0.77 | 1.50 | 1.60 | 1.20 | orf, hypothetical protein |
| ybjH | -0.29 | 0.25 | -1.06 | 0.10 | 0.40 | -1.20 | orf, hypothetical protein |
| ybjM | -0.95 | -2.01 | 0.90 | -1.85 | -1.57 | 1.65 | orf, hypothetical protein |
| ybjN | -0.12 | 0.72 | 0.60 | -1.20 | -0.13 | -0.05 | putative sensory transduction regulator |
| ybjO | -0.41 | 1.01 | 0.59 | -0.15 | 1.37 | 0.30 | orf, hypothetical protein |
| ybjP | 1.03 | -2.01 | -1.25 | 1.45 | -1.23 | -1.50 | putative enzyme |
| ybjT | -0.93 | -1.24 | 0.82 | -1.45 | -0.33 | 1.35 | putative dTDP-glucose enzyme |
| ybjU | -0.84 | 0.71 | 0.80 | -0.45 | 1.30 | 1.40 | putative arylsulfatase |
| ybjW | -1.02 | -1.42 | -1.17 | -0.40 | -1.40 | -1.05 | putative prismane |
| ybjX | 0.01 | 1.86 | -0.49 | 0.10 | 1.93 | 0.05 | putative enzyme |
| ybjZ | 0.22 | 1.56 | 0.75 | 0.05 | 1.97 | 1.25 | putative ATP-binding component of a transport system |
| ycaC | -1.31 | -1.37 | 0.34 | -1.65 | -1.47 | 0.20 | orf, hypothetical protein |
| ycaD | 1.06 | 0.83 | 0.97 | 1.65 | 1.47 | -0.30 | putative transport |
| ycaH | 0.52 | -1.08 | 0.78 | 1.35 | -0.17 | 0.35 | putative EC 1.2 enzyme |
| ycaI | -0.32 | 0.60 | 0.00 | -0.35 | 1.50 | -0.10 | orf, hypothetical protein |
| ycaJ | 0.80 | -0.75 | 1.92 | 1.55 | -0.13 | 1.50 | putative polynucleotide enzyme |
| ycaK | 0.71 | 0.15 | 0.56 | 0.30 | 1.73 | 0.30 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ycaL | -1.58 | -0.20 | -0.05 | -1.70 | 0.50 | -0.10 | putative heat shock protein |
| ycaN | 0.80 | -1.47 | 1.59 | 1.50 | -1.23 | 1.60 | putative transcriptional regulator LYSR-type |
| ycaO | 0.81 | -1.03 | -0.40 | 0.45 | -0.27 | 0.15 | orf, hypothetical protein |
| ycaP | -0.29 | 1.91 | -0.97 | -1.20 | 1.77 | -0.05 | orf, hypothetical protein |
| ycaQ | -0.09 | 2.44 | -0.62 | 0.30 | 1.27 | 0.00 | orf, hypothetical protein |
| ycaR | 0.22 | 1.21 | 2.41 | 1.15 | 1.63 | 1.10 | orf, hypothetical protein |
| ycbB | -0.18 | -0.47 | 0.70 | -0.05 | 0.63 | 0.05 | putative amidase |
| ycbC | -1.14 | -1.49 | -1.45 | -1.60 | -1.13 | -1.15 | orf, hypothetical protein |
| ycbE | 0.45 | 1.42 | 1.86 | 0.40 | 1.17 | 1.20 | putative ATP-binding component of a transport system |
| ycbF | 0.11 | -1.32 | -1.44 | 1.20 | -0.43 | -1.25 | putative chaperone |
| ycbG | -1.31 | -1.90 | 0.72 | -2.10 | -1.27 | 0.30 | putative dehydrogenase |
| ycbK | -0.30 | 1.20 | 0.89 | -0.35 | 1.53 | 1.45 | orf, hypothetical protein |
| ycbL | -0.37 | -0.12 | 0.29 | -1.10 | 0.53 | 0.35 | orf, hypothetical protein |
| ycbM | -1.22 | 0.63 | 1.09 | -0.30 | 1.37 | 1.30 | putative transport system permease protein |
| ycbN | 0.33 | 0.76 | 0.25 | 0.10 | 1.73 | 0.20 | orf, hypothetical protein |
| ycbO | -0.12 | -1.55 | 1.06 | 1.55 | -1.23 | 1.65 | orf, hypothetical protein |
| ycbP | -0.96 | -1.51 | -1.36 | -1.70 | -1.33 | -1.90 | orf, hypothetical protein |
| ycbQ | -0.08 | -3.24 | 0.66 | 0.00 | 0.30 | 0.10 | putative fimbrial-like protein |
| ycbR | 0.20 | -1.38 | 0.44 | 0.05 | -0.20 | 0.05 | putative chaperone |
| ycbS | 0.34 | -1.02 | 0.18 | 1.20 | -0.27 | -0.15 | putative outer membrane protein |
| ycbW | -0.98 | -1.49 | 0.77 | -2.25 | -1.67 | 1.25 | orf, hypothetical protein |
| ycbY | 0.69 | -0.83 | -0.93 | 1.45 | -0.30 | -1.20 | putative oxidoreductase |
| yccA | -2.00 | 1.72 | 0.88 | -1.95 | 1.47 | 1.35 | putative carrier |
| yccC | -3.98 | -0.34 | -0.46 | -1.35 | -0.07 | -0.20 | orf, hypothetical protein |
| yccD | 0.20 | -1.34 | 0.77 | 0.05 | -1.43 | 1.50 | orf, hypothetical protein |
| yccE | -0.84 | 3.32 | -1.41 | 0.30 | 1.20 | -1.50 | orf, hypothetical protein |
| yccF | -0.07 | -1.22 | 1.40 | 0.15 | -0.03 | 1.30 | orf, hypothetical protein |
| yccJ | -1.27 | -0.67 | 0.18 | -5.00 | -0.57 | 0.45 | orf, hypothetical protein |
| yccK | 0.33 | -1.66 | 0.39 | 0.00 | -1.30 | 1.15 | putative sulfite reductase (EC 1.8.-.-) |
| yccM | -1.03 | 1.43 | 0.80 | -0.05 | 1.43 | 1.70 | orf, hypothetical protein |
| yccV | -2.38 | -1.20 | -0.29 | -2.70 | -0.53 | 0.05 | orf, hypothetical protein |
| yccY | 0.91 | 0.00 | -1.38 | -0.15 | 1.13 | -1.20 | putative phosphatase |
| yccZ | -0.08 | 0.75 | -1.23 | -2.20 | 0.63 | 0.05 | putative function in exopolysaccharide production |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ycdB | -0.40 | 1.48 | 0.73 | -0.05 | 1.33 | 0.25 | orf, hypothetical protein |
| ycdC | 0.41 | -0.73 | -1.07 | 1.20 | 0.20 | -0.20 | putative tet operon regulator |
| ycdF | -0.51 | -1.78 | -1.31 | -2.20 | -1.47 | -1.45 | orf, hypothetical protein |
| ycdG | 0.20 | 0.00 | 1.09 | -0.50 | 0.80 | 1.30 | putative transport protein |
| ycdO | 0.29 | -0.83 | -0.71 | 1.30 | 0.00 | -0.05 | orf, hypothetical protein |
| ycdP | 0.24 | -1.34 | 0.77 | -0.20 | -1.53 | 0.05 | orf, hypothetical protein |
| ycdQ | -0.18 | 7.28 | 0.71 | -0.30 | 1.53 | 0.20 | orf, hypothetical protein |
| ycdR | 1.01 | -1.31 | 0.79 | 2.05 | -0.47 | 1.70 | orf, hypothetical protein |
| ycdS | -1.11 | 1.23 | -1.36 | -1.25 | 1.37 | -1.40 | putative outer membrane protein |
| ycdT | 0.71 | 2.56 | 0.63 | 1.70 | 0.60 | 1.20 | orf, hypothetical protein |
| ycdU | 0.57 | 1.09 | 1.37 | 1.25 | 1.50 | 1.15 | orf, hypothetical protein |
| ycdV | 0.72 | -1.12 | -0.88 | 1.80 | -1.47 | -1.30 | putative ribosomal protein |
| ycdW | -0.08 | -1.28 | 0.26 | -1.30 | -0.70 | 0.10 | putative dehydrogenase |
| ycdX | -1.27 | 0.97 | 0.81 | -1.75 | 1.63 | 1.55 | orf, hypothetical protein |
| ycdY | -0.20 | -1.54 | 0.92 | -0.45 | -1.03 | -0.05 | putative oxidoreductase component |
| ycdZ | -2.54 | -2.08 | 0.89 | -2.95 | -1.67 | 0.15 | orf, hypothetical protein |
| yceA | -0.75 | 1.12 | -0.28 | -0.30 | 1.43 | 0.25 | orf, hypothetical protein |
| yceB | -0.09 | -1.38 | -0.88 | -0.25 | -0.43 | -1.35 | orf, hypothetical protein |
| yceC | 1.38 | -1.02 | -0.75 | 0.05 | -0.40 | 0.00 | orf, hypothetical protein |
| yceD | 0.88 | 1.66 | 1.19 | 2.15 | 1.60 | 0.35 | orf, hypothetical protein |
| yceE | 0.18 | -1.27 | 0.75 | 0.45 | -0.50 | 0.35 | putative transport protein |
| yceF | -1.45 | 0.18 | -0.29 | -2.60 | 0.53 | 0.10 | orf, hypothetical protein |
| yceG | 0.70 | -1.06 | 0.63 | 0.10 | -1.23 | 0.05 | putative thymidylate kinase (EC 2.7.4.9) |
| yceH | 0.15 | -0.06 | 0.93 | -0.35 | 0.40 | 1.20 | orf, hypothetical protein |
| yceI | -5.01 | 0.30 | 0.69 | -1.40 | 0.47 | 0.20 | orf, hypothetical protein |
| yceK | -0.09 | 1.31 | -1.26 | -1.40 | -0.27 | -1.20 | orf, hypothetical protein |
| yceL | 2.41 | -0.15 | -2.00 | 2.45 | 0.57 | -1.15 | orf, hypothetical protein |
| yceO | -0.08 | -1.38 | 0.78 | 0.30 | -0.50 | 1.60 | orf, hypothetical protein |
| yceP | -0.83 | 0.04 | 0.01 | -0.60 | 0.23 | 0.25 | orf, hypothetical protein |
| ycfA | 1.86 | -1.12 | -1.41 | 1.65 | -0.27 | -1.55 | orf, hypothetical protein |
| ycfB | -1.68 | 0.80 | 1.26 | -1.50 | 0.23 | 1.35 | orf, hypothetical protein |
| ycfC | -0.85 | 1.51 | 0.79 | -0.20 | 0.63 | 1.25 | orf, hypothetical protein |
| ycfD | 1.05 | 0.10 | -1.24 | 0.40 | -0.57 | -0.20 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ycfF | 0.26 | -2.18 | 1.51 | 0.55 | 0.10 | 1.30 | orf, hypothetical protein |
| ycfH | 0.24 | -1.39 | -1.34 | 0.05 | -0.67 | -1.25 | orf, hypothetical protein |
| ycfJ | 2.36 | 1.42 | 0.73 | 1.25 | 1.60 | 0.25 | orf, hypothetical protein |
| ycfK | -0.79 | -1.29 | -1.36 | 0.20 | -0.50 | -1.25 | orf, hypothetical protein |
| ycfL | 1.96 | 0.63 | 1.14 | 1.20 | 1.40 | 1.45 | orf, hypothetical protein |
| ycfM | -0.89 | 0.58 | 0.02 | -0.85 | 1.53 | -0.35 | orf, hypothetical protein |
| ycfN | -0.13 | 2.47 | -0.35 | 0.20 | 0.03 | 0.15 | putative beta-glucosidase (EC 3.2.1.21) |
| ycfO | 0.68 | -1.72 | 1.56 | -0.35 | -1.23 | 1.35 | orf, hypothetical protein |
| ycfP | 1.78 | 1.12 | 1.76 | 1.05 | 0.37 | 1.25 | orf, hypothetical protein |
| ycfQ | -1.30 | -1.05 | -1.06 | -0.80 | -0.03 | -1.35 | orf, hypothetical protein |
| ycfR | 0.36 | -0.53 | 0.79 | 2.55 | 1.50 | 1.45 | orf, hypothetical protein |
| ycfS | -1.12 | -0.45 | -1.33 | -0.40 | 0.17 | -1.50 | orf, hypothetical protein |
| ycfT | -0.89 | 0.88 | 1.22 | -0.15 | 1.37 | 1.35 | orf, hypothetical protein |
| ycfU | -0.19 | -0.76 | 1.39 | 0.05 | -0.37 | 1.30 | orf, hypothetical protein |
| ycfV | 0.02 | 0.00 | -0.18 | 1.15 | 1.30 | 0.20 | putative ATP-binding component of a transport system |
| ycfW | -0.69 | -1.60 | -1.39 | -1.35 | 1.07 | -1.60 | putative kinase |
| ycfX | 0.28 | -1.01 | -1.31 | -0.15 | -0.23 | -0.20 | putative NAGC-like transcriptional regulator |
| ycgB | -0.23 | 0.13 | -1.32 | 0.05 | 0.43 | -0.10 | putative sporulation protein |
| ycgC | 0.76 | 1.33 | 0.77 | 3.45 | 1.33 | 0.15 | putative PTS system enzyme I |
| ycgE | -0.50 | -0.39 | 0.78 | -0.55 | -1.63 | 1.30 | putative transcriptional regulator |
| ycgJ | 0.69 | 2.73 | -0.19 | 0.30 | 1.47 | -0.05 | orf, hypothetical protein |
| ycgK | -0.17 | 1.02 | -1.32 | -0.25 | 1.47 | -1.05 | orf, hypothetical protein |
| ycgL | 0.51 | -1.44 | 0.83 | 1.15 | -1.20 | 1.20 | orf, hypothetical protein |
| ycgN | 0.57 | 0.36 | 0.46 | 1.45 | 0.33 | 0.30 | orf, hypothetical protein |
| ycgR | -0.78 | -1.40 | -0.27 | -1.55 | -1.67 | 0.05 | orf, hypothetical protein |
| ycgW | 1.59 | -0.94 | -1.23 | 1.15 | -0.13 | -1.50 | orf, hypothetical protein |
| ycgX | -0.48 | 0.28 | 0.63 | 0.10 | -0.27 | 0.05 | orf, hypothetical protein |
| ycgY | 0.00 | 1.97 | -1.08 | -1.50 | 1.53 | -0.05 | orf, hypothetical protein |
| ycgZ | 0.67 | -1.34 | 0.93 | 2.45 | -1.70 | 1.35 | orf, hypothetical protein |
| ychA | -0.02 | 2.29 | 1.38 | -0.05 | -0.23 | 1.40 | orf, hypothetical protein |
| ychB | 0.92 | -0.48 | 1.05 | 1.10 | -0.37 | 1.30 | orf, hypothetical protein |
| ychE | -1.17 | -0.46 | 0.77 | -1.55 | 0.57 | 0.00 | putative channel protein |
| ychF | 1.86 | 4.30 | -0.45 | 1.95 | 2.27 | -0.10 | putative GTP-binding protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ychG | 0.46 | -1.33 | -1.22 | 1.65 | -0.60 | -1.10 | orf, hypothetical protein |
| ychH | -1.18 | -2.64 | -1.28 | -5.00 | -1.33 | -0.35 | orf, hypothetical protein |
| ychJ | -0.40 | 0.69 | -0.08 | -0.05 | 0.33 | 0.05 | orf, hypothetical protein |
| ychK | -0.78 | 0.77 | -1.24 | -1.65 | 1.17 | -1.20 | orf, hypothetical protein |
| ychM | 0.00 | 0.96 | 0.85 | -0.25 | 1.87 | 1.50 | orf, hypothetical protein |
| ychN | 0.90 | 1.65 | 0.89 | 1.25 | 1.13 | 1.20 | orf, hypothetical protein |
| ychP | 0.77 | -0.06 | 0.10 | 1.65 | -0.40 | 0.15 | putative factor |
| yciA | -0.14 | -1.62 | 0.78 | 0.05 | -1.17 | 0.05 | orf, hypothetical protein |
| yciB | -0.51 | 0.96 | 0.95 | -0.20 | 1.33 | 1.15 | orf, hypothetical protein |
| yciC | -0.06 | -0.70 | 0.74 | -0.95 | 1.03 | -0.15 | orf, hypothetical protein |
| yciD | -0.89 | -0.78 | 0.84 | -2.65 | -0.47 | -0.25 | putative outer membrane protein |
| yciE | 0.38 | -1.60 | 0.48 | 0.35 | -1.20 | -0.10 | orf, hypothetical protein |
| yciF | -0.73 | 4.50 | 0.35 | 0.05 | 1.27 | 0.10 | putative structural proteins |
| yciG | 0.00 | 0.00 | 0.76 | -5.20 | 1.23 | 1.30 | orf, hypothetical protein |
| yciH | 1.38 | 2.29 | 1.36 | 3.10 | 1.47 | 1.25 | orf, hypothetical protein |
| yciI | 0.50 | -0.72 | -2.02 | 1.40 | 0.07 | -1.30 | orf, hypothetical protein |
| yciK | -0.86 | -1.28 | -1.22 | -0.20 | -1.47 | -1.40 | putative oxidoreductase |
| yciL | 0.20 | -0.49 | -1.17 | 0.30 | 1.10 | -1.70 | orf, hypothetical protein |
| yciM | 0.30 | -1.87 | 0.87 | 0.10 | 0.30 | 1.60 | putative heat shock protein |
| yciN | 0.92 | 1.14 | -1.32 | -1.05 | 0.50 | -1.25 | orf, hypothetical protein |
| yciO | -0.29 | -1.33 | 0.71 | -2.05 | -1.60 | 0.05 | orf, hypothetical protein |
| yciQ | -1.20 | -0.66 | -0.43 | -0.25 | -1.10 | 0.15 | orf, hypothetical protein |
| yciR | -5.10 | -1.31 | 0.50 | -1.70 | -1.20 | 0.05 | orf, hypothetical protein |
| yciS | -1.69 | -0.88 | 1.08 | -1.55 | 0.23 | 1.95 | orf, hypothetical protein |
| yciV | -0.92 | -1.05 | -0.84 | -1.60 | -0.20 | -0.15 | putative enzymes |
| yciW | -6.61 | 1.08 | -1.01 | -2.20 | 0.33 | -0.15 | putative oxidoreductase |
| ycjC | -0.27 | -0.24 | 0.78 | -0.15 | -0.03 | 1.35 | orf, hypothetical protein |
| ycjD | -0.42 | -0.83 | 0.03 | -0.10 | 0.53 | 0.05 | orf, hypothetical protein |
| ycjF | 1.12 | 0.54 | 0.66 | 1.65 | 0.60 | -0.05 | orf, hypothetical protein |
| ycjG | -0.52 | -1.63 | 1.13 | -0.35 | -1.40 | 1.20 | putative muconate cycloisomerase I (EC 5.5.-.-) |
| ycjI | -0.47 | -1.88 | 0.64 | -0.50 | -1.43 | 0.10 | putative carboxypeptidase |
| ycjJ | 0.35 | 0.68 | -0.58 | -0.05 | 0.60 | 0.05 | putative amino acid |
| ycjL | -0.10 | 1.37 | 0.72 | 0.15 | 1.53 | 1.15 | probable amidotransferase subunit |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ycjM | 1.97 | -1.21 | 0.09 | 1.80 | -0.30 | 0.00 | putative polysaccharide hydrolase |
| ycjO | 0.58 | -1.36 | 0.85 | -0.25 | -0.37 | 1.45 | putative binding-protein dependent transport protein |
| ycjP | 0.14 | -1.89 | -1.07 | 0.05 | -1.47 | -0.10 | putative transport system permease protein |
| ycjQ | 0.85 | -1.01 | -0.96 | 0.20 | -1.17 | -1.20 | putative oxidoreductase |
| ycjS | -0.34 | 0.76 | -1.32 | -1.30 | 1.13 | 0.00 | putative dehydrogenase |
| ycjT | 1.23 | 0.15 | 0.32 | 2.45 | 1.10 | -0.15 | orf, hypothetical protein |
| ycjU | -1.28 | -1.24 | 0.74 | -1.55 | -0.23 | 1.30 | putative beta-phosphoglucomutase |
| ycjV | 0.64 | -1.33 | -1.15 | 0.30 | -0.70 | -1.45 | putative ATP-binding component of a transport system |
| ycjW | -1.24 | -1.24 | 0.58 | -1.55 | -0.20 | 1.20 | putative LACI-type transcriptional regulator |
| ycjX | 2.01 | -1.50 | -1.13 | 1.80 | -1.33 | 0.05 | putative EC 2.1 enzymes |
| ycjZ | 1.22 | -0.03 | -1.11 | 1.25 | -1.17 | -1.45 | putative transcriptional regulator LYSR-type |
| ydaA | -1.01 | -1.63 | 0.89 | -3.60 | -1.57 | 1.30 | orf, hypothetical protein |
| ydaC | 0.00 | 0.00 | 0.93 | 0.25 | 1.73 | -0.05 | orf, hypothetical protein |
| ydaD | 0.94 | -1.34 | 0.76 | 1.60 | -0.40 | 1.20 | orf, hypothetical protein |
| ydaH | 0.73 | -1.35 | -1.30 | 2.05 | -1.27 | -0.30 | putative pump protein (transport) |
| ydaJ | 0.11 | -0.04 | -1.32 | 0.20 | 0.63 | -1.50 | putative aminohydrolase (EC 3.5.1.14) |
| ydaK | 0.16 | 0.00 | -1.42 | 0.15 | -0.30 | -1.15 | putative transcriptional regulator LYSR-type |
| ydaL | 0.00 | 0.72 | 0.74 | -2.50 | 1.80 | 0.15 | orf, hypothetical protein |
| ydaO | -1.26 | 0.23 | -1.28 | -1.20 | -1.10 | -1.55 | orf, hypothetical protein |
| ydaQ | 0.90 | -1.46 | 1.06 | 1.45 | -1.70 | 0.05 | orf, hypothetical protein |
| ydaR | 0.84 | 1.07 | 0.34 | 1.35 | 1.23 | 0.20 | orf, hypothetical protein |
| ydaS | 0.65 | -1.44 | -1.26 | 1.10 | -1.47 | -1.10 | orf, hypothetical protein |
| ydaT | -0.98 | 0.65 | 0.84 | 0.05 | -0.13 | 1.35 | orf, hypothetical protein |
| ydaU | 0.59 | -2.69 | 0.42 | 1.75 | -1.47 | 1.00 | orf, hypothetical protein |
| ydaW | 0.66 | -1.84 | -0.10 | 0.45 | -2.57 | 0.05 | orf, hypothetical protein |
| ydaY | 0.51 | 0.00 | -0.40 | -0.35 | 0.77 | 0.20 | orf, hypothetical protein |
| ydbA | -0.21 | -0.43 | -0.17 | 0.05 | 0.50 | 1.00 | split orf |
| ydbA | 0.00 | 0.00 | 0.77 | -4.90 | 0.27 | 0.20 | split orf |
| ydbC | -1.64 | 1.55 | 0.82 | -1.75 | 1.67 | 1.40 | putative dehydrogenase |
| ydbD | -0.10 | -1.36 | 0.10 | 0.00 | -1.33 | 0.15 | orf, hypothetical protein |
| ydbH | -1.96 | -0.03 | -0.85 | -1.80 | 0.53 | -0.05 | orf, hypothetical protein |
| ydbK | -0.06 | -0.71 | 0.44 | 0.25 | -0.33 | 0.25 | putative oxidoreductase, Fe-S subunit |
| ydbL | 0.02 | -1.12 | -0.05 | -0.10 | -0.33 | 0.05 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ydbO | 0.00 | -1.34 | 0.83 | -2.70 | -2.70 | 1.40 | orf, hypothetical protein |
| ydbP | -2.31 | -1.25 | -0.98 | -2.00 | -0.17 | -1.60 | orf, hypothetical protein |
| ydbS | 0.36 | -1.34 | 1.15 | -0.20 | 0.27 | 1.50 | putative enzyme |
| ydbU | 0.35 | -1.34 | -0.86 | 2.45 | -1.37 | -1.10 | putative enzyme |
| ydcA | -1.02 | 0.75 | 0.36 | -0.50 | -0.40 | -0.10 | orf, hypothetical protein |
| ydcD | -0.18 | 1.51 | 0.84 | 0.20 | 1.70 | 1.10 | orf, hypothetical protein |
| ydcE | 0.87 | 0.66 | 0.93 | 0.00 | 0.37 | -0.20 | orf, hypothetical protein |
| ydcF | 0.80 | 3.32 | 0.81 | 0.15 | 1.27 | 1.20 | orf, hypothetical protein |
| ydcG | -0.97 | -1.48 | 0.78 | -0.40 | -1.30 | 1.35 | putative glycoprotein |
| ydcH | -0.97 | -1.53 | 0.14 | -3.15 | -1.70 | -0.35 | orf, hypothetical protein |
| ydcN | 0.80 | -1.70 | -1.39 | 0.95 | -1.17 | -1.20 | orf, hypothetical protein |
| ydcP | 1.36 | 2.17 | -0.89 | 1.80 | 1.33 | -1.15 | putative collagenase |
| yddA | -0.11 | -1.12 | 0.62 | 0.05 | -0.27 | 0.05 | putative ATP-binding component of a transport system |
| yddB | -1.91 | 1.71 | 0.92 | -1.95 | 1.30 | 2.35 | orf, hypothetical protein |
| yddE | -0.43 | 1.28 | 0.43 | -0.25 | 1.63 | 0.05 | orf, hypothetical protein |
| yddG | 0.73 | -1.34 | -0.68 | 1.35 | 1.17 | -1.20 | orf, hypothetical protein |
| yddM | -1.99 | -1.30 | 0.71 | -1.55 | -1.30 | 0.10 | orf, hypothetical protein |
| ydeA | 0.08 | -1.20 | 2.16 | 1.10 | -1.33 | 1.15 | putative resistance |
| ydeB | 0.40 | 1.46 | 0.91 | -0.50 | 1.93 | 1.65 | orf, hypothetical protein |
| ydeD | -0.02 | -1.18 | 0.39 | 0.15 | 1.40 | 0.10 | orf, hypothetical protein |
| ydeF | -0.87 | -0.51 | -2.95 | -0.25 | 0.60 | -1.25 | putative transport protein |
| ydeH | -0.98 | -0.86 | 0.79 | -1.15 | -0.07 | 1.25 | orf, hypothetical protein |
| ydeI | 0.50 | - 0.68 | 0.80 | 1.85 | 1.50 | 1.45 | orf, hypothetical protein |
| ydeJ | 1.14 | -1.75 | 0.54 | 2.65 | -0.43 | -0.30 | orf, hypothetical protein |
| ydeK | -1.31 | 0.73 | 0.18 | -1.80 | 1.53 | -0.55 | orf, hypothetical protein |
| ydeV | 0.22 | -9.40 | 0.75 | 0.65 | -1.50 | 1.50 | putative kinase |
| ydeW | -0.94 | -1.59 | 0.35 | -0.15 | -1.20 | 0.00 | putative transcriptional regulator, sorC family |
| ydeY | -0.43 | 1.04 | -1.10 | -0.05 | 1.63 | -1.15 | putative transport system permease protein |
| ydeZ | -0.55 | 0.53 | 0.77 | 0.30 | 0.33 | 1.35 | putative transport system permease protein |
| ydfA | 0.00 | 0.00 | 0.77 | -3.85 | 1.33 | 1.50 | orf, hypothetical protein |
| ydfB | -0.34 | -1.38 | -0.82 | -0.20 | 1.07 | 0.00 | orf, hypothetical protein |
| ydfC | 0.70 | -0.97 | -1.34 | 1.55 | -0.10 | -1.35 | orf, hypothetical protein |
| ydfD | 0.45 | -1.54 | 0.74 | 1.65 | -0.33 | 1.35 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ydfE | 0.46 | -1.57 | 0.76 | 2.35 | -0.40 | 1.70 | orf, hypothetical protein |
| ydfG | 0.06 | -1.65 | -1.76 | 0.05 | -1.27 | -1.20 | putative oxidoreductase |
| ydfH | 0.01 | 3.06 | 1.23 | -0.65 | 1.30 | 0.10 | orf, hypothetical protein |
| ydfI | 0.92 | 2.39 | -0.73 | 2.20 | 1.47 | 0.05 | putative oxidoreductase |
| ydfM | 0.45 | -0.14 | -0.07 | 1.75 | 1.10 | 0.30 | orf, hypothetical protein |
| ydfO | 0.01 | -1.26 | -1.02 | 0.00 | -0.37 | -0.10 | orf, hypothetical protein |
| ydgA | -0.34 | 0.39 | -1.07 | -0.35 | 0.30 | -0.15 | orf, hypothetical protein |
| ydgB | -0.28 | -1.05 | 0.19 | 1.70 | -0.47 | -0.05 | putative oxidoreductase |
| ydgC | 0.47 | 0.04 | 0.20 | 0.70 | 0.33 | 0.10 | orf, hypothetical protein |
| ydgO | -0.83 | -1.34 | 0.75 | -0.45 | -0.40 | 1.30 | orf, hypothetical protein |
| ydgQ | -0.62 | -1.29 | -1.02 | -1.50 | -1.87 | -0.10 | orf, hypothetical protein |
| ydgR | -1.53 | 4.28 | 0.68 | -1.25 | 2.20 | 1.00 | putative transport protein |
| ydhA | -0.93 | -1.44 | 1.51 | 0.20 | -1.63 | 1.00 | orf, hypothetical protein |
| ydhB | -0.98 | -1.52 | -1.37 | -1.45 | -1.50 | -1.40 | putative transcriptional regulator LYSR-type |
| ydhC | 1.33 | 0.00 | -1.32 | 2.70 | 1.53 | 0.00 | putative transport protein |
| ydhD | 0.80 | 0.86 | 0.76 | 0.75 | 1.47 | -0.10 | orf, hypothetical protein |
| ydhE | 0.33 | 9.30 | -1.02 | 1.25 | 1.60 | -0.25 | putative transport protein |
| ydhO | 1.39 | -1.35 | 0.81 | 1.75 | -1.33 | 1.30 | putative lipoprotein |
| ydhU | -0.28 | 0.20 | 0.09 | -0.05 | 1.07 | 0.10 | orf, hypothetical protein |
| ydiA | 1.21 | -1.50 | -1.33 | 0.75 | -0.30 | -1.45 | orf, hypothetical protein |
| ydiB | 0.42 | -1.32 | -1.02 | -0.05 | -1.40 | -0.05 | putative oxidoreductase |
| ydiC | 0.48 | 1.37 | -0.57 | 0.35 | 1.40 | -1.10 | orf, hypothetical protein |
| ydiD | 0.68 | -1.16 | 0.94 | 0.35 | -0.50 | 1.05 | putative ligase |
| ydiE | 0.17 | 2.11 | 0.77 | 0.05 | 1.43 | 1.65 | orf, hypothetical protein |
| ydiF | 0.29 | 0.42 | -0.75 | 1.75 | 0.63 | 0.00 | putative enzyme |
| ydiJ | -1.19 | -1.70 | -1.37 | -2.00 | -1.50 | -1.50 | putative oxidase |
| ydiQ | -1.14 | 1.55 | 1.39 | -0.20 | 1.37 | 1.30 | putative transport protein |
| ydiR | 0.00 | 0.00 | 0.00 | -3.25 | 0.40 | 0.05 | putative flavoprotein |
| ydiS | -0.19 | -1.70 | 3.65 | -1.55 | 1.03 | 1.20 | flavoprotein; probably electron transport |
| ydiT | 1.15 | 0.15 | 0.79 | 1.80 | 0.40 | 1.55 | orf, hypothetical protein |
| ydjA | 0.32 | 0.00 | -1.34 | -0.90 | -1.97 | -1.40 | orf, hypothetical protein |
| ydjB | 0.05 | 1.18 | 0.89 | 0.30 | 2.13 | 1.10 | orf, hypothetical protein |
| ydjC | 1.42 | -1.56 | -1.63 | 1.35 | -0.37 | -1.40 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ydjE | 2.79 | 1.10 | 0.55 | 1.40 | 1.33 | 0.10 | putative transport protein |
| ydjJ | -1.11 | 0.79 | 0.82 | -0.20 | 1.23 | 1.35 | putative oxidoreductase |
| ydjS | 0.99 | 0.47 | 0.63 | 0.50 | 0.43 | -0.05 | orf, hypothetical protein |
| ydjX | -1.15 | 1.71 | -1.19 | -0.40 | 1.63 | -0.15 | orf, hypothetical protein |
| ydjY | 0.00 | -1.46 | 0.76 | -3.00 | -1.50 | 1.30 | orf, hypothetical protein |
| ydjZ | 0.21 | 2.15 | 1.24 | 1.35 | 1.53 | 1.30 | orf, hypothetical protein |
| yeaA | -0.26 | -1.22 | -0.52 | -1.80 | -1.13 | -1.15 | orf, hypothetical protein |
| yeaB | -0.05 | -0.07 | -1.32 | -1.40 | 1.57 | -0.05 | orf, hypothetical protein |
| yeaD | 0.41 | 5.82 | -0.84 | 0.00 | 1.30 | -0.05 | orf, hypothetical protein |
| yeaF | -0.03 | 1.01 | 1.41 | -0.25 | 0.40 | -0.15 | orf, hypothetical protein |
| yeaG | -1.08 | -1.02 | 0.58 | -0.55 | -0.40 | -0.15 | orf, hypothetical protein |
| yeaH | 1.14 | -1.48 | 0.82 | 1.55 | -1.40 | 1.55 | orf, hypothetical protein |
| yeaI | -0.88 | 1.29 | 0.70 | -0.40 | 1.37 | 1.25 | orf, hypothetical protein |
| yeaJ | 0.86 | -1.35 | -0.03 | 0.15 | -1.60 | -0.05 | orf, hypothetical protein |
| yeaK | 2.39 | -1.63 | 0.65 | 1.25 | -1.40 | 0.10 | orf, hypothetical protein |
| yeaL | 0.17 | -1.35 | -1.38 | 0.05 | -0.77 | -1.55 | orf, hypothetical protein |
| yeaM | -1.30 | 0.35 | 0.79 | -1.50 | 1.33 | 1.40 | putative ARAC-type regulatory protein |
| yeaN | -0.18 | -1.40 | 0.41 | 0.40 | -1.63 | 0.10 | putative amino acid |
| yeaO | -0.33 | -1.54 | -1.32 | 0.70 | -1.30 | 0.10 | orf, hypothetical protein |
| yeaP | -0.68 | 0.56 | 1.20 | -1.60 | 1.13 | 1.35 | orf, hypothetical protein |
| yeaQ | -1.04 | -2.61 | -1.73 | -2.20 | -1.90 | -1.40 | orf, hypothetical protein |
| yeaR | 0.99 | 1.60 | 1.22 | 2.85 | 1.57 | 1.45 | orf, hypothetical protein |
| yeaS | 2.23 | 16.45 | 1.52 | 1.85 | 1.30 | 1.15 | orf, hypothetical protein |
| yeaT | 0.19 | 0.00 | -1.27 | 0.05 | 1.57 | -1.20 | putative transcriptional regulator LYSR-type |
| yeaU | 1.29 | -1.42 | -0.03 | 0.00 | -1.73 | 0.05 | putative tartrate dehydrogenase |
| yeaV | 0.27 | -0.89 | 0.95 | 1.15 | -0.27 | 0.05 | putative transport protein |
| yeaW | 1.14 | -1.42 | 0.92 | 1.50 | -1.17 | -0.05 | orf, hypothetical protein |
| yeaX | 1.16 | 1.19 | -1.33 | 1.45 | 1.00 | 0.10 | putative diogenase beta subunit |
| yeaZ | 0.11 | -0.65 | -1.27 | 1.05 | -0.10 | -1.40 | orf, hypothetical protein |
| yebA | -0.64 | 0.48 | 1.61 | -0.20 | 0.13 | 1.30 | orf, hypothetical protein |
| yebB | 1.26 | -0.95 | -1.81 | 2.65 | -0.30 | -1.35 | orf, hypothetical protein |
| yebC | 0.67 | 0.48 | 0.19 | 0.60 | -0.07 | -0.05 | orf, hypothetical protein |
| yebE | 0.31 | 3.69 | 0.77 | -0.10 | 2.17 | 0.10 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yebF | 2.62 | 8.91 | 0.27 | 3.95 | 4.10 | 0.20 | orf, hypothetical protein |
| yebG | 2.37 | 8.21 | 1.73 | 4.40 | 3.60 | 1.80 | orf, hypothetical protein |
| yebH | 0.38 | 1.25 | -1.26 | 0.25 | 1.27 | -0.25 | putative enzyme |
| yebI | 1.72 | 2.76 | 0.39 | 1.25 | 1.63 | 0.10 | orf, hypothetical protein |
| yebJ | 0.28 | -0.32 | 1.09 | 1.35 | -0.30 | -1.15 | orf, hypothetical protein |
| yebK | 0.43 | 1.75 | 0.73 | 0.05 | 1.30 | 0.05 | orf, hypothetical protein |
| yebL | -1.51 | 0.33 | 1.59 | -1.55 | -1.13 | 1.15 | putative adhesin |
| yebM | -1.35 | -1.32 | 0.16 | -1.55 | -0.50 | 0.20 | putative ATP-binding component of a transport system |
| yebU | 0.12 | 1.47 | -1.05 | 0.10 | 0.67 | -0.10 | putative nucleolar proteins |
| yecA | -0.43 | -0.45 | 1.05 | -1.15 | 3.23 | 1.55 | orf, hypothetical protein |
| yecC | 0.77 | -1.37 | -0.68 | 0.80 | -0.57 | -1.40 | putative ATP-binding component of a transport system |
| yecD | 0.14 | 0.77 | -1.16 | 1.35 | -1.10 | -1.30 | orf, hypothetical protein |
| yecE | 1.25 | 1.14 | 0.82 | 1.45 | 1.07 | 1.40 | orf, hypothetical protein |
| yecF | 0.69 | 0.78 | 0.78 | -1.05 | 0.43 | -0.20 | orf, hypothetical protein |
| yecG | -0.69 | -1.38 | 0.08 | 0.10 | 1.13 | 1.10 | putative regulator |
| yecH | 0.53 | -1.74 | -0.98 | 0.40 | -1.43 | -0.05 | orf, hypothetical protein |
| yecI | -0.49 | 0.15 | 0.09 | 0.00 | 0.73 | -0.10 | ferritin-like protein |
| yecK | 0.36 | -1.58 | 0.50 | 2.35 | -0.30 | -0.10 | putative cytochrome C-type protein |
| yecM | 0.90 | -1.00 | 0.76 | 1.50 | -0.27 | -0.25 | orf, hypothetical protein |
| yecN | -0.19 | 1.97 | -1.31 | -0.05 | -0.43 | -1.35 | orf, hypothetical protein |
| yecO | -0.85 | 2.77 | -1.25 | -0.20 | 1.40 | -0.40 | orf, hypothetical protein |
| yecP | -0.17 | -1.11 | -1.35 | -0.35 | -0.60 | -1.55 | putative enzyme |
| yecS | -1.28 | -1.19 | 0.93 | -0.15 | -0.40 | 1.30 | putative transport system permease protein (former yecC) |
| yecT | 0.08 | -1.34 | -0.35 | -0.30 | -0.13 | 0.10 | orf, hypothetical protein |
| yedA | 0.31 | 0.33 | -0.76 | -0.10 | 0.50 | -0.05 | putative transmembrane subunit |
| yedD | 0.25 | 1.00 | 1.51 | -0.20 | 0.13 | 1.20 | orf, hypothetical protein |
| yedE | 0.50 | 0.02 | -1.04 | 0.20 | 0.17 | -1.30 | putative transport system permease protein |
| yedF | -0.95 | -1.40 | -0.15 | 0.35 | -1.43 | -0.25 | orf, hypothetical protein |
| yedI | 0.12 | -1.34 | 0.84 | -0.10 | -1.30 | 1.25 | orf, hypothetical protein |
| yedJ | 0.73 | -1.90 | 0.50 | 1.30 | -0.33 | 0.15 | orf, hypothetical protein |
| yedK | 0.21 | -1.38 | 0.81 | 1.60 | -0.63 | 1.55 | orf, hypothetical protein |
| yedL | 0.39 | -1.38 | 0.85 | 0.25 | -0.60 | 1.25 | orf, hypothetical protein |
| yedM | 1.01 | -1.47 | 0.73 | 1.90 | -1.40 | 1.35 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yedN | 0.21 | -0.35 | 0.77 | 0.10 | 0.70 | 1.55 | orf, hypothetical protein |
| yedO | 0.66 | 2.99 | 0.31 | 0.60 | 1.50 | -0.05 | putative 1-aminocyclopropane-1-carboxylate deaminase |
| yedU | -1.74 | -1.10 | 0.59 | -2.45 | 0.47 | 1.10 | orf, hypothetical protein |
| yedV | 0.36 | 1.36 | 0.68 | 0.30 | 1.23 | 0.30 | putative 2-component sensor protein |
| yedW | 0.93 | -1.05 | 0.94 | 1.55 | -0.40 | 1.60 | putative 2-component transcriptional regulator |
| yeeA | -0.49 | -1.36 | 0.67 | -0.25 | -0.40 | -0.05 | orf, hypothetical protein |
| yeeD | 0.06 | -0.41 | 0.61 | -1.30 | -1.47 | -0.20 | orf, hypothetical protein |
| yeeE | -1.78 | -0.99 | 0.80 | -2.00 | -1.90 | -0.15 | putative transport system permease protein |
| yeeF | -0.24 | 0.23 | 0.40 | -0.25 | -0.20 | -0.05 | putative amino acid |
| yeeO | -0.12 | -1.27 | -1.34 | 1.50 | -0.17 | -1.30 | orf, hypothetical protein |
| yeeP | 1.13 | -1.66 | 0.81 | 1.85 | -0.30 | 1.35 | putative histone |
| yeeS | -1.36 | -1.00 | 1.10 | -1.75 | -0.27 | 1.35 | putative DNA repair protein, RADC family |
| yeeT | -0.76 | -0.19 | 1.01 | -0.40 | 1.17 | 1.65 | orf, hypothetical protein |
| yeeU | 0.22 | -1.31 | 0.43 | -0.05 | -0.37 | -0.05 | putative structural protein |
| yeeV | 3.82 | 1.15 | -1.01 | 1.70 | 1.60 | -1.20 | orf, hypothetical protein |
| yeeW | -0.80 | -0.84 | -1.20 | 0.50 | 0.57 | -0.20 | orf, hypothetical protein |
| yeeX | 0.04 | -4.13 | 1.00 | -1.10 | -1.37 | 1.55 | putative alpha helix protein |
| yeeY | 0.93 | -1.29 | -1.40 | 1.40 | -0.60 | -1.15 | putative transcriptional regulator LYSR-type |
| yefJ | -0.59 | 0.92 | 1.15 | -1.45 | 0.50 | 1.30 | putative creatinase (EC 3.5.-) |
| yefM | 0.51 | 1.32 | 0.94 | 0.35 | 1.10 | 1.30 | orf, hypothetical protein |
| yegB | 0.33 | 0.65 | 0.76 | -0.10 | 1.47 | 1.35 | putative transport protein |
| yegD | 1.10 | -1.04 | 1.18 | 0.25 | -0.27 | 1.40 | putative heat shock protein |
| yegE | 1.33 | 0.18 | 0.52 | 1.35 | 0.47 | 0.30 | putative sensor-type protein |
| yegH | -1.24 | -0.76 | -1.46 | -1.40 | 0.17 | -1.10 | putative transport protein |
| yegN | -0.34 | -4.81 | -0.20 | 0.50 | 0.37 | 0.00 | orf, hypothetical protein |
| yegO | 0.35 | 1.52 | -1.61 | 1.45 | 1.77 | -1.40 | orf, hypothetical protein |
| yegQ | 0.23 | -1.76 | 0.70 | -1.60 | -1.53 | 0.20 | orf, hypothetical protein |
| yegT | -0.17 | -1.28 | 0.87 | -0.05 | 1.03 | 1.55 | putative nucleoside permease protein |
| yegW | 0.57 | -1.23 | -1.35 | 1.50 | -0.30 | -1.45 | putative transcriptional regulator |
| yegX | 0.18 | -1.22 | -1.03 | 1.35 | -0.30 | -0.05 | orf, hypothetical protein |
| yehA | 0.36 | -0.89 | 0.56 | 1.45 | 0.30 | 0.00 | putative type-1 fimbrial protein |
| yehB | -1.57 | 2.71 | 0.78 | -2.05 | 1.20 | 1.40 | putative outer membrane protein |
| yehC | -0.45 | 0.65 | -0.03 | 0.40 | 0.43 | 0.00 | putative chaperone |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yehD | 0.52 | -1.25 | 0.67 | 1.35 | -0.33 | 1.15 | putative fimbrial-like protein |
| yehE | -0.94 | -1.51 | 0.67 | -0.25 | -1.27 | 1.15 | orf, hypothetical protein |
| yehI | 0.49 | -1.22 | 0.86 | 1.30 | -1.30 | -0.15 | putative regulator |
| yehL | 0.16 | -1.20 | -1.38 | -0.10 | -0.27 | -1.65 | orf, hypothetical protein |
| yehM | 0.36 | 0.75 | 0.76 | 1.80 | 0.47 | 0.35 | orf, hypothetical protein |
| yehP | 0.00 | 0.00 | 0.77 | -0.65 | 0.70 | 0.00 | orf, hypothetical protein |
| yehQ | 1.67 | 1.39 | -0.58 | 1.30 | 0.40 | 0.05 | orf, hypothetical protein |
| yehR | 0.90 | -1.27 | 0.23 | 1.90 | -1.47 | 0.00 | orf, hypothetical protein |
| yehS | -3.92 | -0.22 | 0.59 | -2.25 | 0.17 | 0.15 | orf, hypothetical protein |
| yehT | -1.02 | -0.64 | -1.49 | -1.30 | 0.53 | -1.55 | orf, hypothetical protein |
| yehU | -1.43 | -1.28 | -0.42 | -1.65 | -0.40 | -1.20 | putative 2-component sensor protein |
| yehV | -1.39 | -1.32 | -1.52 | -1.50 | -0.47 | -1.30 | putative transcriptional regulator |
| yehW | 0.42 | -1.35 | 0.77 | 0.10 | -1.50 | 0.15 | putative transport system permease protein |
| yehX | 0.95 | -0.90 | 0.84 | 2.10 | 0.20 | 1.40 | putative ATP-binding component of a transport system |
| yehY | 0.64 | 2.73 | -1.22 | 0.45 | 1.40 | -0.45 | putative transport system permease protein |
| yehZ | 0.49 | 2.46 | -1.07 | 0.15 | 1.60 | -0.15 | putative transport system permease protein |
| yeiA | -1.06 | 0.71 | 0.49 | -0.15 | 1.73 | 0.05 | putative oxidoreductase |
| yeiB | 0.55 | 0.76 | -1.35 | 1.20 | 0.30 | -1.30 | orf, hypothetical protein |
| yeiC | 1.09 | 1.74 | -0.92 | 3.25 | 1.40 | -1.15 | putative kinase |
| yeiE | -1.34 | 1.34 | 0.64 | -1.45 | 1.17 | 1.15 | putative transcriptional regulator LYSR-type |
| yeiG | -0.16 | 0.69 | -1.41 | 0.10 | 0.47 | -1.30 | putative esterase (EC 3.1.1.-). |
| yeiH | -0.85 | -1.21 | -0.46 | -0.10 | -0.30 | 0.20 | orf, hypothetical protein |
| yeiI | 2.04 | -1.33 | 1.15 | 1.35 | -0.73 | 1.25 | putative kinase |
| yeiJ | 0.87 | -1.32 | -1.14 | 1.45 | -0.57 | -0.10 | putative transport system permease protein |
| yeiK | 0.01 | 2.86 | -1.32 | 0.25 | 1.90 | -1.25 | orf, hypothetical protein |
| yeiL | 0.32 | 0.98 | -1.21 | 0.35 | -0.23 | -0.10 | putative transcriptional regulator |
| yeiM | 0.00 | 0.00 | 0.00 | 0.15 | 0.23 | -1.10 | putative transport system permease protein |
| yeiN | -0.79 | 0.60 | 0.80 | -0.15 | 1.03 | 0.55 | orf, hypothetical protein |
| yeiO | -0.85 | 0.14 | -1.38 | -0.15 | 0.33 | -1.30 | putative transport |
| yeiP | -1.78 | 1.29 | 1.19 | -1.30 | 1.40 | 1.10 | putative elongation factor |
| yeiQ | 0.77 | -1.24 | 1.64 | 1.20 | -0.23 | 1.20 | putative oxidoreductase |
| yeiR | 2.40 | 0.67 | -0.15 | 2.10 | 0.47 | 0.30 | orf, hypothetical protein |
| yejA | 1.90 | 0.11 | 0.92 | 1.55 | 0.43 | 1.20 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yejB | -0.21 | 0.03 | -1.40 | -0.10 | 0.40 | -1.40 | putative transport system permease protein |
| yejE | -2.46 | -1.18 | -1.39 | -1.40 | 0.50 | -1.50 | putative transport system permease protein |
| yejF | -0.01 | -1.35 | 0.75 | -1.40 | -1.47 | 0.05 | putative ATP-binding component of a transport system |
| yejG | -0.25 | 0.25 | 0.56 | -1.50 | 0.40 | 0.15 | orf, hypothetical protein |
| yejH | -1.04 | -1.04 | -1.02 | -1.90 | -0.40 | 0.05 | putative ATP-dependent helicase |
| yejK | -1.07 | -1.19 | -0.34 | -0.40 | -0.70 | 0.05 | orf, hypothetical protein |
| yejL | -0.31 | 3.10 | 1.25 | -1.25 | 1.57 | 1.10 | orf, hypothetical protein |
| yejM | -1.19 | 5.51 | 0.84 | -1.10 | 1.60 | 1.40 | putative sulfatase |
| yejO | -1.02 | -0.30 | -1.31 | -2.60 | 0.33 | -1.40 | putative ATP-binding component of a transport system |
| yfaA | 0.96 | -1.34 | -1.09 | -0.45 | -0.40 | -0.10 | orf, hypothetical protein |
| yfaD | 2.96 | -1.63 | -0.75 | 1.25 | -1.63 | 0.00 | orf, hypothetical protein |
| yfaE | 1.86 | 1.30 | 1.13 | 2.40 | 1.23 | -0.20 | orf, hypothetical protein |
| yfaH | -0.65 | 1.13 | -1.22 | -1.55 | 1.17 | -0.10 | orf, hypothetical protein |
| yfaL | 0.17 | -0.76 | 0.89 | -2.05 | 1.30 | 0.20 | putative ATP-binding component of a transport system |
| yfaO | 0.11 | -2.58 | -0.01 | 0.15 | -1.17 | 0.05 | orf, hypothetical protein |
| yfbB | -0.91 | -1.41 | 1.40 | 0.05 | -1.73 | 1.15 | putative enzyme |
| yfbK | 0.89 | -1.08 | -1.40 | 2.40 | -0.10 | -1.45 | orf, hypothetical protein |
| yfbL | -0.25 | -0.84 | -1.32 | 0.15 | -0.27 | -1.25 | putative aminopeptidase |
| yfbM | -1.13 | -1.63 | 0.77 | -0.10 | -1.33 | 1.35 | orf, hypothetical protein |
| yfbN | 0.38 | 1.43 | 0.76 | 0.35 | 1.47 | 1.20 | orf, hypothetical protein |
| yfbS | -0.26 | 1.10 | -1.48 | -1.85 | 1.47 | -1.45 | putative transport protein |
| yfbT | -0.45 | -1.50 | -1.94 | 0.00 | -1.43 | -1.15 | putative phosphatase |
| yfcA | 0.02 | 0.00 | 0.77 | -1.30 | 0.40 | 1.35 | putative structural protein |
| yfcB | -0.28 | 1.41 | 1.14 | -0.25 | -0.20 | 0.10 | putative adenine-specific methylase |
| yfcC | -0.88 | -1.23 | -0.56 | -0.45 | 0.07 | -1.20 | putative S-transferase |
| yfcE | 0.25 | -0.89 | -0.53 | 1.35 | -1.27 | -1.10 | orf, hypothetical protein |
| yfcF | 0.33 | -1.27 | 0.80 | -0.05 | -0.23 | 2.00 | orf, hypothetical protein |
| yfcG | -1.09 | 0.76 | -1.34 | -0.55 | 1.10 | -1.35 | putative S-transferase |
| yfcI | 1.15 | 0.83 | -1.39 | 1.45 | 1.47 | -1.10 | orf, hypothetical protein |
| yfcS | 0.97 | 0.78 | 0.79 | 1.95 | 1.53 | 0.40 | putative chaperone |
| yfcU | -0.03 | 4.90 | -1.17 | 0.00 | 1.67 | -1.10 | putative outer membrane protein |
| yfdC | -0.36 | -1.36 | -1.16 | 0.15 | -0.57 | -1.30 | putative transport |
| yfdE | 0.18 | -1.32 | 0.49 | 1.15 | -0.60 | 0.55 | putative enzyme |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yfdL | 0.69 | -1.58 | 0.00 | 1.55 | -1.33 | 0.00 | putative RNA polymerase beta |
| yfdM | -0.79 | 1.44 | 0.98 | 0.05 | 1.23 | 1.45 | orf, hypothetical protein |
| yfdN | 0.40 | -1.34 | 0.00 | -0.30 | -0.43 | -1.40 | orf, hypothetical protein |
| yfdO | -0.18 | -0.86 | 1.16 | 1.15 | 1.10 | 1.55 | orf, hypothetical protein |
| yfeA | 0.73 | -1.49 | -0.47 | 0.15 | -1.57 | 0.00 | orf, hypothetical protein |
| yfeC | -1.55 | -1.73 | 0.29 | -1.55 | -1.33 | 0.20 | orf, hypothetical protein |
| yfeD | -0.57 | -1.62 | -1.38 | 0.00 | -1.67 | -1.35 | orf, hypothetical protein |
| yfeG | -1.25 | -1.32 | -0.75 | -1.00 | -1.23 | 0.00 | putative ARAC-type regulatory protein |
| yfeH | 0.01 | -1.80 | 1.33 | 0.05 | -1.10 | 1.60 | putative cytochrome oxidase |
| yfeK | -0.95 | -1.34 | 0.85 | -0.65 | -0.43 | 0.00 | orf, hypothetical protein |
| yfeN | 0.48 | 0.72 | -0.24 | 1.80 | 1.10 | -0.05 | putative sugar hydrolase |
| yfeR | -0.98 | -1.01 | -1.19 | 1.20 | -0.37 | -0.10 | putative transcriptional regulator LYSR-type |
| yfeT | 0.62 | -2.85 | 0.66 | 1.70 | 0.17 | 1.65 | orf, hypothetical protein |
| yfeU | -0.78 | 0.55 | -0.55 | -0.10 | 1.90 | 0.25 | putative regulator |
| yffB | 0.99 | 1.18 | -0.29 | 1.25 | 1.47 | -1.05 | orf, hypothetical protein |
| yffG | -0.16 | 0.70 | 0.45 | 0.05 | 1.73 | -0.10 | putative oxidoreductase, Fe-S subunit |
| yffH | 0.25 | 0.34 | 0.77 | -0.10 | -1.57 | -1.40 | orf, hypothetical protein |
| yfgA | -0.36 | -1.45 | 0.77 | -0.25 | -0.53 | 1.40 | putative membrane protein |
| yfgB | 0.99 | 4.87 | 0.29 | 0.60 | 2.43 | -0.40 | orf, hypothetical protein |
| yfhA | 1.99 | 1.02 | 0.46 | 2.90 | 1.37 | 0.00 | putative 2-component transcriptional regulator |
| yfhB | -0.06 | -0.58 | -0.11 | -0.10 | -0.43 | 0.05 | orf, hypothetical protein |
| yfhC | -0.04 | 0.00 | -0.92 | -1.95 | -0.47 | -0.05 | putative deaminase |
| yfhD | 0.69 | 3.52 | -1.05 | 1.50 | 1.20 | -0.15 | putative periplasmic binding transport protein |
| yfhE | 1.62 | 6.15 | 0.64 | 1.30 | 2.17 | -1.05 | orf, hypothetical protein |
| yfhF | 0.59 | -0.04 | 0.68 | 0.40 | -0.30 | 1.15 | putative regulator |
| yfhG | 1.08 | -1.34 | 0.56 | 0.45 | -0.33 | 1.35 | putative alpha helix protein |
| yfhH | -0.27 | 0.66 | -0.82 | 0.05 | 0.40 | -0.05 | orf, hypothetical protein |
| yfhJ | 0.30 | 3.41 | 1.85 | 1.60 | 2.30 | 1.15 | orf, hypothetical protein |
| yfhK | -0.33 | -2.98 | 1.52 | 1.15 | -1.37 | 1.35 | putative 2-component sensor protein |
| yfhL | 0.57 | -1.76 | 0.96 | 1.25 | -1.40 | 1.20 | orf, hypothetical protein |
| yfhO | -0.01 | 5.46 | 1.36 | -0.25 | 2.90 | 1.60 | putative aminotransferase |
| yfiA | -0.71 | 0.29 | -0.48 | -1.30 | 1.03 | 0.25 | putative yhbH sigma 54 modulator |
| yfiB | -0.22 | 0.00 | -1.28 | -1.30 | 0.43 | -0.10 | putative outer membrane protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yfiC | **0.83** | **-0.85** | **0.58** | 0.60 | 0.53 | 0.40 | putative enzyme |
| yfiD | **0.13** | **-1.46** | **-0.60** | 0.05 | -12.63 | 0.05 | putative formate acetyltransferase |
| yfiE | **-2.06** | **-1.29** | **-0.53** | -1.60 | 0.10 | 0.10 | putative transcriptional regulator LYSR-type |
| yfiF | **-0.77** | **1.13** | **-0.45** | -0.30 | 0.27 | 0.10 | orf, hypothetical protein |
| yfiH | **-0.35** | **0.00** | **-1.27** | -2.75 | 0.27 | -0.25 | orf, hypothetical protein |
| yfiK | **-0.56** | **1.51** | **0.87** | 0.10 | 1.27 | 1.10 | orf, hypothetical protein |
| yfiL | **0.14** | **0.45** | **0.32** | 1.25 | 1.33 | 0.10 | orf, hypothetical protein |
| yfiM | **-1.58** | **-0.58** | **0.84** | -1.40 | 0.53 | 1.35 | orf, hypothetical protein |
| yfiN | **-0.90** | **-1.34** | **0.73** | -1.55 | -0.63 | 1.15 | orf, hypothetical protein |
| yfiP | **-1.32** | **-1.37** | **0.02** | -0.45 | -0.53 | 0.10 | orf, hypothetical protein |
| yfiQ | **-2.29** | **-0.14** | **0.03** | -2.50 | 0.33 | 0.20 | orf, hypothetical protein |
| yfjA | **0.32** | **6.18** | **-0.15** | 0.80 | 3.37 | 0.10 | orf, hypothetical protein |
| yfjB | **1.20** | **-1.91** | **0.23** | 1.35 | 0.33 | 1.30 | orf, hypothetical protein |
| yfjD | **-0.03** | **-1.35** | **0.85** | 1.05 | -1.00 | 1.10 | putative transport protein |
| yfjH | **1.86** | **-1.21** | **0.80** | 1.45 | -0.27 | 1.35 | putative histone |
| yfjI | **0.28** | **0.56** | **0.74** | 1.35 | 1.40 | 1.40 | orf, hypothetical protein |
| yfjJ | **-0.10** | **-1.20** | **0.90** | 0.00 | -0.50 | 0.20 | orf, hypothetical protein |
| yfjK | **0.12** | **0.77** | **0.77** | 1.05 | 0.33 | 1.20 | orf, hypothetical protein |
| yfjL | **-0.23** | **0.77** | **0.74** | -1.40 | -0.30 | 1.50 | orf, hypothetical protein |
| yfjM | **-0.19** | **-1.17** | **0.54** | -0.30 | -0.03 | 1.10 | orf, hypothetical protein |
| yfjN | **-0.57** | **1.03** | **-0.70** | -0.95 | 1.20 | -0.05 | putative cell division protein |
| yfjO | **-0.28** | **-1.68** | **-1.31** | -0.45 | -1.23 | -1.70 | orf, hypothetical protein |
| yfjP | **3.76** | **-1.34** | **1.03** | 2.35 | -0.37 | 1.10 | putative GTP-binding protein |
| yfjQ | **1.18** | **-0.17** | **0.66** | 2.10 | 0.07 | 1.15 | orf, hypothetical protein |
| yfjR | **0.00** | **0.00** | **0.77** | 0.50 | 0.63 | 0.05 | orf, hypothetical protein |
| yfjT | **-1.14** | **-1.24** | **-1.18** | -1.10 | -0.17 | -0.05 | orf, hypothetical protein |
| yfjW | **-2.17** | **-1.47** | **1.43** | -1.50 | 0.20 | 1.30 | orf, hypothetical protein |
| yfjX | **0.82** | **1.95** | **0.32** | 1.55 | 1.77 | -1.35 | orf, hypothetical protein |
| yfjY | **-0.43** | **-0.35** | **0.76** | 1.15 | 0.43 | 1.25 | putative DNA repair protein |
| yfjZ | **2.04** | **0.25** | **0.75** | 1.45 | 0.70 | 1.20 | orf, hypothetical protein |
| ygaA | **0.59** | **-1.39** | **-1.09** | 0.55 | -0.50 | -0.20 | putative 2-component transcriptional regulator |
| ygaC | **1.30** | **-0.52** | **1.66** | 1.30 | 0.37 | 1.20 | orf, hypothetical protein |
| ygaD | **1.60** | **4.12** | **0.71** | 1.50 | 2.23 | 0.30 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ygaE | **-0.10** | **1.29** | **-1.59** | 0.05 | 1.40 | -1.75 | putative transcriptional regulator |
| ygaF | **-0.65** | **-1.42** | **-1.40** | -1.55 | -1.27 | -1.35 | orf, hypothetical protein |
| ygaG | **0.30** | **-2.50** | **-1.01** | 0.15 | -2.40 | -0.05 | orf, hypothetical protein |
| ygaH | **-0.63** | **2.72** | **0.22** | -0.30 | -0.20 | 0.05 | orf, hypothetical protein |
| ygaM | **-0.99** | **0.07** | **-0.82** | -1.55 | 0.50 | 0.00 | orf, hypothetical protein |
| ygaP | **0.06** | **0.60** | **-1.20** | -0.05 | 1.33 | -1.25 | orf, hypothetical protein |
| ygaU | **-1.04** | **-3.35** | **0.67** | -2.90 | -2.00 | 1.40 | orf, hypothetical protein |
| ygbA | **-0.30** | **0.75** | **0.52** | 0.05 | 0.30 | -0.05 | orf, hypothetical protein |
| ygbB | **0.99** | **-0.38** | **-1.33** | 0.20 | 0.27 | -1.25 | orf, hypothetical protein |
| ygbD | **0.97** | **-1.33** | **0.74** | 0.15 | -0.67 | 0.15 | putative oxidoreductase |
| ygbE | **-1.06** | **0.27** | **0.12** | -1.90 | 0.30 | -0.10 | putative cytochrome oxidase subunit |
| ygbF | **-1.21** | **0.88** | **-1.06** | 1.20 | 1.73 | -0.15 | orf, hypothetical protein |
| ygbI | **0.56** | **-1.45** | **0.48** | 1.40 | -1.37 | 1.30 | putative DEOR-type transcriptional regulator |
| ygbL | **0.45** | **-3.38** | **0.65** | 1.05 | -1.63 | 0.00 | putative epimerase |
| ygbM | **-0.72** | **-1.61** | **0.32** | 1.25 | -0.40 | -0.15 | orf, hypothetical protein |
| ygbO | **-1.70** | **-2.87** | **-0.20** | -2.30 | -1.17 | -0.10 | putative hydrogenase subunit |
| ygbP | **-0.10** | **4.52** | **-0.66** | -1.20 | 0.03 | 0.05 | orf, hypothetical protein |
| ygcA | **0.70** | **1.47** | **-0.96** | -0.10 | 1.13 | -1.25 | putative enzyme |
| ygcB | **0.30** | **-1.34** | **0.72** | 0.30 | -0.43 | 1.25 | orf, hypothetical protein |
| ygcE | **0.20** | **1.92** | **-0.04** | 0.05 | 1.47 | -0.20 | putative kinase |
| ygcF | **-0.53** | **0.39** | **0.61** | -1.35 | 1.63 | -0.05 | orf, hypothetical protein |
| ygcG | **1.34** | **1.42** | **1.48** | -1.00 | 1.30 | 1.45 | orf, hypothetical protein |
| ygcK | **0.18** | **0.14** | **-1.20** | 1.25 | 0.70 | -1.25 | orf, hypothetical protein |
| ygcM | **0.06** | **-0.57** | **-0.68** | 0.00 | -0.20 | -1.15 | putative 6-pyruvoyl tetrahydrobiopterin synthase |
| ygcN | **1.06** | **-1.35** | **-0.16** | 0.25 | -1.27 | -0.55 | orf, hypothetical protein |
| ygcO | **-1.01** | **0.12** | **0.75** | -0.30 | -0.30 | 1.20 | orf, hypothetical protein |
| ygcP | **-0.97** | **-1.39** | **-1.15** | -0.45 | -1.20 | -1.40 | putative anti-terminator regulatory protein |
| ygcQ | **-0.70** | **-2.14** | **-0.94** | 1.20 | -1.13 | -0.10 | putative flavoprotein |
| ygcR | **0.40** | **0.02** | **2.55** | 1.40 | -1.30 | 1.10 | putative transport protein |
| ygcS | **0.14** | **1.96** | **0.73** | 1.20 | 1.50 | 1.30 | putative transport protein |
| ygcU | **-3.83** | **-1.28** | **-0.08** | -2.95 | -2.10 | -1.30 | putative oxidoreductase subunit |
| ygcW | **0.68** | **2.56** | **1.56** | 1.50 | 1.33 | 1.40 | putative oxidoreductase |
| ygcX | **-0.23** | **0.76** | **0.82** | -1.45 | 1.33 | 1.65 | putative glucarate dehydratase |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ygcY | 1.03 | 1.59 | 1.65 | 0.20 | 1.37 | 1.40 | putative glucarate dehydratase |
| ygdB | 1.00 | 1.36 | 0.39 | 1.80 | 1.53 | 0.15 | orf, hypothetical protein |
| ygdD | -0.40 | 0.00 | 0.44 | 0.90 | 0.33 | 1.10 | orf, hypothetical protein |
| ygdE | -0.58 | -1.17 | 1.11 | -1.85 | -0.73 | 1.30 | orf, hypothetical protein |
| ygdH | -0.29 | -2.47 | 0.64 | -0.60 | -1.67 | 1.25 | orf, hypothetical protein |
| ygdK | 0.76 | -1.16 | 0.71 | 1.35 | -1.40 | 1.40 | orf, hypothetical protein |
| ygdL | -1.30 | -1.50 | 0.64 | -1.15 | -1.60 | 0.15 | putative enzyme |
| ygdP | -0.55 | 1.11 | 1.43 | -1.70 | 1.17 | 1.35 | putative invasion protein |
| ygeA | 0.75 | 0.66 | 0.88 | 1.35 | 1.33 | 1.30 | putative resistance proteins |
| ygeD | 0.15 | -4.09 | 0.17 | -0.50 | -1.57 | 0.05 | putative resistance proteins |
| ygeF | 0.44 | -2.31 | 0.80 | 0.00 | -1.07 | 1.15 | orf, hypothetical protein |
| ygeG | -1.17 | -1.42 | 0.76 | -0.35 | -1.43 | 1.30 | orf, hypothetical protein |
| ygeH | 0.23 | 1.82 | -0.35 | -0.05 | 1.23 | 0.05 | putative invasion protein |
| ygeK | -0.57 | -1.34 | 0.34 | -0.10 | -1.33 | 3.35 | putative 2-component transcriptional regulator |
| ygeT | 0.86 | 1.29 | -0.23 | 2.30 | 1.50 | 0.20 | putative dehydrogenase |
| ygeV | -0.94 | -0.30 | -1.22 | -1.10 | -0.03 | -0.15 | putative transcriptional regulator |
| ygeW | -0.99 | -1.65 | 0.99 | -1.95 | -1.63 | 1.70 | putative carbamoyl transferase |
| ygeX | -0.99 | -1.34 | 0.94 | -0.95 | -0.40 | 1.55 | putative dehydratase |
| ygeY | -0.65 | -1.38 | -1.19 | 0.05 | -0.63 | -1.25 | putative deacetylase |
| ygfA | -0.19 | 2.44 | 0.55 | -0.45 | 1.33 | 0.05 | putative ligase |
| ygfB | -0.47 | -1.23 | 2.74 | -0.50 | -1.37 | 1.30 | orf, hypothetical protein |
| ygfD | 1.79 | 0.77 | 1.15 | 1.30 | 0.67 | 1.00 | putative nucleotide-binding protein |
| ygfE | -0.34 | -4.15 | -0.06 | -0.05 | -1.57 | -0.55 | orf, hypothetical protein |
| ygfF | -0.36 | 0.77 | 1.70 | 1.00 | 1.33 | 1.35 | putative oxidoreductase |
| ygfG | 0.18 | 2.56 | -1.39 | 0.35 | 1.80 | -1.80 | putative enzyme |
| ygfH | 0.31 | -1.71 | -1.31 | -0.10 | -1.23 | -1.40 | putative coenzyme A transferase |
| ygfI | -1.12 | -1.39 | 0.83 | -0.55 | -1.53 | 1.10 | putative transcriptional regulator LYSR-type |
| ygfJ | -1.59 | -0.26 | 0.10 | -2.00 | 0.23 | 0.05 | orf, hypothetical protein |
| ygfO | -0.94 | -1.13 | -1.20 | -0.25 | -0.17 | -1.30 | putative transport protein |
| ygfP | 0.20 | -1.45 | -1.17 | 0.70 | -1.60 | -1.05 | orf, hypothetical protein |
| ygfQ | -0.27 | 0.65 | -0.13 | 0.55 | 1.53 | 0.05 | orf, hypothetical protein |
| ygfR | 0.15 | 3.51 | 0.41 | -0.35 | 1.20 | 0.25 | putative oxidoreductase |
| ygfS | -0.73 | -1.43 | -1.39 | -0.45 | -1.63 | -1.30 | putative oxidoreductase, Fe-S subunit |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ygfT | -0.09 | -1.93 | 0.53 | -1.35 | -0.37 | 0.00 | putative oxidoreductase, Fe-S subunit |
| ygfU | 0.15 | -1.65 | -1.42 | 0.15 | -1.23 | -1.35 | putative permease |
| ygfY | -1.33 | 0.54 | 0.60 | -2.05 | 0.43 | -0.05 | orf, hypothetical protein |
| ygfZ | -0.13 | -1.60 | -1.40 | -0.25 | -1.20 | -1.20 | orf, hypothetical protein |
| yggA | -0.43 | 0.04 | 0.48 | -1.35 | 0.63 | 0.55 | orf, hypothetical protein |
| yggB | -0.01 | -26.14 | -0.53 | 0.20 | -1.53 | 0.05 | putative transport protein |
| yggC | 0.23 | 1.94 | -0.62 | -0.50 | 1.43 | -0.15 | putative kinase |
| yggD | 0.68 | -0.80 | 0.77 | 0.15 | -0.27 | 0.25 | putative transcriptional regulator |
| yggE | 0.51 | -1.94 | -0.07 | 0.45 | -1.47 | 0.25 | putative actin |
| yggF | 0.41 | -1.33 | 1.15 | 0.15 | 0.30 | 1.35 | orf, hypothetical protein |
| yggG | -2.13 | -1.68 | 0.90 | -1.60 | 0.23 | 1.50 | orf, hypothetical protein |
| yggH | 0.19 | -1.72 | -1.07 | -0.15 | -1.90 | -0.15 | orf, hypothetical protein |
| yggJ | 0.19 | -1.60 | 1.00 | -0.15 | -1.50 | 1.30 | orf, hypothetical protein |
| yggL | -0.71 | 0.89 | 1.67 | -0.05 | 0.27 | 1.65 | orf, hypothetical protein |
| yggM | 0.39 | 0.76 | 0.80 | 0.65 | 1.40 | 1.75 | putative alpha helix chain |
| yggN | 1.73 | 0.33 | -1.28 | 1.60 | 1.40 | -1.10 | orf, hypothetical protein |
| yggP | 0.39 | -1.31 | 0.82 | 0.40 | -0.60 | 1.55 | orf, hypothetical protein |
| yggR | -0.95 | -1.31 | 0.21 | -2.45 | 0.40 | 0.25 | putative protein transport |
| yggS | 0.86 | -1.42 | -1.36 | 1.65 | -1.37 | -1.30 | orf, hypothetical protein |
| yggT | 0.29 | -1.19 | -1.32 | 0.15 | 1.03 | -1.25 | putative resistance protein |
| yggU | 1.77 | 3.67 | -0.92 | 1.65 | 1.27 | -0.05 | orf, hypothetical protein |
| yggV | 0.64 | 0.34 | -0.95 | 1.50 | 0.57 | -0.10 | putative ribosomal protein |
| yggW | -0.19 | -1.73 | -1.39 | -0.10 | -0.27 | -1.40 | putative oxidase |
| yggX | 1.68 | -6.60 | -0.77 | 1.45 | -2.10 | 0.05 | orf, hypothetical protein |
| yghA | 0.98 | 0.57 | -1.08 | 1.85 | 0.17 | -0.10 | putative oxidoreductase |
| yghB | -0.60 | -0.43 | 0.86 | -1.10 | 0.17 | 0.05 | orf, hypothetical protein |
| yghD | -0.35 | -1.57 | 0.05 | 0.30 | -0.80 | 1.10 | putative secretion pathway protein |
| yghE | 1.51 | 0.31 | 1.00 | 1.25 | 0.57 | 1.40 | putative general secretion pathway for protein export (GSP) |
| yghK | -0.88 | 2.70 | -0.40 | -1.50 | 1.63 | -0.05 | putative permease |
| yghQ | 0.54 | 0.77 | -1.30 | 0.40 | 1.83 | -1.20 | orf, hypothetical protein |
| yghR | -1.37 | -0.50 | -0.79 | -0.25 | 0.23 | -1.20 | orf, hypothetical protein |
| yghS | 1.20 | 0.49 | -0.70 | 1.35 | -0.27 | -0.35 | orf, hypothetical protein |
| yghT | -1.10 | -0.28 | 0.19 | -0.45 | 0.43 | 0.20 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ygiA | -0.04 | 0.27 | -1.48 | 0.15 | 1.13 | -1.40 | orf, hypothetical protein |
| ygiB | 0.74 | -0.04 | -1.05 | -1.40 | 0.23 | -0.10 | orf, hypothetical protein |
| ygiC | -7.62 | -1.48 | -1.33 | -1.55 | -1.20 | 0.30 | putative synthetase |
| ygiD | 0.32 | 2.18 | -0.17 | 0.15 | 1.37 | 0.20 | orf, hypothetical protein |
| ygiE | -0.41 | -1.46 | 1.22 | -0.30 | -1.40 | 1.40 | orf, hypothetical protein |
| ygiF | -1.14 | -0.54 | 0.72 | -0.10 | 0.17 | 0.20 | orf, hypothetical protein |
| ygiG | -0.33 | -1.34 | -0.35 | -1.15 | -1.07 | -0.15 | putative kinase |
| ygiH | -0.84 | -1.58 | 0.63 | 0.40 | -1.30 | 0.20 | orf, hypothetical protein |
| ygiL | 0.37 | -1.39 | 0.38 | 1.95 | -1.57 | -0.95 | putative fimbrial-like protein |
| ygiM | 0.24 | 1.41 | 0.90 | 0.25 | 0.03 | 1.50 | orf, hypothetical protein |
| ygiN | 0.52 | -1.77 | -0.02 | 1.90 | -2.33 | 0.25 | orf, hypothetical protein |
| ygiP | 0.50 | -0.39 | 1.03 | 0.20 | 0.00 | 1.15 | putative transcriptional regulator LYSR-type |
| ygiR | 0.98 | -0.84 | -1.02 | 1.85 | -0.20 | -0.10 | orf, hypothetical protein |
| ygiW | -1.29 | -1.22 | -0.32 | -6.60 | -1.00 | -0.15 | orf, hypothetical protein |
| ygiX | 0.68 | -1.36 | 0.56 | 1.95 | -0.70 | -0.35 | putative 2-component transcriptional regulator |
| ygiY | -0.40 | -1.40 | -1.32 | 2.15 | -1.47 | -1.40 | putative 2-component sensor protein |
| ygjD | -0.75 | 0.99 | 0.57 | -0.65 | 1.33 | 0.50 | putative O-sialoglycoprotein endopeptidase |
| ygjE | -1.15 | 1.53 | -1.33 | -0.55 | 1.90 | 0.00 | orf, hypothetical protein |
| ygjF | -0.63 | 0.51 | -1.04 | -0.45 | 0.40 | -0.20 | orf, hypothetical protein |
| ygjG | 0.74 | 0.00 | 0.00 | -1.10 | -0.13 | -0.25 | probable ornithine aminotransferase |
| ygjH | -0.20 | -1.36 | -1.42 | 0.20 | -1.60 | -1.20 | putative tRNA synthetase |
| ygjI | -0.38 | 0.00 | 0.84 | 1.40 | 1.10 | 1.30 | putative oxidoreductase |
| ygjJ | 0.50 | -1.27 | -0.21 | 1.40 | -0.40 | -0.10 | orf, hypothetical protein |
| ygjK | 1.84 | -1.45 | 1.03 | 3.15 | -0.67 | 1.45 | putative isomerase |
| ygjL | 0.37 | 0.76 | 0.75 | 0.25 | 0.30 | 1.40 | putative NADPH dehydrogenase |
| ygjM | 0.41 | 0.97 | -1.12 | 1.65 | 1.23 | -0.10 | orf, hypothetical protein |
| ygjN | 0.35 | -1.26 | -1.11 | 0.65 | -0.23 | -0.10 | orf, hypothetical protein |
| ygjO | -0.82 | -1.34 | -1.29 | -0.10 | -1.13 | -1.35 | putative enzyme |
| ygjP | -0.36 | 1.94 | 0.93 | 0.00 | -0.07 | 1.50 | orf, hypothetical protein |
| ygjQ | -0.98 | -1.63 | -1.15 | -0.05 | -1.23 | -0.05 | orf, hypothetical protein |
| ygjR | -1.12 | -0.33 | -1.33 | -0.40 | 0.57 | 0.10 | orf, hypothetical protein |
| ygjT | -0.53 | -0.01 | 1.30 | 0.00 | 0.73 | 1.55 | putative transport protein |
| ygjU | 1.04 | -0.15 | -1.95 | 1.65 | 0.60 | -1.35 | putative transport protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ygjV | **0.69** | **-1.41** | **-1.14** | 1.40 | -0.37 | -0.15 | orf, hypothetical protein |
| yhaB | **0.47** | **1.83** | **-0.96** | 0.25 | 1.57 | -0.10 | orf, hypothetical protein |
| yhaC | **0.54** | **-1.34** | **1.29** | 0.10 | -0.57 | -0.35 | orf, hypothetical protein |
| yhaD | **0.08** | **-0.67** | **0.76** | -0.50 | -0.07 | 1.10 | orf, hypothetical protein |
| yhaE | **-0.11** | **0.64** | **0.04** | -10.15 | 1.37 | -0.25 | putative dehydrogenase |
| yhaF | **-3.12** | **-1.29** | **-1.58** | -2.30 | -0.63 | -1.55 | orf, hypothetical protein |
| yhaG | **-0.69** | **-1.34** | **0.81** | 0.10 | -0.47 | 1.30 | putative hydrolase |
| yhaH | **0.55** | **-1.20** | **2.52** | 1.65 | -0.63 | 1.30 | putative cytochrome |
| yhaI | **-0.29** | **0.12** | **0.80** | 1.00 | 0.57 | 1.30 | putative cytochrome |
| yhaJ | **1.17** | **-1.29** | **-1.40** | 1.90 | -0.60 | -1.20 | putative transcriptional regulator LYSR-type |
| yhaK | **0.08** | **0.43** | **0.22** | 0.05 | 0.77 | 0.30 | orf, hypothetical protein |
| yhaL | **0.47** | **-1.82** | **-1.58** | 0.35 | -2.17 | -1.25 | orf, hypothetical protein |
| yhaM | **-0.59** | **0.91** | **-1.31** | -1.40 | 1.33 | -0.15 | orf, hypothetical protein |
| yhaN | **0.00** | **0.00** | **-1.16** | -2.00 | 1.30 | 0.05 | orf, hypothetical protein |
| yhaO | **0.10** | **-0.24** | **0.86** | 0.75 | 1.33 | 1.25 | putative transport system permease protein |
| yhaP | **0.54** | **1.56** | **0.41** | 0.25 | -0.23 | 0.35 | putative L-serine dehydratase |
| yhaQ | **-0.59** | **1.52** | **0.76** | 0.20 | 1.30 | 0.45 | putative L-serine dehydratase |
| yhaR | **-0.67** | **-2.11** | **-0.47** | -0.05 | 0.07 | -0.25 | orf, hypothetical protein |
| yhaU | **-0.72** | **-1.38** | **-1.15** | -2.25 | -0.87 | -1.50 | putative transport protein |
| yhaV | **-1.14** | **-7.03** | **-1.19** | -0.90 | -1.50 | -0.20 | orf, hypothetical protein |
| yhbC | **0.42** | **0.52** | **1.52** | 1.35 | 1.00 | 1.10 | orf, hypothetical protein |
| yhbE | **0.16** | **2.53** | **-0.05** | -0.05 | 1.60 | 0.05 | orf, hypothetical protein |
| yhbG | **0.21** | **1.71** | **1.65** | 0.10 | 1.30 | 1.10 | putative ATP-binding component of a transport system |
| yhbH | **-0.41** | **-2.84** | **0.39** | -0.30 | -1.93 | 1.10 | probable sigma-54 modulation protein |
| yhbJ | **0.40** | **-0.41** | **1.16** | 1.15 | 0.27 | 1.15 | orf, hypothetical protein |
| yhbL | **-0.93** | **-0.66** | **0.84** | -0.65 | 0.30 | 1.40 | sigma cross-reacting protein 27A (SCRP-27A) |
| yhbM | **-0.34** | **-0.25** | **0.19** | -1.05 | 0.63 | 0.45 | putative control proteins |
| yhbN | **0.27** | **1.79** | **0.86** | 1.50 | 0.47 | 1.25 | orf, hypothetical protein |
| yhbO | **-0.31** | **2.43** | **0.14** | 0.05 | 1.43 | 0.10 | orf, hypothetical protein |
| yhbP | **0.15** | **1.09** | **0.70** | -0.10 | 1.13 | 0.65 | orf, hypothetical protein |
| yhbQ | **1.40** | **-1.81** | **0.47** | 1.85 | -1.07 | -0.15 | orf, hypothetical protein |
| yhbS | **-1.96** | **-0.45** | **-0.05** | -1.95 | -1.50 | 0.15 | orf, hypothetical protein |
| yhbT | **-0.58** | **-0.83** | **-0.39** | -1.30 | -1.87 | -1.35 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yhbU | 0.31 | -1.13 | 0.74 | 0.00 | 0.57 | 0.00 | putative collagenase |
| yhbV | 0.71 | 1.23 | 0.88 | 1.35 | 0.33 | 0.15 | orf, hypothetical protein |
| yhbW | 0.50 | -1.34 | -1.34 | 1.30 | -0.37 | -1.40 | putative enzyme |
| yhbX | 12.68 | -1.45 | -1.06 | 1.50 | -0.53 | 0.10 | putative alkaline phosphatase I |
| yhbY | 1.54 | 0.21 | -0.87 | 1.60 | 0.23 | -1.40 | orf, hypothetical protein |
| yhbZ | 1.34 | -0.62 | 1.52 | 1.35 | -0.43 | 1.45 | putative GTP-binding factor |
| yhcA | 0.22 | 0.91 | 0.29 | 1.30 | 1.33 | 0.30 | putative chaperone |
| yhcB | 0.32 | -2.66 | 0.11 | 0.35 | -2.07 | 0.00 | orf, hypothetical protein |
| yhcC | -0.43 | -0.49 | -1.34 | -0.25 | -1.23 | -0.15 | orf, hypothetical protein |
| yhcD | -1.04 | -1.64 | -1.32 | -1.30 | -0.40 | -1.25 | putative outer membrane protein |
| yhcE | 0.36 | 0.66 | -0.14 | 0.10 | 1.33 | 1.05 | orf, hypothetical protein |
| yhcF | 0.15 | -1.34 | 1.50 | -0.40 | -0.30 | 1.40 | putative transcriptional regulator |
| yhcG | 0.92 | 2.71 | 1.73 | 1.65 | 1.27 | 1.25 | orf, hypothetical protein |
| yhcH | -0.28 | -1.63 | 0.65 | 1.30 | -1.10 | 0.00 | orf, hypothetical protein |
| yhcI | 0.11 | -1.34 | 0.12 | -0.55 | -0.23 | 0.15 | putative NAGC-like transcriptional regulator |
| yhcJ | -1.00 | -1.37 | 0.37 | -1.85 | -1.13 | 0.10 | putative enzyme |
| yhcK | 0.20 | -0.60 | 0.99 | 1.05 | 0.23 | 1.20 | putative FADA-type transcriptional regulator |
| yhcL | 0.76 | -1.41 | 0.56 | 0.25 | 0.30 | 0.45 | putative transport protein |
| yhcM | 0.99 | -0.35 | -1.34 | 0.45 | 0.47 | -0.20 | orf, hypothetical protein |
| yhcN | 0.45 | 1.65 | 0.68 | 2.90 | 2.40 | -0.15 | orf, hypothetical protein |
| yhcO | -0.76 | 2.02 | 1.37 | 0.55 | 1.30 | 1.25 | orf, hypothetical protein |
| yhcP | 2.06 | 0.35 | -1.31 | 1.95 | -0.23 | -0.40 | orf, hypothetical protein |
| yhcQ | -0.91 | 1.32 | 0.89 | -1.35 | 1.70 | 1.55 | putative membrane protein |
| yhcR | -0.48 | -1.16 | 0.14 | -0.35 | -0.17 | -0.25 | orf, hypothetical protein |
| yhcS | 0.33 | -1.33 | -1.76 | -0.15 | -0.43 | -1.55 | putative transcriptional regulator LYSR-type |
| yhdA | 0.33 | 0.77 | 0.86 | 0.25 | 1.50 | 1.55 | orf, hypothetical protein |
| yhdE | 0.93 | -1.54 | -38.88 | 0.90 | -1.23 | -1.20 | orf, hypothetical protein |
| yhdG | 1.26 | 1.96 | 0.37 | 1.50 | 2.27 | 0.25 | putative dehydrogenase |
| yhdH | -0.23 | -0.77 | 0.95 | -0.70 | -0.17 | 1.55 | putative dehydrogenase |
| yhdJ | 0.50 | 0.62 | 0.77 | 0.60 | 0.60 | 0.00 | putative methyltransferase |
| yhdM | 1.21 | -0.53 | 0.64 | -0.15 | -0.07 | -0.05 | putative transcriptional regulator |
| yhdN | 0.14 | 0.09 | 0.88 | 1.20 | 1.33 | 0.10 | orf, hypothetical protein |
| yhdP | -1.36 | -1.30 | -0.50 | -1.35 | 1.30 | -1.20 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yhdR | 0.29 | -1.23 | 1.35 | 1.25 | -0.27 | 1.40 | orf, hypothetical protein |
| yhdT | 0.19 | -2.23 | 0.41 | 1.40 | -1.20 | 0.50 | orf, hypothetical protein |
| yhdU | -1.11 | 0.13 | 0.77 | -0.55 | 1.07 | 0.60 | orf, hypothetical protein |
| yhdV | -0.22 | 0.83 | 0.36 | -0.05 | 1.07 | 0.20 | orf, hypothetical protein |
| yhdW | 0.64 | -0.84 | 0.72 | 1.05 | -0.23 | -0.15 | putative periplasmic binding transport protein |
| yhdX | 8.21 | -1.27 | -0.19 | 2.25 | -0.23 | -0.05 | putative transport system permease protein |
| yhdY | 0.29 | -1.34 | -0.53 | -0.30 | -0.33 | 0.10 | putative transport system permease protein |
| yhdZ | -0.20 | -1.52 | -1.33 | 0.70 | -1.13 | 0.00 | putative ATP-binding component of a transport system |
| yheA | 0.47 | 1.21 | 0.64 | 1.65 | 1.33 | -0.10 | orf, hypothetical protein |
| yheB | -0.55 | 0.68 | -0.42 | 0.05 | 0.13 | 0.10 | putative enzyme |
| yheD | -0.68 | -0.89 | -1.05 | 0.15 | -0.20 | -1.10 | putative export protein A for general secretion pathway (GSP) |
| yheE | 0.22 | 2.15 | -1.33 | 0.85 | 1.47 | -1.30 | putative general secretion pathway for protein export (GSP) |
| yheF | 1.54 | -1.43 | -1.34 | 0.20 | -0.53 | -1.35 | putative general protein secretion protein |
| yheG | -0.10 | -0.92 | -1.41 | 0.15 | -0.23 | -1.50 | putative general secretion pathway for protein export (GSP) (TYPE II TRAFFIC WARDEN ATPASE) |
| yheH | 0.99 | -0.90 | -0.03 | 2.50 | 0.27 | 0.10 | putative export protein for general secretion pathway (GSP) |
| yheI | -0.89 | -0.94 | -0.73 | 0.30 | -0.10 | 0.00 | putative export protein I for general secretion pathway (GSP) |
| yheJ | -0.97 | -1.34 | 0.54 | -0.55 | -1.30 | 1.15 | putative export protein J for general secretion pathway (GSP) |
| yheK | 1.44 | 2.26 | 0.33 | 1.85 | 0.70 | -1.10 | putative general protein secretion protein |
| yheL | -0.05 | -1.64 | -0.21 | -0.10 | -1.33 | -0.35 | orf, hypothetical protein |
| yheM | 0.23 | 0.29 | -1.55 | 0.10 | 0.47 | -1.45 | orf, hypothetical protein |
| yheN | 0.38 | -1.33 | 0.77 | 1.30 | -1.37 | -0.10 | orf, hypothetical protein |
| yheO | 1.91 | -0.75 | 0.58 | 1.95 | -0.30 | -0.35 | orf, hypothetical protein |
| yheR | 0.76 | -3.24 | 0.24 | 1.75 | -1.53 | 0.05 | putative NAD(P)H oxidoreductase |
| yheS | 2.13 | -1.11 | -0.60 | 2.15 | -0.17 | 0.05 | putative ATP-binding component of a transport system |
| yheT | 1.28 | -0.51 | -0.54 | 1.55 | 0.13 | 0.00 | orf, hypothetical protein |
| yheU | -0.62 | -1.94 | 0.74 | -0.55 | -1.10 | 1.60 | orf, hypothetical protein |
| yhfA | 0.12 | -0.45 | 1.11 | 0.05 | 0.43 | 1.55 | orf, hypothetical protein |
| yhfC | 0.55 | -1.47 | 0.62 | 0.55 | -0.60 | 0.90 | putative transport |
| yhfG | -0.95 | 0.36 | 0.74 | -0.30 | 1.43 | 0.05 | orf, hypothetical protein |
| yhfK | 0.29 | -1.38 | -1.32 | 0.00 | -2.03 | -0.30 | orf, hypothetical protein |
| yhfL | 1.43 | 0.10 | 1.28 | 1.40 | -0.13 | 1.40 | orf, hypothetical protein |
| yhfM | -0.16 | -1.34 | -0.76 | 0.45 | -1.30 | -1.10 | putative amino acid |
| yhfN | 0.42 | -1.34 | -1.34 | 0.50 | -0.07 | -1.05 | putative transport protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yhfO | 0.29 | -1.11 | 0.58 | 1.55 | -0.50 | 0.25 | orf, hypothetical protein |
| yhfP | 1.12 | -1.39 | -0.06 | 3.55 | -0.43 | -0.10 | orf, hypothetical protein |
| yhfQ | 0.87 | 0.62 | -1.30 | 1.60 | 1.20 | -1.15 | putative kinase |
| yhfR | -0.78 | -1.11 | -1.83 | -0.35 | 1.13 | -1.10 | putative transcriptional regulator |
| yhfS | -0.64 | -3.71 | -1.50 | 0.05 | -0.03 | -1.40 | orf, hypothetical protein |
| yhfT | 3.90 | 0.97 | -1.56 | 1.55 | 1.10 | -1.15 | putative transport system permease protein |
| yhfU | 1.94 | 4.16 | -0.57 | 1.95 | 1.63 | 0.15 | orf, hypothetical protein |
| yhfV | 0.30 | 2.63 | 1.11 | -0.10 | -0.30 | -0.15 | putative hydrolase |
| yhfW | -0.24 | 0.35 | 0.74 | 0.65 | 1.40 | 1.75 | putative mutase |
| yhfX | 0.25 | -1.33 | 0.36 | 0.60 | -0.23 | 0.00 | orf, hypothetical protein |
| yhfY | -0.28 | 1.93 | 1.68 | -0.40 | 1.47 | 1.70 | orf, hypothetical protein |
| yhfZ | 0.56 | -1.38 | 0.77 | -0.10 | -2.83 | -0.05 | orf, hypothetical protein |
| yhgA | 0.11 | -0.09 | 1.78 | -0.10 | -0.40 | 1.30 | orf, hypothetical protein |
| yhgE | -1.27 | 0.64 | 1.86 | -0.50 | 0.27 | 1.50 | putative transport |
| yhgF | -0.96 | 0.00 | 0.77 | -1.65 | 1.13 | 0.00 | orf, hypothetical protein |
| yhgG | -1.00 | 0.75 | 0.81 | -2.50 | -1.40 | 1.55 | orf, hypothetical protein |
| yhgH | 0.13 | -1.46 | -0.47 | 0.00 | -0.20 | -1.05 | orf, hypothetical protein |
| yhgI | 0.44 | 3.11 | 0.81 | 1.80 | 1.27 | 0.65 | orf, hypothetical protein |
| yhgJ | 1.52 | 0.27 | 0.79 | 2.20 | 0.67 | 1.30 | orf, hypothetical protein |
| yhgN | 0.15 | 0.48 | -0.06 | 0.40 | -0.13 | 0.10 | orf, hypothetical protein |
| yhhA | -0.07 | -1.19 | -1.37 | 0.25 | -0.40 | -2.15 | orf, hypothetical protein |
| yhhF | 2.50 | 2.16 | 0.09 | 1.50 | -0.30 | 0.05 | orf, hypothetical protein |
| yhhG | -0.25 | -1.47 | -0.43 | 0.20 | -1.73 | 0.05 | orf, hypothetical protein |
| yhhH | 1.67 | -0.22 | 0.59 | 2.25 | 1.37 | 0.15 | orf, hypothetical protein |
| yhhI | -0.27 | 0.66 | -1.04 | 0.00 | 1.43 | 0.00 | putative receptor |
| yhhJ | -0.41 | 0.18 | -1.48 | -0.20 | 0.60 | -1.25 | putative transporter |
| yhhK | 3.63 | -1.45 | -0.79 | 2.30 | -0.53 | -0.35 | orf, hypothetical protein |
| yhhL | 1.09 | -1.57 | -1.33 | 0.25 | 0.47 | 0.05 | orf, hypothetical protein |
| yhhM | 0.10 | 0.37 | 0.53 | 1.70 | 0.27 | 0.35 | putative receptor |
| yhhN | -0.10 | 0.43 | 0.96 | 0.20 | 0.27 | 1.25 | putative enzyme |
| yhhP | 0.10 | -1.76 | 1.01 | -0.25 | -0.20 | 1.15 | orf, hypothetical protein |
| yhhQ | 2.14 | -1.56 | -1.53 | 3.70 | -1.77 | -1.15 | orf, hypothetical protein |
| yhhS | -0.58 | -3.04 | -1.39 | -0.40 | -1.33 | -1.85 | putative transport |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yhhT | 0.64 | -2.31 | -0.76 | 1.75 | -1.10 | 0.05 | orf, hypothetical protein |
| yhhU | 0.20 | 0.04 | 0.21 | 0.55 | 0.40 | -0.20 | orf, hypothetical protein |
| yhhW | 3.13 | -2.19 | 0.82 | 1.55 | -1.60 | 1.40 | orf, hypothetical protein |
| yhhX | 2.27 | -1.07 | -1.34 | 1.40 | -0.17 | -1.30 | putative regulator |
| yhhY | 1.36 | 1.39 | -1.43 | 2.55 | 1.40 | -1.30 | orf, hypothetical protein |
| yhhZ | 0.30 | -1.20 | 0.80 | 0.10 | -0.37 | 1.55 | orf, hypothetical protein |
| yhiD | 0.23 | -2.04 | -0.53 | 0.50 | -1.07 | -1.50 | putative transport ATPase |
| yhiE | -1.05 | 0.57 | 0.76 | -0.25 | 0.50 | 0.05 | orf, hypothetical protein |
| yhiF | 1.29 | -0.95 | -1.17 | 1.70 | -1.07 | -1.05 | orf, hypothetical protein |
| yhiH | 0.00 | -1.34 | 0.81 | -2.00 | -1.17 | 1.30 | putative ATP-binding component of a transport system, fragment 1 |
| yhiI | -0.84 | -1.33 | -0.16 | -0.30 | -0.37 | 0.00 | putative membrane protein |
| yhiJ | -0.67 | -0.11 | 0.79 | 0.05 | 0.20 | 0.10 | orf, hypothetical protein |
| yhiK | -1.63 | 0.90 | -1.30 | -1.20 | 1.17 | 0.15 | orf, hypothetical protein |
| yhiL | -0.70 | 1.40 | -1.34 | 0.50 | 1.30 | -1.60 | orf, hypothetical protein |
| yhiM | 3.76 | -1.29 | -1.21 | 2.20 | -0.33 | -1.10 | orf, hypothetical protein |
| yhiN | -0.24 | 1.88 | -1.17 | 0.30 | 1.57 | -1.20 | orf, hypothetical protein |
| yhiO | -0.75 | 1.27 | 0.78 | -0.55 | 1.23 | 1.45 | orf, hypothetical protein |
| yhiP | -0.59 | 2.76 | 0.77 | -0.60 | 1.27 | 1.25 | putative transport protein |
| yhiQ | -0.28 | -0.17 | -1.51 | 0.15 | 1.47 | -1.15 | orf, hypothetical protein |
| yhiR | 0.68 | -1.55 | -1.35 | 1.50 | -0.27 | -0.20 | orf, hypothetical protein |
| yhiS | -1.02 | 0.71 | -1.12 | -0.05 | 1.40 | -1.40 | orf, hypothetical protein |
| yhiU | -0.55 | 0.77 | 0.38 | 0.85 | 1.30 | 0.15 | putative membrane protein |
| yhiV | -0.29 | 1.23 | 1.30 | 2.65 | 1.70 | 1.30 | putative transport system permease protein |
| yhiW | -0.91 | -1.37 | 0.32 | 0.75 | -0.73 | -0.05 | putative ARAC-type regulatory protein |
| yhiX | -0.17 | -1.01 | 2.01 | 0.75 | -0.50 | 1.20 | putative ARAC-type regulatory protein |
| yhjA | 0.01 | -1.49 | 0.77 | -0.35 | -1.60 | 1.40 | putative cytochrome C peroxidase (EC 1.11.1) |
| yhjB | -0.09 | 6.23 | 1.11 | 0.25 | 2.10 | 1.95 | putative regulator |
| yhjC | 2.71 | 0.76 | 0.79 | 2.40 | 0.33 | -0.35 | putative transcriptional regulator LYSR-type |
| yhjD | -0.51 | -1.33 | 0.15 | -0.10 | -1.20 | 0.25 | orf, hypothetical protein |
| yhjE | 0.28 | 0.63 | -0.76 | 0.80 | 1.43 | 0.00 | putative transport protein |
| yhjG | -0.03 | 0.77 | -1.25 | 0.95 | 1.37 | -0.05 | orf, hypothetical protein |
| yhjH | 1.97 | 0.16 | 0.26 | 1.10 | -0.23 | 0.25 | orf, hypothetical protein |
| yhjJ | -0.06 | 0.42 | 1.25 | -0.45 | -1.33 | 1.40 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yhjK | -0.46 | -0.17 | 0.77 | 0.10 | 1.00 | 1.40 | orf, hypothetical protein |
| yhjL | 3.59 | 0.39 | -1.17 | 0.10 | 1.27 | -0.15 | putative oxidoreductase subunit |
| yhjM | -0.51 | 2.11 | -1.54 | 0.05 | 1.53 | -1.00 | putative endoglucanase |
| yhjN | -0.05 | 1.12 | 0.62 | 0.10 | 1.87 | 0.05 | orf, hypothetical protein |
| yhjO | 2.00 | -0.38 | 0.55 | 2.35 | -0.30 | 0.20 | putative cellulose synthase |
| yhjQ | -0.13 | 0.68 | 0.77 | -0.20 | 0.27 | 0.10 | orf, hypothetical protein |
| yhjR | 8.81 | 1.80 | 0.85 | 1.55 | 1.33 | 1.10 | orf, hypothetical protein |
| yhjS | 0.83 | -0.14 | 0.77 | 2.50 | 0.60 | 1.15 | putative protease |
| yhjT | -0.19 | -5.15 | 1.19 | 0.05 | 0.13 | 1.30 | orf, hypothetical protein |
| yhjU | -0.52 | -1.23 | 0.73 | -0.25 | -0.17 | 1.45 | orf, hypothetical protein |
| yhjV | 0.04 | -1.52 | 1.11 | 0.55 | -1.07 | 1.30 | putative transporter protein |
| yhjW | 0.20 | 0.00 | 0.76 | -0.45 | 0.50 | 1.45 | orf, hypothetical protein |
| yhjX | 0.49 | -0.48 | 0.58 | 0.55 | -0.23 | 0.20 | putative resistance protein |
| yhjY | -0.79 | -1.02 | 2.87 | -0.25 | -0.13 | 1.00 | putative lipase |
| yi21 | -0.45 | 0.74 | -1.25 | -3.15 | 0.63 | -1.45 | IS2 hypothetical protein |
| yi21 | 0.00 | 0.00 | 0.77 | -1.20 | -1.30 | 1.25 | IS2 hypothetical protein |
| yi21 | -0.47 | -0.95 | 0.79 | -18.15 | -0.73 | 1.45 | IS2 hypothetical protein |
| yi22 | -0.14 | -1.61 | -1.33 | 0.10 | -2.37 | -3.45 | IS2 hypothetical protein |
| yi22 | 1.38 | 0.67 | -1.24 | 0.25 | -0.13 | 0.00 | IS2 hypothetical protein |
| yi22 | 0.16 | -0.42 | -0.05 | 1.25 | 1.37 | -0.05 | IS2 hypothetical protein |
| yi41 | 2.39 | -1.54 | 0.82 | 1.75 | -1.47 | 1.35 | IS4 hypothetical protein |
| yi5A | 0.26 | -1.24 | -25.32 | 0.80 | -0.27 | -1.50 | IS150 hypothetical protein |
| yi81 | -0.62 | 0.70 | 0.80 | -0.90 | 2.13 | 1.30 | IS186 hypothetical protein |
| yi82 | -0.33 | 0.30 | -1.35 | -0.15 | 1.57 | -1.45 | IS186 and IS421 hypothetical protein |
| yi91a | -0.87 | -1.38 | 1.08 | -0.50 | -1.73 | 1.15 | IS911 hypothetical protein, variant (IS911A) |
| yi91b | -1.57 | -1.47 | 0.77 | -1.75 | -1.67 | 0.05 | IS911 hypothetical protein (IS911B) |
| yiaA | -0.34 | -1.86 | 0.74 | 1.35 | -1.20 | 0.20 | orf, hypothetical protein |
| yiaB | -0.31 | 0.83 | -1.48 | 1.25 | 1.43 | -1:15 | orf, hypothetical protein |
| yiaC | 0.33 | -1.41 | -1.42 | 0.45 | -1.57 | -1.25 | orf, hypothetical protein |
| yiaD | 2.11 | -1.25 | 1.98 | 1.45 | -0.30 | 1.30 | putative outer membrane protein |
| yiaE | 0.18 | -1.83 | 0.47 | 0.35 | -1.37 | 1.15 | putative dehydrogenase |
| yiaF | 0.28 | -1.38 | 0.84 | 0.20 | -1.50 | -0.05 | orf, hypothetical protein |
| yiaG | -0.34 | -1.23 | 0.86 | -0.50 | -0.33 | 1.20 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yiaH | 0.47 | -1.31 | -1.30 | 0.60 | -0.33 | -0.05 | orf, hypothetical protein |
| yiaI | -1.54 | -1.95 | 0.63 | -0.25 | -1.63 | -0.05 | orf, hypothetical protein |
| yiaJ | 0.13 | -1.17 | 0.52 | 0.30 | -0.30 | 0.00 | putative regulator |
| yiaK | 0.41 | 0.01 | -1.40 | 1.60 | 1.07 | -2.10 | putative dehydrogenase |
| yiaL | 1.00 | 2.88 | 0.94 | 2.15 | 1.33 | 1.20 | putative lipase |
| yiaM | 0.33 | -1.40 | -1.39 | 1.70 | -0.43 | -0.20 | orf, hypothetical protein |
| yiaN | 0.50 | -1.32 | 0.94 | 1.95 | -0.20 | 1.10 | putative membrane protein |
| yiaO | -0.66 | 2.10 | -0.97 | -0.10 | 1.43 | -1.25 | putative solute-binding transport protein |
| yiaT | 0.05 | -0.92 | 2.59 | 0.00 | -0.23 | 1.15 | putative outer membrane protein |
| yiaU | 2.74 | 1.03 | 1.64 | 1.85 | 1.10 | 1.30 | putative transcriptional regulator LYSR-type |
| yiaV | 0.37 | -1.16 | 0.71 | 0.95 | 1.57 | 0.60 | putative membrane protein |
| yiaW | 0.06 | -0.65 | -0.70 | -0.15 | 0.43 | 0.05 | orf, hypothetical protein |
| yiaY | -0.46 | 0.61 | 0.70 | -0.20 | 1.50 | 0.05 | putative oxidoreductase |
| yibA | 0.07 | -1.32 | 0.74 | 0.30 | -0.50 | 1.20 | orf, hypothetical protein |
| yibD | 0.76 | -0.22 | -1.31 | 1.70 | -0.20 | -1.50 | putative regulator |
| yibF | -0.41 | -0.20 | 0.91 | 0.35 | 0.57 | 1.35 | putative S-transferase |
| yibG | 0.25 | 0.98 | 0.77 | 0.45 | 1.67 | 1.55 | orf, hypothetical protein |
| yibH | -0.91 | -1.01 | 0.84 | -0.70 | 0.43 | 1.30 | putative membrane protein |
| yibI | 2.08 | 0.93 | 0.72 | 1.70 | 1.60 | 0.35 | orf, hypothetical protein |
| yibJ | -1.00 | 0.01 | 0.92 | 0.00 | -0.30 | 1.25 | orf, hypothetical protein |
| yibK | -0.66 | 2.26 | -1.29 | -0.40 | 1.30 | -1.20 | orf, hypothetical protein |
| yibL | 0.24 | 0.00 | 0.37 | -0.55 | 1.23 | 0.05 | orf, hypothetical protein |
| yibN | 0.51 | 1.43 | 0.88 | 1.40 | 0.47 | 0.05 | orf, hypothetical protein |
| yibO | -0.17 | 1.28 | 1.47 | -0.60 | 0.60 | 1.05 | putative 2,3-bisphosphoglycerate-independent phosphoglycerate mutase |
| yibP | 2.48 | 0.65 | 0.79 | 1.85 | -0.20 | 1.20 | putative membrane protein |
| yibQ | 0.38 | 0.77 | 0.52 | 0.75 | 1.30 | 0.05 | orf, hypothetical protein |
| yicC | 0.53 | -0.91 | 1.26 | 1.85 | -0.57 | 1.40 | putative alpha helix protein |
| yicE | -0.31 | 0.79 | 0.63 | 0.05 | 1.20 | 1.30 | putative transport protein |
| yicF | 0.57 | -4.28 | -1.27 | 1.85 | -1.80 | -1.30 | putative enzyme |
| yicG | 0.09 | 0.74 | 1.40 | 1.15 | 1.27 | 1.15 | orf, hypothetical protein |
| yicH | -0.15 | 1.93 | -1.34 | 0.20 | 1.23 | -0.10 | orf, hypothetical protein |
| yicI | 0.40 | -1.32 | 1.23 | 0.80 | -0.33 | 1.65 | orf, hypothetical protein |
| yicJ | 0.47 | 0.52 | 0.75 | 1.20 | 1.07 | -0.15 | putative permease |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yicK | 0.04 | -1.27 | 0.08 | 0.20 | -0.13 | 0.30 | two-module transport protein |
| yicL | -0.95 | -1.35 | 0.22 | -0.40 | -1.30 | 0.15 | putative permease transporter |
| yicM | 3.37 | -1.42 | 0.29 | 2.80 | -0.73 | 0.00 | putative transport protein |
| yicN | 1.11 | -0.51 | -1.32 | 1.55 | -0.03 | -0.25 | orf, hypothetical protein |
| yicO | 0.71 | -1.36 | 0.09 | 2.10 | -1.00 | -2.65 | orf, hypothetical protein |
| yicP | 0.24 | 0.76 | 0.48 | -0.15 | -1.10 | -0.20 | probable adenine deaminase (synthesis xanthine) |
| yidA | 0.90 | 0.31 | 0.69 | 1.70 | 0.40 | 1.35 | orf, hypothetical protein |
| yidB | 1.19 | -1.08 | 0.16 | 1.85 | -0.37 | 0.15 | orf, hypothetical protein |
| yidC | -0.01 | 4.97 | 1.89 | 1.15 | 1.93 | 1.40 | 60 KD inner-membrane protein |
| yidE | 0.10 | 1.51 | 0.82 | -0.45 | 1.17 | 1.70 | putative transport protein |
| yidF | 0.44 | -0.84 | -0.21 | -0.45 | 0.37 | 0.00 | putative transcriptional regulator |
| yidG | 0.28 | 0.50 | -1.31 | 0.70 | 1.20 | 0.15 | orf, hypothetical protein |
| yidH | -0.31 | -1.26 | 0.64 | 0.35 | -0.43 | 0.00 | orf, hypothetical protein |
| yidI | 0.85 | -1.37 | 0.60 | 1.55 | -0.70 | 1.15 | orf, hypothetical protein |
| yidJ | 0.31 | 0.76 | 0.77 | 1.75 | 1.80 | 0.00 | putative sulfatase |
| yidK | 0.00 | 0.75 | 0.73 | 0.30 | -0.53 | 1.65 | putative cotransporter |
| yidL | -0.64 | -1.17 | 0.21 | 0.35 | -0.27 | 0.20 | putative ARAC-type regulatory protein |
| yidP | 0.32 | -1.28 | 0.61 | 2.15 | -1.17 | -0.05 | putative transcriptional regulator |
| yidQ | -0.07 | -1.72 | -0.30 | -0.05 | -1.30 | 0.00 | orf, hypothetical protein |
| yidR | 0.61 | -1.10 | 0.55 | 1.30 | 1.07 | -0.05 | orf, hypothetical protein |
| yidS | 0.46 | 2.67 | 0.93 | 2.00 | 1.63 | 0.15 | orf, hypothetical protein |
| yidW | -0.10 | 1.32 | -1.49 | 0.30 | 1.37 | -1.25 | regulator protein for dgo operon |
| yidX | 1.76 | -1.46 | -2.31 | 1.40 | -0.37 | -1.15 | putative replicase EC 2.7.- |
| yidY | -0.22 | -1.41 | 0.68 | 0.15 | -1.20 | 0.25 | putative transport protein |
| yidZ | -1.41 | 1.53 | 0.36 | -1.70 | 1.37 | 0.10 | putative transcriptional regulator LYSR-type |
| yieC | 1.40 | -1.49 | 0.77 | 1.60 | -1.20 | -0.05 | putative receptor protein |
| yieE | 1.78 | 0.00 | -1.31 | 2.35 | 0.27 | -1.55 | orf, hypothetical protein |
| yieF | -0.03 | -1.22 | 0.04 | 0.15 | -1.20 | 0.25 | orf, hypothetical protein |
| yieG | -0.02 | -0.98 | 0.89 | -0.60 | 0.00 | 1.25 | putative membrane |
| yieH | 0.42 | 0.79 | -0.11 | 1.40 | 1.30 | 0.30 | putative phosphatase |
| yieI | 0.24 | -0.08 | 0.90 | 0.30 | 0.60 | 1.30 | orf, hypothetical protein |
| yieJ | -0.49 | 1.36 | 0.74 | -0.80 | 1.43 | 0.10 | orf, hypothetical protein |
| yieK | -0.06 | -0.84 | -1.37 | 0.10 | -0.03 | -0.20 | putative isomerase |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yieL | 0.00 | 0.00 | 1.50 | -1.95 | 0.33 | 1.35 | putative xylanase |
| yieM | 0.07 | 0.81 | 0.57 | 0.00 | 0.63 | -0.05 | orf, hypothetical protein |
| yieN | 0.99 | -1.73 | 0.49 | 0.20 | -1.27 | -0.20 | putative 2-component regulator |
| yieO | -0.46 | -1.58 | -0.68 | -0.05 | -0.37 | -1.30 | putative transport protein |
| yieP | -0.39 | -1.37 | 0.00 | -1.25 | -1.30 | 0.05 | orf, hypothetical protein |
| yifA | -0.16 | -1.18 | 0.81 | -0.15 | 0.13 | 1.50 | orf, hypothetical protein |
| yifB | 0.10 | -1.29 | -0.50 | -0.25 | -0.40 | 0.10 | putative 2-component regulator |
| yifE | 0.90 | -1.39 | 1.03 | 0.90 | -1.73 | 0.45 | orf, hypothetical protein |
| yifK | 1.63 | -1.04 | -1.48 | 1.35 | -0.03 | -1.50 | putative amino acid |
| yifN | 1.33 | 2.34 | 0.97 | 0.40 | 1.70 | -0.10 | orf, hypothetical protein |
| yigA | 0.27 | -1.31 | -0.77 | 1.50 | -0.30 | -1.30 | orf, hypothetical protein |
| yigB | 0.31 | -1.07 | -1.33 | 0.65 | -1.43 | -1.10 | putative phosphatase |
| yigC | 0.32 | 0.80 | -1.36 | 0.50 | 0.33 | -1.25 | putative oxidoreductase |
| yigE | 0.24 | -1.59 | -0.14 | 1.55 | -1.33 | -0.10 | orf, hypothetical protein |
| yigF | 1.94 | 1.27 | 0.51 | 1.70 | 1.17 | 1.30 | orf, hypothetical protein |
| yigG | 0.44 | -1.31 | -0.49 | 1.35 | -0.47 | 0.00 | orf, hypothetical protein |
| yigI | -0.05 | -1.35 | -0.18 | 0.95 | -0.53 | 0.10 | orf, hypothetical protein |
| yigJ | 0.42 | 0.71 | 0.72 | 1.70 | 1.60 | 1.25 | orf, hypothetical protein |
| yigK | -0.35 | 0.92 | -1.53 | 1.10 | 1.40 | -1.40 | orf, hypothetical protein |
| yigL | 2.37 | -0.70 | -0.65 | 0.05 | 0.17 | -1.15 | orf, hypothetical protein |
| yigM | 1.12 | -1.37 | -1.69 | 2.05 | -0.63 | -1.35 | orf, hypothetical protein |
| yigN | 2.74 | -1.77 | 0.14 | 2.30 | -1.37 | -0.45 | putative alpha helix chain |
| yigP | 0.78 | -1.31 | -1.42 | 2.15 | -1.37 | -1.20 | orf, hypothetical protein |
| yigR | -0.06 | -1.22 | 2.05 | 0.10 | -1.27 | 1.50 | orf, hypothetical protein |
| yigU | 1.06 | 2.19 | 1.19 | 1.50 | 1.50 | 1.45 | orf, hypothetical protein |
| yigW | -0.56 | -0.85 | -1.37 | 0.20 | 1.43 | 0.05 | orf, hypothetical protein |
| yigW | 0.18 | 4.77 | 0.48 | -0.45 | 0.03 | -1.40 | orf, hypothetical protein |
| yigZ | 4.16 | 3.30 | 0.77 | 2.95 | 1.33 | 0.00 | orf, hypothetical protein |
| yihA | 0.90 | 1.48 | 2.21 | 1.60 | 1.00 | 1.10 | orf, hypothetical protein |
| yihD | 1.31 | -1.92 | -0.19 | 2.35 | 0.03 | 1.05 | orf, hypothetical protein |
| yihE | 1.64 | -0.72 | -1.38 | 1.75 | -0.20 | -1.65 | orf, hypothetical protein |
| yihF | 1.17 | 3.28 | -1.35 | 2.35 | 2.00 | -2.15 | putative GTP-binding protein |
| yihG | -0.62 | 1.85 | -1.07 | 0.05 | 1.57 | 0.00 | putative endonuclease |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yihI | 0.11 | -1.12 | -0.89 | 0.00 | -0.43 | -1.30 | orf, hypothetical protein |
| yihK | 0.44 | 2.02 | -0.38 | 0.65 | 2.07 | -1.80 | putative GTP-binding factor |
| yihL | 0.11 | 0.83 | -1.08 | 0.60 | 1.40 | -0.15 | putative transcriptional regulator |
| yihM | 0.35 | 1.18 | -1.31 | 1.80 | 1.93 | -1.55 | orf, hypothetical protein |
| yihN | 0.98 | -1.65 | -1.32 | 2.90 | -1.17 | -0.10 | putative resistance protein (transport) |
| yihO | -0.57 | -0.94 | 0.25 | 0.30 | -0.07 | 0.25 | putative permease |
| yihP | 1.89 | -0.37 | 1.29 | 2.00 | 0.30 | 1.50 | putative permease |
| yihQ | 6.96 | -1.36 | -0.30 | 3.15 | -0.43 | -0.55 | putative glycosidase |
| yihR | 0.25 | 3.47 | -0.28 | 0.00 | 1.83 | 0.05 | putative aldose-1-epimerase (EC 5.1.3.3) |
| yihS | -0.74 | -1.28 | -0.93 | 0.60 | -0.43 | -0.20 | orf, hypothetical protein |
| yihT | -0.86 | 1.43 | -1.39 | -0.20 | 1.10 | -1.25 | putative aldolase |
| yihU | 2.05 | -1.43 | 0.41 | 2.75 | -1.43 | 0.15 | putative dehydrogenase |
| yihV | 0.21 | -1.97 | 1.32 | -0.05 | -1.33 | 0.00 | putative kinase |
| yihW | -0.09 | 0.96 | -1.25 | 0.25 | -0.03 | -1.60 | putative DEOR-type transcriptional regulator |
| yihX | 1.22 | -1.69 | -0.76 | 1.30 | -1.10 | 0.00 | putative phosphatase |
| yihZ | -0.12 | -1.67 | -0.30 | 0.30 | -1.60 | 0.05 | orf, hypothetical protein |
| yiiD | 1.56 | -0.16 | 1.06 | 1.85 | 0.27 | 1.15 | putative acetyltransferase (EC 2.3.1.18) |
| yiiE | -0.76 | 0.71 | 0.72 | 0.15 | 1.07 | 1.20 | orf, hypothetical protein |
| yiiF | -0.30 | -1.07 | 1.11 | 0.60 | -0.43 | 0.15 | orf, hypothetical protein |
| yiiG | 0.65 | 3.48 | 0.11 | 1.65 | 1.83 | 0.05 | orf, hypothetical protein |
| yiiL | -0.78 | 0.93 | -1.31 | 0.10 | 1.50 | -0.20 | orf, hypothetical protein |
| yiiM | -0.71 | 2.28 | -1.41 | -0.35 | 1.37 | -1.30 | orf, hypothetical protein |
| yiiP | 1.10 | -1.84 | 0.60 | 1.15 | -1.53 | 0.50 | putative transport system permease protein |
| yiiQ | 0.11 | 0.39 | 1.38 | 0.35 | 1.37 | 1.15 | orf, hypothetical protein |
| yiiR | 0.29 | -0.83 | 0.94 | 0.20 | 0.47 | 1.65 | orf, hypothetical protein |
| yiiS | -0.49 | -1.88 | 0.76 | -0.75 | -1.70 | 1.75 | orf, hypothetical protein |
| yiiT | -1.03 | -1.00 | 0.87 | -1.55 | -0.30 | 1.20 | putative regulator |
| yiiU | 4.51 | -4.49 | 0.44 | 1.55 | -2.33 | 0.60 | orf, hypothetical protein |
| yiiX | -0.76 | -1.12 | 1.17 | -0.15 | -1.20 | 1.35 | orf, hypothetical protein |
| yijC | 0.48 | 0.38 | 1.81 | 1.30 | 0.40 | 1.25 | orf, hypothetical protein |
| yijD | 0.28 | 0.99 | -0.35 | 1.25 | 1.13 | -0.10 | orf, hypothetical protein |
| yijE | -1.04 | 0.79 | 0.55 | -0.40 | 1.13 | 1.15 | orf, hypothetical protein |
| yijF | 0.35 | 1.20 | -0.42 | 1.95 | 1.60 | 0.10 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yijI | **0.81** | **0.00** | **-1.19** | 0.75 | 0.37 | -1.20 | orf, hypothetical protein |
| yijO | **0.43** | **-1.23** | **0.93** | 0.25 | -0.27 | 1.15 | putative ARAC-type regulatory protein |
| yijP | **0.78** | **-1.32** | **-1.28** | 1.20 | -0.33 | -1.55 | orf, hypothetical protein |
| yjaA | **0.50** | **1.35** | **-1.20** | 1.65 | 0.47 | -0.10 | orf, hypothetical protein |
| yjaB | **0.67** | **-1.28** | **1.25** | -0.25 | -0.23 | 1.20 | orf, hypothetical protein |
| yjaD | **-0.32** | **0.95** | **-0.21** | 1.15 | 1.23 | -0.15 | orf, hypothetical protein |
| yjaE | **0.08** | **-1.35** | **-0.15** | 0.30 | -0.50 | -0.25 | putative transcriptional regulator |
| yjaG | **-0.43** | **1.17** | **-1.25** | 0.00 | 1.20 | -0.20 | orf, hypothetical protein |
| yjaH | **0.95** | **3.30** | **-0.12** | 1.55 | 1.53 | 0.10 | orf, hypothetical protein |
| yjaI | **0.36** | **1.52** | **-0.62** | 1.80 | 1.73 | 0.05 | orf, hypothetical protein |
| yjbA | **0.04** | **2.68** | **1.35** | 0.55 | 1.63 | 1.55 | orf, hypothetical protein |
| yjbB | **-0.53** | **1.52** | **1.29** | 0.95 | 1.73 | 1.45 | putative alpha helix protein |
| yjbC | **0.19** | **1.15** | **0.18** | 0.15 | 1.30 | -0.05 | orf, hypothetical protein |
| yjbD | **-0.39** | **-1.47** | **-1.35** | -0.55 | -1.17 | -1.45 | orf, hypothetical protein |
| yjbE | **0.00** | **0.76** | **-1.31** | -0.20 | 1.57 | -0.15 | orf, hypothetical protein |
| yjbF | **-0.92** | **-1.22** | **-1.39** | -0.30 | -0.40 | -1.60 | orf, hypothetical protein |
| yjbG | **-0.99** | **-1.34** | **-0.81** | -0.25 | 0.03 | 0.00 | orf, hypothetical protein |
| yjbH | **0.79** | **-1.19** | **0.73** | 1.30 | -0.40 | 1.40 | orf, hypothetical protein |
| yjbI | **-0.07** | **-1.31** | **-1.30** | 0.00 | -0.33 | 0.05 | orf, hypothetical protein |
| yjbJ | **-0.85** | **-1.96** | **-1.18** | -1.80 | -1.90 | -0.25 | orf, hypothetical protein |
| yjbK | **-1.34** | **-1.51** | **1.16** | -1.65 | -0.03 | 1.20 | putative regulator |
| yjbL | **2.05** | **-0.59** | **0.95** | 2.00 | 0.30 | 1.05 | orf, hypothetical protein |
| yjbM | **0.65** | **-1.72** | **0.34** | 1.60 | -1.20 | -0.10 | orf, hypothetical protein |
| yjbN | **-0.61** | **2.71** | **0.80** | -0.70 | 1.70 | 1.15 | orf, hypothetical protein |
| yjbO | **0.52** | **0.92** | **0.19** | 0.30 | 1.83 | -0.05 | orf, hypothetical protein |
| yjbQ | **-0.41** | **-0.66** | **0.80** | -0.30 | 0.03 | 2.00 | orf, hypothetical protein |
| yjbR | **-0.74** | **-0.40** | **0.64** | -0.60 | 0.50 | 1.10 | orf, hypothetical protein |
| yjcB | **1.24** | **3.88** | **0.90** | 0.20 | 1.90 | -0.10 | orf, hypothetical protein |
| yjcC | **0.00** | **0.00** | **1.30** | -0.45 | 1.53 | 1.40 | orf, hypothetical protein |
| yjcD | **-0.26** | **2.19** | **-1.38** | 0.15 | 1.47 | -1.60 | orf, hypothetical protein |
| yjcE | **-0.03** | **-0.94** | **0.01** | 0.00 | -0.20 | 0.20 | orf, hypothetical protein |
| yjcF | **0.07** | **1.88** | **0.85** | -0.25 | -0.23 | 1.15 | orf, hypothetical protein |
| yjcG | **-0.94** | **-1.33** | **-0.23** | -0.40 | -0.70 | 0.15 | putative transport protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yjcH | **-0.62** | **0.65** | **0.75** | -0.35 | 1.13 | 1.85 | orf, hypothetical protein |
| yjcO | **-0.59** | **-3.00** | **0.79** | -1.45 | 0.07 | 1.50 | orf, hypothetical protein |
| yjcP | **0.05** | **-1.58** | **-0.49** | 0.05 | -1.60 | 0.05 | putative enzyme |
| yjcQ | **0.37** | **0.22** | **-0.19** | 2.00 | 0.50 | 0.00 | putative enzyme |
| yjcR | **0.36** | **0.67** | **0.71** | 1.35 | 0.70 | 1.30 | putative membrane protein |
| yjcS | **-0.62** | **0.86** | **0.78** | -1.20 | 1.73 | 1.40 | orf, hypothetical protein |
| yjcT | **-0.26** | **0.76** | **0.31** | 0.30 | 1.37 | 0.10 | putative NAGC-like transcriptional regulator |
| yjcU | **0.31** | **1.52** | **-1.42** | 0.60 | -0.10 | -1.35 | putative epimerase |
| yjcV | **0.08** | **-1.18** | **0.78** | 1.15 | 1.13 | 0.15 | putative transport system permease protein |
| yjcW | **0.97** | **-0.03** | **0.51** | 2.25 | 1.47 | -0.20 | putative ATP-binding component of a transport system |
| yjcX | **1.25** | **0.54** | **0.67** | 1.65 | 0.47 | 0.25 | putative LACI-type transcriptional regulator |
| yjcZ | **-0.70** | **-2.32** | **1.00** | -1.75 | -1.13 | 1.15 | orf, hypothetical protein |
| yjdA | **-1.39** | **-0.90** | **-0.44** | -2.55 | -0.13 | -1.25 | putative vimentin |
| yjdB | **0.19** | **-1.32** | **0.33** | 0.10 | 0.40 | 0.15 | orf, hypothetical protein |
| yjdC | **-0.14** | **-0.94** | **-0.89** | -0.55 | -0.10 | 0.00 | orf, hypothetical protein |
| yjdE | **0.84** | **-0.98** | **-1.38** | 1.45 | 0.03 | -1.75 | putative amino acid |
| yjdF | **-0.98** | **-2.08** | **0.66** | -0.40 | -1.10 | 0.15 | orf, hypothetical protein |
| yjdG | **-0.56** | **-1.24** | **0.48** | 0.00 | -0.20 | 1.20 | putative 2-component transcriptional regulator |
| yjdH | **-1.11** | **0.56** | **0.74** | 1.10 | 1.13 | 0.05 | putative 2-component sensor protein |
| yjdI | **-0.49** | **-1.15** | **-1.35** | 0.10 | 0.23 | -1.25 | orf, hypothetical protein |
| yjdJ | **-1.00** | **-1.20** | **0.74** | -1.40 | -0.10 | 1.30 | orf, hypothetical protein |
| yjdK | **4.11** | **-1.33** | **-0.47** | 1.35 | -0.43 | 0.15 | orf, hypothetical protein |
| yjdL | **1.35** | **-1.34** | **-0.68** | 1.60 | -0.63 | -0.40 | putative peptide transporter |
| yjeA | **0.86** | **-0.50** | **-1.62** | 1.50 | -0.10 | -1.10 | putative lysyl-tRNA synthetase |
| yjeB | **-0.17** | **-1.40** | **0.68** | -0.45 | -1.20 | 1.55 | orf, hypothetical protein |
| yjeE | **0.13** | **-4.34** | **0.83** | 0.10 | -1.40 | 1.40 | orf, hypothetical protein |
| yjeF | **0.18** | **-1.33** | **-1.03** | -0.85 | -0.17 | -1.25 | orf, hypothetical protein |
| yjeH | **-0.89** | **-2.58** | **-0.02** | -0.65 | -1.50 | 0.05 | putative transport |
| yjeI | **-0.67** | **-1.53** | **0.06** | -1.15 | -1.40 | 0.15 | orf, hypothetical protein |
| yjeJ | **-0.54** | **-2.34** | **1.28** | 1.60 | 0.17 | 1.45 | orf, hypothetical protein |
| yjeK | **0.96** | **-0.93** | **0.20** | 1.50 | -0.27 | 0.40 | orf, hypothetical protein |
| yjeM | **0.00** | **1.47** | **-2.67** | 1.10 | 1.27 | -1.20 | putative transport |
| yjeN | **-0.27** | **0.28** | **-1.35** | 1.55 | 1.20 | -0.20 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yjeO | -0.14 | 0.51 | -0.95 | 0.15 | 1.30 | -0.05 | orf, hypothetical protein |
| yjeP | -0.62 | 1.49 | 0.96 | -0.40 | 1.47 | 1.25 | putative periplasmic binding protein |
| yjeQ | 1.36 | 0.55 | -0.81 | 1.50 | 0.53 | 0.00 | orf, hypothetical protein |
| yjeR | 0.95 | 0.32 | 0.95 | 1.45 | 0.03 | 0.40 | orf, hypothetical protein |
| yjeS | 3.34 | 1.70 | 0.85 | 1.95 | 1.57 | 0.35 | orf, hypothetical protein |
| yjeT | 0.22 | -0.02 | -0.69 | 0.15 | 0.83 | -0.05 | orf, hypothetical protein |
| yjfA | 0.28 | -0.22 | -1.17 | 1.35 | 0.20 | -0.10 | orf, hypothetical protein |
| yjfC | 0.05 | -1.50 | -1.15 | 0.70 | -0.57 | -1.45 | putative synthetase |
| yjfF | 0.00 | -1.42 | 0.82 | -1.95 | -1.57 | 1.30 | putative transport system permease protein |
| yjfG | -0.43 | 1.11 | 0.38 | -1.15 | 1.47 | 0.45 | putative ligase |
| yjfH | -0.52 | -0.14 | 0.74 | -0.20 | -0.27 | 0.15 | orf, hypothetical protein |
| yjfI | -1.18 | -1.43 | 0.55 | -0.60 | -1.40 | 0.30 | orf, hypothetical protein |
| yjfJ | 0.98 | -1.84 | -1.34 | 0.60 | -1.10 | -1.45 | putative alpha helical protein |
| yjfK | -0.74 | -2.24 | -0.03 | 0.35 | -0.03 | -0.05 | orf, hypothetical protein |
| yjfL | -0.58 | -1.64 | 0.81 | 0.60 | 1.10 | 1.35 | orf, hypothetical protein |
| yjfM | 0.33 | 1.35 | -1.29 | 0.45 | 0.37 | -1.20 | orf, hypothetical protein |
| yjfN | -1.08 | 0.77 | 0.04 | -1.25 | 1.53 | 0.00 | orf, hypothetical protein |
| yjfO | -1.21 | -0.93 | -0.78 | -3.30 | 0.07 | 0.05 | orf, hypothetical protein |
| yjfP | 1.37 | -1.89 | -0.56 | 2.75 | -1.23 | -0.80 | orf, hypothetical protein |
| yjfQ | 3.28 | -1.49 | 0.88 | 1.45 | -1.47 | 2.35 | putative DEOR-type transcriptional regulator |
| yjfR | -0.04 | -1.30 | 1.45 | 1.60 | -0.43 | 1.20 | orf, hypothetical protein |
| yjfY | 0.56 | -1.34 | 0.80 | 0.05 | -1.53 | 1.25 | orf, hypothetical protein |
| yjfZ | -0.62 | -1.06 | 0.76 | 0.00 | -0.03 | 1.70 | orf, hypothetical protein |
| yjgA | 0.89 | -1.94 | -0.08 | 0.10 | -1.90 | -0.55 | putative alpha helix protein |
| yjgB | -0.73 | -1.23 | 0.73 | 0.35 | -0.40 | 1.85 | putative oxidoreductase |
| yjgD | 0.15 | 0.50 | 1.61 | 1.20 | 0.33 | 1.70 | orf, hypothetical protein |
| yjgF | -3.16 | -5.87 | -2.00 | -1.75 | -3.07 | -1.35 | orf, hypothetical protein |
| yjgG | 2.38 | -1.31 | -1.18 | 1.80 | -0.53 | -1.05 | orf, hypothetical protein |
| yjgH | -0.38 | 1.53 | -1.24 | 0.35 | 1.37 | -0.25 | orf, hypothetical protein |
| yjgI | 0.00 | -1.18 | 0.70 | -3.00 | 0.53 | -0.10 | putative oxidoreductase |
| yjgJ | 0.36 | 0.00 | 0.77 | 0.25 | 0.40 | 1.60 | orf, hypothetical protein |
| yjgK | -0.94 | -1.27 | -0.68 | -0.60 | -0.53 | -0.05 | orf, hypothetical protein |
| yjgL | -1.15 | 2.10 | 0.59 | -0.20 | 1.23 | 0.30 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yjgN | -0.92 | -1.17 | 1.06 | 0.05 | -0.37 | 0.25 | orf, hypothetical protein |
| yjgP | -0.50 | -1.24 | -1.54 | 0.15 | -0.33 | -1.10 | orf, hypothetical protein |
| yjgQ | -0.11 | -1.45 | 0.47 | -0.05 | -1.30 | 0.00 | orf, hypothetical protein |
| yjgR | 0.86 | 1.29 | 0.19 | 1.95 | 1.53 | 0.25 | orf, hypothetical protein |
| yjgW | 2.25 | 3.91 | 1.72 | 2.90 | 1.53 | 1.15 | orf, hypothetical protein |
| yjgX | 0.46 | 1.01 | 0.85 | 1.20 | 1.10 | 0.15 | orf, hypothetical protein |
| yjgY | 2.74 | -2.99 | 0.74 | 2.80 | -1.67 | -0.65 | orf, hypothetical protein |
| yjgZ | 0.57 | -1.12 | -0.29 | 2.65 | -0.20 | 0.15 | orf, hypothetical protein |
| yjhA | 0.00 | -0.40 | -0.37 | -1.75 | 0.57 | 0.05 | orf, hypothetical protein |
| yjhB | 0.02 | 1.15 | 0.76 | 0.55 | 1.33 | 0.25 | putative transport protein |
| yjhC | -2.37 | -1.66 | 0.79 | -2.00 | -1.83 | 1.20 | putative dehydrogenase |
| yjhD | 0.56 | 0.74 | 0.61 | 1.90 | 1.17 | 0.00 | orf, hypothetical protein |
| yjhE | -0.86 | -1.27 | 1.24 | 0.20 | -0.13 | 1.15 | orf, hypothetical protein |
| yjhF | -0.15 | -1.40 | 1.03 | 1.05 | -0.57 | 1.25 | putative transport system permease |
| yjhG | 0.42 | -0.36 | 0.89 | 1.25 | 0.13 | 1.30 | putative dehydratase |
| yjhH | 0.53 | -1.22 | -1.21 | -0.05 | 0.63 | -1.40 | putative lyase |
| yjhI | 0.34 | 1.35 | 0.76 | 0.25 | 1.33 | 1.55 | putative regulator |
| yjhP | -0.48 | -0.87 | -1.32 | -0.15 | 0.13 | 0.05 | putative methyltransferase |
| yjhQ | 0.81 | -1.11 | 0.00 | 0.90 | 0.40 | 0.15 | orf, hypothetical protein |
| yjhR | 0.78 | 0.76 | -0.16 | 2.25 | -0.23 | 0.10 | putative frameshift suppressor |
| yjhS | 1.81 | -1.34 | 1.52 | 2.15 | -1.43 | 1.25 | orf, hypothetical protein |
| yjhT | 0.52 | 3.41 | -1.31 | 1.25 | 1.40 | -1.05 | orf, hypothetical protein |
| yjhU | -1.11 | 0.60 | 0.97 | -0.45 | 0.83 | 1.25 | orf, hypothetical protein |
| yjiA | 0.19 | -1.74 | 0.49 | 0.30 | -1.37 | 1.10 | orf, hypothetical protein |
| yjiC | 1.88 | 1.04 | -1.40 | 1.65 | 1.17 | -1.30 | orf, hypothetical protein |
| yjiD | -1.24 | -1.48 | -0.46 | -1.40 | -0.47 | -0.25 | orf, hypothetical protein |
| yjiE | 4.57 | -1.62 | 0.12 | 1.70 | -1.43 | 0.05 | putative transcriptional regulator LYSR-type |
| yjiG | 0.53 | -1.34 | 1.24 | 0.90 | -1.50 | 1.20 | orf, hypothetical protein |
| yjiH | 0.44 | -0.25 | 0.56 | 1.35 | 0.23 | 0.20 | orf, hypothetical protein |
| yjiI | -0.55 | -1.35 | 0.27 | -0.10 | -0.57 | 0.20 | orf, hypothetical protein |
| yjiJ | -0.65 | -1.09 | -1.14 | 0.00 | 1.13 | -1.25 | putative transport protein |
| yjiK | -0.91 | -1.03 | -0.09 | -0.20 | 0.30 | -0.15 | orf, hypothetical protein |
| yjiL | -2.26 | -0.96 | -0.49 | -1.65 | -0.03 | 0.15 | putative enzyme |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yjiM | 0.94 | -1.34 | 0.79 | -0.30 | -0.23 | 1.75 | orf, hypothetical protein |
| yjiN | 0.09 | 0.19 | 0.13 | 0.35 | 0.57 | -0.20 | orf, hypothetical protein |
| yjiO | -0.91 | 0.32 | -0.18 | -0.35 | 1.30 | -0.05 | putative transport protein |
| yjiP | 0.29 | 0.00 | -0.46 | -0.15 | 0.13 | 0.20 | orf, hypothetical protein |
| yjiQ | 1.48 | -1.35 | -1.41 | 1.50 | -0.30 | -1.15 | orf, hypothetical protein |
| yjiR | -0.45 | -1.41 | 1.48 | -1.35 | -0.80 | 1.20 | putative regulator |
| yjiS | 1.15 | -3.13 | 0.27 | 0.15 | -1.20 | 0.15 | orf, hypothetical protein |
| yjiT | -0.06 | -0.97 | -1.06 | 0.05 | 1.07 | -0.15 | orf, hypothetical protein |
| yjiU | -0.16 | -1.54 | 0.22 | 0.15 | -1.13 | -0.10 | orf, hypothetical protein |
| yjiW | 0.50 | -1.58 | -0.82 | 2.60 | -1.47 | 0.05 | orf, hypothetical protein |
| yjiX | 0.27 | 0.76 | 0.76 | 0.75 | 0.27 | 1.75 | orf, hypothetical protein |
| yjiY | 0.40 | 6.38 | 0.89 | 9.10 | 1.47 | 1.25 | putative carbon starvation protein |
| yjiZ | 0.02 | -0.73 | 1.07 | -0.15 | 0.10 | 1.30 | putative transport protein, cryptic, orf, joins former yjiZ and yjjL |
| yjjA | -0.70 | -1.00 | 0.24 | 0.05 | -0.07 | -1.05 | putative glycoprotein |
| yjjB | -1.05 | 0.22 | -0.55 | -0.30 | 1.23 | 0.05 | orf, hypothetical protein |
| yjjG | -0.45 | -1.20 | -1.17 | 0.80 | 0.27 | -0.10 | putative phosphatase |
| yjjI | -0.63 | 0.57 | -1.35 | 0.10 | 1.17 | -1.55 | orf, hypothetical protein |
| yjjJ | 0.70 | 0.00 | 0.00 | 1.10 | 0.47 | 0.20 | orf, hypothetical protein |
| yjjK | -1.22 | 0.95 | 1.01 | -1.10 | 0.33 | 1.30 | putative ATP-binding component of a transport system |
| yjjM | -0.16 | 0.86 | 1.32 | 1.15 | 1.37 | 1.15 | orf, hypothetical protein |
| yjjN | 0.35 | -2.20 | -1.33 | 1.20 | -1.17 | -0.10 | putative oxidoreductase |
| yjjP | 1.78 | -1.27 | -0.73 | 1.15 | -0.43 | 0.05 | putative structural protein |
| yjjQ | -0.90 | 1.57 | -1.32 | 0.15 | 1.63 | -1.30 | putative regulator |
| yjjT | 0.28 | 1.11 | -1.33 | 1.75 | 0.00 | -1.30 | putative enzyme |
| yjjU | 1.93 | -1.23 | -1.33 | 1.70 | -0.37 | -2.00 | orf, hypothetical protein |
| yjjV | 1.16 | -1.41 | 1.64 | 1.55 | -1.40 | 1.20 | orf, hypothetical protein |
| yjjW | -1.03 | -1.97 | -0.88 | 1.80 | -1.37 | -0.05 | putative activating enzyme |
| yjjX | 0.13 | 0.50 | -0.27 | 1.15 | 1.23 | 0.15 | orf, hypothetical protein |
| yjjY | 2.23 | -1.52 | -1.35 | 1.75 | -1.10 | -1.55 | orf, hypothetical protein |
| ykfA | 0.00 | -1.05 | 0.00 | -2.30 | 0.17 | 0.10 | putative GTP-binding protein |
| ykfB | 1.32 | -1.45 | 0.76 | 2.00 | -1.00 | 1.20 | orf, hypothetical protein |
| ykfC | 0.98 | 1.05 | 0.77 | 0.50 | 0.40 | -0.15 | orf, hypothetical protein |
| ykfD | 0.35 | 0.55 | 1.40 | 0.00 | -0.47 | 1.40 | putative amino acid |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ykfE | -0.85 | -3.37 | 1.06 | -1.65 | -1.70 | 1.45 | orf, hypothetical protein |
| ykfF | 0.31 | -1.19 | -0.46 | 1.25 | -1.07 | -1.40 | orf, hypothetical protein |
| ykfG | 0.00 | 0.00 | -0.73 | -3.65 | 0.30 | -1.50 | putative DNA repair protein |
| ykgA | 1.91 | -1.47 | 0.07 | 1.75 | -1.53 | 0.05 | putative ARAC-type regulatory protein |
| ykgB | -0.67 | 1.41 | -1.24 | -0.10 | 2.00 | 0.00 | orf, hypothetical protein |
| ykgC | -1.40 | -1.43 | -0.87 | -1.75 | -0.70 | -1.20 | putative oxidoreductase |
| ykgD | -0.23 | -1.23 | 0.74 | 0.05 | -0.27 | 0.15 | putative ARAC-type regulatory protein |
| ykgE | -0.99 | -1.38 | -0.59 | -3.45 | -1.43 | -1.15 | putative dehydrogenase subunit |
| ykgF | -0.54 | 0.55 | 0.98 | -1.55 | 1.23 | 1.30 | orf, hypothetical protein |
| ykgG | 0.04 | -1.84 | -0.32 | -0.25 | -1.40 | 0.10 | putative transporter |
| ykgH | -0.40 | -1.53 | 0.42 | 0.15 | -1.00 | 0.00 | orf, hypothetical protein |
| ykgI | 0.89 | -1.38 | -1.32 | -0.15 | -1.27 | -1.15 | orf, hypothetical protein |
| ykgJ | 0.60 | 2.10 | 0.79 | -0.30 | 0.60 | -0.90 | putative ferredoxin |
| ykgK | 0.16 | 2.65 | 0.89 | 0.05 | 1.30 | 0.00 | putative regulator |
| ykgL | 1.03 | 1.75 | -0.95 | 1.35 | 1.30 | -0.10 | orf, hypothetical protein |
| ykgM | 2.35 | 1.13 | -0.05 | 2.45 | 1.17 | 0.00 | putative ribosomal protein |
| ylaB | -1.26 | 2.82 | 0.33 | -1.45 | 1.63 | 0.20 | orf, hypothetical protein |
| ylaC | -2.98 | 0.68 | 0.34 | -2.40 | 1.27 | -0.30 | orf, hypothetical protein |
| ylaD | -1.02 | -1.93 | 0.83 | -0.60 | 0.37 | 0.05 | putative transferase |
| ylbA | -3.16 | -1.36 | 0.78 | -1.20 | -1.63 | 1.25 | orf, hypothetical protein |
| ylbB | -0.96 | 0.76 | -1.33 | -0.30 | 0.33 | -4.85 | putative hydantoin utilization protein |
| ylbC | -0.56 | -1.23 | 0.76 | -0.05 | -0.23 | 1.40 | putative malate dehydrogenase (EC 1.1.1.37) |
| ylbE | -0.99 | -1.53 | -0.66 | -1.75 | -1.63 | 0.05 | orf, hypothetical protein |
| ylbF | 0.89 | -0.57 | 0.61 | -0.25 | -0.30 | 2.60 | putative carboxylase |
| ylcA | -0.97 | 0.00 | -1.33 | -2.85 | 0.43 | -1.60 | putative 2-component transcriptional regulator |
| ylcB | 0.94 | 0.71 | -1.29 | -0.30 | 0.23 | -0.05 | putative resistance protein |
| ylcC | 0.13 | -1.60 | 0.40 | 0.35 | -1.23 | 0.25 | orf, hypothetical protein |
| ylcD | 0.27 | 0.89 | 1.11 | -1.85 | 0.37 | 1.75 | putative resistance protein |
| ylcE | 1.25 | 0.48 | -1.51 | 2.30 | -1.43 | -1.30 | orf, hypothetical protein |
| yleA | 0.72 | 2.48 | 1.09 | 0.80 | 0.43 | 1.25 | orf, hypothetical protein |
| yleB | 0.09 | -1.26 | -1.35 | 1.25 | -0.70 | -1.45 | orf, hypothetical protein |
| yliG | -0.99 | -1.21 | 0.90 | -1.85 | -0.13 | 1.45 | orf, hypothetical protein |
| yliI | -0.72 | -1.43 | -1.33 | 0.00 | -0.40 | -0.20 | putative dehydrogenase |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yliJ | -0.01 | 1.90 | -0.19 | -0.55 | 1.37 | 0.15 | putative transferase |
| yljA | 0.27 | -0.71 | -0.24 | -0.35 | -0.03 | 0.05 | orf, hypothetical protein |
| ymbA | 1.20 | -1.40 | 0.41 | 1.25 | -1.73 | 0.35 | orf, hypothetical protein |
| ymcA | 0.66 | -1.40 | 0.71 | 0.15 | -1.50 | 0.00 | orf, hypothetical protein |
| ymcB | 0.76 | -0.98 | -1.48 | 0.10 | -0.33 | -0.05 | orf, hypothetical protein |
| ymcC | 0.38 | -1.41 | 0.67 | 1.85 | -0.63 | -0.20 | putative regulator |
| ymcD | 1.40 | 2.09 | 0.90 | 1.10 | 1.43 | 1.55 | orf, hypothetical protein |
| ymdC | 1.20 | -1.30 | 1.04 | 1.40 | -0.33 | 1.50 | putative synthase |
| ymdD | -0.46 | 1.17 | -1.32 | 0.45 | 1.70 | 0.30 | orf, hypothetical protein |
| ymfA | 0.51 | 1.17 | -1.27 | 0.00 | 1.57 | -0.20 | orf, hypothetical protein |
| ymfC | 0.06 | -1.29 | -0.65 | -0.30 | -1.30 | 0.10 | orf, hypothetical protein |
| ymfD | -0.83 | 1.35 | 0.06 | 1.65 | 1.47 | 0.30 | orf, hypothetical protein |
| ymfE | -0.60 | 0.76 | 0.46 | -0.10 | 1.27 | 0.40 | orf, hypothetical protein |
| ymfH | 1.06 | 2.33 | 0.06 | 8.50 | 0.53 | -0.10 | orf, hypothetical protein |
| ymfI | -0.38 | -1.17 | -1.34 | -0.35 | -0.27 | -1.75 | orf, hypothetical protein |
| ymfJ | 2.34 | 1.97 | 0.91 | 17.15 | 2.10 | 1.25 | orf, hypothetical protein |
| ymfL | 1.85 | -0.79 | 0.43 | 6.20 | -0.03 | 1.25 | orf, hypothetical protein |
| ymfM | 1.49 | -0.67 | -1.58 | 3.55 | -0.40 | -1.45 | orf, hypothetical protein |
| ymfN | 4.52 | 1.11 | 0.70 | 2.15 | 1.20 | 0.10 | orf, hypothetical protein |
| ymfO | 4.94 | -1.27 | 0.05 | 2.05 | -1.50 | 0.10 | orf, hypothetical protein |
| ymfR | 1.37 | -1.03 | 0.60 | 3.20 | -0.10 | -0.20 | orf, hypothetical protein |
| ymgA | 1.26 | -1.37 | 0.95 | 2.15 | -0.50 | 1.20 | orf, hypothetical protein |
| ymgB | 9.82 | 1.41 | -1.23 | 4.05 | 1.13 | -0.20 | orf, hypothetical protein |
| ymgC | 0.45 | -1.31 | 0.69 | 3.65 | -0.57 | 1.20 | orf, hypothetical protein |
| ymgE | -1.02 | -1.67 | -1.41 | -1.05 | -2.03 | -1.35 | orf, hypothetical protein |
| ymjA | 1.31 | 0.65 | 0.46 | 1.55 | -1.03 | -1.35 | orf, hypothetical protein |
| ynaE | -1.05 | -1.48 | -1.32 | -2.00 | -1.73 | -1.30 | orf, hypothetical protein |
| ynaF | -1.61 | -11.56 | -1.08 | -4.95 | -3.33 | -1.10 | putative filament protein |
| ynaJ | 0.12 | 0.08 | 0.48 | 0.05 | -0.10 | 1.25 | orf, hypothetical protein |
| ynbD | 1.81 | 1.37 | -1.32 | 1.35 | 1.87 | -0.20 | putative enzymes |
| ynbE | 1.12 | 1.33 | -0.18 | 0.15 | 1.17 | 0.25 | orf, hypothetical protein |
| ynbF | 0.39 | -1.25 | 0.87 | -1.40 | -0.63 | 1.55 | orf, hypothetical protein |
| yncB | -0.78 | -2.09 | 0.25 | 0.85 | -1.20 | 1.10 | putative oxidoreductase |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yneB | **0.47** | **-1.33** | **0.71** | 0.55 | 0.20 | -0.10 | orf, hypothetical protein |
| yneH | **-0.76** | **0.66** | **-0.30** | -0.20 | 1.13 | 0.15 | putative glutaminase |
| yneJ | **-1.01** | **1.46** | **-0.84** | -0.05 | 1.43 | -0.05 | putative transcriptional regulator LYSR-type |
| ynfC | **1.24** | **3.54** | **-0.20** | 1.15 | 1.57 | 0.15 | orf, hypothetical protein |
| ynfL | **1.94** | **-0.36** | **0.75** | 0.20 | 1.33 | 0.10 | putative transcriptional regulator LYSR-type |
| ynfM | **0.03** | **1.62** | **-0.37** | 0.30 | 1.33 | -0.20 | putative transport protein |
| ynhA | **0.05** | **0.00** | **0.78** | -0.40 | 1.67 | 1.70 | orf, hypothetical protein |
| ynhC | **0.00** | **-1.31** | **-0.90** | -1.70 | 0.30 | 0.00 | orf, hypothetical protein |
| ynhD | **-0.96** | **0.12** | **0.70** | -1.45 | -1.13 | 0.10 | putative ATP-binding component of a transport system |
| ynhE | **-0.05** | **0.00** | **-1.21** | -1.95 | 1.27 | -0.20 | orf, hypothetical protein |
| ynhG | **-0.78** | **-1.45** | **-1.31** | -0.30 | -2.20 | -1.55 | orf, hypothetical protein |
| yniC | **0.21** | **-1.04** | **0.51** | -0.35 | 1.30 | 0.30 | putative phosphatase |
| ynjA | **0.00** | **-1.42** | **-1.34** | -2.40 | -1.37 | -1.45 | orf, hypothetical protein |
| yoaE | **-1.62** | **0.12** | **-1.12** | -1.90 | 0.27 | -1.10 | putative transport protein |
| yoaF | **0.06** | **-1.01** | **1.24** | -1.55 | 0.13 | 1.20 | orf, hypothetical protein |
| yoaG | **-1.05** | **-1.88** | **0.81** | -0.45 | -1.10 | 1.65 | orf, hypothetical protein |
| yodB | **0.10** | **-0.10** | **-1.26** | 0.50 | 0.60 | -0.30 | putative cytochrome |
| yohC | **1.27** | **0.47** | **-0.44** | 1.40 | 0.43 | 0.10 | orf, hypothetical protein |
| yohD | **-0.61** | **-2.27** | **-1.58** | -0.65 | -1.27 | -1.30 | orf, hypothetical protein |
| yohF | **1.91** | **-0.90** | **0.41** | 1.40 | 0.03 | -0.30 | putative oxidoreductase |
| yohG | **0.37** | **-1.31** | **-1.33** | 0.85 | -0.40 | -1.65 | putative channel |
| yohH | **0.00** | **0.18** | **1.46** | -1.40 | 0.37 | 1.50 | orf, hypothetical protein |
| yohI | **-1.45** | **-0.99** | **1.67** | -1.50 | -0.57 | 1.30 | putative regulator protein |
| yohJ | **-1.65** | **-1.45** | **-0.87** | -2.25 | -0.17 | -0.05 | orf, hypothetical protein |
| yohK | **-2.83** | **-1.62** | **-1.34** | -1.40 | -0.40 | 0.00 | putative seritonin transporter |
| yohL | **0.00** | **-1.34** | **-0.08** | -2.10 | -1.70 | 0.10 | orf, hypothetical protein |
| yohM | **0.40** | **-1.17** | **-0.96** | 2.20 | -0.17 | -1.15 | orf, hypothetical protein |
| yojH | **0.14** | **0.76** | **-1.36** | -0.70 | -0.40 | -1.55 | orf, hypothetical protein |
| yojI | **-0.97** | **-1.33** | **-1.32** | -1.75 | -0.67 | 0.05 | putative ATP-binding component of a transport system |
| yojL | **0.06** | **-1.33** | **-1.32** | -0.35 | -1.37 | -1.35 | orf, hypothetical protein |
| yojN | **-0.47** | **-1.10** | **0.31** | -1.30 | -1.80 | -0.10 | putative 2-component sensor protein |
| ypfH | **0.05** | **1.76** | **0.74** | 0.00 | 1.30 | 1.25 | orf, hypothetical protein |
| ypfI | **-0.74** | **-1.35** | **-1.32** | 0.05 | 0.33 | -1.80 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yphA | 0.74 | -1.40 | 1.37 | 1.35 | -0.37 | 1.30 | orf, hypothetical protein |
| yphB | 0.86 | 0.69 | 2.34 | 2.90 | 0.43 | 1.30 | orf, hypothetical protein |
| yphC | 0.25 | -0.46 | -0.88 | -0.25 | 0.43 | 0.00 | putative oxidoreductase |
| yphD | -0.31 | -0.04 | -0.20 | 0.40 | 0.40 | 0.20 | putative transport system permease protein |
| yphE | 0.12 | 0.69 | 0.89 | 0.05 | 0.57 | 1.75 | putative ATP-binding component of a transport system |
| yphF | 0.39 | 0.19 | 0.81 | 0.25 | -0.20 | 1.30 | putative LACI-type transcriptional regulator |
| yphG | 0.44 | 1.99 | 1.24 | 1.80 | 1.83 | 1.40 | orf, hypothetical protein |
| yphH | -1.38 | -0.33 | -0.55 | -0.80 | 1.10 | 0.15 | putative NAGC-like transcriptional regulator |
| ypjA | 0.66 | 0.00 | -0.69 | -0.40 | 0.30 | -1.05 | putative ATP-binding component of a transport system |
| ypjE | -0.50 | -1.32 | -1.27 | 0.05 | -0.57 | -0.10 | orf, hypothetical protein |
| ypjF | 0.69 | 0.51 | 1.50 | 0.60 | 1.27 | 1.15 | orf, hypothetical protein |
| yqaB | 0.06 | -1.41 | -1.13 | 1.15 | -1.70 | -1.20 | putative phosphatase |
| yqcB | -0.28 | -1.63 | -0.16 | 0.05 | -1.07 | 0.05 | orf, hypothetical protein |
| yqcD | 0.06 | 2.89 | -1.33 | 1.15 | 1.37 | -0.15 | orf, hypothetical protein |
| yqcE | -0.33 | 0.43 | -1.48 | 0.40 | 1.30 | -1.15 | putative transport protein |
| yqeA | 0.29 | 1.38 | -1.33 | 0.10 | 2.20 | -0.05 | putative kinase |
| yqeF | 0.18 | -1.40 | 0.71 | 0.80 | -0.63 | -0.10 | putative acyltransferase |
| yqeH | -1.16 | -1.52 | -1.21 | -0.20 | -1.10 | -0.20 | orf, hypothetical protein |
| yqeI | -0.91 | 1.48 | -1.05 | -0.30 | 1.27 | -0.05 | putative sensory transducer |
| yqeJ | 0.89 | 0.76 | -1.23 | -0.05 | 1.37 | -1.55 | orf, hypothetical protein |
| yqeK | 0.20 | -0.08 | -1.33 | 1.10 | 0.63 | -1.15 | orf, hypothetical protein |
| yqfB | -0.04 | -1.32 | -1.33 | 0.00 | -0.37 | -1.35 | orf, hypothetical protein |
| yqfE | 2.17 | -1.32 | 0.73 | 1.80 | -0.10 | 1.40 | orf, hypothetical protein |
| yqgA | -0.33 | -1.34 | -1.18 | 1.15 | -1.53 | -0.05 | putative transport protein |
| yqgB | 0.64 | 1.13 | 0.97 | 1.25 | 0.67 | -0.10 | orf, hypothetical protein |
| yqgC | -0.34 | 1.55 | -1.50 | -1.35 | 1.53 | -1.20 | orf, hypothetical protein |
| yqgD | 1.40 | 1.67 | -0.49 | 1.40 | 1.23 | -1.20 | orf, hypothetical protein |
| yqgE | -0.03 | 6.09 | -1.35 | 0.40 | 1.23 | -1.30 | orf, hypothetical protein |
| yqgF | 0.64 | -2.16 | -0.80 | 1.25 | -1.60 | -0.15 | orf, hypothetical protein |
| yqhA | -0.37 | 1.84 | 0.85 | -0.60 | 1.50 | 1.70 | orf, hypothetical protein |
| yqhC | 0.92 | -1.20 | 0.83 | 2.30 | -0.30 | 1.10 | putative ARAC-type regulatory protein |
| yqhD | 0.56 | 1.19 | 0.74 | 1.90 | 1.87 | 1.35 | putative oxidoreductase |
| yqhE | -0.75 | -0.60 | 0.77 | -0.35 | 1.13 | 0.15 | orf, hypothetical protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yqhG | 0.15 | 0.12 | -1.41 | 0.10 | -0.10 | -1.55 | orf, hypothetical protein |
| yqhH | 1.99 | -0.47 | -0.17 | 1.70 | 0.40 | -0.10 | orf, hypothetical protein |
| yqiA | 2.81 | -0.57 | -1.40 | 1.50 | 0.10 | -1.40 | orf, hypothetical protein |
| yqiB | 0.73 | -1.37 | -1.24 | -0.10 | -1.47 | -0.20 | putative enzyme |
| yqiE | -0.28 | -1.10 | 0.86 | 0.00 | -0.43 | -0.50 | orf, hypothetical protein |
| yqiG | 1.46 | -1.26 | 0.57 | 0.20 | -0.23 | 0.10 | putative membrane protein |
| yqiH | -0.76 | -1.26 | 0.86 | 0.00 | -0.20 | 1.20 | putative membrane protein |
| yqiI | 1.04 | 0.85 | 0.89 | 1.50 | 1.37 | 0.00 | orf, hypothetical protein |
| yqjA | -1.34 | -1.29 | 0.39 | -1.25 | -1.57 | 1.25 | orf, hypothetical protein |
| yqjB | 3.76 | -1.21 | 0.85 | 1.90 | -0.47 | 1.05 | orf, hypothetical protein |
| yqjC | 0.02 | -1.79 | -1.20 | -0.40 | -1.47 | -0.15 | orf, hypothetical protein |
| yqjD | -0.94 | -1.27 | -1.20 | -5.55 | -1.70 | -1.25 | orf, hypothetical protein |
| yqjE | -0.93 | -3.85 | -1.44 | -3.10 | -1.93 | -1.35 | orf, hypothetical protein |
| yqjF | 0.60 | -0.15 | 0.28 | 0.35 | 0.67 | 1.10 | orf, hypothetical protein |
| yqjG | 0.18 | 1.47 | 0.18 | -1.15 | 1.53 | 0.25 | putative transferase |
| yqjH | 2.05 | -1.45 | 1.43 | 2.00 | -0.60 | 1.35 | orf, hypothetical protein |
| yqjI | -0.01 | 1.25 | 1.06 | -0.10 | 0.67 | 1.25 | orf, hypothetical protein |
| yraH | 0.69 | 2.58 | -2.91 | 1.70 | 1.20 | -1.35 | putative fimbrial-like protein |
| yraI | 0.44 | 1.29 | 0.81 | 2.15 | 1.37 | 1.40 | putative chaperone |
| yraJ | 1.44 | -1.28 | 1.09 | 1.55 | -0.27 | 1.30 | putative outer membrane protein |
| yraK | 0.47 | 0.00 | -1.09 | 0.25 | -0.27 | -1.25 | putative fimbrial protein |
| yraL | -1.21 | 0.78 | -1.38 | -0.40 | -0.17 | -1.20 | orf, hypothetical protein |
| yraM | 0.00 | -1.56 | 0.75 | -2.50 | -2.50 | -0.20 | putative glycosylase |
| yraN | 0.36 | 0.19 | -0.24 | 1.20 | 0.43 | 0.00 | orf, hypothetical protein |
| yraO | 0.79 | -0.08 | 0.14 | -0.10 | 0.27 | 1.05 | orf, hypothetical protein |
| yraP | 0.09 | -1.34 | 0.74 | -0.75 | -0.67 | 1.45 | putative periplasmic protein |
| yraQ | 0.25 | -1.42 | 0.73 | -0.40 | -2.00 | -0.15 | orf, hypothetical protein |
| yraR | 0.66 | 0.53 | -1.25 | 1.50 | 0.73 | -1.40 | orf, hypothetical protein |
| yrbA | 2.85 | 0.79 | 1.00 | 1.55 | -0.03 | 1.35 | orf, hypothetical protein |
| yrbB | 1.69 | 5.72 | -0.95 | 1.50 | 2.10 | -1.10 | orf, hypothetical protein |
| yrbC | -0.02 | 2.43 | 0.56 | 1.15 | 1.23 | 0.40 | orf, hypothetical protein |
| yrbD | 1.57 | 3.15 | 0.82 | 1.55 | 1.77 | -0.20 | orf, hypothetical protein |
| yrbE | 1.20 | -0.70 | 0.81 | 1.40 | -0.10 | 1.65 | orf, hypothetical protein |

| GENE | FC | | | d(i) | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| yrbF | 4.80 | 2.13 | -1.14 | 1.45 | 1.43 | -0.15 | putative ATP-binding component of a transport system |
| yrbG | 0.22 | -1.30 | 0.38 | 0.20 | -1.10 | 1.30 | orf, hypothetical protein |
| yrbH | 1.76 | 0.31 | -1.27 | -0.10 | 0.53 | -1.25 | putative isomerase |
| yrbI | -0.55 | 0.29 | 0.85 | -0.45 | 1.23 | 1.30 | orf, hypothetical protein |
| yrbK | -0.39 | -0.83 | 0.75 | -0.50 | -0.17 | 0.10 | orf, hypothetical protein |
| yrbL | -1.47 | -2.28 | 0.76 | -2.50 | -1.93 | 1.40 | orf, hypothetical protein |
| yrdA | -0.11 | 0.24 | -0.92 | -0.20 | -1.20 | -1.15 | putative transferase |
| yrdB | -0.05 | -1.30 | 1.44 | 0.10 | -1.33 | 1.10 | orf, hypothetical protein |
| yrdC | 0.12 | 1.32 | 1.23 | 0.40 | -0.20 | 1.50 | orf, hypothetical protein |
| yrdD | 0.42 | -1.71 | -0.11 | 0.10 | -1.67 | -0.15 | putative DNA topoisomerase |
| yrfA | -0.07 | 1.12 | -1.28 | 1.25 | 1.23 | 0.10 | orf, hypothetical protein |
| yrfB | 1.14 | 1.76 | 1.11 | 2.85 | -0.27 | 1.25 | orf, hypothetical protein |
| yrfC | -0.04 | -1.01 | 0.38 | 0.35 | -0.07 | -0.05 | orf, hypothetical protein |
| yrfD | -0.19 | -1.34 | -1.33 | 1.35 | -0.70 | -0.05 | orf, hypothetical protein |
| yrfE | -0.16 | 2.22 | 0.75 | -0.05 | 1.33 | 1.15 | orf, hypothetical protein |
| yrfF | 0.27 | -1.30 | 0.29 | 0.45 | -1.17 | 0.10 | putative dehydrogenase |
| yrfG | 1.75 | 1.26 | 0.55 | 1.90 | 0.30 | -0.30 | putative phosphatase |
| yrfH | 0.38 | 0.22 | -1.33 | 1.40 | -0.20 | -1.60 | orf, hypothetical protein |
| yrfI | 0.55 | -1.22 | 0.92 | 1.55 | -0.57 | -0.10 | orf, hypothetical protein |
| yrhA | 0.72 | -0.83 | 0.81 | 1.75 | 0.20 | 1.20 | orf, hypothetical protein |
| yrhB | 0.69 | -1.43 | -0.09 | 1.75 | -0.43 | 0.20 | orf, hypothetical protein |
| ysgA | -0.21 | 0.85 | 0.34 | 1.25 | -0.33 | 0.05 | putative enzyme |
| yshA | 0.00 | 0.75 | 0.73 | -0.20 | 1.43 | 1.30 | orf, hypothetical protein |
| ytfA | 0.19 | -1.22 | -1.25 | -0.25 | -0.20 | -1.15 | orf, hypothetical protein |
| ytfB | -0.18 | -1.05 | 0.63 | 0.10 | -0.17 | -0.10 | orf, hypothetical protein |
| ytfE | 0.88 | -1.73 | -0.25 | 2.60 | -1.37 | 0.15 | orf, hypothetical protein |
| ytfF | 0.19 | -0.87 | -0.39 | 0.55 | 1.17 | 0.10 | putative transmembrane subunit |
| ytfG | 1.33 | -0.40 | 0.84 | 1.20 | 0.10 | 1.05 | putative oxidoreductase |
| ytfH | 0.58 | -2.29 | 0.41 | 1.20 | -0.37 | 0.15 | orf, hypothetical protein |
| ytfI | 1.39 | -1.56 | -1.47 | 1.60 | -1.63 | -0.15 | orf, hypothetical protein |
| ytfJ | -0.65 | -1.10 | -1.42 | -1.25 | -0.40 | -1.55 | orf, hypothetical protein |
| ytfK | -0.44 | -4.47 | -1.03 | -1.65 | -1.97 | -0.15 | orf, hypothetical protein |
| ytfL | 0.11 | 2.73 | 0.28 | 0.10 | 1.50 | 0.25 | putative transport protein |

| GENE | FC | | | *d(i)* | | | Possible function |
|---|---|---|---|---|---|---|---|
| | wt | dam | dammutS | wt | dam | dammutS | |
| ytfM | **1.85** | **0.88** | **-0.19** | 1.75 | 0.37 | -1.20 | orf, hypothetical protein |
| ytfN | **-0.02** | **-1.55** | **-1.02** | -2.35 | -3.23 | 0.00 | orf, hypothetical protein |
| ytfP | **0.28** | **-1.58** | **-1.49** | 0.25 | -1.60 | -1.25 | orf, hypothetical protein |
| ytfQ | **-1.24** | **1.29** | **0.76** | -2.25 | 1.53 | -1.45 | putative LACI-type transcriptional regulator |
| ytfR | **-0.32** | **0.70** | **-0.52** | 0.50 | 0.47 | -1.60 | putative ATP-binding component of a transport system |
| ytfS | **0.00** | **-1.34** | **0.77** | -1.05 | -0.13 | 1.15 | putative ATP-binding component of a transport system |
| ytfT | **0.58** | **0.23** | **-0.04** | 1.90 | 1.20 | 0.25 | putative transport system permease protein |
| yzgL | **0.07** | **1.39** | **-0.15** | 0.30 | 1.63 | 0.05 | orf, hypothetical protein |
| zipA | **-0.97** | **-1.42** | **0.54** | -0.95 | -1.57 | -0.15 | cell division protein involved in FtsZ ring |
| zntA | **0.74** | **0.19** | **1.36** | 0.35 | 0.30 | 1.75 | zinc-transporting ATPase |
| zwf | **0.13** | **-1.13** | **-0.51** | 0.05 | -1.40 | 0.00 | glucose-6-phosphate dehydrogenase |