

## Genetics III: Human Genetics

### 51. Human Genetics

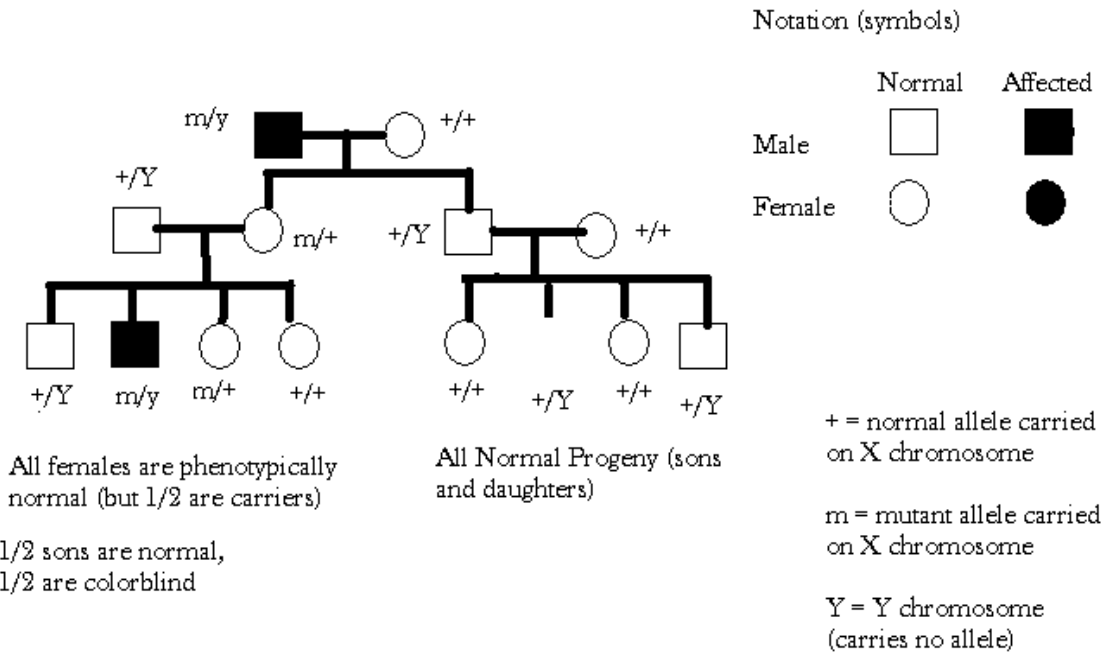
Pedigrees are used to show the inheritance of human genetic diseases.

A pedigree in which one can trace the pattern of inheritance of a genetic trait.

#### Modes of inheritance of genetic diseases

##### 1) X-linked (sex-linked) inheritance (X-linked recessive trait)

###### a) Pedigree:



In X-linked traits with a recessive phenotype, females are carriers. Carrier females have the mutant allele, but do not exhibit the trait.

###### b) Characteristics of an X-linked inherited trait:

1) Predominantly affects males - males only need 1 copy of mutant allele to show trait.

(trait is rare in females - they need to be  $m/m$  to show the trait - occurs if affected male marries carrier female)

2) Affected males ( $m/y$ ) do not transmit trait to sons (do not transmit mutant allele)

3) The trait "skips" generations - Females are unaffected carriers - carry the mutant allele, but do not exhibit the trait, therefore they appear phenotypically normal.

4) Carrier females can transmit the trait (mutant allele) to  $\frac{1}{2}$  sons and  $\frac{1}{2}$  daughters.

5) Affected females transmit mutant allele to all sons and all daughters (daughters become carriers)

Why are males predominantly affected by sex-linked traits?

- Need only 1 mutant copy of gene to exhibit trait

Males:  $\frac{m}{Y}$   $X^m$  affected males lack good copy of gene

Females:  $\frac{m}{+}$   $X^m$  carrier females still have good copy of gene

$\frac{+}{+}$   $X^+$

Examples: red-green color-blindness, hemophilia

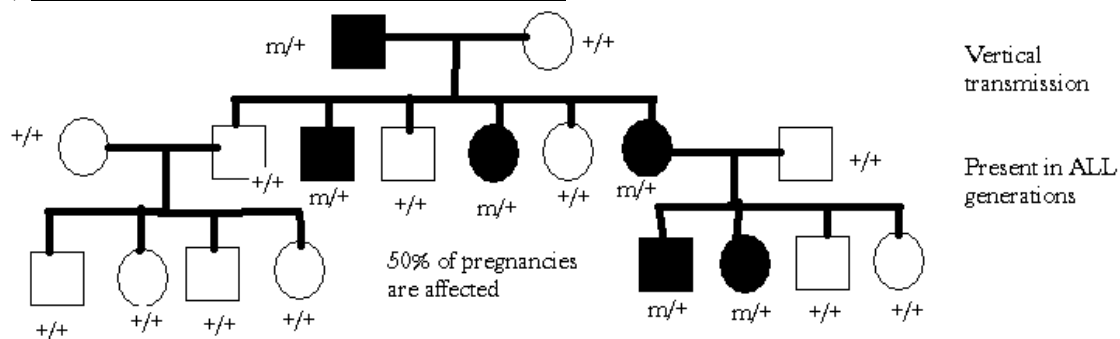
Genes that are affected in these diseases are carried on X chromosomes.

## 2) Autosomal Dominant Inheritance

Autosomes (non sex chromosomes)

Humans have 22 pairs of autosomes and 1 pair of sex chromosomes

### a) Pedigree of an autosomal dominant trait



### b) Characteristics of an Autosomal Dominant Trait (e.g. Huntingtons Disease)

- 1) Heterozygotes are affected - only 1 copy of allele necessary to be affected with trait
- 2) Trait is present in every generation (does not "skip")
- 3) Affects males and females equally
- 4) Affected individuals m/+ transmit trait to 50% of progeny. If affected is m/m ALL children get the trait.
- 5) Unaffected individuals never transmit trait.

Huntington's Disease - brain degeneration - occurs 40-50 years old.

Huntington's disease is a disease that shows full penetrance - which means that if you have the mutant allele - always have the disease phenotype.

For most diseases however, if you are m/+ you will get disease with certain probability.

This is due to incomplete penetrance - having mutant allele does not mean that you will always get the disease phenotype. Heterozygotes (m/+) show trait with probability  $p < 100\%$

Examples of disease that show incomplete penetrance:

Colon cancer: ~80% of individuals with m/+ genotype will develop cancer

Type I diabetes (juvenile onset diabetes): shows ~30% penetrance

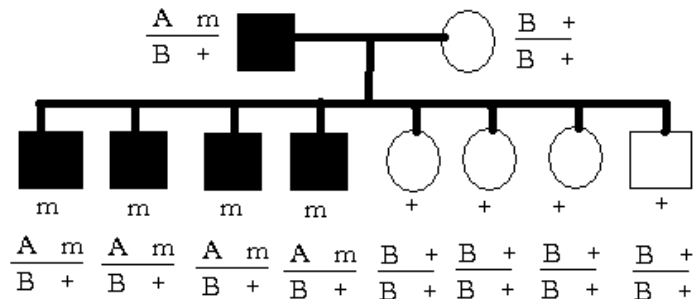
Breast Cancer: ~85% of individuals with mutant allele develop breast cancer.

Two genes implied: BRAC1, BRAC2 (Breast Cancer). Genes found in chromosome #17

It is inherited in an autosomal dominant fashion.

Use linkage to other genes to trace and find these mutant genes

Example: Pedigree showing the inheritance of a mutant gene (m)



A and B are MUTANT ALLELES of some gene with sequence differences (DNA spelling differences)

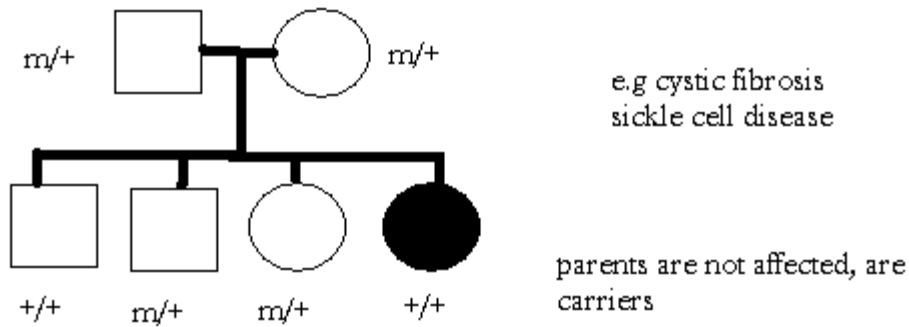
mutant allele A is transmitted with mutant allele m  
 mutant allele B is transmitted with wild-type allele +

Since phenotype of mutant allele A is always seen with phenotype of mutant allele of disease gene (m), we can say that A is linked to m, therefore it is close to it on the chromosome. Likewise, B must be linked to the wild-type allele.

If A is seen with wild-type phenotype or B is seen with the mutant (disease) phenotype, we can assume that recombination has occurred.

### 3) Autosomal Recessive Inheritance

a) pedigree:



1/4 wild type, 1/2 carriers, 1/4 affected

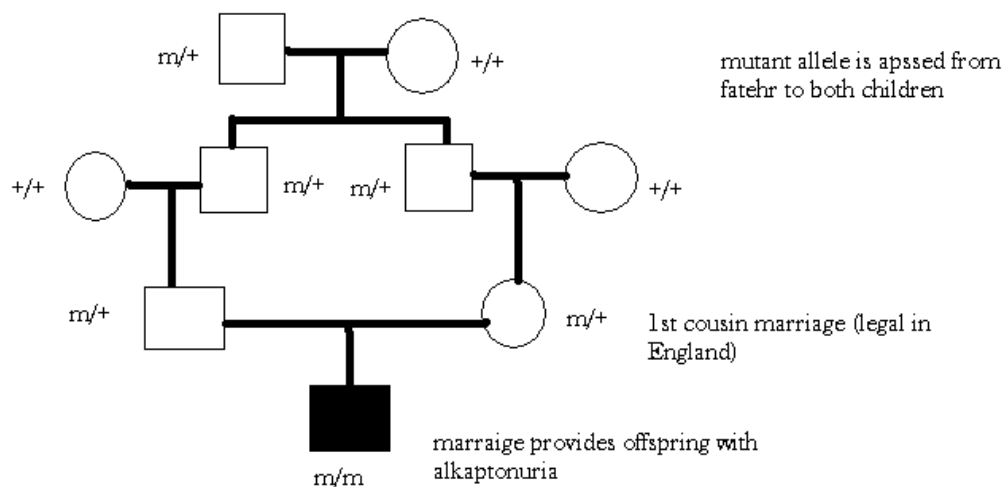
b) Characteristics of an autosomal recessive trait:

- 1) Not present in every generation, in a large pedigree may be only 1 or 2 persons affected
- 2) Parents not usually affected - 1/4 of progeny are affected
- 3) Offspring of affected not usually affected (not usually transmitted to next generation)
- 4) Affects both males and females equally

This type of inheritance was studied by: Archibald Garrod (English Physician ~1900's)

Garrod studied patients with the disease alkaptonuria -

- phenotype of alkaptonuria is that person's urine turns black upon exposure to air
- studied patients with alkaptonuria and found that 8/17 were children of 1<sup>st</sup> cousin marriages
- this led Garrod to believe that alkaptonuria was a genetic disease



- Inbreeding increases the chance that a disease allele (m) that is rare in the population, becomes heterozygous (m/m)
- Many rare diseases are the result of inbreeding; e.g. albinism cases are due to 1<sup>st</sup> cousin marriages.

Garrod investigated why the urine of alkaptonurics turned black upon exposure to air.

- found that patients with alkaptonuria excreted large amounts of homogentisic acid (HGA), which turns black upon exposure to air.
- he hypothesized that HGA was produced from the breakdown of proteins, especially amino acids phenylalanine and tyrosine
- HGA oxidizes (upon exposure to air) and turns into a black substance

Garrod tested his hypothesis by feeding patients:

- 1) High protein diet → result: increased amounts of HGA in urine
- 2) Phenylalanine → result: increased HGA in urine
- 3) Tyrosine → result: increased HGA in urine
- 4) HGA → result: quantitative increase of HGA in urine.

Garrod proposed that there was a pathway in humans that involved the breakdown of amino acids and also suggested that the alkaptonuria (genetic disease) was due to a block in the breakdown of HGA.

Proteins →→Phenylalanine→Tyrosine→→HGA→XX Product Z

Garrod hypothesized that the disease was due to a biochemical defect. HGA builds up because the enzyme to breakdown HGA is missing in alkaptonuria patients.

Hypothesis: Genetic Disease due to Biochemical Defect.

Garrod realized that genes could encode enzymes, which create biochemical reactions.

He called diseases like alkaptonuria "Inborn errors of Metabolism"

Garrod's work led to the work of Beadle and Tatum who in 1942 developed the notion that one gene corresponds to one enzyme.