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Regulation and dysregulation of chromosome structure in cancer

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Summary

Cancer arises from genetic alterations that produce dysregulated gene expression programs. Normal gene regulation occurs in the context of chromosome loop structures called insulated neighborhoods, and recent studies have shown that these structures are altered and can contribute to oncogene dysregulation in various cancer cells. We review here the types of genetic and epigenetic alterations that influence neighborhood structures and contribute to gene dysregulation in cancer, present models for insulated neighborhoods associated with the most prominent human oncogenes, and discuss how such models may lead to further advances in cancer diagnosis and therapy.

Introduction

The idea that structural alterations of chromosomes may cause disease is nearly as old as the chromosome theory of inheritance (Boveri, 1914). The first discovery of a chromosomal translocation, the Philadelphia chromosome, in the blood cells of a leukemia patient (Nowell and Hungerford, 1960), stimulated further study of the potential roles of chromosome structural alterations in the neoplastic state of cancer cells. Such studies revealed that structural alterations of chromosomes often contribute to dysregulation of cellular gene expression programs in cancer cells (Rabbitts, 1994; Vogelstein and Kinzler, 2004). More recently, chromosome conformation capture technologies, which detect DNA interactions genome-wide, have led to important new insights into the roles that chromosome structures play in normal gene control and have revealed how various alterations in chromosome structure contribute to gene dysregulation in disease (Bickmore and van Steensel, 2013; Bonev and Cavalli, 2016; Corces and Corces, 2016; de Laat and Duboule, 2013; Dixon et al., 2016; Gibcus and Dekker, 2013; Gorkin et al., 2014; Groschel et al., 2014; Hnisz et al., 2016a; Krijger and de Laat, 2016: Lupianez et al., 2015: Merkenschlager and Nora, 2016: Ong and Corces. 2014; Phillips-Cremins and Corces, 2013; Valton and Dekker, 2016).

Recent studies have revealed that interphase chromosomes are organized into thousands of DNA loops, which are anchored, in part, through the interactions of CTCF proteins that bind to two separate sites in DNA and also bind one another, and these CTCF-CTCF interactions are reinforced by the cohesin complex. These loops generally contain one or more genes together with the regulatory elements that operate on the genes. The loop anchors constrain the regulatory elements to act predominantly on genes within the loop. In this manner, the anchors insulate genes and their regulatory elements from other regulatory elements located outside the neighborhood, and thus the CTCF-CTCF anchored loop structures have been called "insulated neighborhoods".

Here we review recent evidence that genetic and epigenetic alterations can disrupt insulated neighborhoods in cancer cells and thereby contribute to the transformed phenotype. We present models for insulated neighborhoods associated with prominent human oncogenes, and identify neighborhoods that are altered based on cancer genome sequence data. Finally, we discuss how knowledge of insulated neighborhoods may lead to further advances in cancer diagnosis and therapy.

Chromosome structures

Interphase chromosomes are organized in a hierarchy of structures, and these can play important roles in transcriptional regulation (Figure 1). Detailed descriptions of the

various layers of genome organization and the history of this field can be found in other excellent reviews (Bickmore and van Steensel, 2013; Cavalli and Misteli, 2013; de Laat and Duboule, 2013; Dekker and Heard, 2015; Dixon et al., 2016; Gibcus and Dekker, 2013; Gorkin et al., 2014; Merkenschlager and Nora, 2016). We provide here a brief description of the layers of chromosome structural organization as background to the recent concept that chromosome loops are a structural and functional unit of gene control in mammalian cells.

Chromosomes in interphase nuclei tend not intermingle, but occupy distinct regions within the nuclear space (Figure 1). In situ hybridization and microscopy techniques revealed that these "chromosome territories" are a general feature in mammalian nuclei and that the territorial organization of chromosomes is maintained through cell division, although the positions of chromosome territories can be reshuffled (Cremer and Cremer, 2010). At present, the mechanisms that maintain chromosome territories are unknown.

Chromosome conformation capture technologies initially revealed that interphase chromosomes are partitioned into megabase sized folding entities that were termed "topologically associating domains" (TADs) (Figure 1) (Dixon et al., 2012; Nora et al., 2012). TADs are regions of DNA that show high frequency interactions relative to regions outside the TAD boundaries. Early studies reported about 2,000 TADs, which tend to have similar boundaries in all human cell types and contain on average 8 genes whose expression is weakly correlated (Dixon et al., 2015; Dixon et al., 2012). TADs were postulated to help constrain interactions between genes and their regulatory sequences (Dixon et al., 2012). The initial studies produced data at approximately 40kb resolution, which was not sufficient to determine the mechanistic basis of TAD formation and maintenance, although an abundance of CTCF bound sites was noted at TAD boundaries (Dixon et al., 2012).

Insights into the relationship between chromosome structure and gene regulation have emerged from studies that focused on the roles of chromosome-structuring proteins in DNA interactions, and used chromatin contact mapping technologies that provided a high resolution view of DNA contacts associated with those proteins (Figure 1) (DeMare et al., 2013; Dowen et al., 2014; Handoko et al., 2011; Ji et al., 2016; Phillips-Cremins et al., 2013; Splinter et al., 2006; Tang et al., 2015; Tolhuis et al., 2002). These studies showed that chromosomes are organized into thousands of DNA loops, formed by the interaction of DNA sites bound by the CTCF protein and occupied by the cohesin complex. The anchors of these CTCF-CTCF loops function to insulate enhancers and genes within the loop from enhancers and genes outside the loop. These CTCF-CTCF loops have thus been called insulated neighborhoods, but they have also been called sub-TADs, loop domains, and CTCF-contact domains (Dowen et al., 2014; Phillips-Cremins et al., 2013; Rao et al., 2014; Tang et al., 2015). For the purposes of this review, we will use the term "insulated neighborhoods" to describe these loops.

The Insulated Neighborhood model

Insulated neighborhoods are formed by an interaction between two DNA sites bound by the transcription factor CTCF and the cohesin complex (Figure 1) (Hnisz et al., 2016a). In human embryonic stem cells (ESCs), there are at least 13,000 insulated neighborhoods, which range from 25 kb to 940 kb in size and contain from 1–10 genes (Ji et al., 2016). The median insulated neighborhood is ~190kb and contains three genes. These numbers can vary depending on assumptions made when filtering

genomic data, but provide an initial description of genomic loops that is useful for further analysis.

Several lines of evidence argue that the CTCF-bound anchor sites of insulated neighborhoods insulate genes and regulatory elements within a neighborhood from those outside the neighborhood. Genome-wide analysis indicates that the majority (>90%) of enhancer-gene interactions occur within insulated neighborhoods (Dowen et al., 2014; Hnisz et al., 2016b; Ji et al., 2016). Perturbation of insulated neighborhood anchor sequences leads to changes in gene expression in the vicinity of the altered neighborhood boundary (Dowen et al., 2014; Ji et al., 2016; Narendra et al., 2015; Sanborn et al., 2015). Insulated neighborhood boundary elements are coincident with the endpoints of chromatin marks that spread over regions of transcriptional activity or repression (Dowen et al., 2014). These lines of evidence indicate that the insulating function of the neighborhood loop anchors contributes to normal gene regulation.

Insulated neighborhoods, and the CTCF-CTCF loops that form them, are largely maintained during development, and the subset of CTCF sites that form neighborhood loop anchors show little genetic variation in the germ-line (Hnisz et al., 2016a). However, allele-specific CTCF binding contributes to the formation of allele-specific insulated neighborhoods at imprinted genes (Hnisz et al., 2016a), and cell type-specific CTCF binding and neighborhoods appear to make some contribution to cell-specific transcriptional programs (Bunting et al., 2016; Narendra et al., 2015; Splinter et al., 2006; Tolhuis et al., 2002; Wang et al., 2012).

Although the descriptions of CTCF-CTCF loops and TADs to this point may imply to the reader that these are static structures, several lines of evidence suggest that they are dynamic. Both CTCF and cohesin dynamically interact with DNA, and as described below, their binding is influenced by a variety of different factors and post-translational modifications. Modeling studies suggest that chromatin contact mapping data represent an assembly of configurations that can differ between individual cells in the cell population, between time points within the same cell, and between alleles of a locus within the same cell (Figure 2) (Fudenberg et al., 2016; Giorgetti et al., 2014; Imakaev et al., 2012; Naumova et al., 2013). Consequently, the loop models displayed in this review and in other reports represent the predominant configurations deduced from cell population data or, in some cases, a combination of configurations that are inferred from the data.

Insulated neighborhoods cover the majority of the genome, and thus genes that play prominent rules in cancer biology are typically found within insulated neighborhoods. These genes include, but are not limited to, *KRAS*, *NRAS*, and *BRAF*, which are members of the RAS and RAF pathway (Figure 3A-C) (Bos, 1989; Downward, 2003); *MYC*, the most frequently overexpressed and amplified human oncogene (Figure 3D) (Beroukhim et al., 2010); *TP53*, which encodes the P53 protein and is the most frequently mutated gene in all cancers (Figure 3E) (Lawrence et al., 2014); EGFR , which encodes the epidermal growth factor receptor, a major drug target (Figure 3F) (Lynch et al., 2004); CD274, or Programmed death-ligand 1 (PD-L1), and the gene encoding its receptor PDCD1, which are immune checkpoint targets for cancer immunotherapy (Figure 3G-H) (Hamid et al., 2013; Pardoll, 2012). More detailed information on the structures of these loci is provided in Supplementary Figure 1. These models rely on data from a cell line, but provide the reader with one view of the structural features of these loci and a potential foundation for further exploration of these structures in primary cells of various cancer types.

Regulators of Insulated Neighborhood structure

The proteins that are best understood to contribute to insulated neighborhood anchor structures are CTCF and cohesin, as discussed in more detail below. There are additional factors that have been implicated in establishing, maintaining or modifying insulated neighborhood anchor structures (Figure 4). These include Structural Maintenance of Chromosomes (SMC) proteins such as condensin II, the CTCF-like protein BORIS, Poly (ADP-Ribose) polymerase (PARP), DNA methylation, noncoding RNA species, and the process of transcription by RNA Polymerase II.

CTCF

CTCF is a Zinc-finger transcription factor that was originally identified as a repressor of the c-MYC oncogene (Baniahmad et al., 1990; Lobanenkov et al., 1990). CTCF is conserved in eukaryotes from *Drosophila* to *Homo sapiens*, is essential for embryonic development in mammals, and is ubiquitously expressed in all cells (Ghirlando and Felsenfeld, 2016). CTCF has long been described as a component of insulators, which are DNA elements that can block the ability of enhancers to activate genes when placed between them (Bell et al., 1999). Several recent reviews provide more detailed information and historical perspective on CTCF (Ghirlando and Felsenfeld, 2016; Merkenschlager and Odom, 2013; Ong and Corces, 2014; Phillips and Corces, 2009).

Several lines of evidence suggest that CTCF contributes to the formation and maintenance of chromosome structures such as TADs and the insulated neighborhoods that comprise TADs. The majority of the boundary regions of topologically associating domains (TADs) are bound by CTCF (Dixon et al., 2015; Dixon et al., 2012; Nora et al., 2012), and global depletion of CTCF perturbs the insulating properties of TADs (Zuin et al., 2014). The CTCF protein is able to form homodimers and thus physical interactions between two CTCF molecules bound at two genomic locations can participate in the formation of DNA loops (Hou et al., 2008; Palstra et al., 2003; Splinter et al., 2006; Yusufzai et al., 2004).

Chromatin immunoprecipitation and sequencing (ChIP-Seq) experiments indicate that approximately 50,000-80,000 sites are bound by CTCF in mammalian genomes (Kim et al., 2007). However, functional assays of insulator function found that only a minority of these sites act as insulators (Liu et al., 2015) or participate in formation of insulated neighborhood boundaries (Ji et al., 2016). It is possible that two CTCF sites need to be in a specific orientation in order for the CTCF proteins to interact and have insulating function (Dekker and Mirny, 2016; Fudenberg et al., 2016; Sanborn et al., 2015).

The ability of CTCF to bind its DNA sequence motif and participate in insulator function is influenced by DNA methylation and protein modification (Figure 4A). CTCF binds to hypomethylated regions of the genome (Mukhopadhyay et al., 2004) and mechanistic studies of the H19/IGF2A imprinted locus revealed that methylation of DNA is sufficient to prevent CTCF binding to the methylated allele (Bell and Felsenfeld, 2000; Hark et al., 2000; Kanduri et al., 2000; Szabo et al., 2000). CTCF can be poly(ADP-ribosyl)ated (PARylated), and at the imprinted *H19/IGF2A* locus, PARylation of CTCF regulates its insulator function (Figure 4A), which is associated with its ability to form DNA loops at the locus (Yu et al., 2004). Studies in *Drosophila* have identified additional proteins that interact with CTCF, including DNA helicases, nucleophosmin and topoisomerase (Phillips-Cremins and Corces, 2013), but whether such proteins associate with CTCF in human cells and modulate its function remains to be investigated.

Transcription by RNA polymerase II has been reported to evict CTCF from specific sites (Lefevre et al., 2008) and various RNA species can enhance or reduce CTCF binding at specific loci. The Tsix, Xite, and Xist RNAs produced during X chromosome inactivation can recruit CTCF to the X-inactivation center (Kung et al., 2015), whereas the Jpx RNA evicts CTCF from the Xist promoter (Sun et al., 2013)(Figure 4A). An antisense transcript (*Wrap53*) produced at the *TP53* locus was found to contribute to CTCF binding (Saldana-Meyer et al., 2014) (Figure 4A).

The CTCF gene has an ortholog in mammals called CTCFL or BORIS, which may also participate in DNA loops. While CTCF is ubiquitously expressed in all cell types, the expression of BORIS is thought to be restricted to male germ cells (Loukinov et al., 2002). BORIS appears to bind the same DNA sequence as CTCF and its expression is mutually exclusive with CTCF during germ cell development (Loukinov et al., 2002).

Cohesin

Cohesin is a multiprotein complex that belongs to the family of Structural Maintenance of Chromosome (SMC) family of proteins (Figure 4B), whose members are conserved both in prokaryotes and eukaryotes (Nasmyth and Haering, 2009). Cohesin consists of a tripartite ring of three subunits - SMC1, SMC3 and RAD21 - which in human cells is bound by accessory factors that include STAG1 or STAG2. Cohesin was initially studied for its role in sister chromatid cohesion, and later found to play important roles in gene regulation (Dorsett and Merkenschlager, 2013; Hirano, 2006; Merkenschlager and Odom, 2013; Nasmyth and Haering, 2009; Uhlmann, 2016).

Cohesin forms a ring whose internal dimensions are sufficient to entrap two DNA molecules, which provides a model to explain how it contributes to DNA loops, but it is also possible that two connected cohesin rings function in DNA loop formation (Nasmyth and Haering, 2009). Cohesin is loaded onto DNA by the SMC-loading factor NIPBL (Figure 4C), which is associated with the Mediator cofactor, which mediates interactions between enhancers and promoters at active genes (Kagey et al., 2010). Disruption of cohesin perturbs enhancer-promoter interactions and gene expression (Kagey et al., 2010; Seitan et al., 2011; Zuin et al., 2014).

Cohesin is also associated with CTCF-bound sites and contributes to insulation when two CTCF-bound sites interact to form the anchors of a DNA loop (Parelho et al., 2008; Rubio et al., 2008; Wendt et al., 2008). The SMC-loading factor NIPBL is not found at CTCF sites, so it is possible that cohesin is loaded at transcriptionally active sites and then migrates to CTCF bound sites, where further movement is inhibited. The STAG1/2 subunits of cohesin can engage in direct physical interaction with CTCF (Xiao et al., 2011), which may contribute to stable CTCF-cohesin association. DNA loop extrusion models have been proposed to account for the formation of DNA loops; these models posit that where cohesin rings) would drive cohesin migration to two CTCF-bound sites where, if the sites were properly oriented for CTCF-CTCF interaction, the DNA loop would be anchored (Dekker and Mirny, 2016; Fudenberg et al., 2016; Sanborn et al., 2015).

The regulation of cohesin has been studied primarily in the context of its role in sister chromatid cohesion, but these regulatory features may also contribute to cohesin regulation in enhancer-promoter and CTCF-CTCF interactions. For example, the SMC3 subunit of cohesin can be acetylated by the ESCO family of acetyltransferases and deacetylated by HDAC8, and the acetylation is important for normal retention of cohesin on DNA and sister chromatid cohesion (Figure 4C) (Deardorff et al., 2012). Furthermore,

cohesin is removed from chromatin in the mitotic prophase by the unloading factor Wapl, and depletion of Wapl leads to gross chromosome organization defects in interphase nuclei (Tedeschi et al., 2013).

Additional SMC complexes have been implicated in the control of chromosome organization. Vertebrate cells have two condensin complexes (Figure 4B). Although condensin I is excluded from interphase nuclei, condensin II is loaded, like cohesin, onto interphase chromatin by Nipbl at active enhancer-promoter interactions (Dowen et al., 2013). The contributions of condensin II to gene regulation, DNA looping, and larger chromosome structures are not yet understood.

Mutations in structuring components and neighborhood boundaries in cancer

Translocations of large portions of chromosome arms have been described for decades in tumor cells, but only recently were mutations in chromosome structure regulators and their binding sites described and appreciated for their potential impact on specific chromosome structures. In this section we describe the spectrum of mutations that have been described that impact neighborhood regulators and neighborhood boundary sites in tumor genomes, and review evidence suggesting that these mutations contribute to tumor development (Table 1, Supplementary Table 1).

CTCF mutations

Mutations in the CTCF gene have been reported in breast cancer, endometrial cancer (Lawrence et al., 2014; Walker et al., 2015), prostate cancer (Filippova et al., 1998), Wilms' tumor (Filippova et al., 2002), and head and neck carcinomas (Lawrence et al., 2014). These mutations are predominantly missense or nonsense and thus predicted to impair CTCF function (Lawrence et al., 2014). Some tumor cell mutations occur within the Zinc fingers of CTCF and may selectively perturb certain neighborhoods because they affect CTCF binding at only a subset of sites (Filippova et al., 2002). Loss of a CTCF allele can occur in some tumor types, suggesting that CTCF may act as a haplo-insufficient tumor suppressor (Filippova et al., 1998). Consistent with this notion, mice heterozygous for the CTCF gene display an increased susceptibility to develop tumors in various radiation and chemical- based cancer induction models (Kemp et al., 2014). Dysregulated expression of the germ line specific CTCF ortholog BORIS has been reported in several cancer types (Simpson et al., 2005), but it is not yet clear that this contributes to tumorigenesis.

Cohesin mutations

Mutations in the cohesin complex occur in acute myeloid leukemia (AML) (Cancer Genome Atlas Research et al., 2013), myeloid dysplastic syndrome (MDS) (Kon et al., 2013), bladder cancer (Guo et al., 2013), breast cancer (Stephens et al., 2012), colorectal cancer (Barber et al., 2008) and Ewing sarcoma (Crompton et al., 2014), among others (Table 1, Supplementary Table 1). In AML, mutations in all four cohesin subunits (SMC1A, SMC23, RAD21 and STAG2) have been reported, whereas in solid tumors mutations of the STAG2 subunit occur most frequently. The majority of mutations in the cohesin subunits are missense, nonsense or truncating (Lawrence et al., 2014), suggesting a loss-of-function effect, which is consistent with the reduced level of DNA-bound cohesin reported in cohesin-mutant AML cells (Kon et al., 2013).

Recent studies indicate that the tumor-promoting effect of at least a subset of cohesin alterations are linked to its roles in gene regulation and chromosome structure rather

than its roles in proper chromosome segregation. The classic role of cohesin in sister chromatid cohesion would predict that cohesin mutations in cancer contribute to the neoplastic state through defects in chromosome segregation and consequent aneuploidy. However, modeling of SMC3 mutations that occur in AML has revealed no association with chromosome segregation defects and aneuploidy, but rather with alteration of the gene expression program of the leukemia cells (Mazumdar et al., 2015; Mullenders et al., 2015; Viny et al., 2015). Furthermore, analysis of STAG2 mutant bladder cancer did not reveal any association of the STAG2 mutation with chromosome segregation defects and aneuploidy.

CTCF binding site mutations

Nucleotide substitutions in the DNA binding site of CTCF occur in the genomes of several cancer types (Supplementary Table 1), and such substitutions appear to be especially enriched in CTCF binding sites that form insulated neighborhood boundaries. Nucleotide substitutions in CTCF binding sites have been reported in colorectal cancer (Katainen et al., 2015), gastrointestinal cancer (Umer et al., 2016), esophageal cancer (Hnisz et al., 2016b), liver cancer (Hnisz et al., 2016b; Katainen et al., 2015), and melanoma (Poulos et al., 2016). Although the functional impact of these mutations has not been investigated in depth, the observation that insulated neighborhood boundary CTCF sites are conserved and show limited germ line variation (Ji et al., 2016), together with evidence that some of these mutations are recurrent, suggests that many of the somatic CTCF site mutations in tumor cells contribute to the neoplastic state by perturbing insulated neighborhoods.

Epigenetic alteration of CTCF binding

Because DNA hypermethylation is a feature of many cancer types and DNA methylation reduces CTCF binding, insulated neighborhood structures may be compromised in cells with hypermethylated DNA (Supplementary Table 1). Indeed, in a subset of gliomas that harbor mutations in the *IDH1* gene, tumor-specific hypermethylation is associated with the disruption of CTCF binding, alteration of chromosome structure, and dysregulation of oncogene expression (Flavahan et al., 2016).

Mutations in regulators of CTCF and cohesin

Several regulators of CTCF and cohesin have been recently implicated in cancer, and it is possible that mutations of some of these regulators contribute to the neoplastic state through alteration of insulated neighborhoods. For example, nucleophosmin, a direct physical interaction partner of CTCF is frequently mutated in AML (Cancer Genome Atlas Research et al., 2013). Many non-coding RNA species are implicated in cancer development (Lin and He, 2017), and CTCF interacts with thousands of RNAs, some of which impact its binding to DNA (Kung et al., 2015), so it is plausible that dysregulation of non-coding RNAs in tumor cells contributes to alterations of chromosome structures. ESCO1, the enzyme that acetylates cohesin is mutated in a subset of endometrial cancers (Price et al., 2014). In summary, defects in a diverse set of mechanisms may contribute to alterations of chromosome structure in cancer cells.

Impacts of neighborhood alterations in cancer

The structural and functional impact of mutations in chromosome structuring components and in neighborhood boundaries is only beginning to be studied in cancer, but it is useful nonetheless to consider models that explain how these mutations can

contribute to gene dysregulation in tumor cells (Figure 5). In some instances, these models are supported by experimental data and in others, they are predictive and await further study.

About half of T cell acute lymphoblastic leukemias contain mutations that activate the *TAL1* oncogene (Armstrong and Look, 2005; Van Vlierberghe and Ferrando, 2012). In a subset of these leukemias, the *TAL1* oncogene is activated by microdeletions that remove the boundary of an insulated neighborhood containing the *TAL1* gene. The disruption of the boundary leads to inappropriate contacts between the *TAL1* gene and regulatory elements normally located outside the *TAL1* neighborhood (Figure 5A) (Hnisz et al., 2016b). Similar microdeletions that disrupt an insulated neighborhood boundary also occur encompassing the *LMO2* oncogene in these T cell leukemias (Hnisz et al., 2016b).

Epigenetic alteration of CTCF binding sites at insulated neighborhood anchors can also lead to oncogene activation. A subset of gliomas harbor a mutation in the *IDH1* gene, and this mutation is associated with DNA hypermethylation (Cancer Genome Atlas Research et al., 2015; Dang et al., 2009). A recent study found that in *IDH1* mutant gliomas, methylation of an insulated neighborhood boundary encompassing the *PDGFRA* oncogene leads to a loss of the insulating property of the neighborhood, inappropriate contacts between *PDGFRA* and an upstream enhancer normally located outside the *PDGFRA* neighborhood, and elevated expression of *PDGFRA* (Figure 5A) (Flavahan et al., 2016).

Our understanding of insulated neighborhoods in normal gene control suggest additional models for the impact of genetic or epigenetic alterations of neighborhood structures in gene dysregulation in neoplastic cells; these have yet to be reported in cancer cells and thus serve merely as predictions. For example, alterations of neighborhood boundaries or their components may lead to the activation of silent oncogenes by enabling enhancers within the neighborhood to activate genes that are normally located outside the neighborhood (Figure 5B). Genetic or epigenetic perturbation of insulated neighborhood s (Figure 5C) (Dowen et al., 2014), and thus potentially loss of expression of a tumor suppressor. A minority of enhancers and promoters are bound by CTCF, and contacts between such enhancer-promoter pairs can be facilitated by CTCF-CTCF interactions (Guo et al., 2015), so disruption of these interactions can contribute to gene dysregulation (Figure 5D). Because the process of transcription and the presence of RNA species can affect CTCF binding, altered transcription in the cancer state may also be responsible for changes in neighborhood structure and function.

Future challenges: chromosome structures in cancer diagnostics and therapy

Genetic and epigenetic alterations of insulated neighborhoods can lead to dysregulation of prominent oncogenes that drive tumorigenesis. These new insights suggest new approaches to identify mechanisms associated with gene dysregulation in cancer and new approaches to target dysregulated expression of oncogenes and tumor suppressors.

Neighborhood alteration in cancer: identification of oncogenes and dependencies

Somatic mutations and epigenetic alterations that perturb insulated neighborhood boundaries may be useful to identify oncogenes and dependencies in cancers whose development and progression is not well understood. The finding that insulated

neighborhood boundary alterations occur at oncogene loci in leukemia and gliomas (Flavahan et al., 2016; Hnisz et al., 2013) suggests that neighborhoods with recurrently altered boundaries can identify new oncogenic drivers.

Cancer cells can become highly dependent on certain gene products during cancer progression. The disrupted neighborhood around *PDGFRA* in *IDH1* mutant glioma cells is associated with the sensitivity of these cells to PDGFRA inhibitors (Flavahan et al., 2016). This suggests that cancer dependencies engendered by similar mechanisms will be revealed through investigation of neighborhood alterations in cancer cells. Progress here will require improved understanding of the mutational landscape of non-coding regions of the genome where most neighborhood boundaries are located, and the epigenetic mechanisms that impact neighborhood boundary function.

Cancer susceptibility

Although cancer development occurs as a consequence of somatic alterations of the genome, DNA variants in the germ line contribute to the susceptibility of cancer development. Recent evidence that DNA polymorphisms in non-coding DNA are linked to cancer predisposition (Oldridge et al., 2015), that rare germ line variants occur in insulated neighborhood CTCF sites (Ji et al., 2016), and that such variants can impact neighborhoods (Tang et al., 2015) indicate that some of the genetic variation that contributes to cancer susceptibility may occur in insulated neighborhoods.

Epigenetic editing of CTCF anchors

Targeted disruption of CTCF binding and neighborhood integrity, with predictable effects on gene dysregulation, has been demonstrated through targeted methylation with a dCas9-DNA-metyltransferase-3 fusion protein (Liu et al., 2016). Targeted demethylation with a dCas9-TET fusion protein reversed this effect, allowing CTCF binding and insulated neighborhood formation (Liu et al., 2016). This suggests that targeted methylation and demethylation of CTCF binding sites could be used to alter CTCF-CTCF loops that form either insulated neighborhoods or enhancer-promoter interactions. Such epigenetic editing tools might evolve to be useful for therapeutic purposes in cancer and in other diseases where gene dysregulation is key to the disease state.

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Figure legends

Figure 1. Chromosome structures

Hierarchy of chromosome structures: chromosome territories, Topologically Associating Domains (TADs), and Insulated Neighborhoods. The experimental methods typically used to identify these structures are listed on the right side.

Figure 2. Insulated neighborhood models

Dynamics and heterogeneity of insulated neighborhoods inferred from chromatin contact data. Displayed are schematic representations of the experimental data, and models of their interpretation. Insulated neighborhoods are thought to be dynamic, and alternative neighborhood configurations indicated by the experimental data may occur in different cells of the population or within the same cell at different times or on different alleles within the same cell.

Figure 3. Insulated neighborhoods containing genes with prominent roles in cancer

(A-H) Models of Insulated Neighborhoods identified from high confidence interactions detected in CTCF ChIA-PET data in GM12878 cells (Tang et al., 2015). Insulated neighborhoods are depicted as arcs, with those containing the gene of interest in red. The length of the largest such neighborhood is noted. CTCF binding profiles (ChIP-Seq) are displayed in gene tracks below the insulated neighborhood arcs. ChIP-Seq data is from (ENCODE Project Consortium et al., 2012), and read density is measured as reads per million mapped reads. The genes with prominent roles in cancer are depicted as black arrows and identified in black font. Only a subset of neighborhoods at each locus is shown for simplicity; more detailed information can be found in Supplementary Figure 1.

The genomic coordinates (hg19 genome assembly) of the displayed loci are:

- (A) KRAS, chr12:23,328,472-26,234,964
- (B) NRAS, chr1:114,471,740-116,063,184
- (C) BRAF, chr7:140,149,898-141,280,727
- (D) MYC, chr8:127,797,231-130,842,492
- (E) TP53, chr17:7,398,136-7,751,726
- (F) EGFR, chr7:54,800,278-56,193,912
- (G) CD274, chr9:4,706,510-5,693,885
- (H) PDCD1, chr2:241,704,545-243,199,373

Figure 4. Chromosome structure regulators

(A) Regulatory mechanism and their impact on the chromosome structure regulator CTCF.

(B) Schematic models of the composition of the SMC family members cohesin, condensin I, and condensin II.

(C) Regulatory mechanism and their impact on the chromosome structure regulator cohesin

(D) Model of DNA loop formation by loop extrusion

Figure 5. Insulated neighborhood models for gene regulation and dysregulation in cancer

(A) Disruption of an insulated neighborhood boundary leads to upregulation of gene that was in the neighborhood due to inappropriate contact with an enhancer that was outside the neighborhood.

(B) Disruption of an insulated neighborhood boundary leads to upregulation of gene that was outside the neighborhood due to inappropriate contact with an enhancer that was inside the neighborhood.

(C) Disruption of an insulated neighborhood boundary leads to downregulation of a gene that used to be inside the neighborhood.

(D) Disruption of a CTCF anchor that mediates enhancer-promoter interactions within a neighborhood leads to downregulation of a gene within the neighborhood.

Table 1. Mutations in structuring components and neighborhood boundaries in cancer

Listed are cancer types in which mutations in CTCF, subunits of cohesin, and cohesin regulators have been reported. Only studies that included at least 100 samples, and mutations that reached an at least 3% frequency are displayed. The complete list of mutations is displayed in Supplementary Table 1.

Supplementary Figure 1. Insulated neighborhoods around prominent human oncogenes

Displayed are chromatin interaction data and ChIP-seq, and their annotation in GM12878 cells. From top to bottom: (1) HiC interaction matrices, shown in brown color scale (data from (Rao et al., 2014), visualized with http://higlass.io). (2) Annotation of contact domains, which are higher resolution version of Topologically Associating Domains (TADs) derived from the Hi-C data, shown as black bars below the Hi-C interaction matrices. (3) Annotation of insulated neighborhoods identified using CTCF ChIA-PET data, displayed as thin bars. The neighborhoods that contain the genes highlighted in black are highlighted in green. (4) High confidence CTCF-CTCF interactions identified in CTCF ChIA-PET data (in purple), originally from (Tang et al., 2015). The high confidence interactions annotated as insulated neighborhoods that contain the genes highlighted in black are highlighted in green. The length of the largest such neighborhood is displayed for orientation. (5) CTCF ChIP-seg signal is shown in blue, measured in reads per million (data from (ENCODE Project Consortium et al., 2012)). (6) The orientation of the strongest CTCF motif under each CTCF ChIP-Seq peak is displayed as black bars. "+" indicates that the strongest motif is oriented from left to right on the top (i.e. "+" strand). "-" indicates that the strongest motif is oriented from

right to left on the bottom (i.e. "-" strand), (data from (Hnisz et al., 2016b)). (7) Simplified Refseq gene annotations. The oncogene is shown in black, other genes in grey.

The genomic coordinates (hg19 genome assembly) of the displayed loci are:

- (A) KRAS, chr12:23,328,472-26,234,964
- (B) NRAS, chr1:114,471,740-116,063,184
- (C) BRAF, chr7:140,149,898-141,280,727
- (D) MYC, chr8:127,797,231-130,842,492
- (E) TP53, chr17:7,398,136-7,751,726
- (F) EGFR, chr7:54,800,278-56,193,912
- (G) CD274, chr9:4,706,510-5,693,885
- (H) PDCD1, chr2:241,704,545-243,199,373

Supplementary Table 1. Mutations in structuring components and neighborhood boundaries in cancer

Listed are cancer types in which mutations in CTCF, subunits of cohesin, and cohesin regulators have been reported.

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ch	Layer of romsome structure	Typical method used to identify		
	Chromosome territory	Microscopy		
E Co E	Topologically Associating Domain (TAD)	Hi-C 5C		
Anchor Cohesin CTCF Enhancer Gene	Insulated neighborhood	ChIA-PET hiChIP		



Alternative neighborhood configurations that occur in different cells of the population or within the same cell at different times or on different alleles within the same cell



















Factor	Cancer Type	Type of mutation	Effect on gene	Hits	Samp	le Size Frequen	cy References
CTCF	Endometrial cancer	unreported	unreported		46	248	18.5 Lawrence et al., Nature, 2014
CTCF	Endometrial cancer, endometrioid		frameshift, missense, splice, read through		136	538	25.3 Walker et al., Journal of the National Cancer Institute, 2015
CTCF	Head and neck cancer	unreported	unreported		12	384	3.1 Lawrence et al., Nature, 2014
CTCF	Uterine corpus endometrial carcinoma	substitution, indel	unreported		43	230	18.7 Kandoth et al., Nature, 2013
ESCO1	Endometrial cancer	substitution	nonsense, missense		4	107	3.7 Price et al., PLoS ONE, 2013
NIPBL	Colorectal cancer	substitution, indel	missense, frameshift		4	132	3 Barber et al., PNAS, 2008
NIPBL	Urothelial carcinoma	substitution	nonsense, missense, exon junction		5	131	3.8 Cancer Genome Atlas Research Network, Nature, 2014
RAD21	Acute myeloid leukemia	substitution, indel	frameshift, nonsense, splice		7	157	4.5 Kon et al., Nature Genetics, 2013
RAD21	Acute myeloid leukemia	unreported	unreported		6	196	3.1 Lawrence et al., Nature, 2014
RAD21	Urothelial carcinoma	substitution	missense, nonsense		5	131	3.8 Cancer Genome Atlas Research Network, Nature, 2014
SMC1A	Acute myeloid leukemia	substitution	missense, nonsense		7	200	3.5 Cancer Genome Atlas Research Network, NEJM, 2013
SMC1A	Acute myeloid leukemia	substitution	unreported		7	200	3.5 Kandoth et al., Nature, 2013
SMC1A	Acute myeloid leukemia	unreported	unreported		7	196	3.6 Lawrence et al., Nature, 2014
SMC1A	Colorectal cancer	substitution	missense		4	132	3 Barber et al., PNAS, 2008
SMC3	Acute myeloid leukemia	substitution	missense, nonsense		7	200	3.5 Cancer Genome Atlas Research Network, NEJM, 2013
SMC3	Acute myeloid leukemia	substitution, indel	missense, nonsense, splice, frameshift		14	450	3.1 Thota et al., Blood, 2014
SMC3	Acute myeloid leukemia	substitution	unreported		7	200	3.5 Kandoth et al., Nature, 2013
SMC3	Acute myeloid leukemia	unreported	unreported		7	196	3.6 Lawrence et al., Nature, 2014
STAG1	Urothelial carcinoma	substitution	missense, exon junction		4	131	3.1 Cancer Genome Atlas Research Network, Nature, 2014
STAG2	Acute myeloid leukemia	substitution, indel	frameshift, nonsense, splice		10	157	6.4 Kon et al., Nature Genetics, 2013
STAG2	Acute myeloid leukemia	substitution	nonsense		6	200	3 Cancer Genome Atlas Research Network, NEJM, 2013
STAG2	Acute myeloid leukemia	substitution, indel	nonsense, frameshift, splice, deletion		23	450	5.1 Thota et al., Blood, 2014
STAG2	Acute myeloid leukemia	substitution, indel	nonsense, frameshift, splice, missense, deletion		24	299	8 Lindsley et al., Blood, 2015
STAG2	Acute myeloid leukemia	substitution	unreported		6	200	3 Kandoth et al., Nature, 2013
STAG2	Acute myeloid leukemia	unreported	unreported		6	196	3.1 Lawrence et al., Nature, 2014
STAG2	Acute myeloid leukemia, de novo	unreported	frameshift, nonsense, missense		10	197	5.1 Kihara et al., Leukemia, 2014
STAG2	Bladder cancer	substitution, indel	missense, nonsense, exon junction, framshift		25	111	2.5 Solomon et al., Nature Genetics, 2013
STAG2	Bladder cancer	substitution, indel	missense, nonsense, frameshift, deletion, splice		67	307	21.8 Taylor et al., Human Molecular Genetics, 2014
STAG2	Ewing's sarcoma	substitution, indel, duplication	nonsense, missense, exon junction, frameshift, exon duplication		19	112	17 Tirode et al., Cancer Discovery, 2014
STAG2	Ewing's sarcoma	substitution, indel, duplication	nonsense, missense, exon junction, frameshift, exon duplication, in-frame deletion		41	199	20.6 Tirode et al., Cancer Discovery, 2014
STAG2	Gliobastoma multiforme	substitution, indel	unreported		12	290	4.1 Kandoth et al., Nature, 2013
STAG2	Gliobastoma multiforme	unreported	unreported		12	291	4.1 Lawrence et al., Nature, 2014
STAG2	Glioblastoma	unreported	unreported		12	291	4.1 Brennan et al., Cell, 2013
STAG2	Myelodysplastic syndromes	substitution, indel	frameshift, nonsense, splice		13	224	5.8 Kon et al., Nature Genetics, 2013
STAG2	Myelodysplastic syndromes	substitution, indel	missense, nonsense, frameshift, splice		30	386	7.8 Thota et al., Blood, 2014
STAG2	Myelodysplastic syndromes	substitution, indel	splice, nonsense, frameshift		9	150	6 Walter et al., Leukemia, 2013
STAG2	Myelodysplastic syndromes	unreported	unreported		71	944	7.5 Haferlach et al., Leukemiea, 2014
STAG2	Myelodysplastic syndromes/Myeloproliferat	substitution	missense, nonsense, splice		6	169	3.6 Thota et al., Blood, 2014
STAG2	Renal cell carcinoma, papillary	unreported	unreported		8	157	5.1 Cancer Genome Atlas Research et al., NEJM, 2016
STAG2	Urothelial carcinoma	substitution, indel	nonsense, missense, exon junction, frameshift		14	131	10.7 Cancer Genome Atlas Research Network. Nature. 2014

Supplementary Table 1

CICF		. hards after a
CTCF	Acute iymphoblastic leukemia. Down syndrome-related	substitution
CTCF	Acute megakaryoblastic leukemia, non-Down syndrome-related	
CTCF	Acute myeloid leukemia	substitution
CTCF	Acute myeloid leukemia	substitution
CTCF	Acute myeloid leukemia Bladder cancer, transitional cell carcinoma	substitution indel
CTCF	Breast adenocarcinoma	substitution, indel
CTCF	Breast cancer	indel
CTCF	Breast cancer	unreported
CTCF	Breast cancer Breast cancer	
CTCF	Breast cancer	
CTCF	Breast cancer, invasive ductal carcinoma	indel
CTCF	Clear cell renal cell carcinoma	
CTCF	Colorectal cancer	substitution
CTCF	Endometrial cancer endometrioid	unieporteu
CTCF	Endometrial cancer, MSI negative	substitution, indel
CTCF	Endometrial cancer, MSI positive	substitution, indel
CTCF	Endometrial cancer, MSI positive	substitution, indel
CTCF	Endometrial cancer, serous	substitution
CTCF	Head and neck cancer	unreported
CTCF	Myelodysplastic syndromes	unreported
CTCF	Prostate cancer	
CTCF	Urothelial carcinoma	substitution
CTCF	Uterine corpus endometrial carcinoma	substitution, indel
CTCF	Wilms' tumor	
ESCO1	Chronic myelomonocytic leukemia	substitution
ESCO1	Colorectal cancer	substitution
ESCO1	Endometrial cancer	substitution
ESCO1	Multiple myeloma	substitution
ESCO1	Urothelial carcinoma	substitution
ESCO2	Acute myeloid leukemia	substitution
ESCO2	Clear cell renal cell carcinoma	
ESCO2	Colorectal cancer	substitution
ESCO2	Myelodysplastic syndromes	substitution
ESCO2	Wyelouysplastic synuromes Urothelial bladder cancer	substitution
ESCO2	Urothelial carcinoma	substitution
HDAC8	Urothelial carcinoma	substitution
MAU2	Urothelial bladder cancer	substitution, indel
NIPBL	Acute megakaryoblastic leukemia, bown syndrome-related	indel
NIPBL	Acute myeloid leukemia	substitution
NIPBL	Bladder cancer, transitional cell carcinoma	substitution
NIPBL	Breast cancer	substitution
NIPBL	Clear cell renal cell carcinoma	substitution
NIPBL	Colorectal cancer	substitution, indel
NIPBL	Colorectal cancer	substitution
NIPBL	Glioma	
NIPBL	Myelodysplastic syndromes	unreported
NIPBL	Urothelial bladder cancer	substitution
NIPBL	Urothelial carcinoma	substitution
PDS5A	Breast cancer Clear cell renal cell carcinoma	substitution
PDS5A	Colorectal cancer	substitution
PDS5A	Multiple myeloma	substitution
PDS5A	Urothelial carcinoma	substitution
PDS5B	Acute myeloid leukemia	substitution
PDS58	Acute myeloid leukemia	substitution, indel
PDS5B	Acute myeloid leukemia	indel
PDS5B PDS5B PDS5B	Acute myeloid leukemia Bladder cancer, transitional cell carcinoma Breast cancer	indel substitution substitution indel
PDS5B PDS5B PDS5B PDS5B	Acute myeloid leukemia Bladder cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia	indel substitution substitution, indel substitution
PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B	Acute myeloid leukemia Bladder cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell renal cell carcinoma	indel substitution substitution, indel substitution
PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B	Acute myeloid leukemia Bladder cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal cancer Swinof cancera padiatic	indel substitution substitution, indel substitution substitution, splice
PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58	Acute myelooi leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal cancer Exing's sarcoma, pediatric Myelodysolatic: syndromes	indel substitution substitution, indel substitution substitution, splice substitution substitution
PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B	Acute myelioù leukema Biadder cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal cancer Eving's sarcoma, pediatric Myelodysplastic syndromes Myelodysplastic syndromes	indel substitution, indel substitution substitution substitution substitution substitution unreported
PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B PDS5B	Acute myelooi leukema Biadder cancer, transitional cell carcinoma Breast cancer Orvnnic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectai canco Colorectai canco Ostare cell renal cell artic Myelodysplastic syndromes Myelodysplastic syndromes Myelogysplastic syndromes	indel substitution, indel substitution substitution substitution substitution unreported substitution
PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58 PDS58	Acute myeliod leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal cancer Eving's sarcoma, pediatric Myelodysplastic syndromes Myelodysplastic syndromes Myelogrobiferative neoplasms Myelogrobiferative neoplasms	indel substitution substitution, indel substitution substitution substitution substitution substitution substitution substitution
PDSSB	Acute myelooi leukema Biader cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Chronic myelomonocytic leukemia Chronic myelomonocytic leukemia Chronic myelomona Eving's sarcman, pediatric Myelodysplastic syndromes Myelogropoliferative neoplasms Myelogropoliferative neoplasms Urothelial Jander cancer Urothelial Jander cancer	indel substitution substitution, indel substitution substitution substitution substitution substitution substitution substitution
PDSSB RAD21	Acute myoloal leukemia Biadder cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal cancen Ewing's sarcoma, pediatric Myelodysplastic syndromes Myelogropilferative neoplasms Unyeloproliferative neoplasms Myeloproliferative neoplasms Myeloproliferative neoplasms Acute megalaryoblastic leukemia, Down syndrome-related	indel substitution, indel substitution, indel substitution substitution substitution unreported substitution substitution substitution substitution
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PDSSB PDSSB </td <td>Acute myelooi leukemia Biader cancer, transitional cell carcinoma Breast cancer Ornonic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal cancon Bwiedoxplastic syndromes Myelodoxplastic syndromes Myelopoifierative neoplasms Myelopoifierative neoplasms Myelopoifierative neoplasms Myelopoifierative neoplasms Myelopoifierative neoplasms Acute megola leukemia Acute myeloi leukemia</td> <td>indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel</td>	Acute myelooi leukemia Biader cancer, transitional cell carcinoma Breast cancer Ornonic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal cancon Bwiedoxplastic syndromes Myelodoxplastic syndromes Myelopoifierative neoplasms Myelopoifierative neoplasms Myelopoifierative neoplasms Myelopoifierative neoplasms Myelopoifierative neoplasms Acute megola leukemia Acute myeloi leukemia	indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel
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PDSSB RAD21 RAD21 RAD21 RAD21 RAD21	Acute myeloia leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Charce and transit cell carcinoma Desire and cell carcinoma Sening's sarcman, pediatric Myelokryslastic syndromes Myelogrofiferative neoplasms Myelogrofiferative neoplasms Urothelial carcinoma Acute myeloi leukemia Acute myeloi leukemia Acute myeloi leukemia Acute myeloi leukemia Acute myeloi leukemia	indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel
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PDS58 RAD21 RAD21	Acute myelooi leukemia Biadder cancer, transitional cell carcinoma Breast cancer Dronic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal cancer Biwleg's sarcoma, pediatric Myelodysplastic syndromes Myelogroifferative neoplasms Urothelia blader cancer Urothelia ladater cancer Urothelia carcinoma Acute myeloio publistic leukemia, Down syndrome-related Acute myeloi deukemia Acute myeloi leukemia Acute myeloi leukemia	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel
PDS58 PDS58	Acute myelioi leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell real carcinoma Cell real cell carcinoma Cell real cell carcinoma Myeloporoliferative neoplasms Myeloporoliferative neoplasms Myeloporoliferative neoplasms Urothelial carcinoma Acute myeloi leukemia Acute myeloi leukemia	indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution
PDS58 PDS58	Acute myeloia leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myeloimonocytic leukemia Clear cell renal cell carcinoma Colorectal canco Myeloitypalastic syndromes Myeloitypalastic syndromes Myeloitypalastic syndromes Myeloitypalastic syndromes Myeloitypaliet eneoplasms Urothelial biader cancer Urothelial biader cancer Acute myeloid leukemia Acute myeloid leukemia Chronic myelogenous leukemia Chronic myelogenous leukemia	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution indel substitution indel substitution indel substitution
PDS58 PDS58	Acute myelooi leukemia Biadder cancer, transitionia (ell carcinoma Breast cancer Chronic myelokomoncytic leukemia Clear cell renal cell carcinoma Colorectal cancer Ewing's sarcoma, pediatric Myelodysplastic syndromes Myelodysplastic syndromes Myeloproliferative neoplasms Urothelial biader cancer Urothelial biader cancer Urothelial acterioma Acute myeloid leukemia Acute myeloid leukemia Chronic myelomooscytic leukemia	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution
PDS58 PDS58	Acute myelioal leukemia Biadder cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal canco Diorectal canco Biadder cancer, transitional cell Acute myeloal positis proformas Myelogonofistrative neoplasms Myelogonofistrative neoplasms Myelogonofistrative neoplasms Myelogonofistrative neoplasms Myelogonofistrative neoplasms Myelogonofistrative neoplasms Myelogonofistrative neoplasms Acute myeloal feukemia Acute myeloal feukemia Chronic myelogonous feukemia Chronic myelogonous feukemia Chronic myelogonous feukemia Chronic myelogonous feukemia Chronic myelogonous feukemia	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution substitution substitution
PDS58 PDS58	Acute myeloia leukemia Biadder cancer, transitional cell carcinoma Breast cancer Ornonic myeloiomocrytic leukemia Clear cell renal cell carcinoma Colorectal cancer Ewing's sarcoma, pediatric Myelodoysplastic syndromes Myelogroilferative neoplasms Urothelia blader cancer Urothelia ladarker cancer Urothelia ladarker cancer Urothelia ladarker cancer Urothelia ladarker cancer Urothelia ladarker cancer Autet myeloial elukemia Autet myeloial elukemia Cartori myeloigenous leukemia Chronic myeloionocytti elukemia Colorectal cancer Ewing's arcoma, pediatric Myelodoysplastic syndromes	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution substitution substitution substitution substitution substitution substitution indel substitution
PDS58 PDS58	Acute myelioa leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell real carcinoma Clear cell real carcinoma Carcell real cell carcinoma Carcell real cell carcinoma Myeloporoliferative neoplasms Myeloporoliferative neoplasms Urothelial carcinoma Acute myeloi leukemia Acute myeloi leukemia Carte myeloi neumemia Caronic myelomos leukemia Chronic myelomos leukemia Myelodysplastic syndromes Myelodysplastic syndromes	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution
PDS58 PDS58	Acute myelioal leukemia Biadder cancer, transitional cell carcinoma Breast cancer Chronic myeliomoncytic leukemia Clear cell renal cell carcinoma Colorectal cancer Hyeliodypalastic syndromes Myeliopyiliseris syndromes Myeliopyiliseris syndromes Myeliopyiliseris eneplasms Unorthelial carcinoma Acute myelio Huekemia Acute myelio Huekemia Carte myelio Huekemia Chronic myelogenous Huekemia	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution substitution substitution inserion substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution indel substitution indel substitution
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PDS58 PDS58	Acute myelioi leukemia Biadder cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell renal cell carcinoma Colorectal canco Divertal canco Ewing's systema, perfamilie Wyelogrofilerative neoplasms Myelogrofilerative neoplasms Urothelial carcinoma Acute myeloi leukemia Acute myeloi leukemia Caute myeloi leukemia Chronic myelogenous leukemia Ch	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution insertion substitution substitution indel substitution indel substitution substitution substitution substitution
PDS58 PDS58	Acute myelioi leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myeleiomoncytic leukemia Clear cell real cell carcinoma Colorectal cancer Myelodysplastic syndromes Myelodysplastic syndromes Myelogrofilerative neoplasms Urothelial blader cancer Urothelial blader cancer Urothelial carcinoma Acute myelod reukemia Acute myelod reukemia Acute myelod leukemia Acute myelod leukemia Carcer myelod leukemia Acute myelod leukemia Carcer myelod leukemia Chronic myelogenous leukemia Chronic myelog	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution
PDS58 PDS58	Acute myelioi leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell real carcinoma Clear cell real carcinoma Carcell real cell carcinoma Carcell real cell carcinoma Myeloporoliferative neoplasms Myeloporoliferative neoplasms Urothelial carcinoma Acute myeloi leukemia Acute myeloi leukemia Carte myeloi leukemia Acute myeloi leukemia Carte myeloi neukemia Carten myeloi myelomos leukemia Carten myeloi neukemia Carten myeloi sukemia Chronic myelomos leukemia Chronic myelomos leukemia Acute myeloi leukemia Acute myeloi leukemia Acute myeloi leukemia Acute myeloi leukemia Acute myeloi leukemia	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution insertion substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution
PDS58 PDS58	Acute myelio leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myeloionocytic leukemia Clear cell renal cell carcinoma Colorectal cancer Weidoxplastic syndromes Myeloioxplastic syndromes Myeloioxplastic syndromes Myeloioxplastic syndromes Myeloioxplastic syndromes Myeloioxplastic syndromes Myeloioxplastic leukemia Acute myeloi leukemia Caute myeloi leukemia Chronic myelogenous leukemia Acute myeloi leukemia Acute myeloi leukemia Acute myeloi leukemia Acute myeloi leukemia Acute myeloi leukemia	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution
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PDS58 PDS58	Acute myelio leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Clear cell real cal carcinoma Clear cell real cell carcinoma Carcent enal cell carcinoma Carcent enal cell carcinoma Carcent enal cell carcinoma Myeloprofilerative neoplasms Myeloprofilerative neoplasms Urothelial carcinoma Acute myelol elukemia Acute myelol elukemia Carcen myelol myelonas cell carcinoma Carcent myelonas cell carcinoma Carcent enyelon elukemia Acute myelol elukemia Chronic myelognosis leukemia Chronic myelognosis leukemia Chronic myelopolosis leukemia Chronic myelopolosis leukemia Chronic myelopolosis leukemia Chronic myelopolosis leukemia Acute myelol feukemia Acute myelol feukemia	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution
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PDS58 PDS58	Acute myelio leukemia Bidef cancer, transitional cell carcinoma Breast cancer Chronic myelosinonocytic leukemia Concerte leukenicanoma Octore et leukenicanoma Bidef cancer, transitional cell Myelodysplastic syndromes Myelogropiferative neoplasms Wyelogropiferative neoplasms Urothelial acricoma Acute myeloi leukemia Acute myeloi leukemia Colorectal cancer Urotheil acroma Myelodysplastic syndromes Myelodysplastic syndromes Myelodysp	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution
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PDS58 PDS58	Acute myelio leukemia Directi cancer Directi cancer	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution
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PDS58 PDS58	Acute myelio leukemia Breast cancer Chronic myelomonocytic leukemia Clear cell real cal carcinoma Clear cell real cell carcinoma Colorectal cancer Myelogrofilerstive neoplasms Myelogrofilerstive neoplasms Myelogrofilerstive neoplasms Urothelial carcinoma Acute myelol elukemia Acute mye	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution
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PDS58 PDS8 PDS58 P	Acute myelio leukemia Biader cancer, transitional cell carcinoma Breast cancer Chronic myelomonocytic leukemia Cear cell real cell carcinoma Cear cell real cell carcinoma Cear cell real cell carcinoma Cear cell real cell carcinoma Myeloporoliferative neoplasms Myeloporoliferative neoplasms Urothelial carcinoma Acute myeloi leukemia Acute myeloi leukemia Cartor myeloi neosi bukama Coronic myelomoos leukemia Coronic myelomoos leukemia Chronic myelomos leukemia Chronic myelomos leukemia Acute myeloi leukemia Acute myeloi leukemia Chronic myelomos leukemia Chronic m	indel substitution, indel substitution substitution substitution substitution substitution substitution substitution substitution substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution
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missense, splice, deletion
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unreported
unreported
missense, insertion
unreported
deletion
missense
unreported
missense missense, nonsense
missense

	Sample Size	Frequency	References
1 10	23 49	4.3 20.4	Mullighan et al., Nature 2011 Yoshida et al., Nature Genetics, 2013
4	19	21.1	Yoshida et al., Nature Genetics, 2013
1	8 200	12.5	Ding et al., Nature, 2012 Cancer Genome Atlas Research Network, NEJM, 2013
1	50	2	Dolnik et al., Blood, 2012
18	763	2.4	Kandoth et al., Nature, 2013
1	100	1	Stephens et al., Nature, 2012
20	4	2.2	Fillipova et al., Genes Chromosomes Cancer, 1998
1	31	3.2	Fillipova et al., Cancer Research, 2002
1	18	5.6	Aulmann et al., Breast Cancer Resarch and Treatment, 2003
2	417	0.5	Cancer Genome Atlas Research et al., Nature, 2013 Seshagiri et al., Nature, 2012
46	248	18.5	Lawrence et al., Nature, 2014
136 9	538	25.3	Walker et al., Journal of the National Cancer Institute, 2015 Zighelboim et al., Human Mutation, 2014
3	8	37.5	Zighelboim et al., Human Mutation, 2014
36	98	36.7	Le Gallo et al., Nature Genetics, 2012
1	92	1.1	Cromptom et al., Cancer Discovery, 2014
12	584 944	1.3	Haferlach et al., Leukemiea, 2014
1	41	2.4	Fillipova et al., Cancer Research, 2002 Voshida et al. Nature Genetics, 2013
3	131	2.3	Cancer Genome Atlas Research Network, Nature, 2014
43	230	18.7	Kandoth et al., Nature, 2013 Fillipova et al., Cancer Research, 2002
1	88	1.1	Kon et al., Nature Genetics, 2013
2	417	0.5	Cancer Genome Atlas Research et al., Nature, 2013 Seshagiri et al., Nature, 2012
4	107	3.7	Price et al., PLoS ONE, 2013
3	203	0.8	Cancer Genome Atlas Research Network, Nature, 2014
1	200	0.5	Cancer Genome Atlas Research Network, NEJM, 2013
1	450	0.2	Cancer Genome Atlas Research et al., Nature, 2013
1	72	1.4	Seshagiri et al., Nature, 2012 Kon et al., Nature, Constice, 2012
1	944	0.4	Haferlach et al., Leukemiea, 2014
1	77	1.3	Balbás-Martínez et al., Nature Genetics, 2013
1	131	0.8	Cancer Genome Atlas Research Network, Nature, 2014 Cancer Genome Atlas Research Network, Nature, 2014
2	77	2.6	Balbás-Martínez et al., Nature Genetics, 2013 Yoshida et al., Nature Genetics, 2013
1	157	0.6	Kon et al., Nature Genetics, 2013
1	200	0.5	Cancer Genome Atlas Research Network, NEJM, 2013 Guo et al., Nature Genetics, 2013
2	100	2	Stephens et al., Nature, 2012
4	417	1.6	Cancer Genome Atlas Research et al., Nature, 2013
4	132	3	Barber et al., PNAS, 2008
19	820	2.3	Ceccarelli et al., Cell, 2016
1	224	0.4	Kon et al., Nature Genetics, 2013 Haferlach et al. Leukemiea. 2014
2	77	2.6	Balbás-Martínez et al., Nature Genetics, 2013
5	131	3.8	Cancer Genome Atlas Research Network, Nature, 2014 Stephens et al., Nature, 2012
4	417	1	Cancer Genome Atlas Research et al., Nature, 2013
3	203	4.2	Lohr et al., Cancer Cell, 2012
2	131	1.5	Cancer Genome Atlas Research Network, Nature, 2014
1	200	0.5	Cancer Genome Atlas Research Network, NEJM, 2013
2	450 299	0.4	Thota et al., Blood, 2014 Lindslev et al., Blood, 2015
1	99	1	Guo et al., Nature Genetics, 2013
2	100	1.1	Stephens et al., Nature, 2012 Kon et al., Nature Genetics, 2013
5	417	1.2	Cancer Genome Atlas Research et al., Nature, 2013
1	92	4.2	Cromptom et al., Cancer Discovery, 2014
1	386	0.3	Thota et al., Blood, 2014 Haferlach et al., Leukemiea, 2014
1	77	1.3	Kon et al., Nature Genetics, 2013
1	55	1.8	Thota et al., Blood, 2014 Balbás-Martínez et al., Nature Genetics, 2013
1	131	0.8	Cancer Genome Atlas Research Network, Nature, 2014
11	49	22.4	Yoshida et al., Nature Genetics, 2013 Kon et al., Nature Genetics, 2013
5	200	2.5	Cancer Genome Atlas Research Network, NEJM, 2013
4	450	2.4	Thota et al., Blood, 2014
8	299	2.7	Lindsley et al., Blood, 2015
4	200	2.5	Kandoth et al., Nature, 2013
6	196	3.1	Lawrence et al., Nature, 2014 Kibara et al., Leukemia, 2014
1	99	1	Guo et al., Nature Genetics, 2013
1	64 53	1.6	Kon et al., Nature Genetics, 2013 Rocquain et al. American Journal of Hematology. 2010
2	72	2.8	Seshagiri et al., Nature, 2012
2	224	0.9	Kon et al., Nature Genetics, 2013
7	386	1.8	Thota et al., Blood, 2014
15	944	0.6	Thota et al., Blood, 2014
1	77	1.3	Balbás-Martínez et al., Nature Genetics, 2013 Cancer Genome Atlas Research Network, Nature, 2014
2	389	0.5	Thol et al., Blood, 2014
2	49 157	4.1	Yoshida et al., Nature Genetics, 2013 Kon et al., Nature Genetics, 2013
7	200	3.5	Cancer Genome Atlas Research Network, NEJM, 2013
5	450	1.1	Thota et al., Blood, 2014 Lindslev et al., Blood, 2015
1	24	4.2	Welch et al., Cell ,2012
7	200 196	3.5	Kandoth et al., Nature, 2013 Lawrence et al., Nature, 2014
4	83	4.8	Huether et al., Nature Communications, 2014
5	197 99	2.5	Kihara et al., Leukemia, 2014 Guo et al., Nature Genetics, 2013
1	40	2.5	Huether et al., Nature Communications, 2014
1	101 64	3.1	stepnens et al., Nature, 2013 Kon et al., Nature Genetics, 2013
1	417	0.2	Cancer Genome Atlas Research et al., Nature, 2013
4	132 72	3	Barber et al., PNAS, 2008 Seshagiri et al., Nature, 2012
1	112	0.9	Tirode et al., Cancer Discovery, 2014
1	92	1.1	Jones et al., Nature, 2012
10	944	1.1	Haferlach et al., Leukemiea, 2014 Ralbás-Martínez et al., Nature Consting, 2012
3	131	1.3	Cancer Genome Atlas Research Network, Nature, 2014
1	102	1	Stephens et al., Nature, 2014

Hits

SMC1B	Clear cell renal cell carcinoma		unreported	2	417	0.5 Cancer Genome Atlas Research et al., Nature, 2013
SMC1B	Colorectal cancer	substitution	missense, nonsense	3	72	4.2 Seshagiri et al., Nature, 2012
SMC1B	Multiple myeloma	substitution	missense	1	203	0.5 Lohr et al., Cancer Cell, 2014
SMC1B	Myelodysplastic syndromes, del(5q)		missense	1	2	50 Pellagatti et al., Leukemia, 2014
SMC1B	Urothelial bladder cancer	substitution	missense, exon junction	4	77	5.2 Balbás-Martínez et al., Nature Genetics, 2013
SMC1B	Urothelial carcinoma	substitution	missense	2	131	1.5 Cancer Genome Atlas Research Network, Nature, 2014
SMC3	Acute megakaryoblastic leukemia, Down syndrome-related		splice	1	49	2 Yoshida et al., Nature Genetics, 2013
SMC3	Acute myeloid leukemia	substitution	missense	1	8	12.5 Ding et al., Nature, 2012
SMC3	Acute myeloid leukemia	substitution	missense	1	157	0.6 Kon et al., Nature Genetics, 2013
SMC3	Acute myeloid leukemia	substitution	missense, nonsense	7	200	3.5 Cancer Genome Atlas Research Network, NEJM, 2013
SMC3	Acute myeloid leukemia	substitution	missense	5	389	1.3 Thol et al., Blood, 2014
SMC3	Acute myeloid leukemia	substitution, indel	missense, nonsense, splice, frameshift	14	450	3.1 Thota et al., Blood, 2014
SMC3	Acute myeloid leukemia	substitution	missense	4	299	1.3 Lindsley et al., Blood, 2015
SMC3	Acute myeloid leukemia	substitution	missense	1	24	4.2 Welch et al., Cell ,2012
SMC3	Acute myeloid leukemia	substitution	splice	1	7	14.3 Walter et al., NEJM, 2012
SMC3	Acute myeloid leukemia	substitution	unreported	7	200	3.5 Kandoth et al., Nature, 2013
SMC3	Acute myeloid leukemia	unreported	unreported	7	196	3.6 Lawrence et al., Nature, 2014
SMC3	Acute myeloid leukemia, de novo	unreported	missense, insertion	4	197	2 Kihara et al., Leukemia, 2014
SMC3	Bladder cancer, transitional cell carcinoma	substitution	nonsense, exon junction	2	99	2 Guo et al., Nature Genetics, 2013
SMC3	Clear cell renal cell carcinoma		unreported	5	417	1.2 Cancer Genome Atlas Research et al., Nature, 2013
SMC3	Colorectal cancer	substitution	missense	1	130	0.8 Barber et al. PNAS 2008
SMC3	Colorectal cancer	substitution	missense	3	72	4.2 Seshagiri et al. Nature. 2012
SMC3	Medulloblastoma	substitution	splice	1	125	0.8 Jones et al., Nature, 2012
SMC3	Mvelodvsplastic syndromes	substitution	missense	3	224	1.3 Kon et al. Nature Genetics 2013
SMC3	Mvelodvsplastic syndromes	substitution indel	missense splice deletion	3	386	0.8 Thota et al. Blood 2014
SMC3	Myelodysplastic syndromes	substitution	missense splice	2	150	1 3 Walter et al. Leukemia 2013
SMC3	Myelodysplastic syndromes	upreported	unreported	16	944	1.7 Haferlach et al. Leukemiea 2014
SMC3	Myelodysplastic syndromes/Myeloproliferative neoplasms	substitution	solice	1	169	0.6 Thota et al. Blood 2014
SMC2	Urotholial bladdor cancor	substitution	micronro	1	77	1.2 Palbás Martínoz et al. Nature Constics 2012
SMC2	Urothelial carcinema	substitution	missense	2	121	1.5 Dalbas-Watchiez et al., Nature Genetics, 2013
STACI	A suba superior la concentra	substitution indel	missense farmerhift	2	200	1.9 Thei stal. Diand 2014
STAGE	Acute myeloid leukenna	substitution, inder	missense, mamesmit	2	369	2 Cup et al., blobus, 2014
STAGE	Diaduler cancer, transitional cell carcinoma	substitution	missense	2	102	2 Guo et al., Nature Genetics, 2015
STAGI	Breast cancer	substitution	missense	1	103	1 Stephens et al., Nature, 2015
STAGI	Chronic myelomonocytic leukemia	substitution	missense	1	88	1.1 Kon et al., Nature Genetics, 2013
STAG1	Clear cell renal cell carcinoma		unreported	4	417	1 Cancer Genome Atlas Research et al., Nature, 2013
STAG1	Colorectal cancer	substitution	missense	4	72	5.6 Seshagiri et al., Nature, 2012
STAG1	Ewing's sarcoma	substitution	missense	1	112	0.9 Tirode et al., Cancer Discovery, 2014
STAG1	Multiple myeloma	substitution	missense	2	203	1 Lohr et al., Cancer Cell, 2014
STAG1	Myelodysplastic syndromes	substitution	missense	1	224	0.4 Kon et al., Nature Genetics, 2013
STAG1	Myelodysplastic syndromes	substitution	nonsense	1	386	0.3 Thota et al., Blood, 2014
STAG1	Myelodysplastic syndromes	unreported	unreported	2	944	0.2 Haferlach et al., Leukemiea, 2014
STAG1	Urothelial bladder cancer	substitution	missense	5	77	6.5 Balbás-Martínez et al., Nature Genetics, 2013
STAG1	Urothelial carcinoma	substitution	missense, exon junction	4	131	3.1 Cancer Genome Atlas Research Network, Nature, 2014
STAG2	Acute megakaryoblastic leukemia, Down syndrome-related		nonsense, splice, indel, deletion	9	49	18.4 Yoshida et al., Nature Genetics, 2013
STAG2	Acute megakaryoblastic leukemia, non-Down syndrome-related		missense, nonsense	2	19	10.5 Yoshida et al., Nature Genetics, 2013
STAG2	Acute myeloid leukemia	substitution, indel	frameshift, nonsense, splice	10	157	6.4 Kon et al., Nature Genetics, 2013
STAG2	Acute myeloid leukemia	substitution	nonsense	6	200	3 Cancer Genome Atlas Research Network, NEJM, 2013
STAG2	Acute myeloid leukemia	substitution, indel	missense, frameshift, nonsense	5	389	1.3 Thol et al., Blood, 2014
STAG2	Acute myeloid leukemia	substitution, indel	nonsense, frameshift, splice, delection	23	450	5.1 Thota et al., Blood, 2014
STAG2	Acute myeloid leukemia	substitution, indel	nonsense, frameshift, splice, missense, deletion	24	299	8 Lindslev et al., Blood, 2015
STAG2	Acute myeloid leukemia	substitution	nonsense	1	24	4.2 Welch et al., Cell .2012
STAG2	Acute myeloid leukemia	indel	frameshift	1	7	14.3 Walter et al. NEIM 2012
STAG2	Acute myeloid leukemia	substitution	splice	1	15	6.7 Walter et al., Leukemia, 2013
STAG2	Acute myeloid leukemia		deletion	1	51	2 Rocquain et al. American Journal of Hematology, 2010
STAG2	Acute myeloid leukemia	substitution	unreported	6	200	3 Kandoth et al. Nature 2013
STAG2	Acute myeloid leukemia	upreported	unreported	6	196	3.1 Jawrence et al. Nature 2014
STAG2	Acute myeloid leukemia de novo	unreported	frameshift nonsense missense	10	197	5.1 Kibara et al. Leukemia 2014
STAG2	Bladder cancer	substitution indel	missense nonsense evon junction framshift	25	111	22.5 Solomon et al. Nature Genetics 2013
STAG2	Bladder cancer	substitution, indel	missense nonsense frameshift deletion solice	67	307	21.8 Taylor et al. Human Molecular Genetics 2014
STAG2	Bladder cancer	upreported	unrenorted	10	99	10.1 Lawrence et al. Nature 2014
STAG2	Bladder cancer transitional cell carcinoma	substitution indel	nonsense missense exon junction	11	99	11.1 Guo et al. Nature Genetics 2013
STAG2	Bladder cancer, transitional cell carcinoma	CNV deletion	deletion	5	99	5 1 Guo et al. Nature Genetics, 2013
31/(02	Bladder urotholial carrinoma	substitution indel	uproported	10	09	10.2 Kandoth et al. Nature 2012
STAG2		substitution, inder	ponconco	11/	50	10.2 Kalidoth et al., Nature, 2015
STAG2	Broast cancor	CUDCTITUTIOD	nonsense	1	104	1 STODDODC OF 31 MOTUFO (1116
STAG2 STAG2 STAG2	Breast cancer Broast cancer	substitution	uproported	1	104	1 Stephens et al., Nature, 2016
STAG2 STAG2 STAG2	Breast cancer Breast cancer	unreported	unreported	1 11 2	104 892	1 Stephens et al., Nature, 2016 1.2 Lawrence et al., Nature, 2014
STAG2 STAG2 STAG2 STAG2 STAG2	Breast cancer Breast cancer Chronic myelogenous leukemia	substitution unreported substitution	unreported nonsense for a selice	1 11 2	104 892 64	1 Stephens et al., Nature, 2016 1.2 Lawrence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 10.2 Kon et al., Nature Genetics, 2013
STAG2 STAG2 STAG2 STAG2 STAG2 STAG2	Breast cancer Breast cancer Chronic myelogenous leukemia Chronic myelomonocytic leukemia Chronic melositatione and cancer	substitution unreported substitution substitution, indel	unreported nonsense frameshift, nonsense, splice	1 11 2 9	104 892 64 88	1 Stepnens et al., Nature, 2016 1.2 Lawrence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 10.2 Kon et al., Nature Genetics, 2013 1.2 Kon et al., Nature Genetics, 2013
STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2	Breast cancer Breast cancer Chronic myelogenous leukemia Chronic myelomonocytic leukemia Clear cell renal cell carcinoma	substitution unreported substitution substitution, indel	unreported nonsense frameshift, nonsense, splice unreported	1 11 2 9 7	104 892 64 88 417	1 Stephens et al., Nature, 2016 1.2 Lawrence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 10.2 Kon et al., Nature Genetics, 2013 1.7 Cancer Genome Atlas Research et al., Nature, 2013
STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2	Breast cancer Breast cancer Chronic myelogenous leukemia Chronic myelomonocytic leukemia Clear cell rena cell cancionma Colorectal cancer	substitution substitution substitution, indel substitution	umeported norsense frameshift, nonsense, splice umreported umreported missense	1 11 2 9 7 4	104 892 64 88 417 72	1 Stephenes et al., Nature, 2016 1.2 Lawrence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 10.2 Kon et al., Nature Genetics, 2013 1.7 Cancer Genome Attas Research et al., Nature, 2013 5.6 Seshagiri et al., Nature, 2012
STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2	Breast cancer Breast cancer Chronic myelogenous Jeukemia Chronic myelogenous Jeukemia Celar cell renal cell carcinoma Colorectal cancer Ewing's sarcoma	substitution unreported substitution substitution, indel substitution substitution	urreported nonsense frameshift, nonsense, splice urreported missense 5' UTR	1 11 2 9 7 4 1	104 892 64 88 417 72 24	1 Stephens et al., Nature, 2016 12 Lavvence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 10.2 Kon et al., Nature Genetics, 2013 1.7 Cancer Genome Atlas Research et al., Nature, 2013 5.6 Sensagiri et al., Nature, 2012 4.2 Solomon et al., Science, 2011
STAG2 ST	Breast cancer Breast cancer Ornoric myelogenous leukemia Chronic myelomonocytic leukemia Clear cell rena cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's sarcoma	substitution unreported substitution substitution, indel substitution substitution, indel, duplication	umeported norsense frameshift, nonsense, splice umeported wissense S' UTR nonsense, missense, exon junction, frameshift, exon duplication	1 11 2 9 7 4 1 19	104 892 64 88 417 72 24 112	1 Stephenis et al., Nature, 2016 12 Lavarence et al., Nature, 2016 102 Kon et al., Nature, Genetics, 2013 107 Cancer Genome, Atlas Research et al., Nature, 2013 56 Seshagint et al., Nature, 2012 42 Solomon et al., Science, 2011 17 Truche et al., Cancer Discovery, 2014
STAG2 ST	Breast cancer Breast cancer Chronic myelogenous leukemia Character et real cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma	substitution unreported substitution substitution substitution substitution, indel, duplication substitution, indel, duplication	umeported nonsense frameshift, nonsense, splice umeported missense 5 UTR nonsense, missense, exon junction, frameshift, exon duplication nonsense, missense, exon junction, frameshift, exon duplication, in-frame deletion	1 11 2 9 7 4 1 19 41	104 892 64 88 417 72 24 112 199	1 Stephens et al., Nature, 2016 12 Lavvence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 10.2 Kon et al., Nature, Genetics, 2013 1.7 Cancer Genome Atlas Research et al., Nature, 2013 5.6 Seshajeri et al., Nature, 2014 2.5 Gostajeri et al., Nature, 2014 2.5 Giroda et al., Cancer Discovery, 2014 2.6 Tiroda et al., Cancer Discovery, 2014
STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2	Breast cancer Breast cancer Chronic myelogenous leukemia Chronic myelogenous leukemia Celore cell ena cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma	substitution unreported substitution, indel substitution substitution, indel, duplication substitution, indel, duplication substitution, indel substitution, indel	umeported nonsense frameshift, nonsense, splice umeported visconse S'UTR nonsense, missense, exon junction, frameshift, exon duplication nonsense, missense, exon junction, frameshift, exon duplication, in-frame deletion exon junction, nonsense, frameshift, duplication, deletion, 3' UTR	1 11 2 9 7 4 1 19 41 14 3	104 892 64 88 417 72 24 112 199 65 11	1 Stephenis et al., Nature, 2016 12 Lawrence et al., Nature, 2016 13 Likon et al., Nature, 2016 10 Z Kon et al., Nature, 2016 13 Z Kon et al., Nature, 2016 15 Sestinger et al., Nature, 2011 14 Solomon et al., Science, 2011 15 Gridde et al., Cancer Discovery, 2014 21 Solomot et al., JCAN 2014
STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2 STAG2	Breast cancer Breast cancer Ohronic myelogenous leukemia Ohronic myelonoorchic leukemia Olear cell enal cell carcinoma Colorectal cancel Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma	substitution unreported substitution substitution substitution substitution substitution, indel, duplication substitution, indel substitution, indel substitution, indel	umeported nonsense frameshift, nonsense, splice umeported S' UTR onsense, missense, exon junction, frameshift, exon duplication nonsense, missense, exon junction, frameshift, exon duplication, in-frame deletion exon junction, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense exon junction frameshift	1 11 2 9 7 4 1 19 41 14 3 8	104 892 64 88 417 72 24 112 199 65 11 96	1 Stephens et al., Nature, 2016 12 Lavarence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 1.0 Cancer Genome Atlas Research et al., Nature, 2013 5.6 Seshajeri et al., Nature, 2014 4.2 Solomon et al., Science, 2011 1.7 Trode et al., Cancer Discover, 2014 20.6 Trode et al., Concer Discover, 2014 21.5 Rohl et al., PLoS Genetics, 2014 27.3 Agelopoulos et al., Clinical Cancer Research, 2015 8.3 Common et al. Lacaret
STAG2 STAS	Breast cancer Breast cancer Chronic myelogenous leukemia Chronic myelomonocytic leukemia Celar cell rena cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma	substitution unreported substitution, indel substitution substitution substitution substitution, indel, duplication substitution, indel substitution, indel substitution, indel	umeported nonsense frameshift, nonsense, splice umeported S'UTR nonsense, missense, exon junction, frameshift, exon duplication nonsense, missense, exon junction, frameshift, exon duplication, in-frame deletion exon junction, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense	1 11 2 9 7 4 1 19 41 14 3 8	104 892 64 88 417 72 24 112 199 65 11 96	1 Stephenis et al., Nature, 2016 12 Lavarence et al., Nature, Genetics, 2013 107 Kon et al., Nature, Genetics, 2013 107 Cancer Genome Atlais Research et al., Nature, 2011 56 Seshagin et al., Nature, 2012 42 Solomon et al., Science, 2011 17 Trode et al., Cancer Discovery, 2014 205 Trode et al., Cancer Discovery, 2014 215 Konit et al., PuSG Benetics, 2016 213 Konit et al., Colincal Cancer Research, 2015 83 Comptione et al., Clinical Cancer Assession, 2015 83 Comptione et al., Cancer Discovery, 2014
STAG2 STAS	Breast cancer Breast cancer Chronic myelogenous leukemia Charoit myelogenous leukemia Clarcell renal cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma	substitution unreported substitution substitution substitution substitution substitution, indel, duplication substitution, indel substitution, indel substitution, indel substitution, indel	umeported nonsense frameshift, nonsense, splice umeported S' UTR nonsense, missense, exon junction, frameshift, exon duplication nonsense, missense, exon junction, frameshift, exon duplication, exon junction, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense nonsense, missense, exon junction, frameshift umeported	1 11 2 9 7 4 1 19 41 14 3 8 12	104 892 64 88 417 72 24 112 199 65 11 96 290	1 Septents et al., Nature, 2016 12 Lavarence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 1.7 Cancer Genome Atlas Research et al., Nature, 2013 5.6 Seshagir et al., Nature, 2014 4.2 Solomon et al., Science, 2011 1.7 Triode et al., Cancer Discovery, 2014 20.6 Trode et al., Cols Centics, 2014 21.5 Roht et al., PLoS Genetics, 2014 23.4 Saydopoulos et al., Clinical Cancer Discovery, 2014 3.4 Kandoh et al., Nature, 2013 3.5 Roht et al., Cancer Discovery, 2014 3.5 Roht et al., Kature, 2013
5TAG2 5T	Breast cancer Breast cancer Chronic myelogenous leukemia Chronic myelomocychic leukemia Clear cell renal cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's sarcoma Ewing's marcoma, pediatric Giobastoma multiforme	substitution unreported substitution substitution substitution substitution, indel, duplication substitution, indel, duplication substitution, indel substitution, indel substitution, indel substitution, indel	umeported nonsense frameshift, nonsense, splice umeported S'UTR nonsense, missense, exon junction, frameshift, exon duplication nonsense, missense, exon junction, frameshift, exon duplication, in-frame deletion exon junction, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense, missense, exon junction, frameshift umeported umeported	1 11 2 9 7 4 1 19 41 14 3 8 12 12	104 892 64 88 417 72 24 112 199 65 11 96 290 290 291	1 Stephenis et al., Nature, 2016 12 Lavarence et al., Nature, Genetics, 2013 10 Kon et al., Nature, Genetics, 2013 10 Cancer Genome, Atlais Research et al., Nature, 2011 56 Seshagin et al., Nature, 2012 42 Solomon et al., Science, 2011 17 Truche et al., Cancer Discovery, 2014 206 Truche et al., Cancer Discovery, 2014 215 Snoth et al., HoSG Genetics, 2014 213 Agelopoulos et al., Clinical Cancer Research, 2015 83 Comptione et al., Clinical Cancer Research, 2015 41 Lavarence et al., Nature, 2014 41 Lavarence et al., Nature, 2014
STA62 S	Breast cancer Breast cancer Chronic myelogenous leukemia Charoic myelomoacytic leukemia Clast cell real cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's Sarcoma Ewing's Ewing's Sarcoma Ewing's Sarcoma Ewing's Sarcoma Ewing's Sarco	substitution unreported substitution substitution substitution substitution substitution, indel, duplication substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel unreported unreported	umeported nonsense frameshift, nonsense, splice umeported S' UTR nonsense, missense, exon junction, frameshift, exon duplication nonsense, missense, exon junction, frameshift, exon duplication, in-frame deletion exon junction, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense nonsense, missense, exon junction, frameshift umeported umeported	1 11 2 9 7 4 1 19 41 14 3 8 12 12 12	104 892 64 88 417 72 24 112 199 65 11 96 290 291 291 291 291	1 Septents et al., Nature, 2016 12 Lavarence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 1.7 Cancer Genome Atlas Research et al., Nature, 2013 5.5 Geshagir et al., Nature, 2012 4.2 Solomon et al., Science, 2011 1.7 Trode et al., Cancer Discovery, 2014 20.6 Trode et al., Concer Discovery, 2014 21.5 Rohl et al., IJOLS Genetics, 2014 23.3 Rombodios et al., Clinical Cancer Research, 2015 8.3 Comgtone et al., Cancer Discovery, 2014 4.1 Kandeth et al., Nature, 2013 4.1 Lavarence et al., Cancel Sciencery, 2014 4.1 Lavarence et al., Cancel Sciencery, 2014 4.1 Lavarence et al., Nature, 2013 4.1 Bornen et al., Cancel Sciencery, 2014 4.1 Cancer Research, 2013 4.1 Bornen et al., Cancel Sciencer, 2014 4.1 Cancer Research, 2013 4.1 Bornen et al., Cancel Sciencer, 2014 4.1 Bornen et al., Sc
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5TAG2 5T	Breast cancer Breast cancer Chronic myelogenous leukemia Charoic myelomoacytic leukemia Clast cell real cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's sarcoma Ewing'sarcoma Ewing'sarcoma Ewing'sarcoma Ewing's sarcoma Ewing'sarco	substrution umported substrution substrution substrution substrution, indel, duplication substrution, indel, duplication substrution, indel substrution, indel substrution, indel umported umported substrution, indel	urreported nonsense frameshift, nonsense, splice urreported S' UTR nonsense, missense, exon junction, frameshift, exon duplication nonsense, missense, exon junction, frameshift, exon duplication, in-frame deletion exon junction, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense nonsense, missense, exon junction, frameshift urreported urreported urreported	1 11 2 9 7 4 1 19 41 14 3 8 12 12 12 12 15 1	104 892 64 88 417 72 24 112 199 65 11 96 290 291 291 291 291 291 291 291	1 Septents et al., Nature, 2016 12 Lavarence et al., Nature, 2014 3.1 Kon et al., Nature Genetics, 2013 1.0 Cancer Genome Atlas Research et al., Nature, 2013 5.6 Seshagir et al., Nature, 2012 4.2 Solomon et al., Science, 2011 1.7 Triode et al., Cancer Discovery, 2014 20.6 Trode et al., Cancer Discovery, 2014 21.5 Rohl et al., IDuS Genetics, 2014 23.8 Agelopoulos et al., Clinical Cancer Research, 2015 8.3 Comgtome et al., Cancer Discovery, 2014 4.1 Lavarence et al., Nature, 2013 4.1 Lavarence et al., Nature, 2014 4.1 Bernnan et al., Cancel Discovery, 2014 4.1 Bernnan et al., Cancel Discovery, 2014 4.1 Bernnan et al., Cancel Discovery, 2014 4.1 Bernnan et al., Cancel, 2016 3.8 Comgtome et al., Nature, 2013 3.8 Coccarellie et al., Nature, 2014 4.1 Bernnan et al., Cancel, 2016 5.0 Longes et al., Nature, 2015 5.0 Longes et al., Nature, 2014 5.0 Longes et al., Nature, 2015 5.0 Longes et al., Na
STA62 STA62	Breast cancer Breast cancer Chronic myelogenous leukemia Chronic myelomocychi cleukemia Clear cell renal cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's sarcoma Ewin	substitution umeported substitution substitution substitution, indel, duplication substitution, indel, duplication substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel umeported umeported iumeported indel	umeported nonsense frameshift, nonsense, splice umeported viscense S'UTR nonsense, missense, exon junction, frameshift, exon duplication, in-frame deletion exon junction, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense nonsense, missense, exon junction, frameshift umeported umeported umeported umeported nonsense	1 1 1 2 9 7 4 1 19 41 14 3 8 12 12 12 12 12 1 1	104 892 64 88 417 72 24 112 199 65 11 96 290 291 291 820 291 820 291 822 48 828	1 Stephenis et al., Nature, 2016 12 Lavarence et al., Nature, 2016 12 Lavarence et al., Nature, Genetics, 2013 107 Kont et al., Nature, Genetics, 2013 107 Cancer Genome, Atlas Research et al., Nature, 2013 56 Seshagin et al., Nature, 2012 42 Solomon et al., Science, 2011 17 Triode et al., Cancer Discovery, 2014 206 Tirode et al., Cancer Discovery, 2014 215 Sondi et al., I-Dis Genetics, 2014 213 Agelopoulos et al., Clinical Cancer Research, 2015 83 Comptione et al., Cancer Discovery, 2014 41 Lavarence et al., Nature, 2013 41 Lavarence et al., Nature, 2014 41 Bernann et al., Calle (2013) 18 Geccarelli et al., Colló 08 Jones et al., Nature, 2012 21 Siolomon et al., Science, 2011
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5TA62 5T	Breast cancer Breast cancer Chronic myelogenous leukemia Chronic myelomoxocytic leukemia Clear cell renal cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's sarcoma Ewi	substitution umeported substitution substitution substitution, indel, duplication substitution, indel, duplication substitution, indel, duplication substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel	umeported nonsense frameshift, nonsense, splice umeported visconses, missense, splice visconses, missense, son junction, frameshift, exon duplication, in-frame deletion exon junction, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense, missense, exon junction, frameshift, deletion, 3' UTR frameshift, nonsense, missense, umeported umeported umeported umeported nonsense frameshift, nonsense, applice frameshift, the splice frameshift	1 11 2 9 7 4 1 19 41 14 41 3 8 12 12 12 12 15 1 1 2 13	104 892 64 88 417 72 24 112 199 65 111 96 290 291 291 291 820 291 221 820 293 224 82 203 224	1 Septents et al., Nature, 2016 12 Lavarence et al., Nature, 2016 12 Lavarence et al., Nature, 2014 10 Z hon et al., Nature, 2016 10 Z hon et al., Nature, 2018 10 Z hon et al., Nature, 2018 10 Z hon et al., Saince, 2011 11 Tirode et al., Cancer Discovery, 2014 20 G Tirode et al., Cancer Discovery, 2014 21 S fondi et al., IAGS Genetics, 2014 21 Agelopoulos et al., Clinical Cancer Resarch, 2015 23 Groupton et al., Cancer Discovery, 2014 21 Lavarence et al., Nature, 2013 41 Lavarence et al., Nature, 2014 41 Brennan et al., Call Course 21 Solomo et al., Nature, 2014 41 Bernan et al., Call 2014 31 Geocarelli et al., Call 2015 31 Geocarelli et al., Call 2016 31 Solomo et al., Nature, 2012 21 Solomo et al., Stence, 2011 11 Lohr et al., Cancer Cell, 2013
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5TA62 5T	Breast cancer Breast cancer Chronic myelogenous leukemia Chronic myelomoxocyti cluckemia Clear cell renal cell carcinoma Colorectal cancer Ewing's sarcoma Ewing's Sarcoma Ewi	substitution umreported substitution substitution substitution, indel, duplication substitution, indel, duplication substitution, indel substitution, indel substitution, indel substitution, indel substitution indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel substitution, indel	urreported nonsense frameshift, nonsense, splice urreported vissense 5' UTR nonsense, missense, son junction, frameshift, eson duplication, in-frame deletion eson junction, nonsense, frameshift, duplication, deletion, 3' UTR frameshift, nonsense, manshift, duplication, deletion, 3' UTR frameshift, nonsense, missense, eson junction, frameshift urreported urreported urreported urreported missense frameshift, nonsense, splice missense, nonsense, splice missense, nonsense, frameshift, splice	1 11 2 9 7 4 1 19 41 14 3 8 12 12 12 12 12 12 12 12 12 12 13 300 9 9	104 892 64 88 417 72 24 119 65 11 96 65 11 96 5290 291 820 291 820 125 48 203 224 386 150	1 Septents et al., Nature, 2016 12 Lavarence et al., Nature, 2014 3.1 Kon et al., Nature, Genetics, 2013 107 Kon et al., Nature, Genetics, 2013 107 Cancer Genome, Atlas Research et al., Nature, 2013 5.6 Seshagin et al., Nature, 2012 4.2 Solomon et al., Science, 2011 107 Trode et al., Cancer Discovery, 2014 20.6 Trode et al., Cancer Discovery, 2014 21.5 Ronit et al., IAGS Genetics, 2014 21.3 Ronit et al., IAGS Genetics, 2014 4.1 Kandoth et al., Mature, 2013 4.1 Lavarence et al., Nature, 2014 4.1 Lavarence et al., Nature, 2014 4.1 Brennan et al., Calle, 2014 4.1 Brennan et al., Calle, 2014 4.1 Brennan et al., Calle, 2014 3.6 Geocarelli et al., Coll, 2014 3.6 Socomet et al., Nature, 2012 1.5 Solom et al., Science, 2011 1. Lohr et al., Cancer Cell, 2014 3.6 Kont et al., Nature, 2013 3.6 Thota et al., Block, 2014 6 Walter et al., Leukema, 2013
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