# PATTERN OF SINGLE GENE INHERITANCE

GENETIC VESION TEAM

**Pattern of single gene inheritance**

- ❖ Genotype: is a genetic constitution that exists in the genome.

- ❖ Phenotype: the apparent or the reflection of genotype

physical, clinical , cellular, or biochemical manifestation

Of genotype.

- ❖ Allele: a different form of the gene, some genes have two forms, while others have three forms and some genes have hundreds of forms.

- ❖ Regardless of how many forms of this gene are in certain populations within cells only two alleles are present.

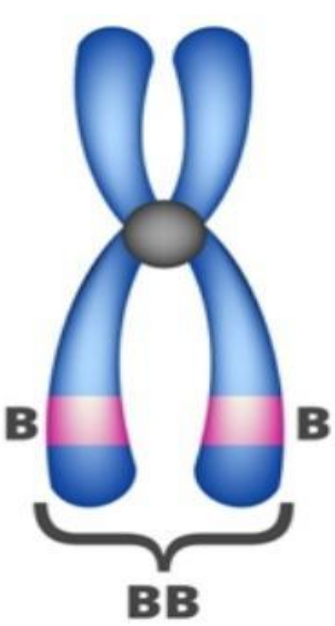
Why two alleles?

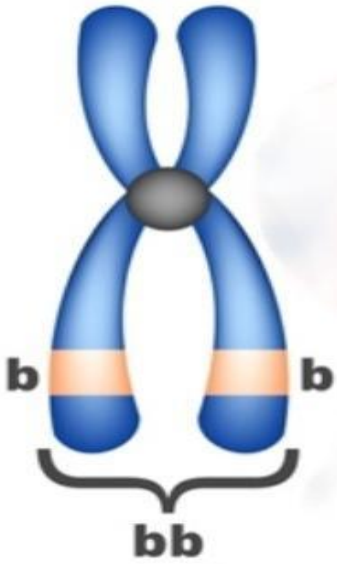
→human is a diploid organism

- ❖ morphometric aspects: are the different measurements of human face, these measurements are the final results of interactions between genes products.

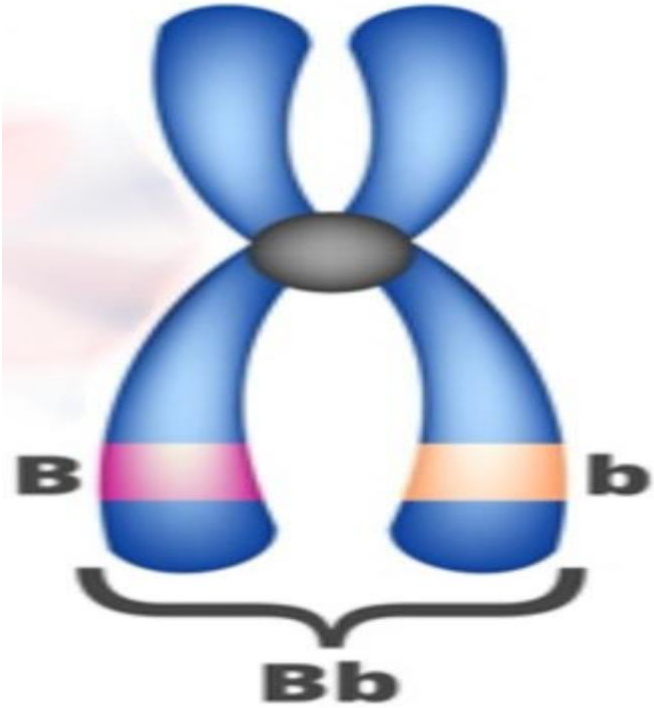
- ❖ homozygous: at the two loci for the same gene for the same gene, we have two similar alleles

BB or bb



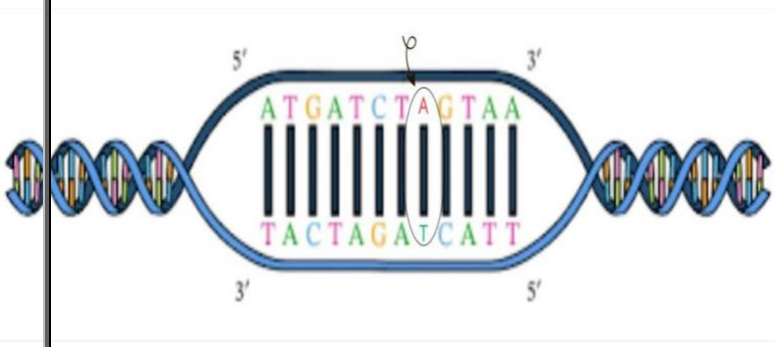




Heterozygous: at two loci for the same gene we have different alleles.

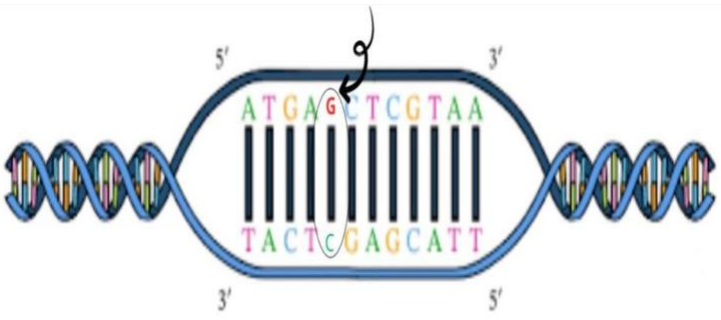


**Compound heterozygous**: for the same gene we have two different.

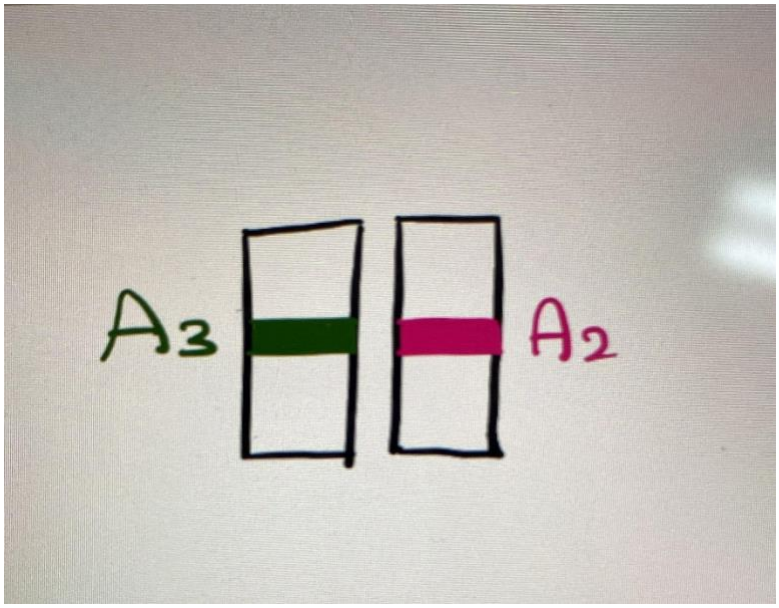
Alleles each have mutations that differ from the other allele


A2




A3




**Compound Heterozygous Genotype**

**The difference between heterozygous and compound heterozygous**

- in heterozygous there is one wild type allele and one mutant allele, in compound heterozygous there are two mutant alleles each has mutation that differs from the other allele.

- The effect of compound heterozygous is similar to two homozygous recessive, but in homozygous recessive the two alleles both have the same mutation.

- **Hemizygous**: one copy of something, like human male XY only has one X chromosome.

- X chromosomes carry genes, because a male has one X chromosome he has only one copy of these genes except genes that exist on pseudo autosomal regions which have two copies.
- **Pseudo autosomal regions: short regions of homology between the mammalian X and Y chromosomes.**

- Single gene disorders: disorders result from problems in a single gene

also called Mendelian disorders why?

→Because Mendel laws apply to them.

All disorders that result from mutation in a single gene were recorded in A book called **Mendelian Inheritance in Man by Victor Mckusick.**

- Pleiotropy: one mutation causes multiple phenotypes.

- Penetrance : In some cases, gene mutation occurs but the phenotype does not appear.

Two individuals might have the same mutation and the disease phenotype appears in one and does not appear in the other individual.

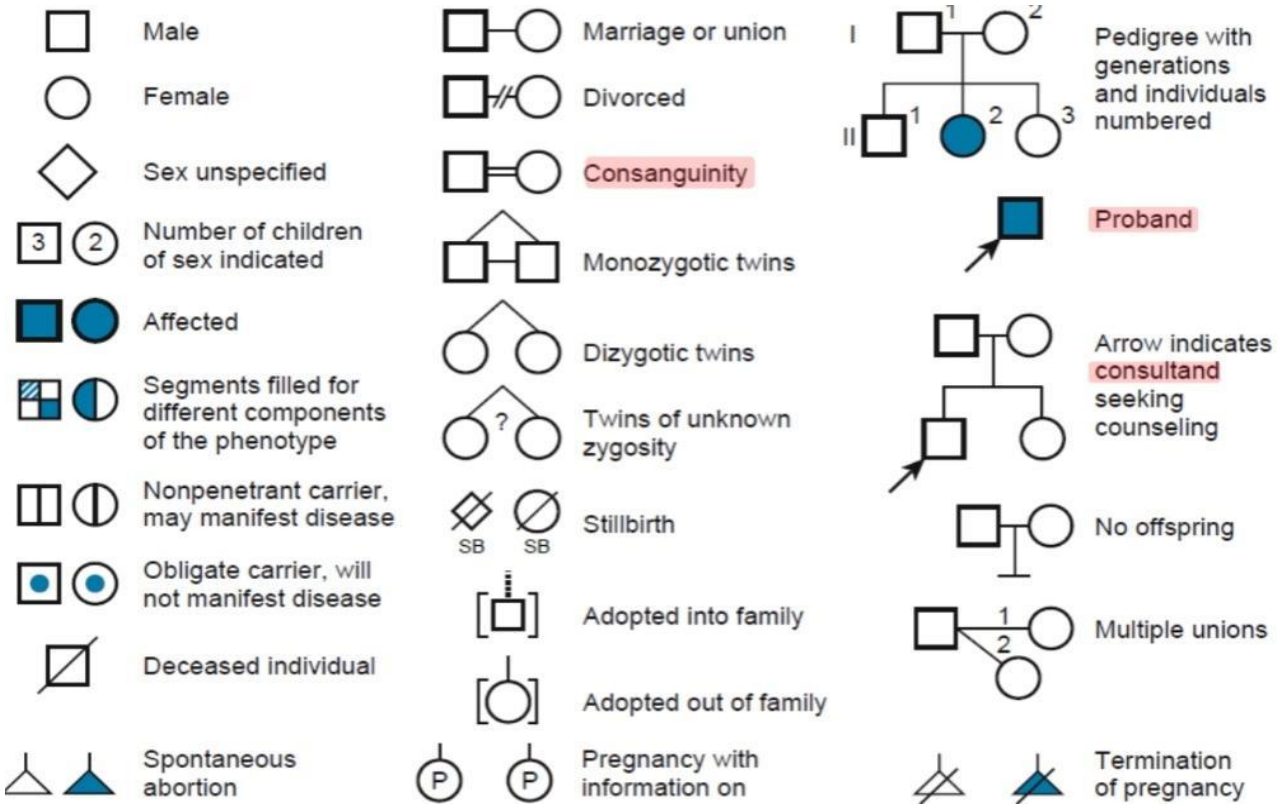
If the mutation occurs and phenotype appears we call it **full or complete penetrance.**

if the phenotype of mutation does not appear we call it **incomplete penetrance.**

- **80% penetrance** means if we have 100 individuals that have the same mutation, mutation phenotype will appear in 80 individuals, and 20 individuals will not show the disease phenotype.

- Expressivity: differences in phenotypes, might happen in two individuals have the same mutation and each has a different phenotypes, individual 1 shows moderate phenotype but individual 2 show sever phenotype.

- Congenital: present with birth .




Deceased individual = dead person

Consanguinity = Relative marriage

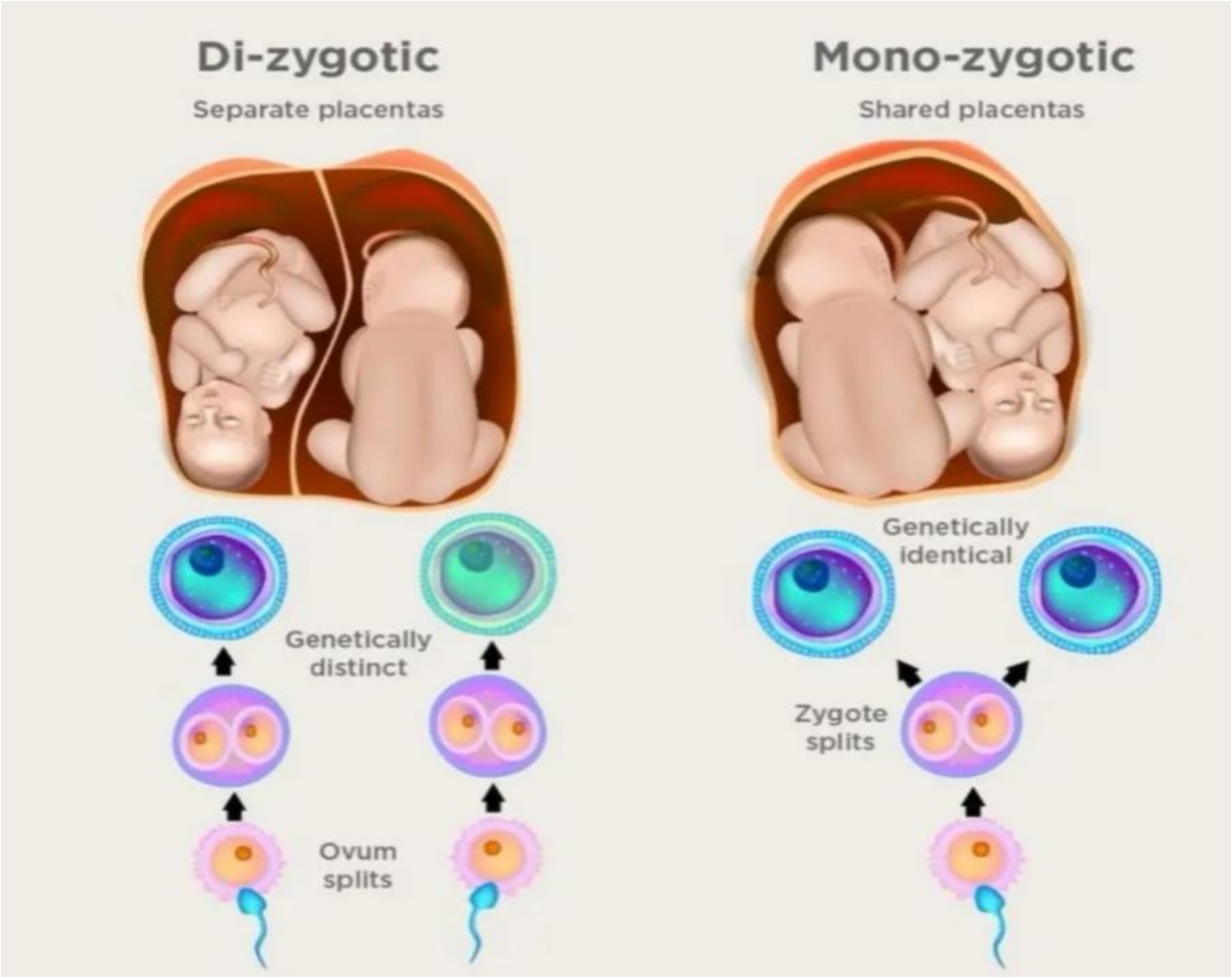
Still birth = loss pregnancy, the fetus is born dead.

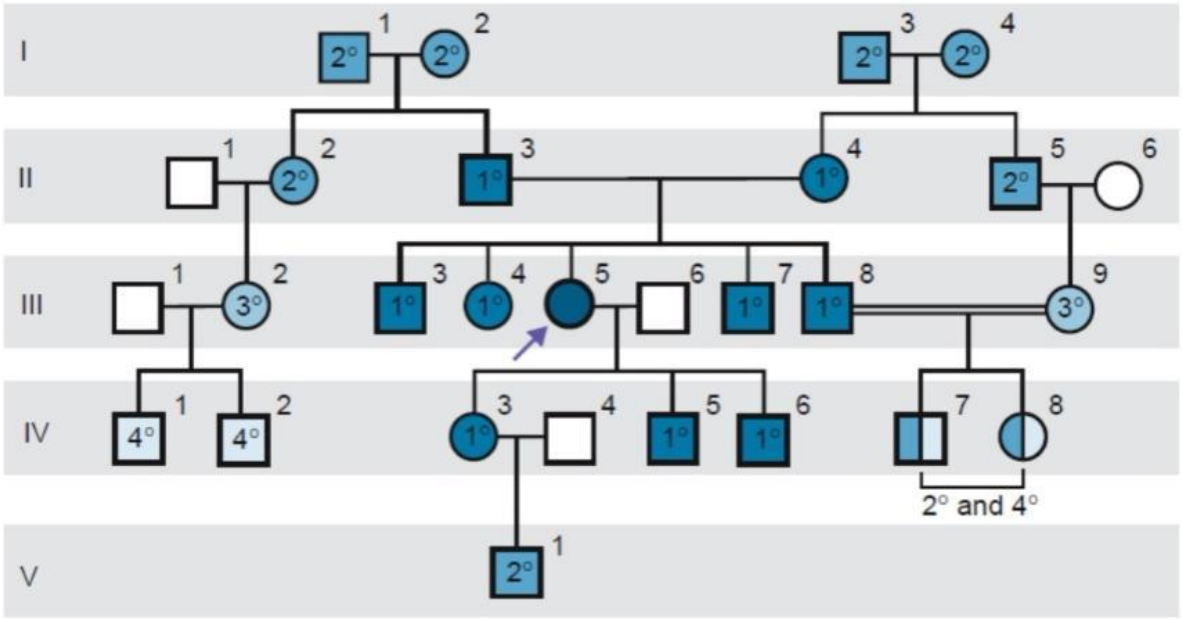
Proband = the first individual discover in  a Family who affected with specific disease or trait.

Consultand = a person who ask the doctor if he had a heritable disease or not.

Mono Zygote twins : result from fertilization of single egg by a single sperm, and the zygote split to two cells each give embryo.

Dizygotic twins ( Fraternal twins): result from fertilization of two eggs by two different sperms during the same pregnancy.






Look at this pedigree, numbers inside squares and circles are related to degree of relativeness.

First-degree relatives ( 1°) : mother, fathers, brothers, sisters, brothers, sons and  daughters.

Second-degree relatives(2°): grandfather, grandmother, paternal uncles and maternal uncles, paternal aunts, and maternal aunts.

Third-degree relatives(3°): cousins.

To determine the relative's degree we need a reference point, for example

you, the degree of relatives in respect to you is different from your

father, grandfather is second degree to you, but grandfather is first degree respect to your father.

- **Siblings**: brothers and sisters
- **The First cousin** : is the direct cousin
- **The second cousins** : are the children of your parent's first cousins
- The First cousin once removed: If your first cousin has a married your daughter.
- Consanguineous: relative marriage.
- **Sporadic**: a new mutation that was not found in the family generation.

→Complications of discerning inheritance pattern

Sometimes it is not easy to distinguish the pattern of gene inheritance :

1-lethal disorders affecting the fetus, the disorder affects the embryo and it could kill the embryo before the diagnosis

2- variable is age onset , some diseases are age-affected, at the beginning the patient appears normal and you record him as normal in pedigree, but after some time the phenotype of the disease appears.

3-reduced penetrance. Some individuals have the mutation, but the disease/phenotype does not appear, and you are going to classify these individuals as normal, but they carry the mutation.

4- variable is the family size

**As the size of a family increases it becomes more easy to trace the mutation and draw the correct pedigree**.

**Recessive disease** : two mutations ( two mutant alleles) must exist to allow expression of the mutation, one allele is not enough.

**Dominant disease** : only one mutation is sufficient to express the disease.

**Incomplete dominant**: There is a difference in the phenotype between an individual who has only one copy of mutation from another individual who has two copies of mutation.

**→Aa is different from AA.**

**Pure dominant** : the phenotype of only one copy of the mutation is the same phenotype for two copies of the mutation

**→Aa=AA**

In most cases, the disorders are **incompletely dominant.**

**Co-dominant : both alleles express themselves.**

- Blood groups are excellent examples of multiple alleles, according to ABO system has three alleles IA , IB, and I but within **our cells only two alleles present.**
- Also, shows complete dominant IA is completely dominant to i , And IB is completely dominant to i
- IAIA =IAi ( pure dominant )
- Codominant: IA and IB

Autosomal recessive inheritance

- ❖ Two mutant alleles must exist to express disorders, only 1 allele is not enough
- ❖ **In autosomal recessive disorders, there is no vertical transmission ( not All generations in the family have the disease)**

- ❖ We have three cases

Case 1

Carrier with carrier

| Carrier by Carrier | | Parent 2 Genotype R/r Gametes | | |
|---|---|---|---|---|
| | | R | r | Risk for Disease |
| Parent 1 Genotype R/r | Gametes R | R/R | R/r | ¼ Unaffected (R/R)<br>½ Unaffected carriers (R/r)<br>¼ Affected (r/r) |
| | Gametes r | R/r | r/r | |

The probability of offsprings: 25% non-affected RR , 50% carrier ( non affected) Rr, and 25% affected rr.

Case 2

Carrier with affected

| Carrier by Affected | | Parent 2 Genotype r/r Gametes: r | Parent 2 Genotype r/r Gametes: r | Risk for Disease |
|---|---|---|---|---|
| Parent 1 Genotype R/r | Gametes: R | R/r | R/r | ½ Unaffected carriers (R/r)<br>½ Affected (r/r) |
| | Gametes: r | r/r | r/r | |

Probability of offspring : 50% affected and 50% carrier

Case 3

Affected with affected

| Affected by Affected | | Parent 2 Genotype r/r Gametes: r | Parent 2 Genotype r/r Gametes: r | Risk for Disease |
|---|---|---|---|---|
| Parent 1 Genotype r/r | Gametes: r | r/r | r/r | All affected (r/r) |
| | Gametes: r | r/r | r/r | |

A**ll offspring are affected**

## Autosomal recessive pedigree

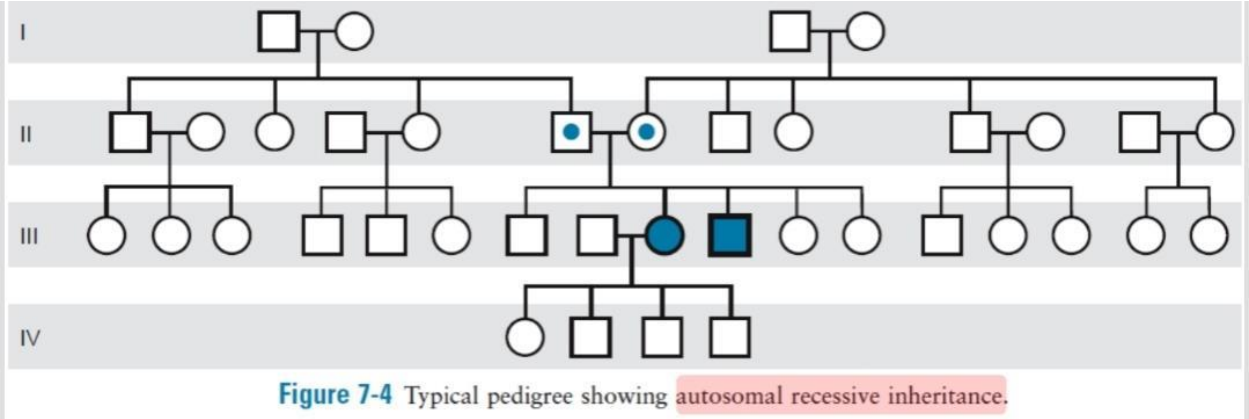



Figure 7-4 Typical pedigree showing autosomal recessive inheritance.

## Sex influence autosomal recessive disorders

- The incidence rate in one sex is higher than in the other sex.

- Hemochromatosis is a sex-influenced autosomal recessive disorder ,which causes an increase in iron absorption which leads to iron accumulation in tissues.

- **Males are 5-10 times more susceptible to become affected.**

**Its thought that there are many reasons :**

1) that females lose large quantities of blood during menstruation, so a lot

of iron will be lost, but males don't undergo menstruation

2) males consume more meats

3) males consume more alcoholic beverages.

Multiple factors play a role.

Another example is cystic which is the common autosomal recessive disease Xeroderma pigmentosum is a rare autosomal recessive disease-related to repair the system, it is rare; because both parents need to be carriers, but in consanguinity the probability increases.

**20% of xeroderma pigmentosum is due to consanguinity, however, it does not mean that consanguinity always causes diseases.**

Consanguinity cases are a 2-fold risk, but not necessary all consanguinities cause the disease.

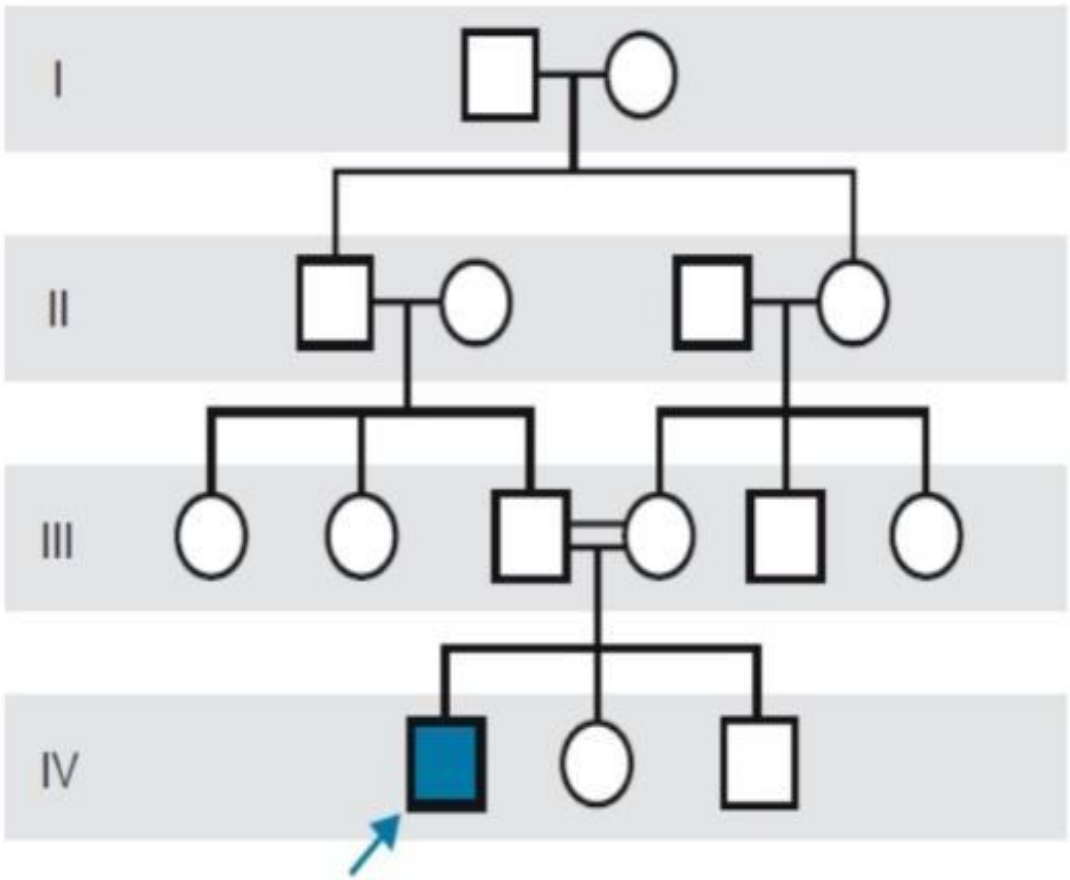



**Figure 7-5** Pedigree in which parental consanguinity suggests autosomal recessive inheritance. *Arrow* indicates the proband.

## Autosomal dominant disorders

- ❖ One mutant allele is enough to cause the disorder

We Have two cases

1 affected with unaffected

| Affected by Unaffected | | | Parent 2 Genotype d/d Gametes: d | Parent 2 Genotype d/d Gametes: d | Risk for Disease |
|---|---|---|---|---|---|
| Parent 1 Genotype D/d | Gametes | D | D/d | D/d | ½ Affected (D/d)<br>½ Unaffected (d/d) |
| | | d | d/d | d/d | |

Probability offsprings : 50% affected and 50% non affected

2 affected with affected

| Affected by Affected | | Parent 2 Genotype D/d Gametes: D | Parent 2 Genotype D/d Gametes: d | Risk for Disease |
|---|---|---|---|---|
| Parent 1 Genotype D/d Gametes | D | D/D | D/d | Strictly dominant<br>¾ Affected (D/D and D/d)<br>¼ Unaffected (d/d) |
| | d | D/d | d/d | Incompletely dominant<br>¼ Severely affected (D/D)<br>½ Affected (D/d)<br>¼ Unaffected (d/d) |

Result offspring: DD, Dd , Dd, and dd

Now it depends on the gene if the relationship between the two alleles is strictly dominant, the phenotype results from

DD=Dd

if the relationship between alleles is incomplete dominant

the phenotype of DD is different from the phenotype of Dd, DD is more severe because it has two mutations ( two mutant alleles )

- ❖ In the case of pure dominant:75% were affected and 25% unaffected (normal).

- ❖ In the case of incomplete dominant: 25% were severely affected, 50% affected and 25% unaffected.

To distinguish an autosomal dominant pedigree from a recessive pedigree, in an autosomal dominant pedigree there is vertical transmission which means the disease is present in all generations.

The affected individuals are equal to 50% between males and females.

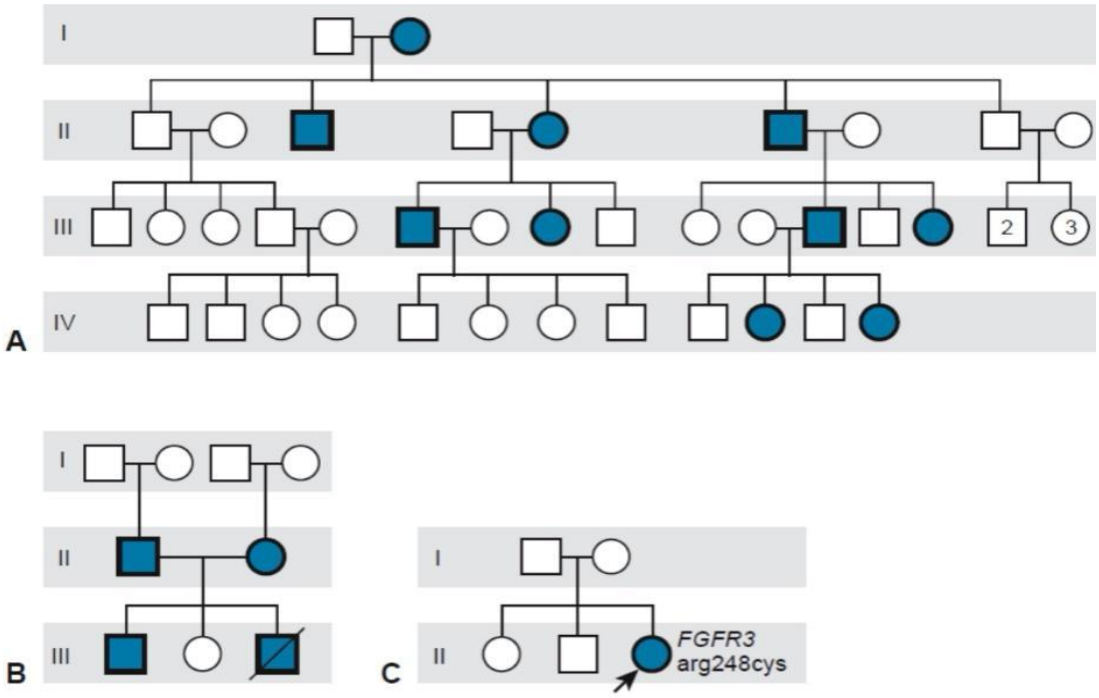



**Figure 7-6** A, Pedigree showing typical inheritance of a form of adult-onset progressive sensorineural deafness (DFNA1) inherited as an autosomal dominant trait. B, Pedigree showing inheritance of achondroplasia, an incompletely dominant (or semidominant) trait. C, Pedigree showing a sporadic case of thanatophoric dwarfism, a genetic lethal, in the proband *(arrow)*.

Achondroplasia: reduce bone growth.

It is an autosomal dominant disorder and it shows incomplete dominant, this mutation occurs in gametogenesis, the parents could be normal and during gametogenesis, the mutation occurs and is transmitted to offspring, if the person has two mutations it is more severe and he  die at an early stage.

**Thanatophoric dwarfism:** is a genetically lethal disorder, the affected individual die before reaching a reproductive age, so the mutation will not be transmitted.

## Sex-limited autosomal disorders

- ❖ Only expressed in one sex and isn't express in the other sex.
- ❖ **Male limited precocious puberty :** ( early adult ) is only expressed in males

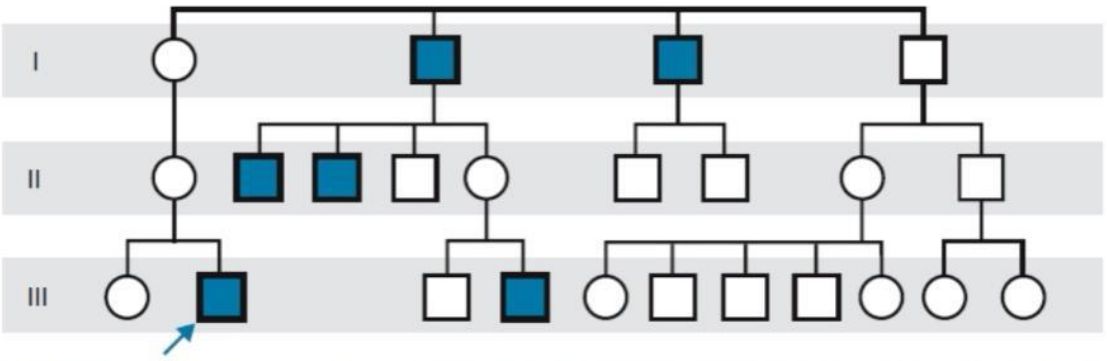



**Figure 7-8** Part of a large pedigree of male-limited precocious puberty in the family of the child shown in Figure 7-7. This autosomal dominant disorder can be transmitted by affected males or by unaffected carrier females. Male-to-male transmission shows that inheritance is autosomal, not X-linked. Transmission of the trait through carrier females shows that inheritance cannot be Y-linked. *Arrow* indicates proband.

Look at this pedigree, there is a male-to-male transmission which means it is not X-linked, also it is not Y-linked because there is a son of an affected male and he isn't affected, females are the only carriers not affected by this disease.

## Effect of incomplete dominant, variable expressivity, and new mutations

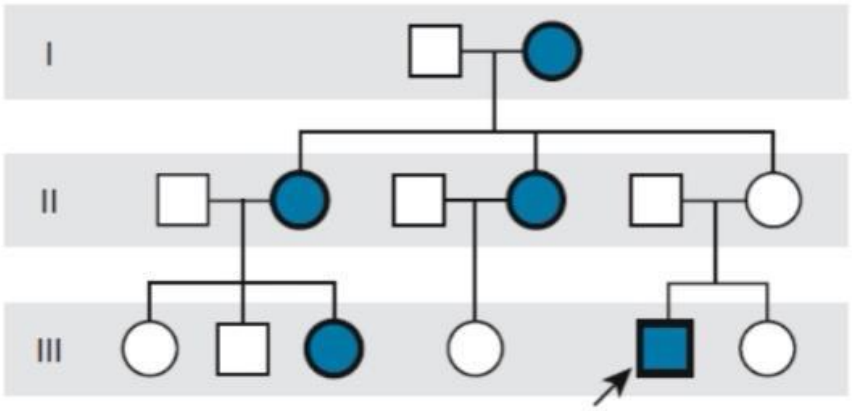



**Figure 7-10** Pedigree of split-hand deformity demonstrating failure of penetrance in the mother of the proband *(arrow)* and his sister, the consultand. Reduced penetrance must be taken into account in genetic counseling.

Look at this pedigree, it's autosomal dominant because the disease is present In all generations, but if you look at generation 2, individual 2 is an affected female and has an unaffected male so it isn't X-linked disease.

If you look to proband he had been affected by the disease, but his parents are not affected, so the explanation for this:

1) A new mutation arose during gametogenesis and this mutation wasn't

exist in parents

2) one of the parents shows incomplete penetrance .

**Neurofibromatosis is age-dependent**, early stage the patient appears normal, but later he becomes affected also this disease is high expressivity.

## Fitness

- ❖ Is the measure of the impact of mutation on reproduction.

**0 fitness**

it is genetically lethal, and the affected individual not reach the reproductive age, so the mutation does not transmit to the next generation.

Example: thanatophoric dwarfism.

All thanatophoric dwarfism individuals receive new mutations from gametogenesis.

**1 fitness**

Late-onset, not affecting reproduction, also can transmit.

Example: progressive hearing loss.

- **Some  mutations are intermediate between 0 and 1**

## X linked inheritance

X chromosome contains 1100 genes

800 genes are protein-coding

300 associated with X-linked phenotypes.

Male XY female XX

Males are either affected or unaffected

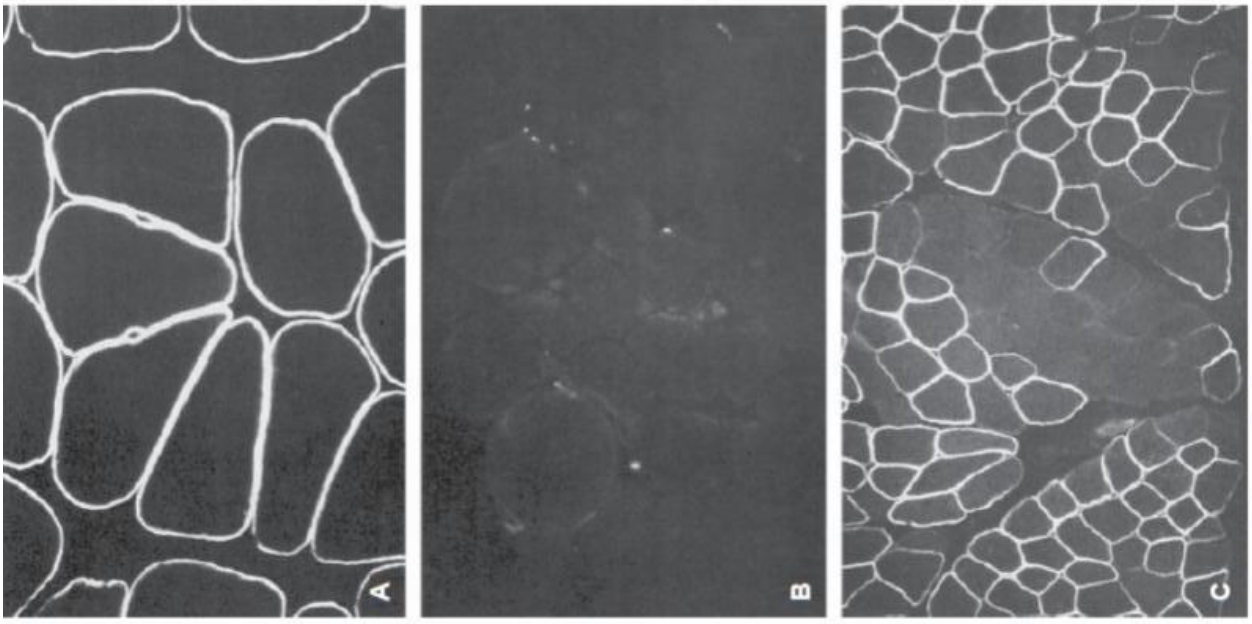
Females could be homozygous or heterozygous

Also, X inactivation plays a role.

If the mutation is recessive only one copy is enough to affect males, but for females it must be two copies.

If the mutation dominant one allele is enough to express the disease .

The effect of X inactivation in X-linked disease , we are going to focus on heterozygous females, for example, Duchene muscular dystrophy which is a X linked recessive disease, dystrophin is a protein that surrounds muscle cells .



in Figure A we have a normal female, in Figure B we have a

male with complete loss of dystrophin, in figure C we have a carrier female ( has a normal allele and mutant allele and each is carried at different X chromosome ).

during X inactivation it randomly selects one of the X chromosomes, so the effect depends on how many X chromosomes are selected (active ) that carry  mutation, so because this process is random

we have three possibilities

1) complete affected female

2 complete un-affected female

3 intermediate ( the severity depends on how many cells contain the X chromosome which carries the mutant allele).

## X linked recessive

hemophilia A: no blood clotting

generally, it is restricted to males because only one copy is enough to cause disease in males.

| Affected Male by Noncarrier Female | | Female Genotype $X_H/X_H$ Gametes | | |
|---|---|---|---|---|
| | | $X_H$ | $X_H$ | Risk for Disease |
| Male Genotype $X_h/Y$ Gametes | $X_h$ | $X_H/X_h$ | $X_H/X_h$ | All female carriers ($X_H/X_h$) |
| | Y | $X_H/Y$ | $X_H/Y$ | All males unaffected ($X_H/Y$) |
| **Unaffected Male by Carrier Female** | | **Female Genotype $X_H/X_h$ Gametes** | | |
| | | $X_H$ | $X_h$ | Risk for Disease |
| Male Genotype $X_H/Y$ Gametes | $X_H$ | $X_H/X_H$ | $X_H/X_h$ | ¼ Noncarrier female ($X_H/X_H$)<br>¼ Carrier female ($X_H/X_h$) |
| | Y | $X_H/Y$ | $X_h/Y$ | ¼ Normal male ($X_H/Y$)<br>¼ Affected male ($X_h/Y$) |

The wild-type allele at the X-linked hemophilia locus is denoted as $X_H$ with an uppercase H, and the mutant allele is denoted as $X_h$ with a lowercase h.

as we said previously the heterozygous individual could be:

complete affected

incomplete affected

intermediate

it depends on how many cells carry the mutant copy of the gene, sometimes heterozygous h cells carry the mutation, and cells that carry normal allele are equal.

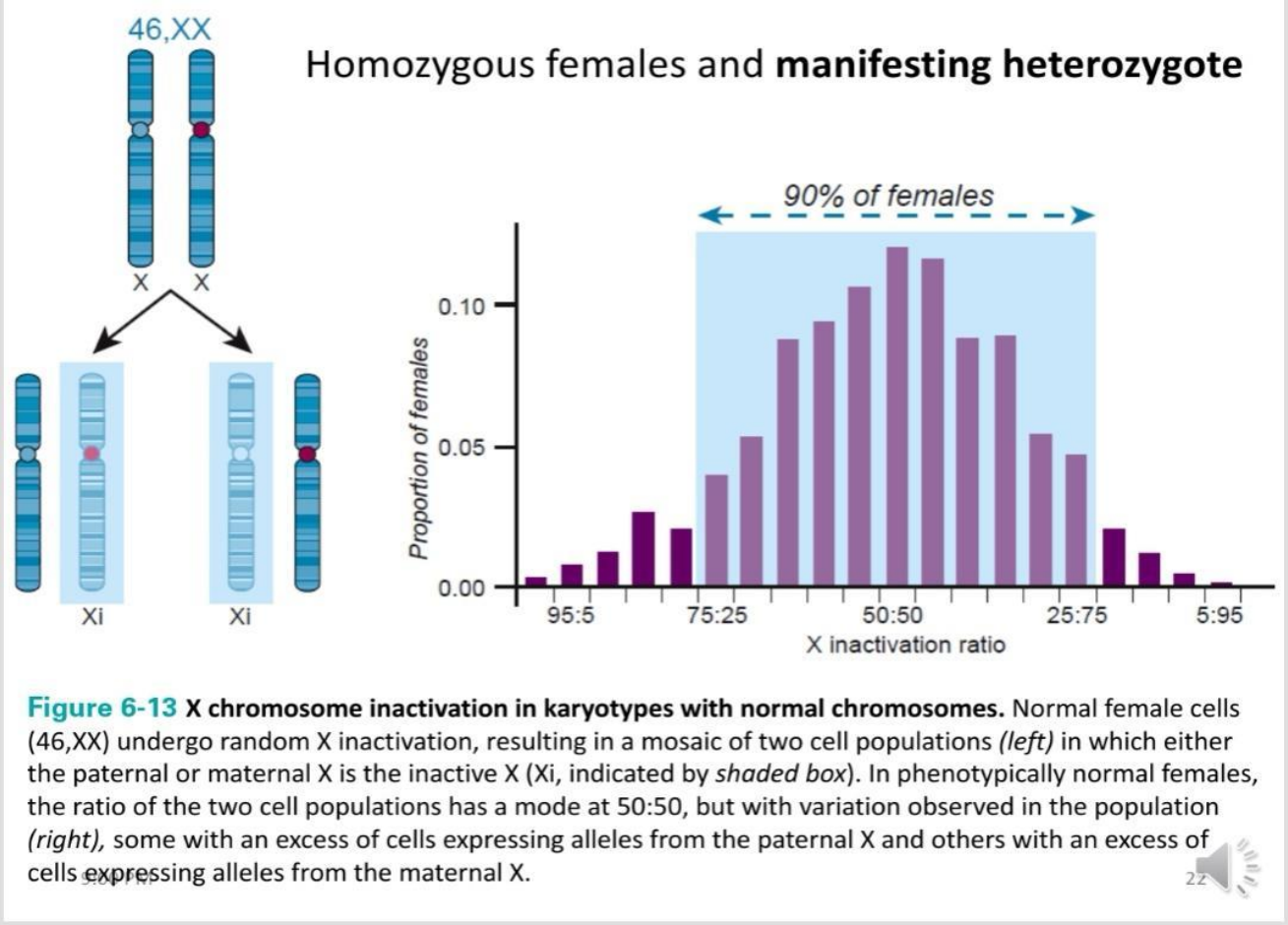



**Figure 6-13 X chromosome inactivation in karyotypes with normal chromosomes.** Normal female cells (46,XX) undergo random X inactivation, resulting in a mosaic of two cell populations *(left)* in which either the paternal or maternal X is the inactive X (Xi, indicated by *shaded box*). In phenotypically normal females, the ratio of the two cell populations has a mode at 50:50, but with variation observed in the population *(right),* some with an excess of cells expressing alleles from the paternal X and others with an excess of cells expressing alleles from the maternal X.

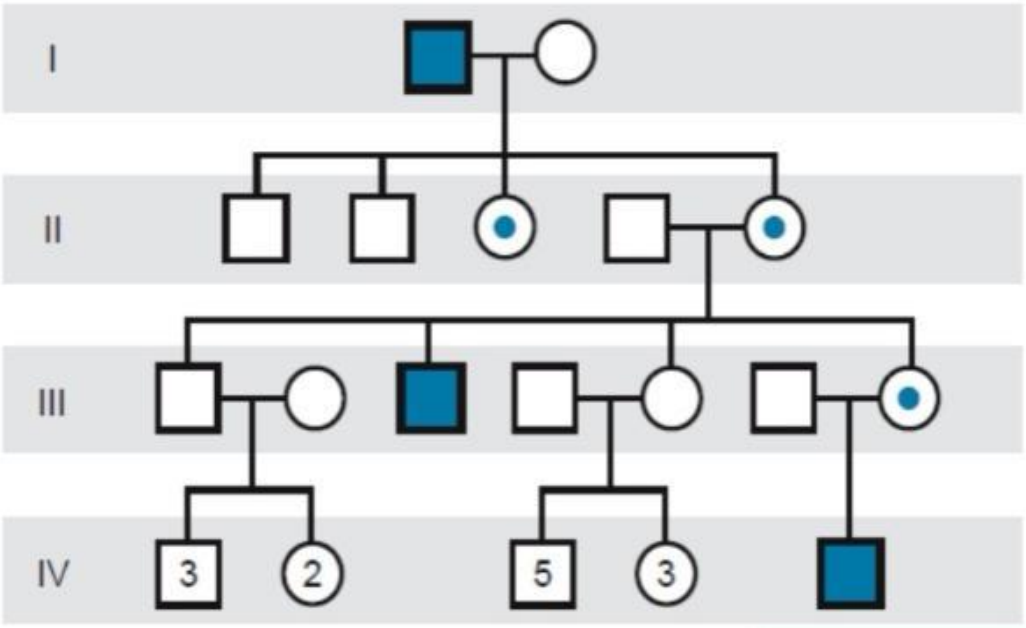



**Figure 7-12** Pedigree pattern demonstrating an X-linked recessive disorder such as hemophilia A, transmitted from an affected male through females to an affected grandson and great-grandson.

## X linked dominants

- ❖ One copy of the mutation is enough to express the disease
- ❖ There is no male-to-male transmission; because the male takes the Y chromosome from his father.
- ❖ For affected males, all daughters will affected.

X-Linked Dominant Inheritance

| Unaffected Male by Affected Female | | Female Genotype $X_D/X_d$ Gametes | | |
|---|---|---|---|---|
| | | $X_D$ | $X_d$ | Risk for Disease |
| Male Genotype $X_d/Y$ Gametes | $X_d$ | $X_D/X_d$ | $X_d/X_d$ | ¼ Affected females ($X_D/X_d$)<br>¼ Unaffected females ($X_d/X_d$) |
| | Y | $X_D/Y$ | $X_d/Y$ | ¼ Affected males ($X_D/Y$)<br>¼ Unaffected males ($X_d/Y$) |
| **Affected Male by Noncarrier Female** | | **Female Genotype $X_d/X_d$ Gametes** | | |
| | | $X_d$ | $X_d$ | Risk for Disease |
| Male Genotype $X_D/Y$ Gametes | $X_D$ | $X_D/X_d$ | $X_D/X_d$ | All females affected ($X_D/X_d$) |
| | Y | $X_d/Y$ | $X_d/Y$ | All males unaffected ($X_d/Y$) |

The wild-type allele at the hypophosphatemic rickets locus is denoted as $X_d$, and the mutant allele is denoted as $X_D$.

## X linked dominant with male lethality

## X-linked dominant with male lethality

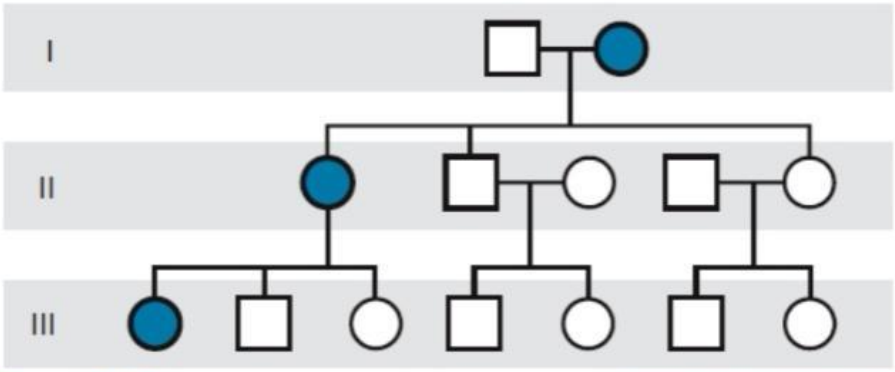



**Figure 7-14** Pedigree pattern demonstrating X-linked dominant inheritance of a disorder that is lethal in males during the prenatal period.

## Rett syndrome
## *MECP2*

If you look at the pedigree the disease only affects females and doesn't affect males.

Actually, the disease also affects the males at prenatal stage, the embryo dies while still in the uterus

, because it is so severe, but females can exist in heterozygous and can survive to adulthood.

## X linked dominant with male sparing.

Males are not affected by the disease, the disease only affects females, with no clear-cut explanations,

Example: **familial female epilepsy and cognitive impairment** is an X-linked dominant, as we said only females

are affected by this disease, the best explanation is that mosaicism female (Heterozygous) has two populations of neurons one has the surface protein essential to communication between neurons and other

the population lacks the protein, so the communication between cells

is disrupted (miscommunication)

But in males, this protein is uniform and completely lacking, so no mismatch.

Also, other proteins will work.

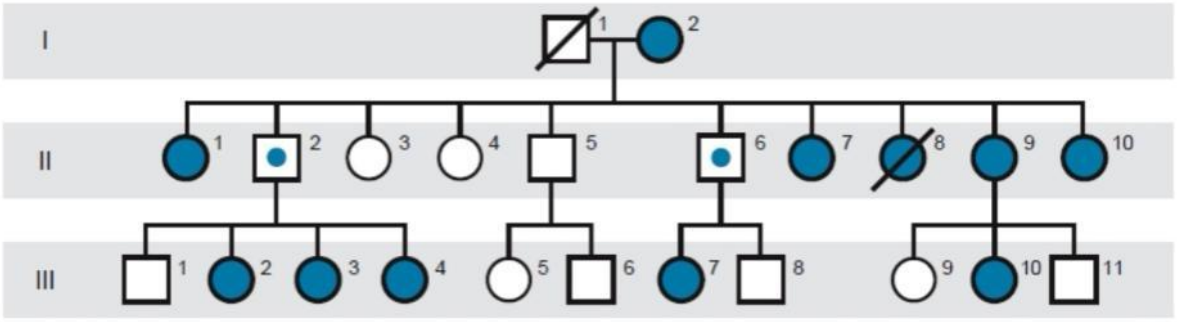



**Figure 7-15** Pedigree pattern of familial female epilepsy and cognitive impairment, demonstrating its X-linked dominant inheritance with sparing of males hemizygous for a premature termination mutation in the protocadherin 19 gene.

Duchene muscular dystrophy has fitness 0, which means the affected

individual dies before reaching the reproductive age

All affected individuals get a new mutation from from carrier mother.

Hemophilia A has a fitness of 70%

Of the 100 affected individuals, 70 could reach reproductive age and

transmit the mutation to the next generation.

## Pseudo autosomal inheritance

Is similar to Autosomal inheritance, but the genes present in pseudo autosomal regions that exist at the X and Y chromosomes.

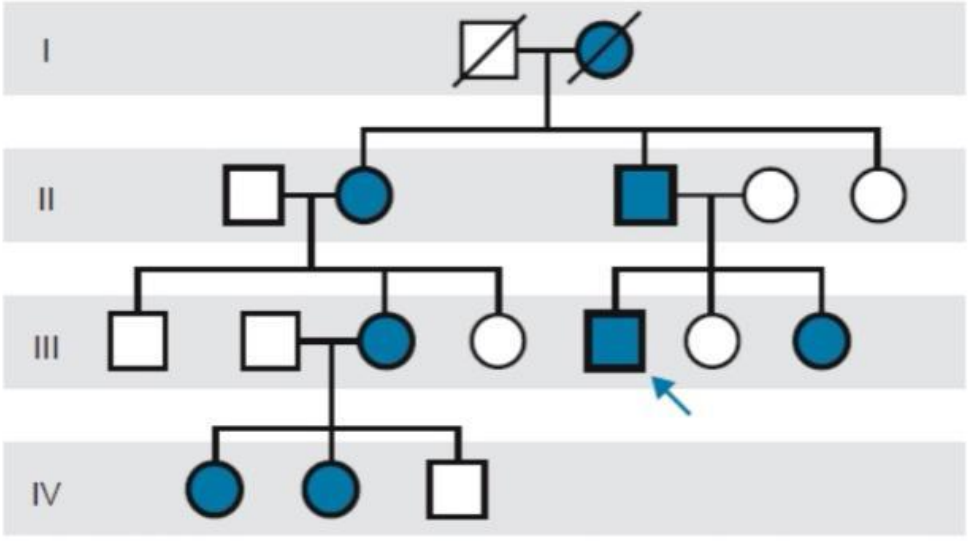



**Figure 7-16** Pedigree showing inheritance of dyschondrosteosis due to mutations in *SHOX*, a pseudoautosomal gene on the X and Y chromosomes. The *arrow* shows a male who inherited the trait on his Y chromosome from his father. His father, however, inherited the trait on his X chromosome from his mother.

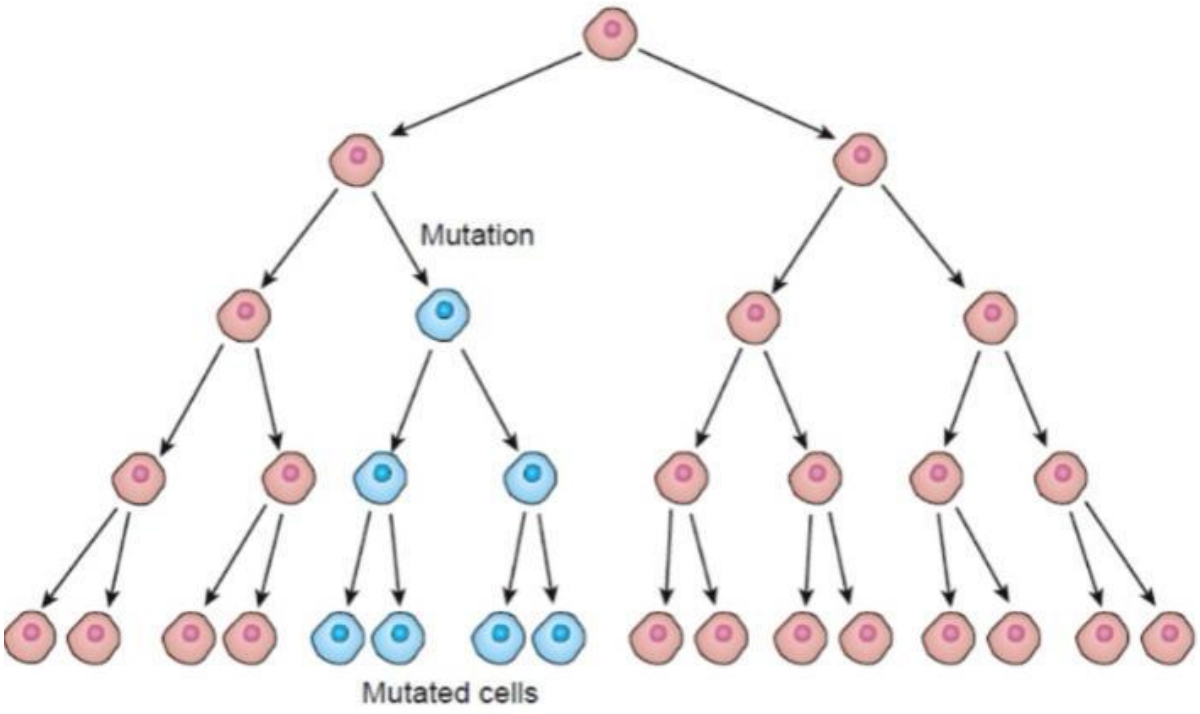
**Mosaicism**

Differences in genetic material in cells within the same body

A mixture of two populations of cells that differ in genotypes.

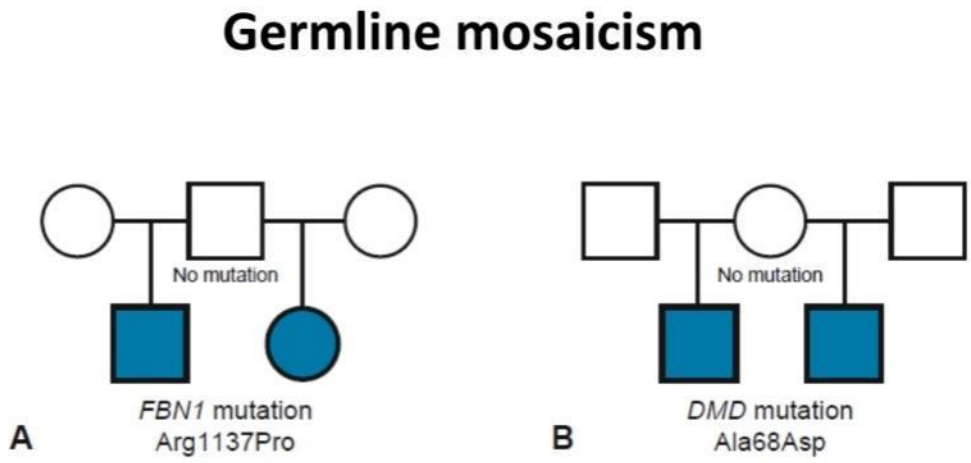
Somatic mosaicism: mutation at the stage of growth, the mutation could

occur in the cell, and this cell divides and produces a population of cells that carry the mutation and also a normal population of cells already exists.




**Germline mosaicism**

At gametogenesis cells that give gametes at the mitotic phase before reaching the meiotic phase, mutation occurs in some of these cells, two population of cells arise.




How can we distinguish a germline mutation from other mutations?

When an individual marries more than one time and each time he has a son or daughter who is affected by mutation.

Note: if you isolate the blood sample from the father you can't detect the mutation because of the mutation in Germline.

The difference between new mutation and germline mutation, germline mutation occurs more than one time, but new mutations occur one time.

**Parent-of-origin effects on inheritance patterns**

**Unusual inheritance pattern due to genomic imprinting**

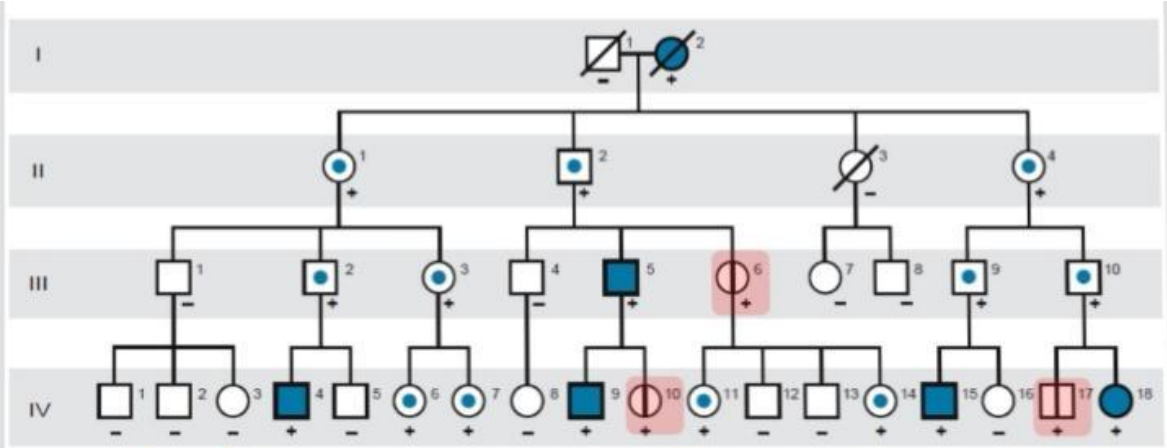


**Figure 7-19** Pedigree of a family with paraganglioma syndrome 1 caused by a mutation in the *SDHD* gene. Individuals II-1, II-2, II-4, III-2, III-3, III-9, III-10, IV-6, IV-7, IV-11, and IV-14 each inherited the mutation from their mothers but are unaffected. However, when the males in this group pass on the mutation, those children can be affected. In addition to the imprinting, the family also demonstrates the effect of reduced and age-dependent penetrance in the children (III-6, IV-10, IV-17) of heterozygous fathers. The + and − symbols refer to the presence or absence of the *SDHD* mutation in this family.

Affected only if the mutation is inherited from the father

It is related to genomic imprinting, some genes only express at the paternal chromosome and others only express at the maternal chromosome.

Each gene has two copies within our cells, for example, gene X, gene X

only expresses at the paternal X chromosome, and doesn’t express at maternal chromosome.

If the mutation occurs in gene X that is present at the paternal chromosome and the mutation is transmitted to offspring, the mutation does not appear because this allele is not expressed at the paternal chromosome ( Already inactivated), but if the mutation occurs at the other copy of gene X that is present at the maternal chromosome, the mutation will transmit and also appear.

Dynamic mutations

Abnormal expansion of repeats ( usually triplets or more )

Polyglutamine disorder and Huntington's disease affect individuals after 40 years.

The features of Huntington's disease

- Anticipation: mutation increases when transmitted from generation to the next.

- Paternal transmission bias: the expansion from father greater than

mother.

Normally repeats between 9- 35 CAG

Affected ≥40

Between 36-39, usually unaffected but high risk of expansion during

transmission special from father we call it reduce penetrance stage or pre-mutation.

Usually transmitted from father to child.

As CAG repeats increases, the age at which individuals become affected decreases.

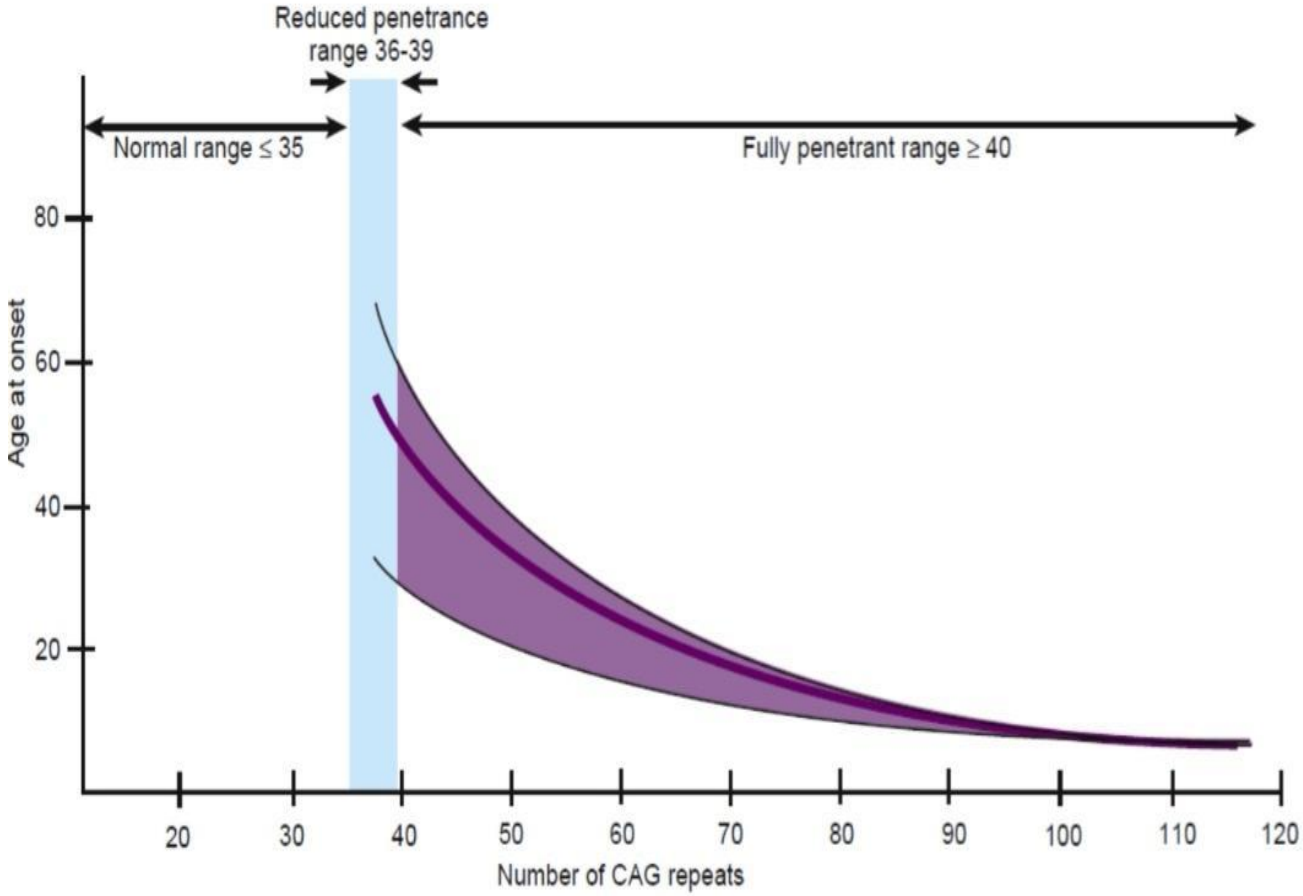



**Figure 7-20** Graph correlating approximate age of onset of Huntington disease with the number of CAG repeats found in the *HD* gene. The *solid line* is the average age of onset, and the *shaded area* shows the range of age of onset for any given number of repeats. *See Sources & Acknowledgments.*

## Fragile X syndrome

Another type of Dynamic mutation, in Huntington's disease, repeats

present in the coding sequence, but in fragile X, Repeats present in 5' UTR.

Usually transmitted from mother to child.

The most common **heritable** form of moderate intellectual disability is **fragile X**

Penetrance in females in the 50%-60% range

Frequency 1 in 3000-4000 male births

CGG in the 5’ UTR of FMR1

Normal ≤55 repeats

Affected >200 repeats

Permutation 56-200

The most common form of moderate intellectual ability disorder is **down syndrome**.

Relationship between the number of repeats in pre-mutation allele and Frequency of expression in Heterozygous female.

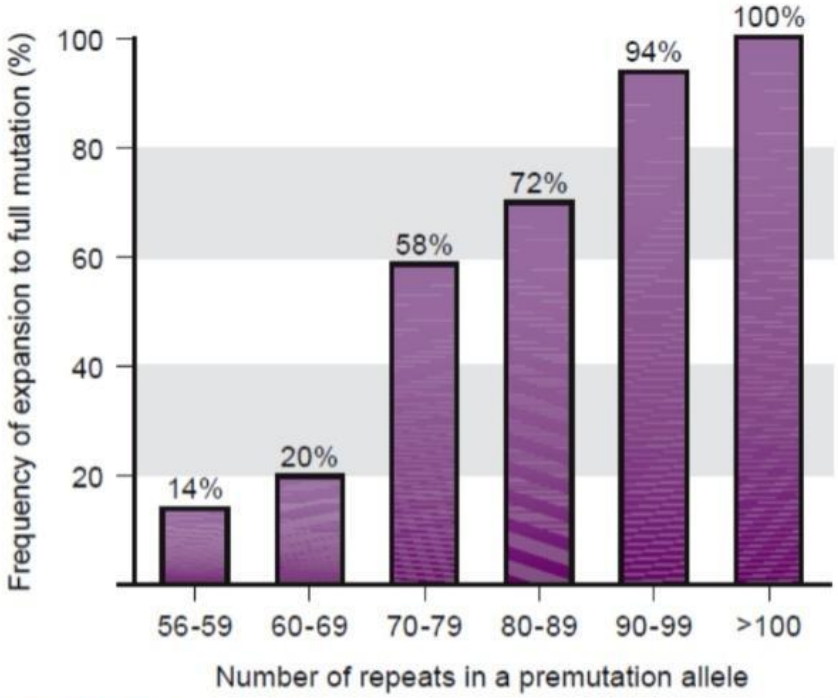



**Figure 7-23** Frequency of expansion of a premutation triplet repeat in *FMR1* to a full mutation in oogenesis as a function of the length of the premutation allele carried by a heterozygous female. The risk for fragile X syndrome to her sons is approximately half this frequency, because there is a 50% chance a son will inherit the expanded allele. The risk for fragile X syndrome to her daughters is approximately one-fourth this frequency, because there is a 50% chance a daughter would inherit the full mutation, and penetrance of the full mutation in a female is approximately 50%. *See Sources & Acknowledgments.*

If the number of repeats is greater than 100, 100% of this pre-mutation will expand to full mutation and the Probability of affected offspring is 50%

## Maternal inheritance of mt-DNA

Mitochondria only inherited from the mother

Both males and females could be affected by mutation in mitochondria

DNA, but male doesn't transmit mitochondria DNA.

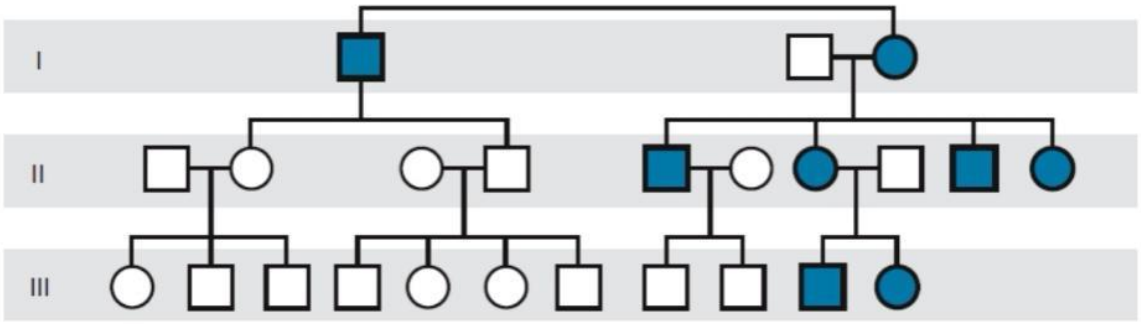



**Figure 7-24** Pedigree of Leber hereditary optic neuropathy, a form of adult-onset blindness caused by a defect in mitochondrial DNA. Inheritance is only through the maternal lineage, in agreement with the known maternal inheritance of mitochondrial DNA. Note that no affected male transmits the disease.

### Replicative segregation

Varies in the ratio of affected mitochondria and normal mitochondria that

transmit to offspring

Homoplasmy: all mitochondria present within the cell have the same

genotype

Heteroplasmy: some mitochondria have mutation and others don’t

have a mutation, so different genetic constitution of mt-DNA that

present within the same cell.

Mitochondrial genetic bottleneck: a small fraction of mitochondria will.

Give DNA to the next generation.

Does the disease occur or not?

It depends on the percentage of defective mitochondria within the cell, if excess the threshold the disease occur.

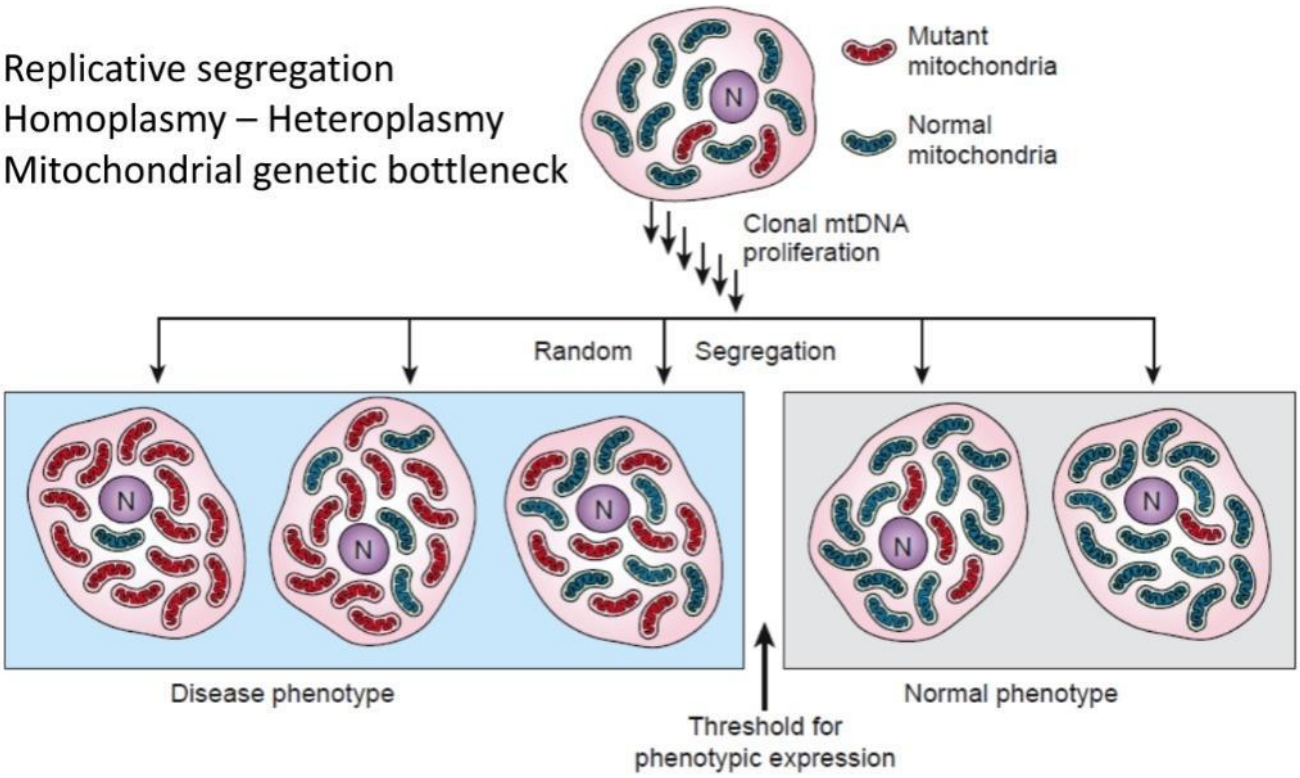



**Figure 7-25** Replicative segregation of a heteroplasmic mitochondrial mutation. Random partitioning of mutant and wild-type mitochondria through multiple rounds of mitosis produces a collection of daughter cells with wide variation in the proportion of mutant and wild-type mitochondria carried by each cell. Cell and tissue dysfunction results when the fraction of mitochondria that are carrying a mutation exceeds a threshold level. mtDNA, Mitochondrial DNA; N, nucleus.

Allelic heterogeneity: differences between alleles, default conditions

Different alleles cause the disease

Example: compound Heterozygous.

Locus heterogeneity: mutation in different genes causes the same disease.

Clinical or phenotypic heterogeneity: different mutations in the same the gene causes different Diseases