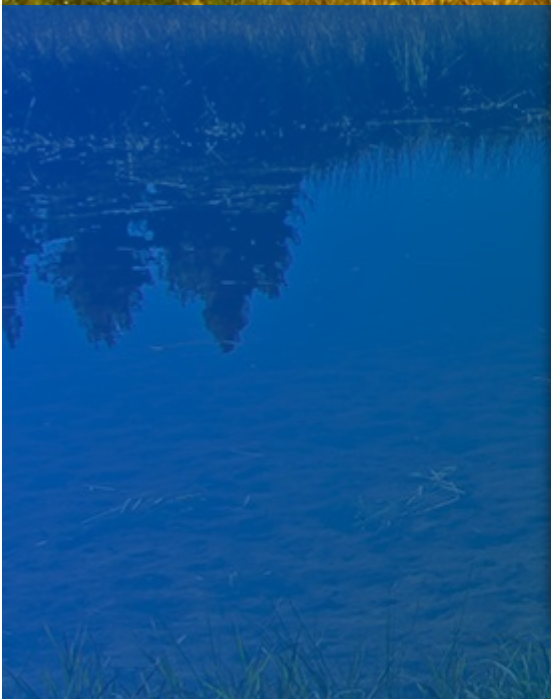


اجازه ندهید دیروز،
وقت امروز شما را بگیرد!

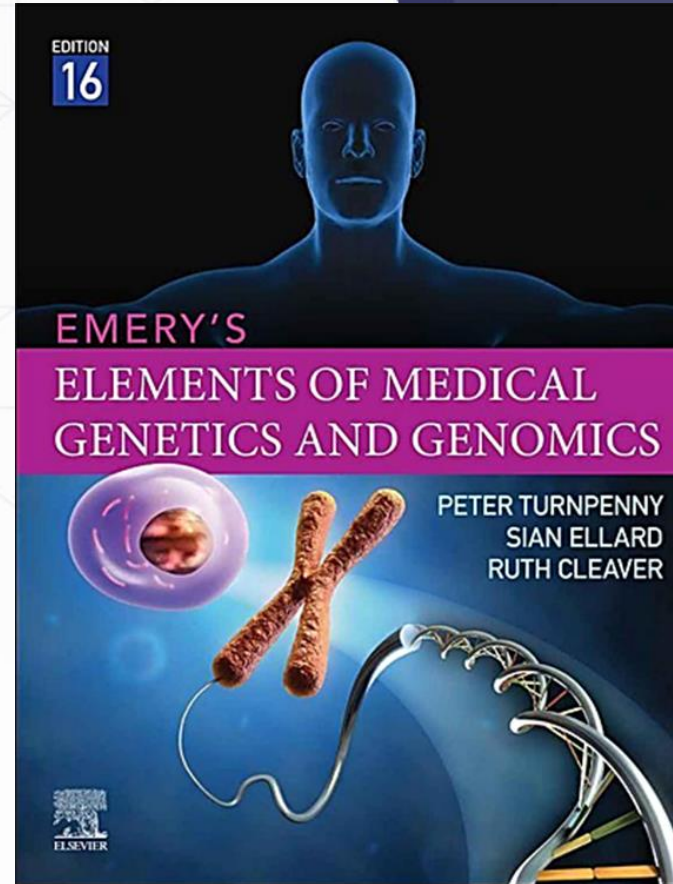




Patterns of Inheritance

Chapter 6:

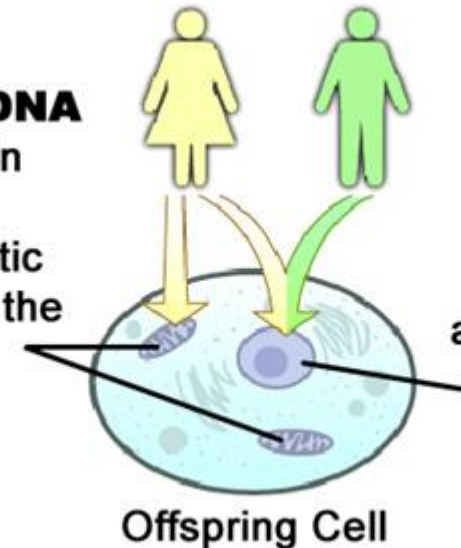
- Family Studies
- Mendelian Inheritance
- Multiple Alleles and Complex Traits
- Anticipation
- Mosaicism
- Uniparental Disomy
- Genomic Imprinting
- Mitochondrial Inheritance



Patterns of Inheritance:

- Single-gene or Mendelian inheritance
- Multifactorial genetic inheritance
- Sex-linked inheritance
- Digenic inheritance
- Somatic mosaicism
- Gonadal mosaicism
- Uniparental disomy
- Genomic imprinting
- Mitochondrial inheritance

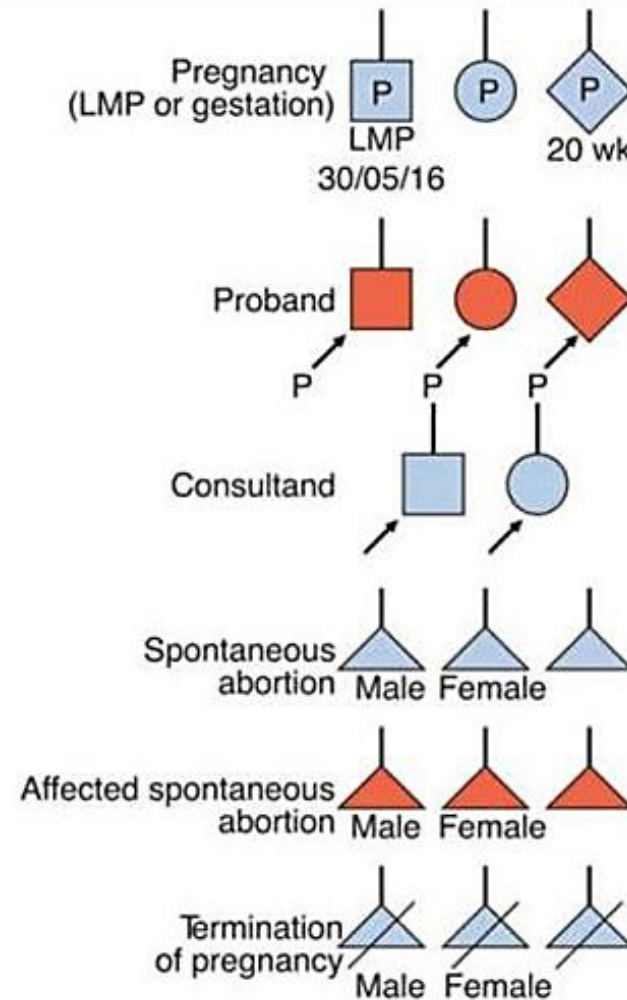
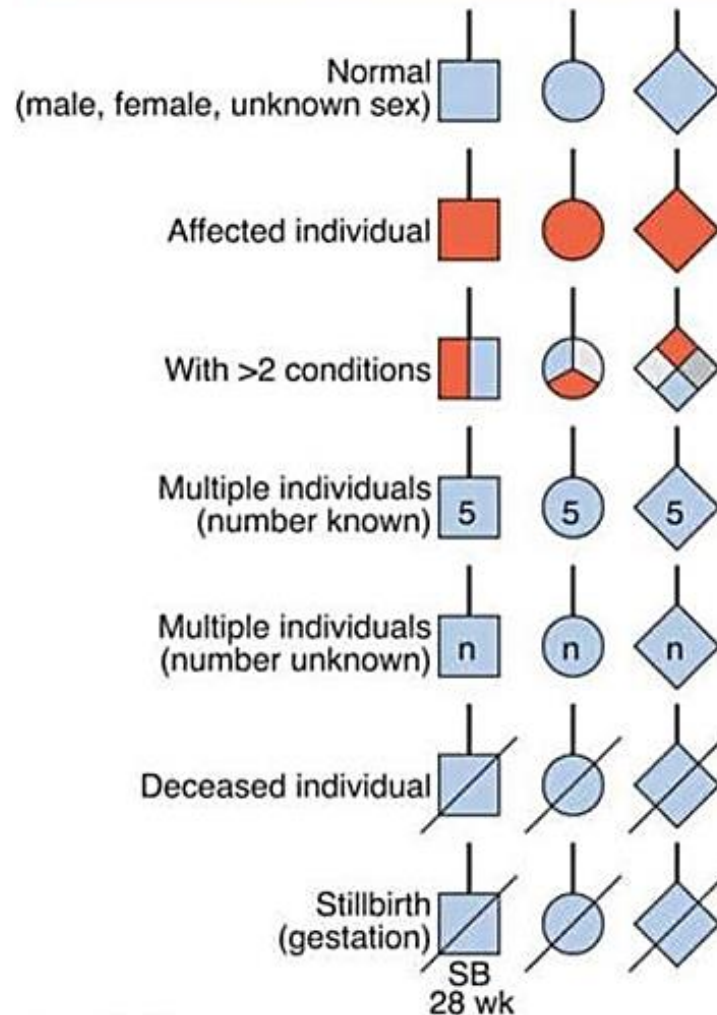
Mitochondrial DNA (mtDNA) is found in cell mitochondria and contains genetic material only from the **mother**.



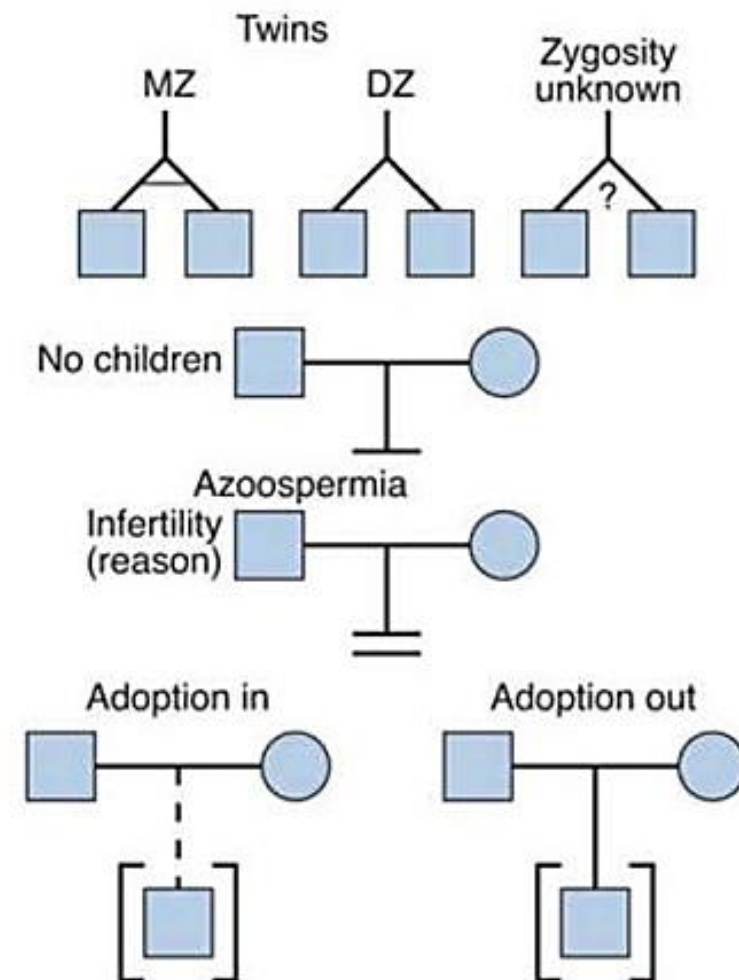
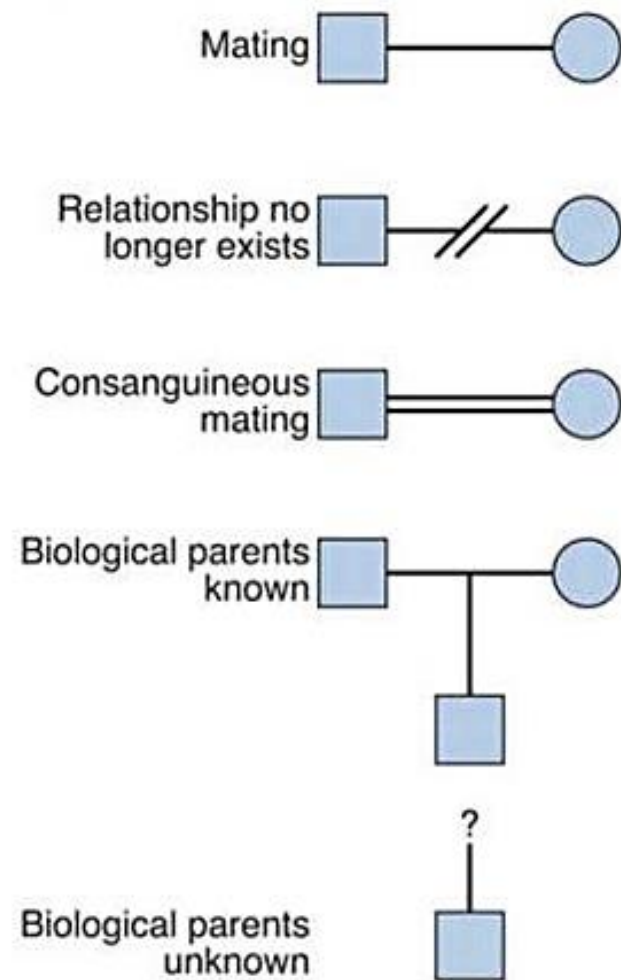
Nuclear DNA (nuDNA) is found in the cell nucleus and contains genetic material from **both parents**.

Symbols used to represent individuals and relationships in family trees. DZ, LMP, MZ.

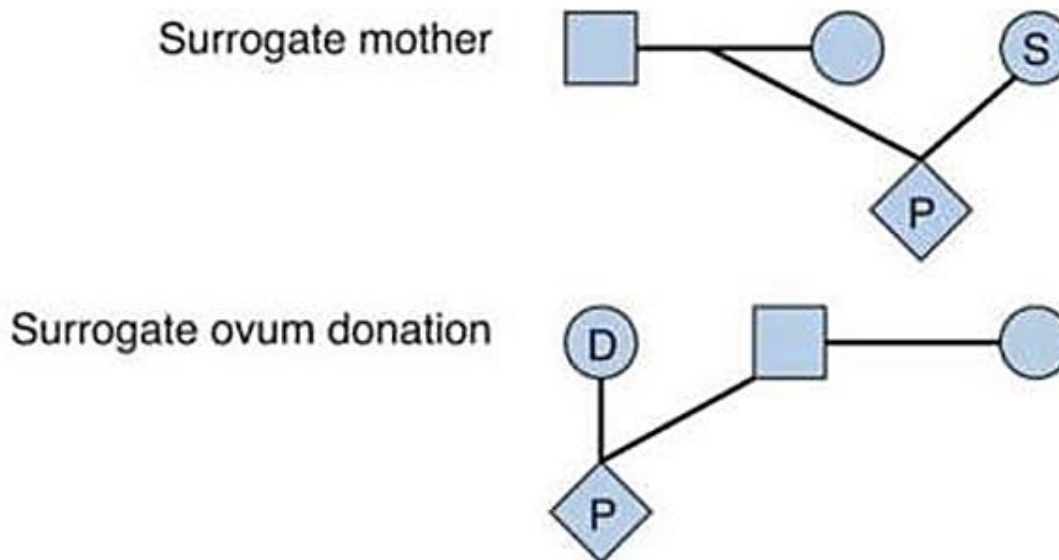
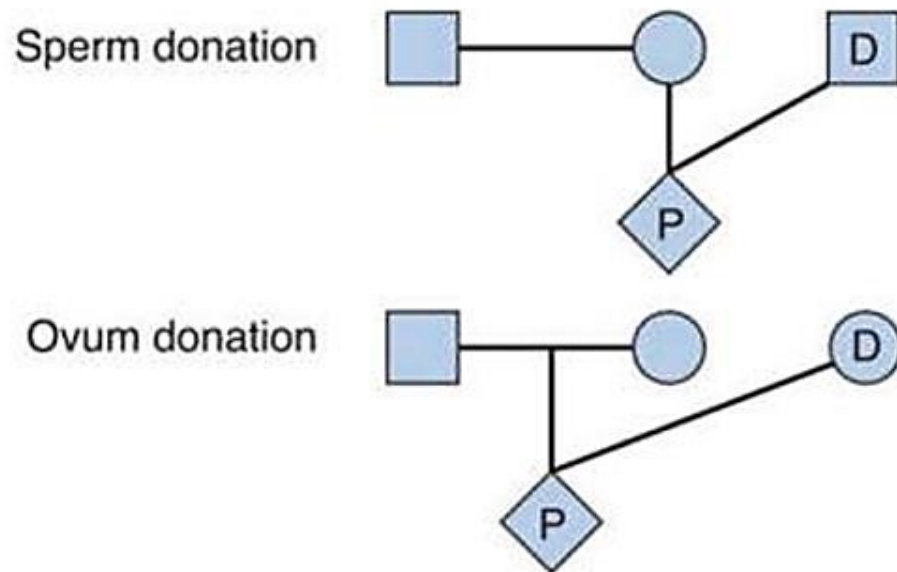
Individuals



Relationships



Assisted reproductive scenarios



Mendelian Inheritance

Modern genetics was founded by the **Austrian priest Gregor Johann Mendel** (*The father of genetics*) in the 19th century (1865).



More than 16,000 traits or disorders in humans exhibit **single-gene** unifactorial or **mendelian** inheritance:

- A trait or disorder determined by **a gene on an autosome** is said to show **autosomal inheritance**.
- A trait or disorder determined by **a gene on one of the sex chromosomes** is said to show **sex-linked inheritance**.

Autosomal Dominant (AD) Inheritance

- “Vertical” transmission
- Confirmed when male–male (i.e., father to son) transmission has occurred.

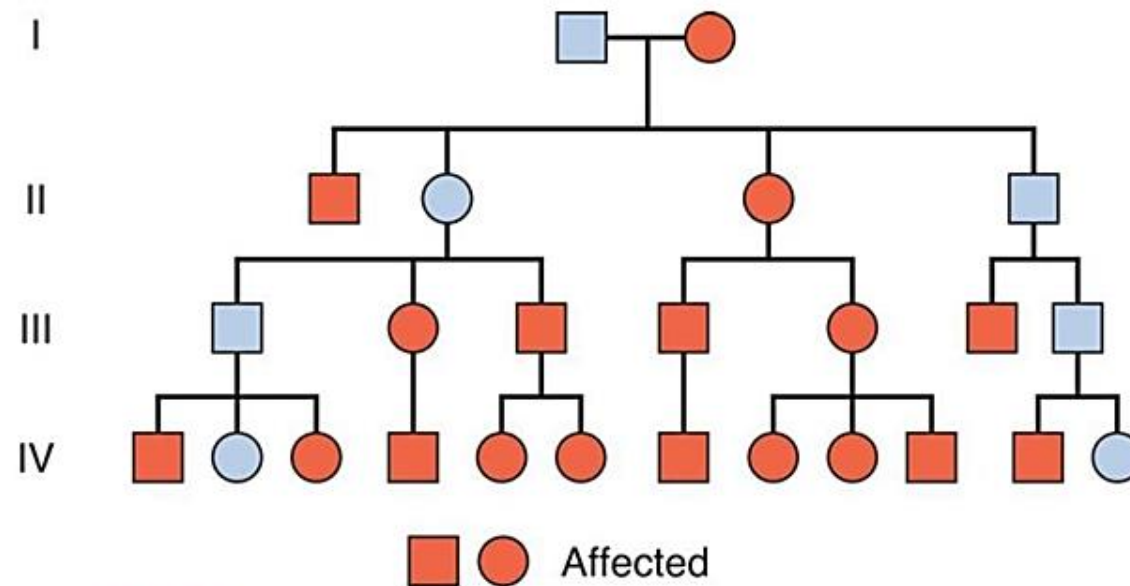


FIG. 6.2 Family tree of an autosomal dominant trait. Note the presence of male-to-male transmission.



Neurofibromatosis

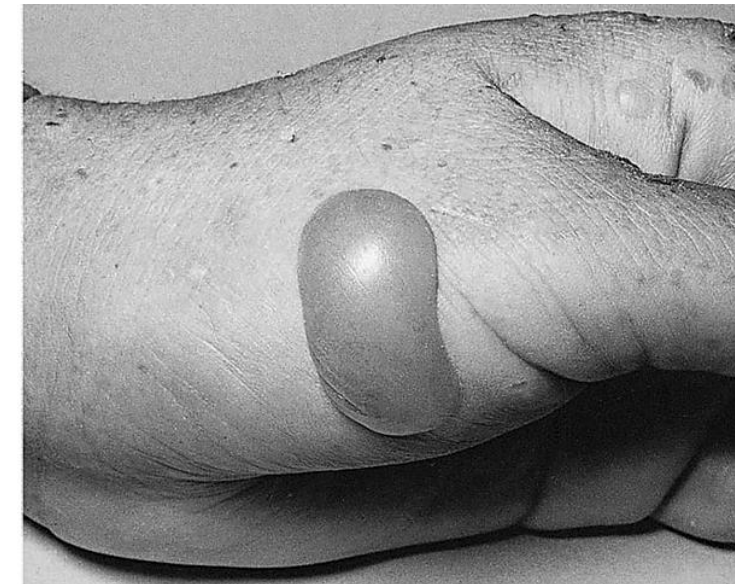


FIG. 6.3 Blistering skin lesions on the hand in porphyria variegata

Genetic Risks in AD Inheritance

- Any child born to a person affected with a dominant condition has a 1 in 2 (**50%**) chance of **inheriting** it and being similarly affected.

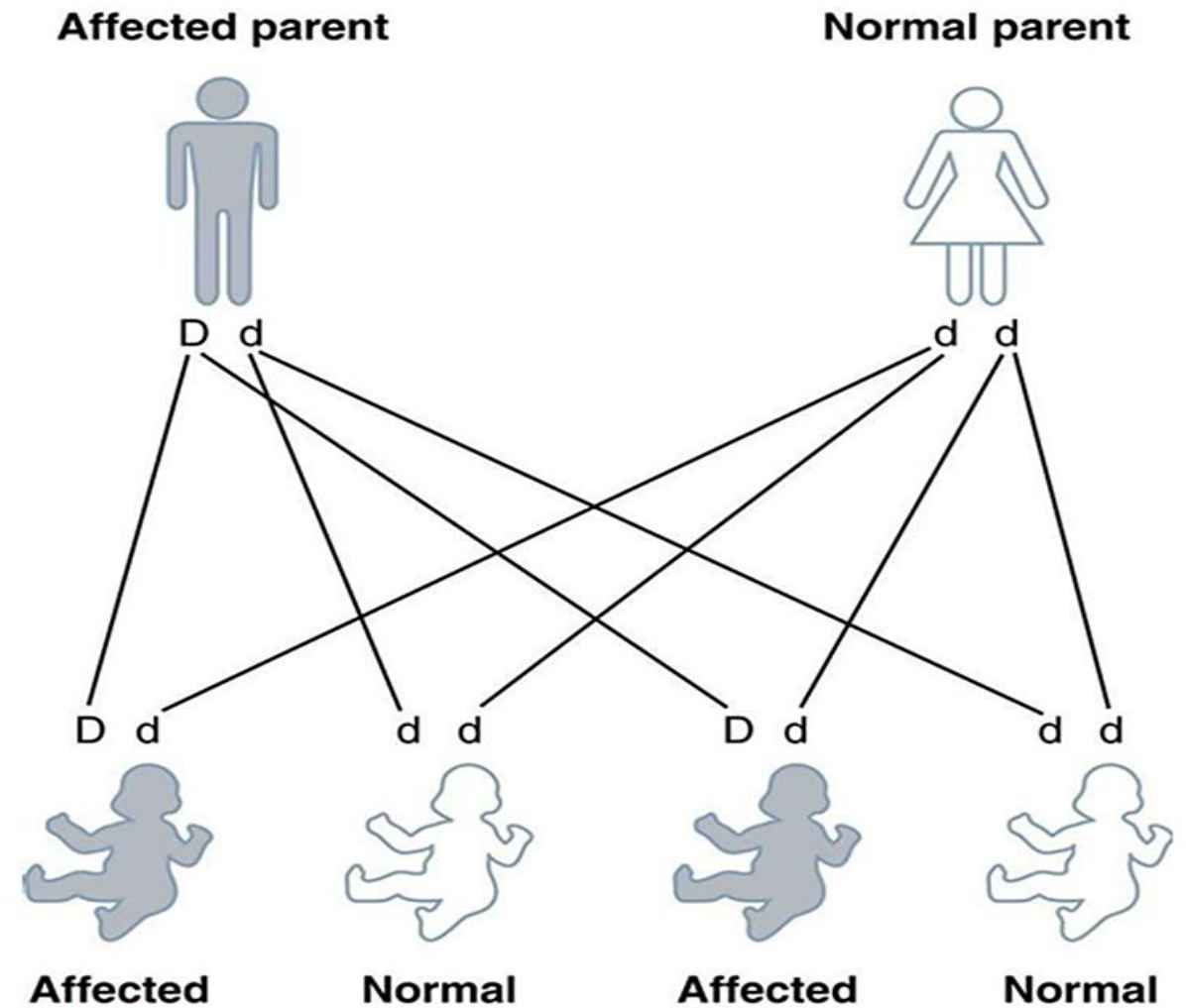


FIG. 6.4 Segregation of alleles in autosomal dominant inheritance. D represents the mutated allele, whereas d represents the normal allele.

Pleiotropy

Pleiotropy (plī'ätṛəpē):

Is a type of genetic expression in which **only one gene** affects **multiple traits**. A **classic example** of pleiotropy is

Tuberous Sclerosis Complex (TSC), also known as tuberous sclerosis (AD inheritance):

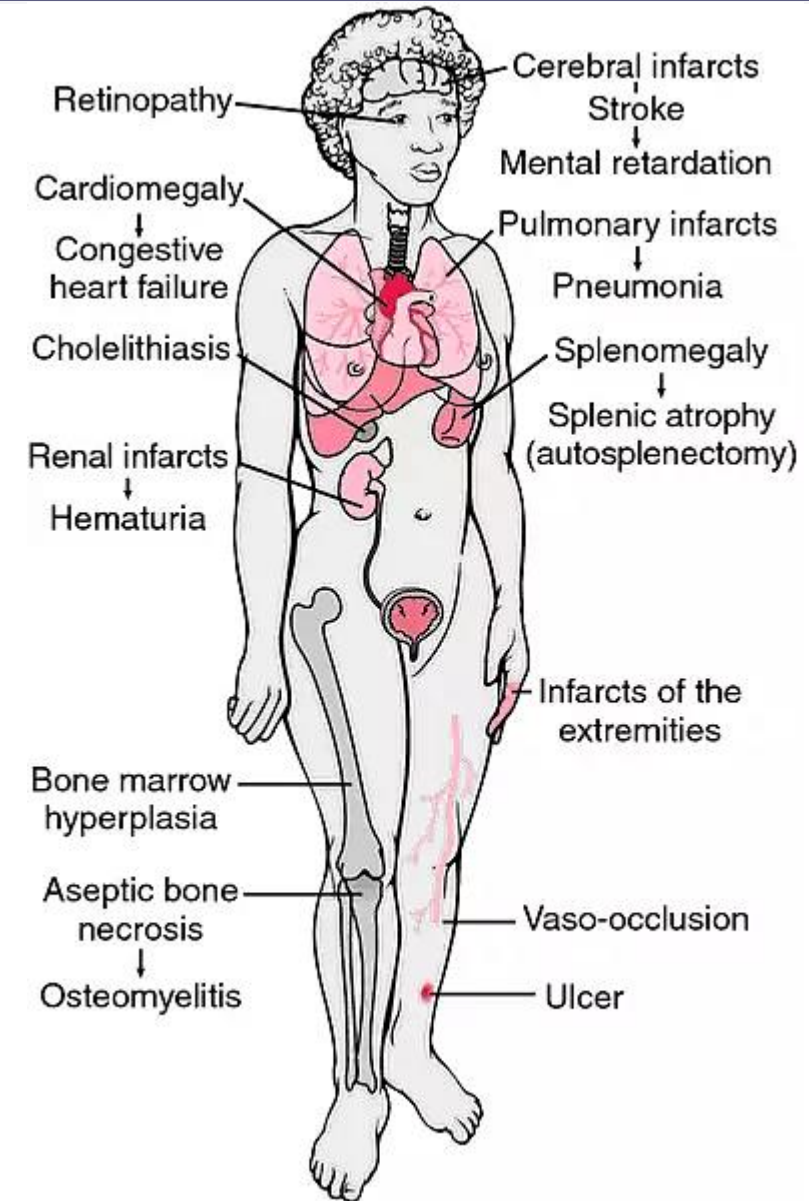
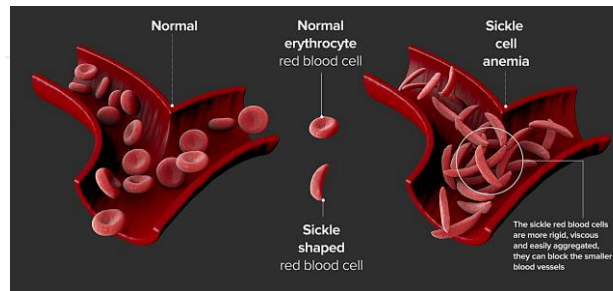
- ❑ A **rare** genetic disease that causes **non-cancerous (benign) tumors** to grow in the **brain and several areas of the body**, including the spinal cord, nerves, eyes, lung, heart, kidneys, and skin.
- ❑ Learning difficulties, epilepsy, **a facial rash** known as **adenoma sebaceum** (histologically composed of **blood vessels and fibrous tissue** known as **angiokeratoma**), or **subungual fibromas**.
- ❑ **Some** affected individuals have **all features**, whereas others may have **almost none**.



Pleiotropy

Another **classic** example of pleiotropy is **Sickle-cell Anemia**.
The gene mutation that results in **sickle-shaped red blood cells (AR)** also leads to other affected traits.

- Breathing problems (shortness of breath or pain when breathing or both)
- Extreme tiredness
- Headache or dizziness
- Painful erections in males
- Weakness or a hard time moving some parts of your body
- Yellowish skin color (jaundice)
- Spleen infarction



Pleiotropy

The **remarkably diverse syndromes** that can result from **different variants** in **the same gene**, for example:

Mutations in **LMNA** gene (which encodes lamin A/C) may cause:

- **Dominant inheritance diseases:** Emery-Dreifuss muscular dystrophy, a form of limb girdle muscular dystrophy, dilated cardiomyopathy with conduction abnormality, Dunnigan type familial partial lipodystrophy, and Hutchinson-Gilford progeria
- **Recessive inheritance diseases:** Charcot-Marie-Tooth disease and mandibuloacral dysplasia
- Sometimes an individual with a **variant** is entirely **normal**.
- Mutations in **X-linked filamin A (FLNA)** gene may cause:
 - **X-linked dominant:** Oto palato-digital syndrome, Melnick-Needles syndrome, and frontometaphyseal dysplasia, periventricular nodular heterotopia.
 - A form of X-linked dominant **epilepsy** in women, called **periventricular nodular heterotopia**

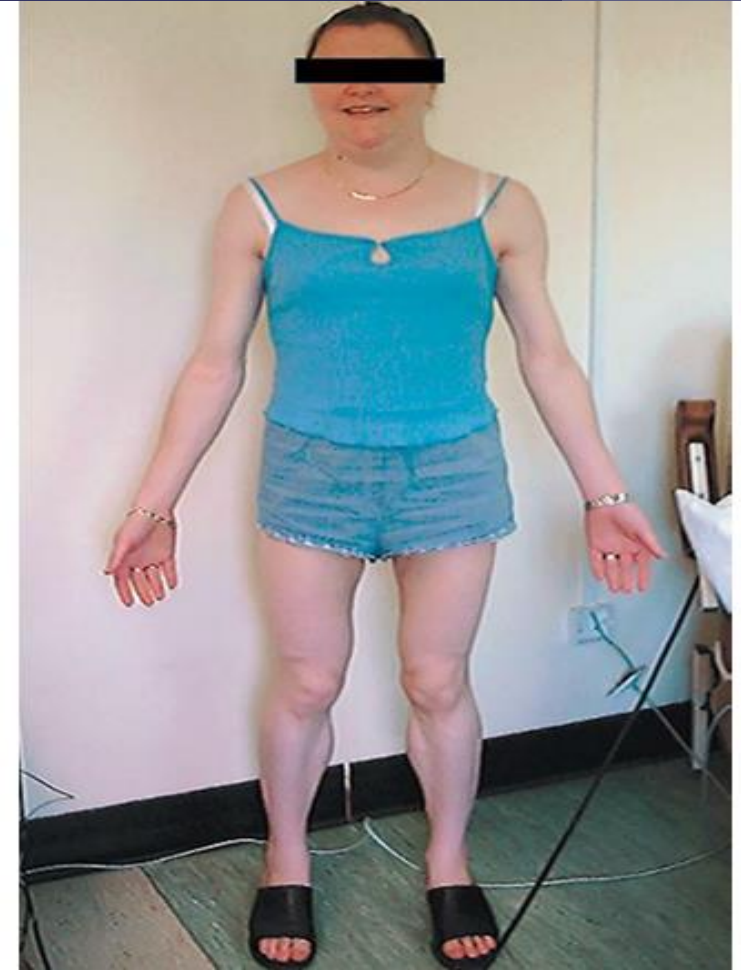


FIG. 6.6 Dunnigan-type familial partial lipodystrophy attributed to a variant in the gene encoding **LAMIN A/C**. The patient **lacks adipose tissue**, especially in the distal limbs.

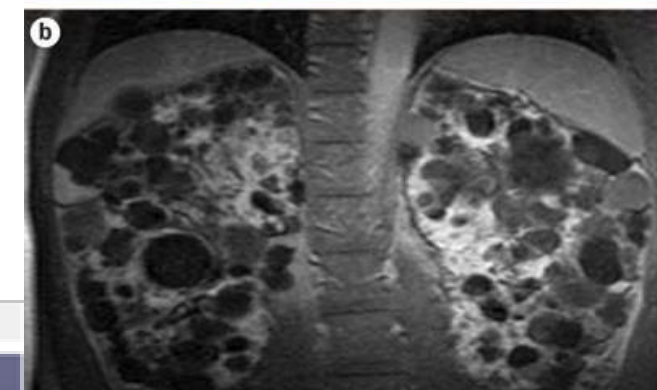
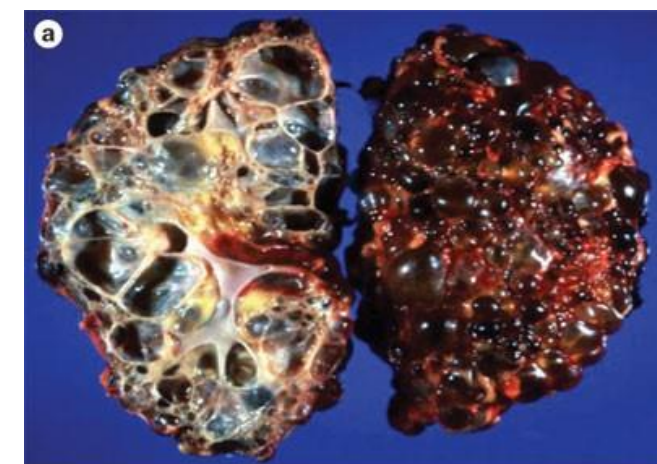
Variable Expressivity

Both **incomplete penetrance** and **variable expressivity** are probably due to a combination of **genetic**, **environmental**, and **lifestyle** factors.

The clinical features in **autosomal dominant disorders** can show striking variation **from person to person**, even in the same family. Refers to **the series of signs and symptoms** that can occur in **different people** with the **same genetic condition**.

➤ **Polydactyly**

- In autosomal dominant **Polycystic kidney disease (PKD)**: Some affected individuals develop **renal failure in early adulthood** whereas others **have just a few renal cysts** that do not affect renal function significantly.



Reduced Penetrance

Some individuals with a particular disease-causing mutation or genotype fail to express most if not all features of the disease in question, a phenomenon that is known as '**reduced (or incomplete) penetrance**': *"skips a generation"*

- **HD (Huntington's disease)** gene containing **between 36 and 39 repeats** are in the 'reduced penetrance' range. **Some** people in this range will **develop symptoms** of the disease, **while others won't**.
- **Polydactyly** in humans (extra fingers and/or toes)
- Many people with a variant in the **BRCA1** or **BRCA2** gene associated with an increased cancer risk will develop **cancer** during their lifetime, but some people will not.



FIG. 6.7 The baby in this picture has **Treacher-Collins syndrome**, resulting from a variant in **TCOF1 (treacle ribosome biogenesis factor 1)**. The mandible is small, the palpebral fissures slant downward, there is usually a defect (coloboma) of the lower eyelid, the ears may show microtia, and hearing impairment is common. The condition follows autosomal dominant inheritance but is very variable—the baby's mother also has the variant, but she shows no obvious signs of the condition.

New Variants

- No preceding family history: Sudden” appearance must be considered
- **Achondroplasia**, in which parents usually have normal stature.
- A result of a pathogenic heterozygous gene variant in **FGFR3** gene is called a **de novo variant**.
- New **heterozygous variants** have been associated with older-than-average fathers. Traditionally, this is believed to be a consequence of **the large number of mitotic divisions that male gamete stem cells undergo** during a man’s reproductive lifetime.
- **Craniosynostosis Syndromes**: Wilkie’s group in Oxford demonstrated that causative **gain-of-function variants** in **FGFR2** confer a **selective advantage to spermatogonial stem cells**, so that mutated cell lines **accumulate in the testis**.



Codominance

- Two allelic traits that are both expressed in the heterozygous state.
- In persons with blood group AB it is possible to demonstrate both A and B blood group substances on the red blood cells, so the A and B blood groups are therefore codominant.

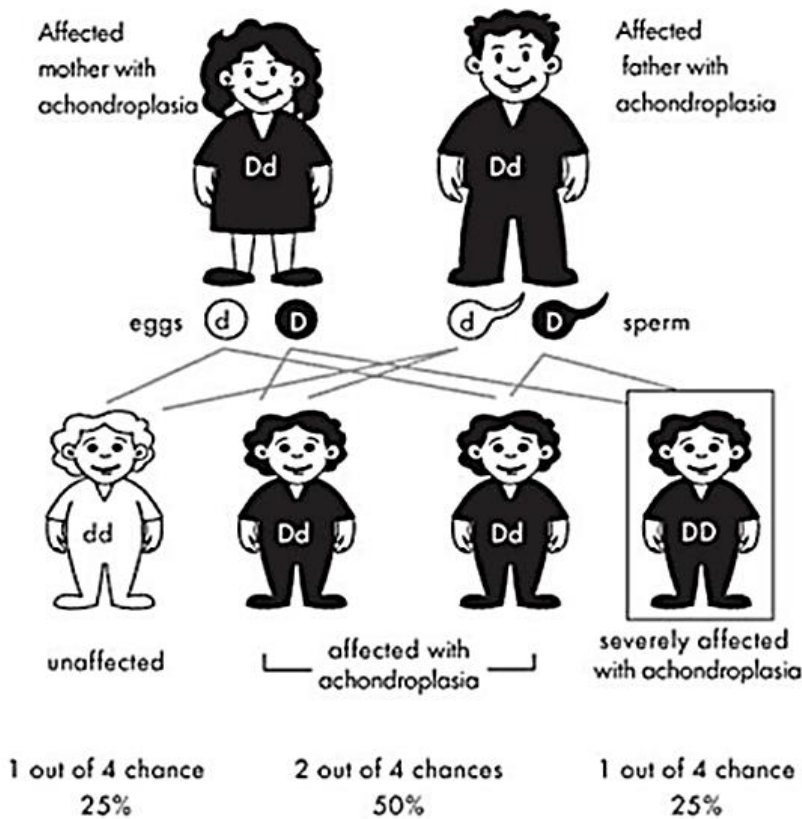


	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in plasma			None	
Antigens in red blood cell				None

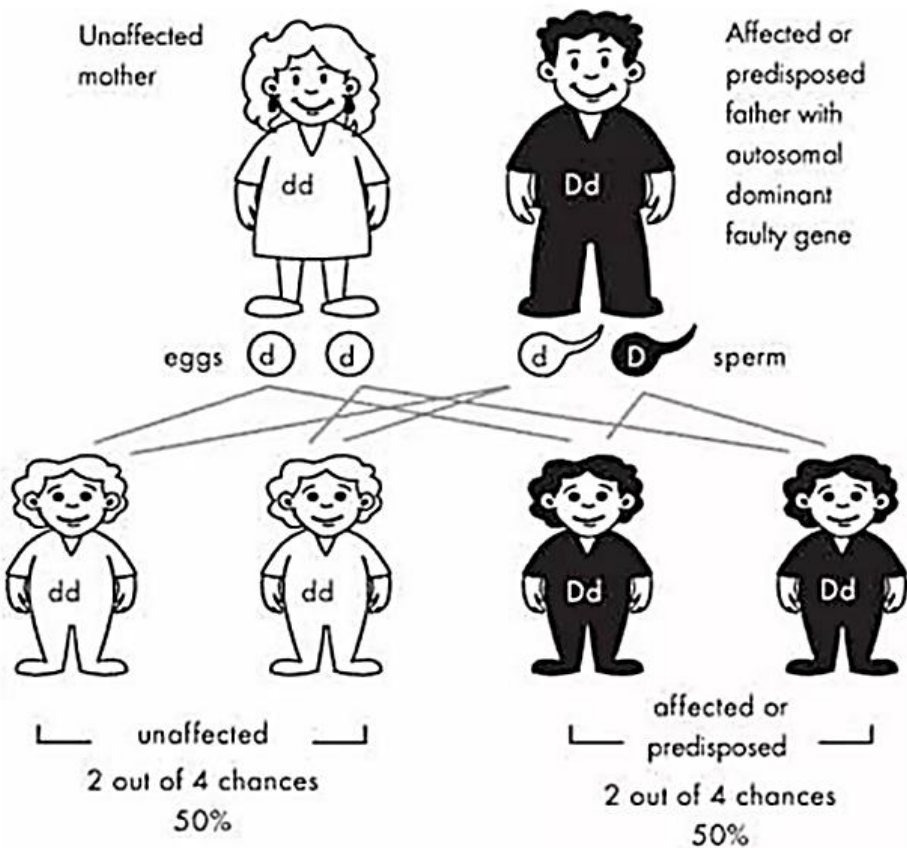
Homozygosity for Autosomal Dominant Traits

- ❑ The **rarity** of most autosomal dominant conditions means that they **usually occur only in the heterozygous state**.
- ❑ Occasionally, however, children are born to couples where **both parents are heterozygous** for a dominantly inherited disorder.
- ❑ Such offspring are at risk of being homozygous for the gene variants. In some instances, affected individuals appear either:
 - ❑ Be **more severely affected**, as with *Achondroplasia (Dwarfism)*
 - ❑ An **earlier age of onset**, as in *Familial hypercholesterolemia*
 - ❑ **Not more severely affected than heterozygotes**, as in *Huntington disease* and *Myotonic dystrophy*
- ❑ These different phenotypic effects may be explained by the nature of the variant: whether they are **gain or loss-of-function**.

Homozygosity in Achondroplasia



Incompatible with life

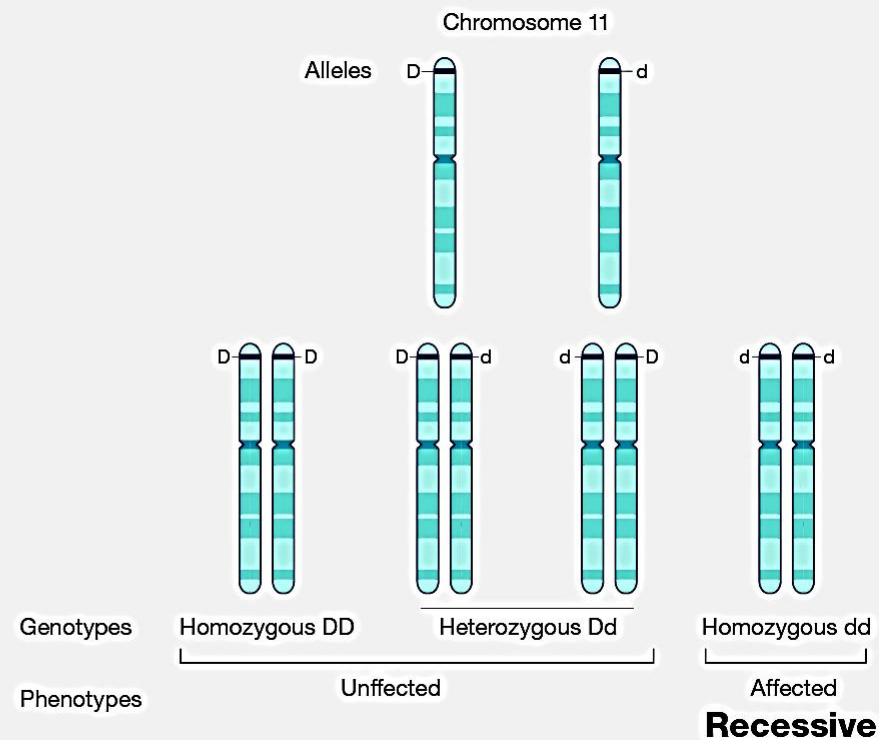
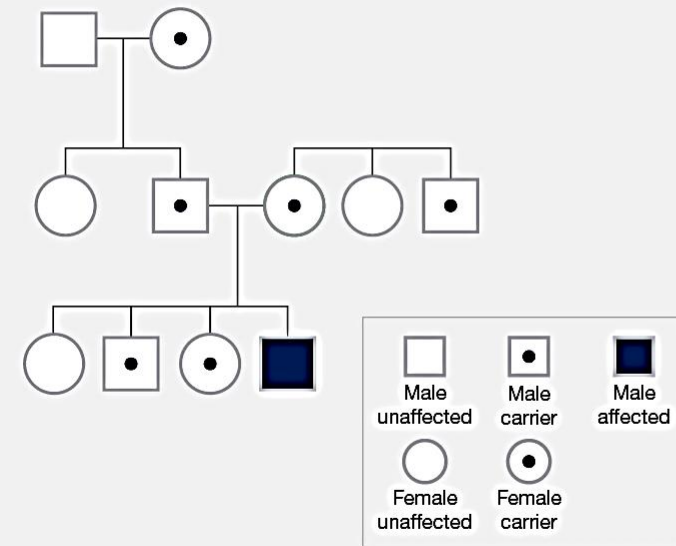


Compatible with life

Autosomal Recessive Inheritance



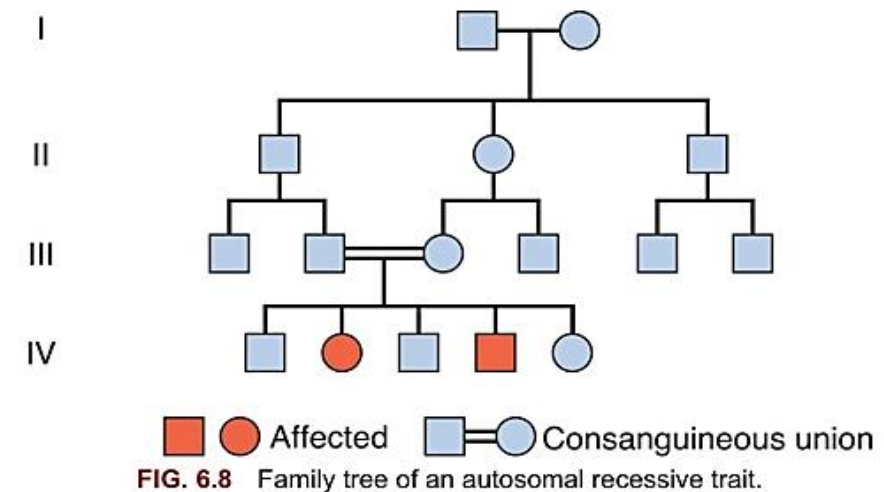
Sickle cell anemia



“Horizontal” Transmission:
All the affected individuals in a family are usually in a single sibship (i.e., brothers and sisters).

Consanguinity

- ❖ Enquiry into the family history of individuals affected with **rare recessive** conditions might reveal that **their parents are related** (i.e., consanguineous).
- ❖ The **rarer** a **recessive trait or disorder**, the **greater** the frequency of **consanguinity** among the parents of affected individuals.
- ❖ In **cystic fibrosis**, the most common “**serious**” **autosomal recessive disease** in **western Europeans**, the frequency of parental consanguinity is only slightly greater than that seen in the general population.
- ❖ By contrast, when Bateson and Garrod originally described the **very rare alkaptonuria**, they observed that a quarter or more of the parents were **first cousins**, and rightly reasoned that rare alleles are more likely to “meet up” in the offspring of cousins than unrelated parents.
- ❖ In large inbred kindreds, an autosomal recessive condition may be present in more than one branch of the family.



➤ **Consanguinity**: Mating between relatives

➤ **Coefficient of Relationship (R)**:

The probability that two individuals share a specific gene (allele) inherited from a common ancestor. For example, a parent and child have a coefficient of relationship of 0.5, while siblings have a coefficient of 0.5 as well.

➤ **Coefficient of Inbreeding (F)**:

This represents the probability that an individual inherits two copies of the same allele (one from each parent) that are identical by descent (IBD) from a common ancestor. In other words, it measures the level of inbreeding in an individual.

➤ **A**: Ancestor

$$R = 2F$$

$$F = \sum \left(\frac{1}{2}\right)^{ni} + (1+FA)$$

Degree of Consanguinity

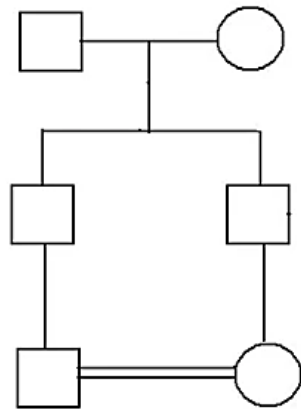
5° = 5 degrees of separation

							Gr (X5) grand-parent 7°
						Gr (X4) grand-parent 6°	Gr (X4) grand- uncles/ aunts 8°
					Gr (X3) grand-parent 5°	Gr (X3) grand- uncles/ aunts 7°	1 st cousin 5x removed 9°
				Great-great- grand-parent 4°	Gr-gr-grand- uncles/ aunts 6°	1 st cousin 4x removed 8°	2 nd cousin 4x removed 10°
			Great-grand- parent 3°	Gr-grand- uncles/ aunts 5°	1 st cousin 3x removed 7°	2 nd cousin 3x removed 9°	3 rd cousin 3x removed 11°
		Grandparent 2°	Grand- uncles/ aunts 4°	1 st cousin twice removed 6°	2 nd cousin twice removed 8°	3 rd cousin twice removed 10°	4 th cousin twice removed 12°
	Parent 1°	Aunts & Uncles 3°	1 st cousin once removed 5°	2 nd cousin once removed 7°	3 rd cousin once removed 9°	4 th cousin once removed 11°	5 th cousin once removed 13°
You 0°	Siblings 2°	1 st cousin 4°	2 nd cousin 6°	3 rd cousin 8°	4 th cousin 10°	5 th cousin 12°	6 th cousin 14°
Children 1°	Nephews/ nieces 3°	1 st cousin once removed 5°	2 nd cousin once removed 7°	3 rd cousin once removed 9°	4 th cousin once removed 11°	5 th cousin once removed 13°	6 th cousin once removed 15°
Grandchildren 2°	grand- nephews/ nieces 4°	1 st cousin twice removed 6°	2 nd cousin twice removed 8°	3 rd cousin twice removed 10°	4 th cousin twice removed 12°	5 th cousin twice removed 14°	6 th cousin twice removed 16°
Great-grand- children 3°	great-grand- nephew/ niece 5°	1 st cousin 3x removed 7°	2 nd cousin 3x removed 9°	3 rd cousin 3x removed 11°	4 th cousin 3x removed 13°	5 th cousin 3x removed 15°	6 th cousin 3x removed 17°

Genetic Risks

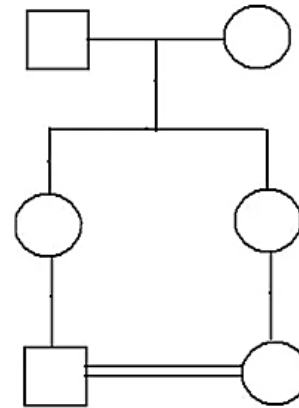
$$R = 2F$$

$$F = \sum \left(\frac{1}{2}\right)^{ni} + (1+FA)$$

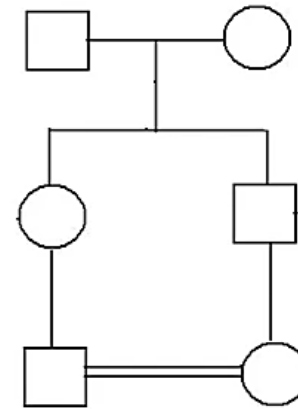


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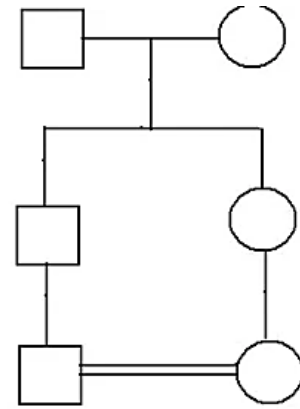
paternal parallel first cousins
father brother daughter
 $F=0.0625$



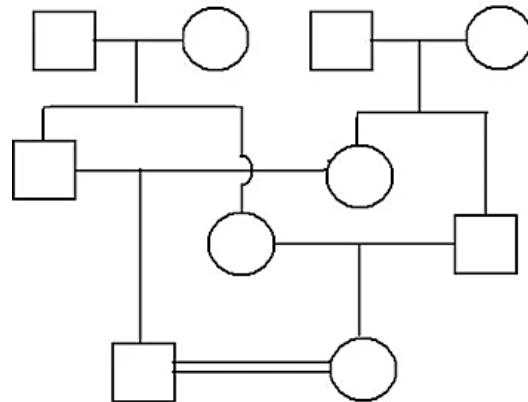
maternal parallel first cousins
mother sister daughter
 $F=0.0625$



cross first cousins
mother brother daughter
 $F=0.0625$

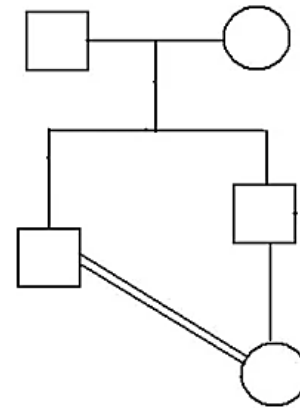


cross first cousins
father sister daughter
 $F=0.0625$

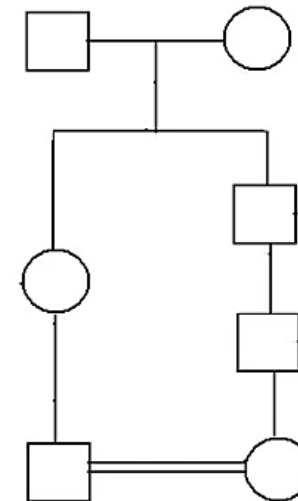


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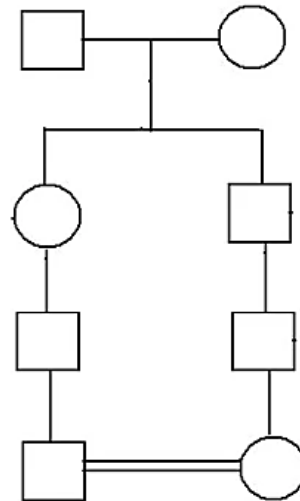
double first cousins
 $F=0.125$



uncle-niece
 $F=0.125$



first cousins once removed
 $F=0.03131$



second cousins
 $F=0.0156$

Pseudodominance

- ❖ If an individual who is **homozygous** for an **autosomal recessive** condition has **children** with a carrier of the same condition, their offspring have a 1 in 2 (50%) chance of being affected.
- ❖ Such a pedigree is said to exhibit pseudodominance.

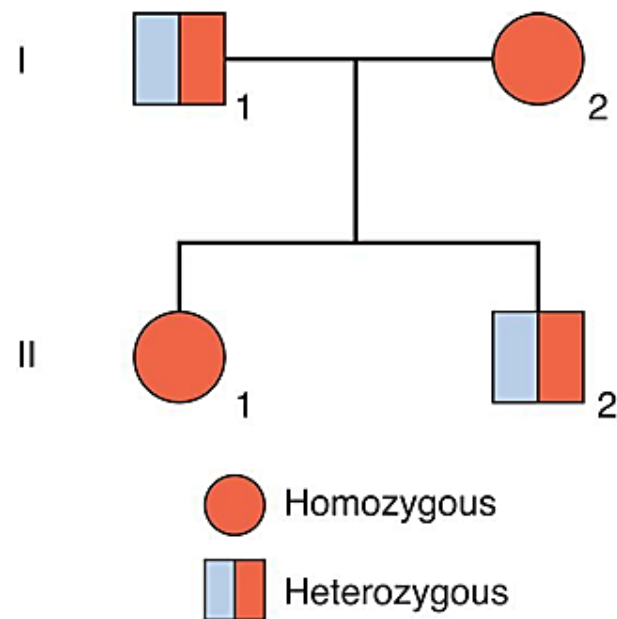


FIG. 6.10 A pedigree with a woman (I2) homozygous for an autosomal recessive disorder whose husband is heterozygous for the same disorder. They have a homozygous affected daughter, so that the pedigree shows pseudodominant inheritance.

Heterogeneity

□ *Locus heterogeneity / Genocopy*

The same phenotype from different genetic loci

- **Double heterozygotes**
 - Early-onset sensorineural hearing loss/deafness
 - Autosomal recessive retinitis pigmentosa

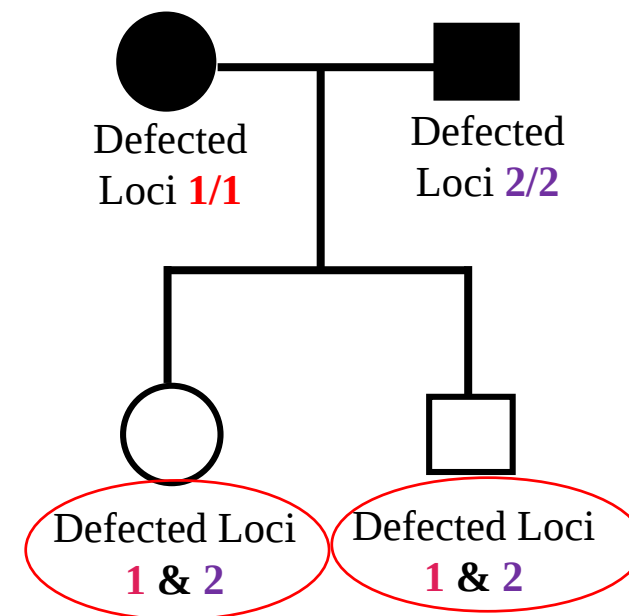
□ *Variant/ Allelic heterogeneity*

Two or more different variants at the same locus

- **Compound heterozygotes**
 - β -thalassemia

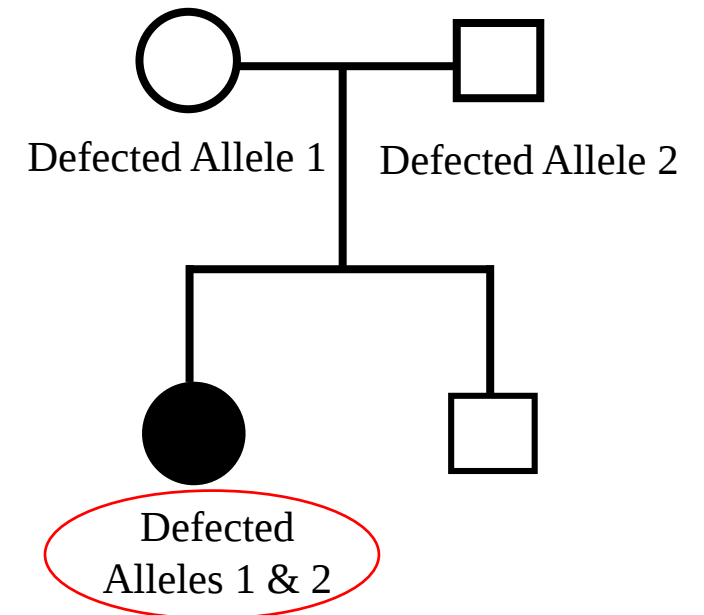
Locus Heterogeneity

- ❖ Some clinical conditions occur due to variants in **more than one gene**, thus demonstrating locus heterogeneity.
 - For example, **early-onset sensorineural hearing loss/deafness** most **commonly** follows **autosomal recessive** inheritance.
 - There are families in which **all children** born to **parents with autosomal recessive deafness** have **normal hearing** because they are **double heterozygotes** (or carriers).
 - The parents are therefore homozygous for gene variants at **different loci**. In fact, there are **more than 80 genes or gene loci** known to be implicated in **recessively inherited deafness**.
- ❖ A similar story applies to **autosomal recessive retinitis pigmentosa**.
- ❖ Disorders with **the same phenotype** from **different genetic loci** are known as **genocopies**, whereas when **the same phenotype** results from **environmental causes**, it is known as a **phenocopy**.



Variant/ Allelic Heterogeneity

- ❖ **Compound heterozygotes:** Heterogeneity can also occur **at the allelic level**. In the majority of **single-gene disorders**, for example, **β -thalassemia**, a large number of different variants have been identified as being responsible.
- ❖ Individuals who have **two different variants at the same locus** are known as **compound heterozygotes**, constituting what is known as **allelic heterogeneity**.
- ❖ **Most** individuals affected with an **autosomal recessive** condition are **compound heterozygotes** rather than **true homozygotes**, **unless their parents are related**, in which case they are likely to be homozygous for **the same variant by descent**, that is, inherited from a common ancestor.



Sex-Linked Inheritance

❖ Genes that are located on **the sex chromosomes**.

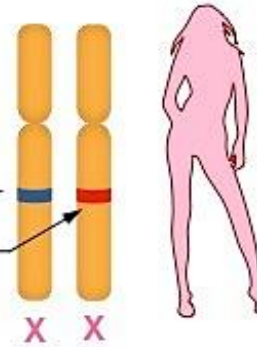
✓ X-linked

✓ Y-linked / holandric inheritance

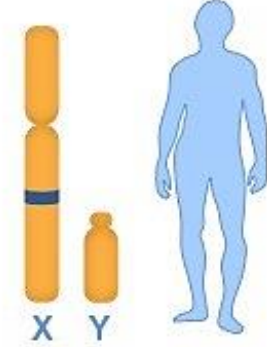
Parents:

X-linked gene

- Normal allele
- Defective allele

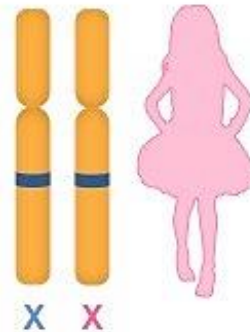


Normal - *carrier*

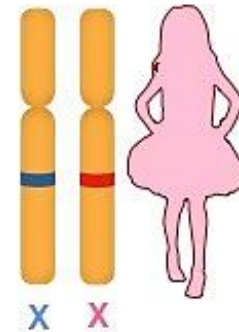


Normal

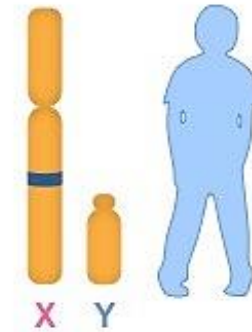
Possible offspring:



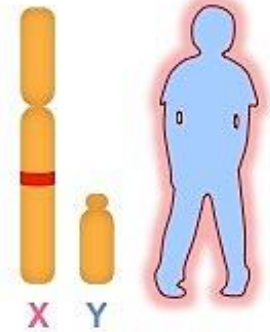
Normal



Normal - *carrier*



Normal



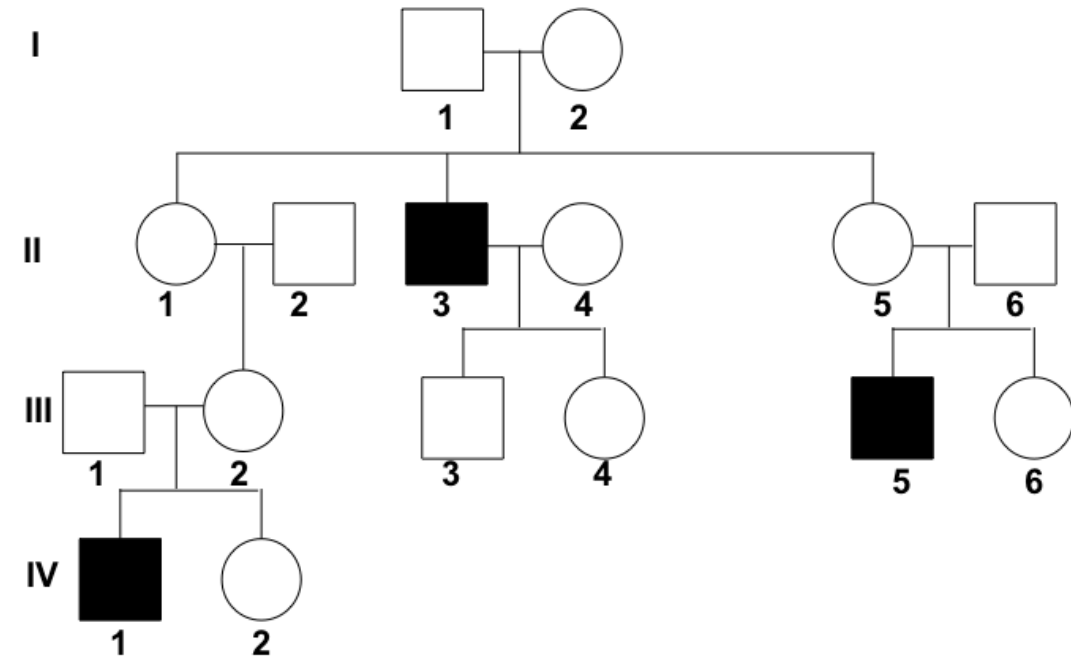
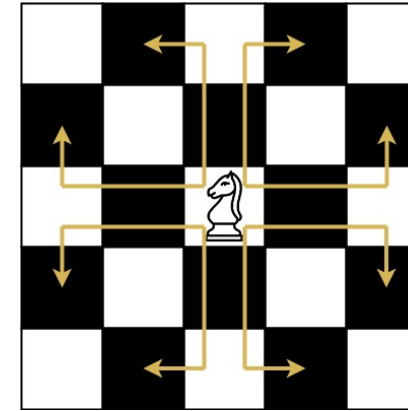
Affected

Inherits alleles from both parents,
recessive trait can be masked (carriers)

Inherits allele from mother only,
recessive trait **cannot** be masked

X-Linked Recessive Inheritance

- ❖ Usually manifests only in **males**.
- ❖ A **male** with a **variant allele** on his single X **chromosome** is said to be **hemizygous** for that allele.
- ❖ Are transmitted by (usually) **healthy heterozygous female** carriers to **affected males**, as well as by
- ❖ **Affected males** have their **obligate carrier daughters**, with a consequent **risk to male grandchildren** through these daughters
- ❖ This was sometimes referred to as a “**diagonal**” or “**knight’s move**” pattern of transmission.



Genetic Risks at X-Linked Recessive Inheritance

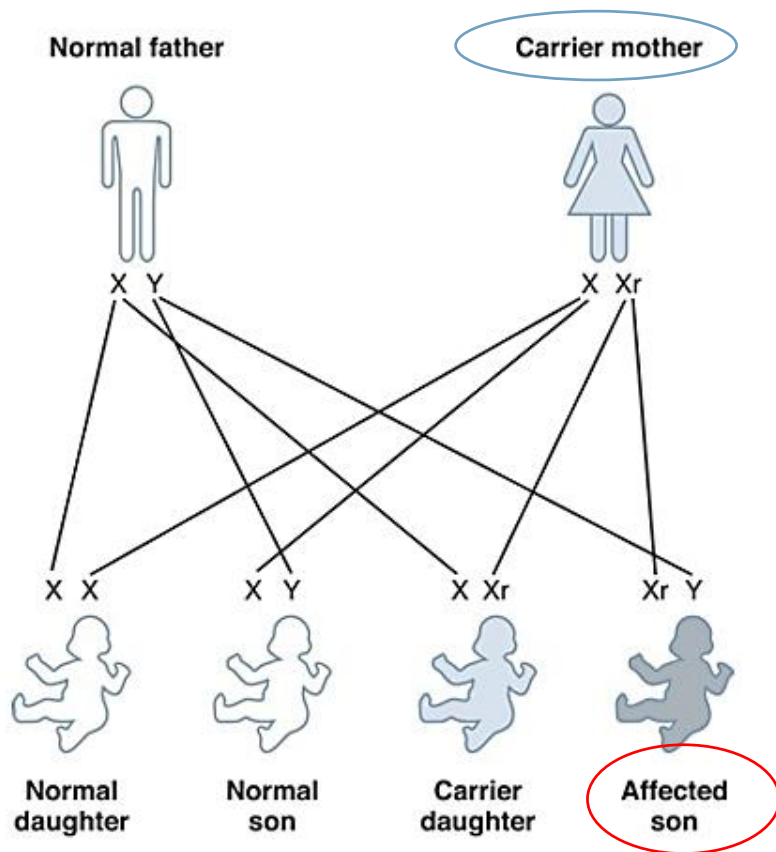


FIG. 6.13 Segregation of alleles in X-linked recessive inheritance, relating to the offspring of a carrier female. **r** represents the mutated allele.



FIG. 6.14 Boy with **Duchenne muscular dystrophy**; note the enlarged **calves** and wasting of the thigh muscles.

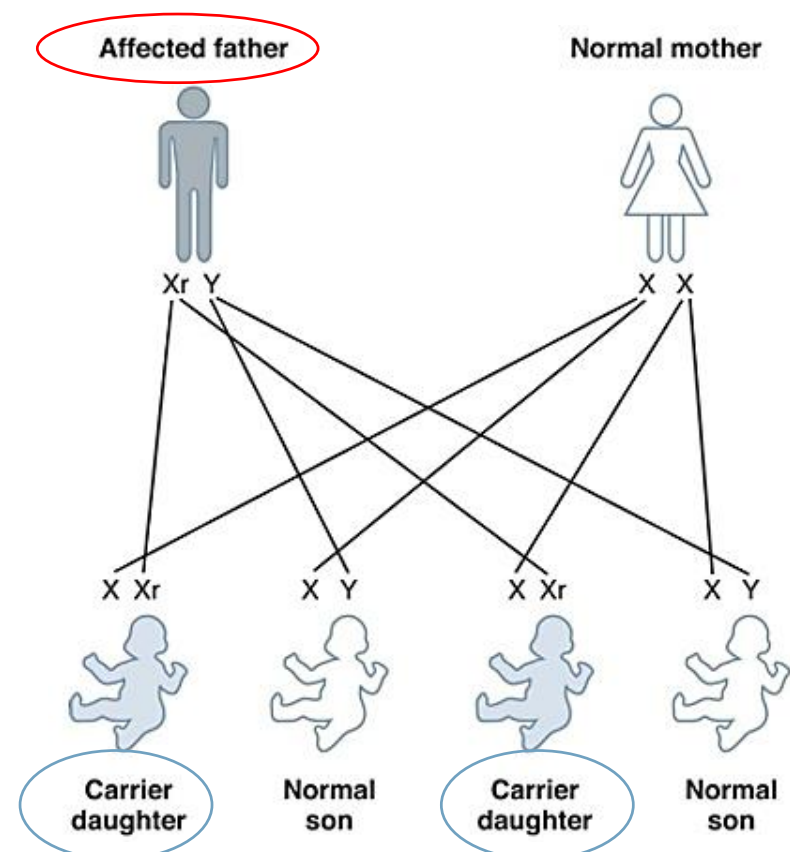
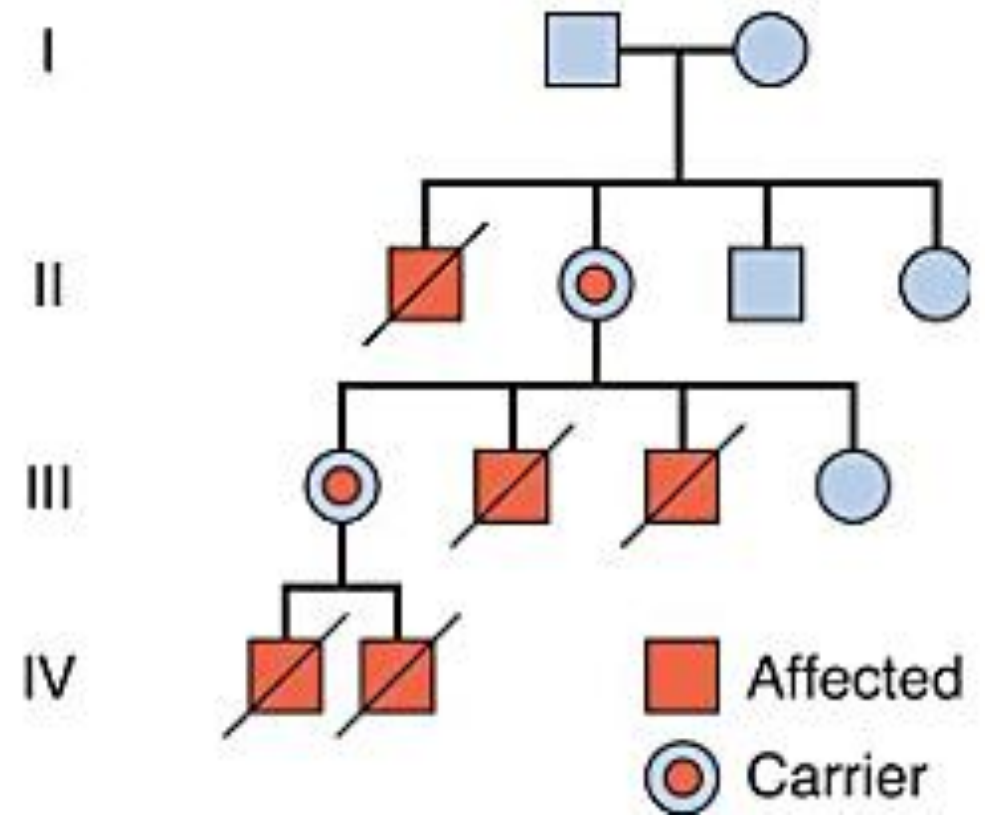


FIG. 6.12 Segregation of alleles in X-linked recessive inheritance, relating to the offspring of an affected male. **r** represents the mutated allele.

X-Linked Recessive Inheritance

FIG. 6.15 Family tree of *Duchenne muscular dystrophy (DMD)*, with the disorder being transmitted by carrier females and *affecting males, who do not survive to transmit the disorder*.



Variable Expression in Heterozygous Females

- ❖ In **X-linked conditions**, heterozygous females may have a **mosaic phenotype** with a mixture of features of the **normal** and **variant alleles**.
- ❖ In **X-linked ocular albinism**, the iris and ocular fundus of affected males lack pigment.
- ❖ Careful examination of the ocular fundus in females heterozygous for ocular albinism reveals a mosaic pattern of pigmentation.
- ❖ This is explained by *the random process of X-inactivation*.
- ❖ In the **pigmented** areas the **normal gene** is on the **active X** chromosome, and in **depigmented** areas the **variant allele** is on the **active X** chromosome.



FIG. 11.1 The fundus of a carrier of X-linked **ocular albinism** showing a mosaic pattern of retinal pigmentation.

Variable Expression in Heterozygous Females

- The patient has a variant in a gene on one of **her X chromosomes**; The **pigmented areas** indicate tissue in which the **normal X** chromosome has been **inactivated**.
- This developmental pattern follows **Blaschko's lines**.



FIG. 6.18 ***Mosaic pattern of skin pigmentation*** in a female with the **X linked dominant disorder, Incontinentia Pigmenti.**

Females Affected with X-Linked Recessive Disorders

- Sometimes a woman may manifest features of an X-linked recessive trait.
- There are several possible explanations:
 - **Homozygosity for X-Linked Recessive Disorders**
 - **Skewed X-Inactivation**
 - **Numerical X-Chromosome Abnormalities**
 - **X-Autosome Translocations**

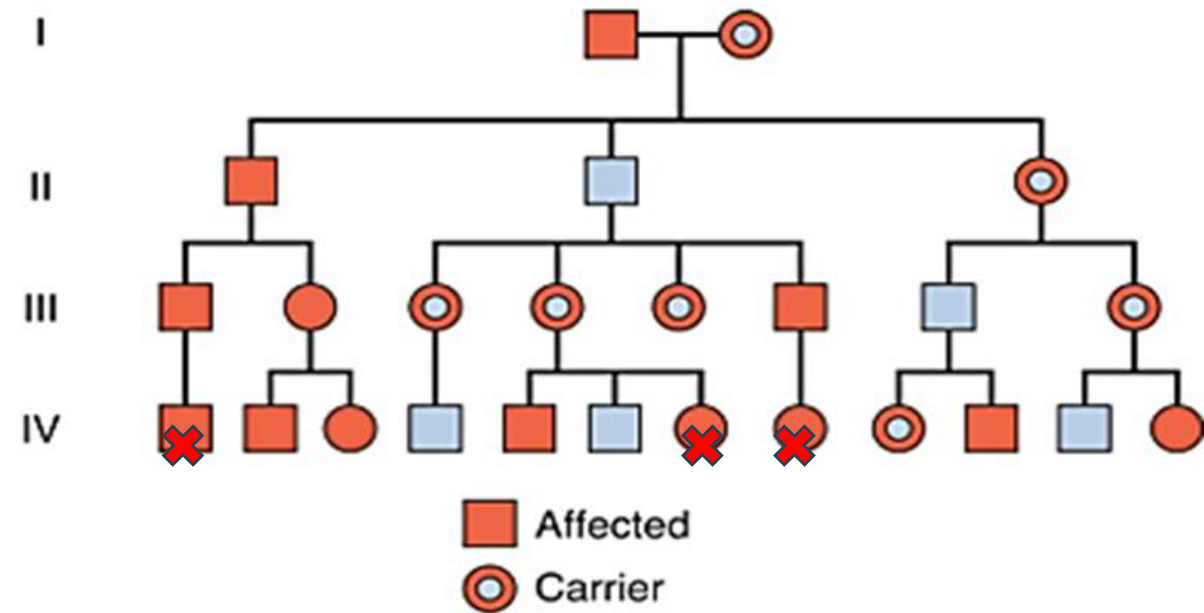
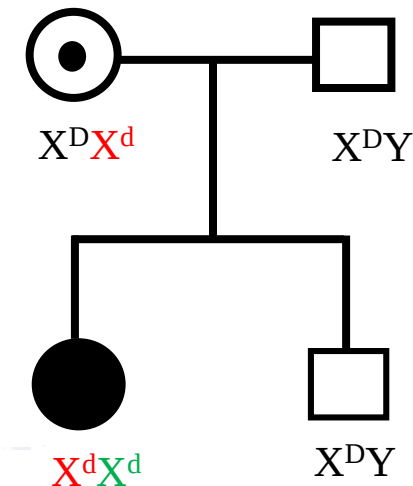
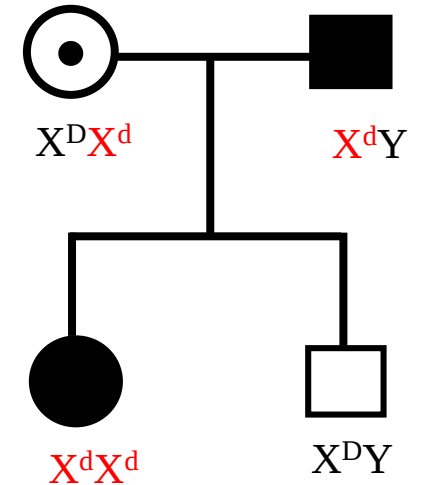


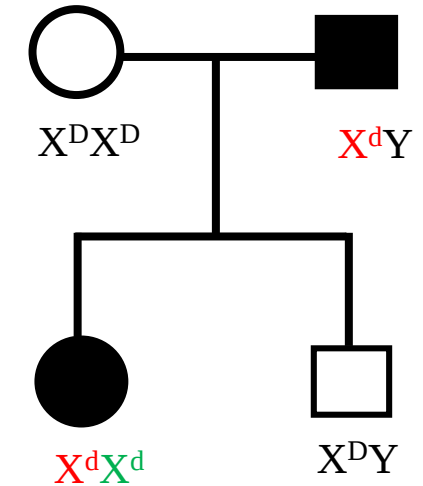
FIG. 6.11 Family tree of an **X-linked recessive** trait in which affected males reproduce.

Homozygosity for X-Linked Recessive Disorders

- ❑ A **common** X-linked recessive trait is **red-green color blindness**: The inability to distinguish between the colors red and green.
- ❑ Approximately **8% of males** are red-green color-blind
- ❑ Because of the high frequency of this allele in the population, approximately **1 in 150 women** are red-green color-blind by:
 - ❑ Virtue of both parents having the allele on the X chromosome.
 - ❑ A female could also be homozygous if her **father was affected** and **her mother was normal**, but a **new variant** occurred on the X chromosome **transmitted to the daughter**.
 - ❑ It could happen if **her mother was a carrier** and **her father was normal**, but a **new variant** occurred on the X chromosome **transmitted to his daughter**: but these scenarios are **rare**.



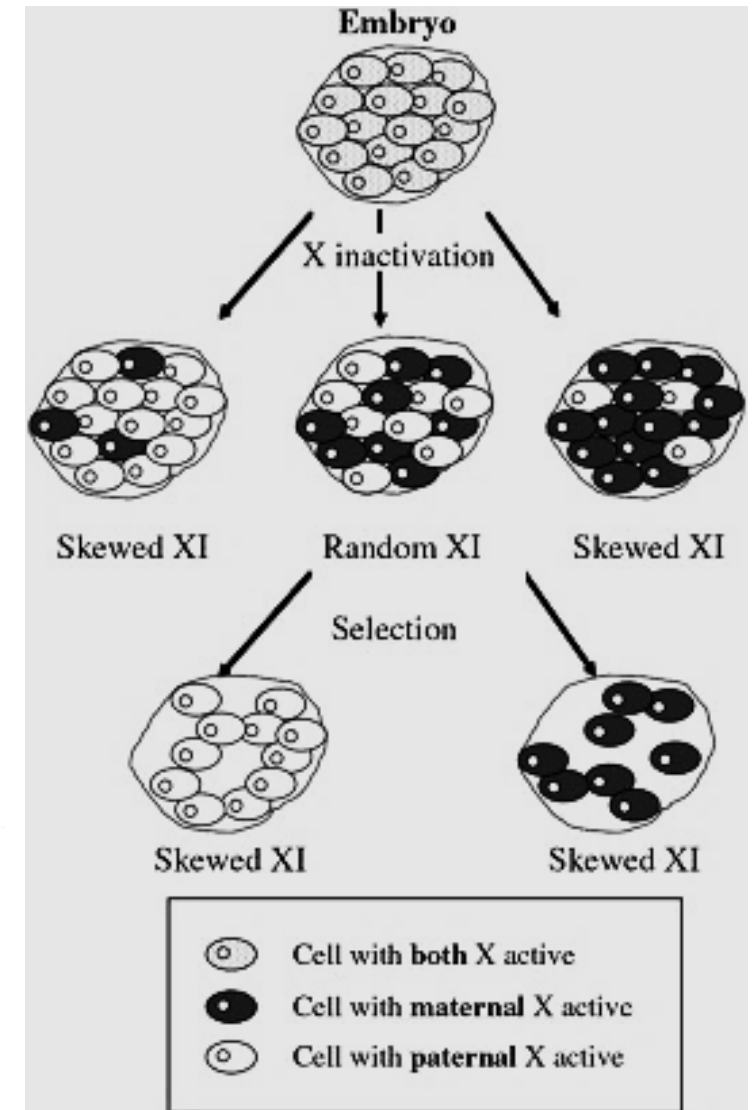
A new variant in **father** gametogenesis



A new variant in **mother** gametogenesis

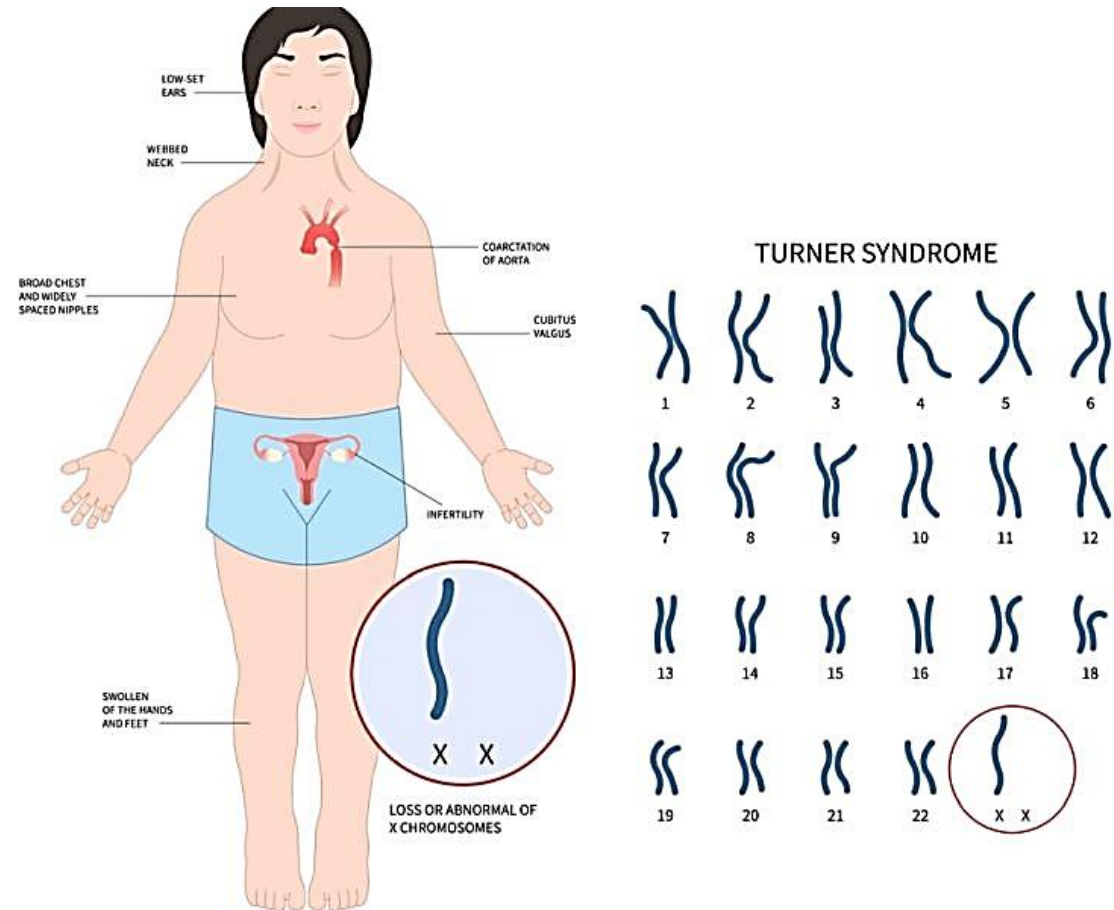
Skewed X-Inactivation

- ❖ The process of **X-inactivation usually** occurs **randomly**, there being an equal chance of either of the two X chromosomes in a **heterozygous female** being inactivated in any one cell.
- ❖ After X inactivation in **embryogenesis**, therefore, in roughly **half the cells** one of the X chromosomes is active, whereas in the other half it is the other X chromosome that is active.
- ❖ **Sometimes this process is not random**, allowing for the possibility that the active X chromosome in most of the cells of a heterozygous female carrier is the one bearing the variant allele. If this happens, a carrier female would exhibit some of the symptoms and signs of the disease and be a so-called **manifesting heterozygote/ carrier**.
- ❖ This occasionally occurs in **Duchenne muscular dystrophy** and **hemophilia A**, for example.



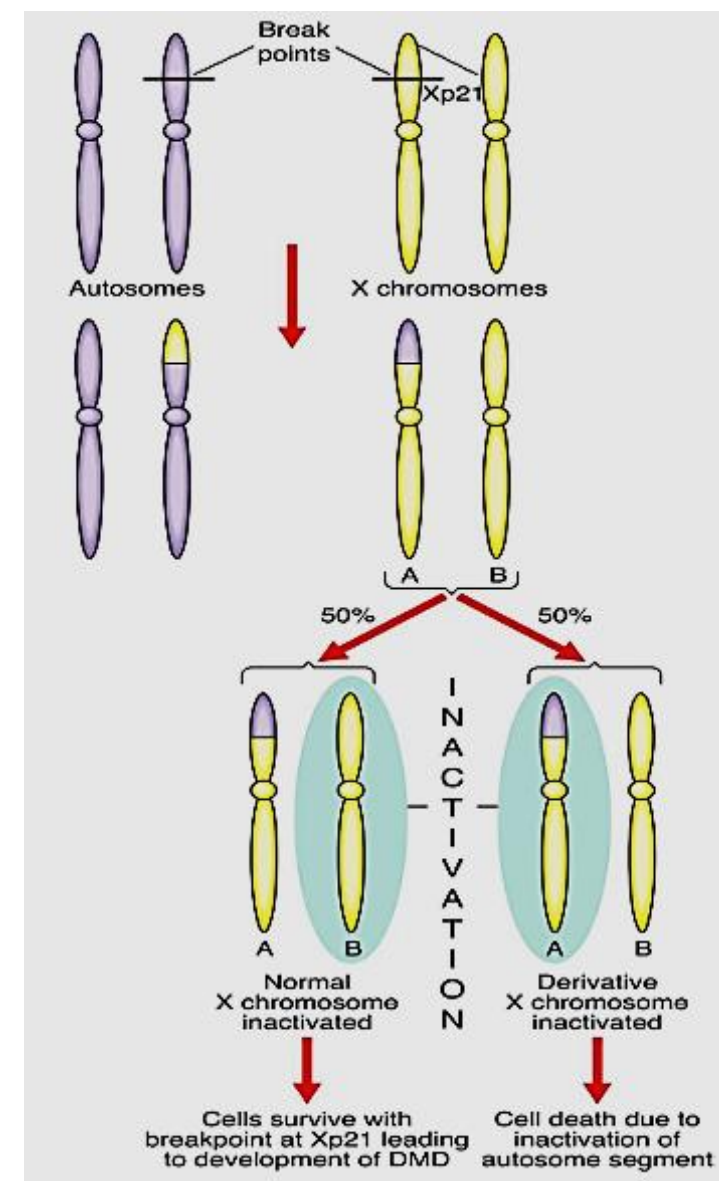
Numerical X-Chromosome Abnormalities

- A carrier with an X-linked recessive **variant** that has **a single X** chromosome (i.e., **Turner syndrome**)
- Women with **Turner syndrome** and **hemophilia A**, or **Duchenne muscular dystrophy**, have been reported.



X-Autosome Translocations

- X-Autosome Translocations Females with a translocation involving one of the **X chromosomes** and an **autosome** can be affected with an X-linked recessive disorder.
- If the **breakpoint** of the translocation **disrupts an X chromosome gene**, then a female can be affected. This is because the X chromosome involved in the translocation survives preferentially so as to maintain functional disomy of the autosomal genes.
- The observation of females affected with **Duchenne muscular dystrophy (DMD)** and having X autosome translocations involving the same region of **Xp** helped to **map the Duchenne muscular dystrophy gene**.



X-Linked Dominant Inheritance

- The *heterozygous female/male* who has the variant allele on his single X chromosome.
- Superficially this *resembles an autosomal dominant trait* because both the daughters and sons of an affected female have a 1 in 2 (50%) chance of being affected.
- However, in *X-linked dominant inheritance* an affected *male transmits the trait to his daughters but not to his sons*, resulting in *an excess of affected females* and *no direct male-to-male* transmission.

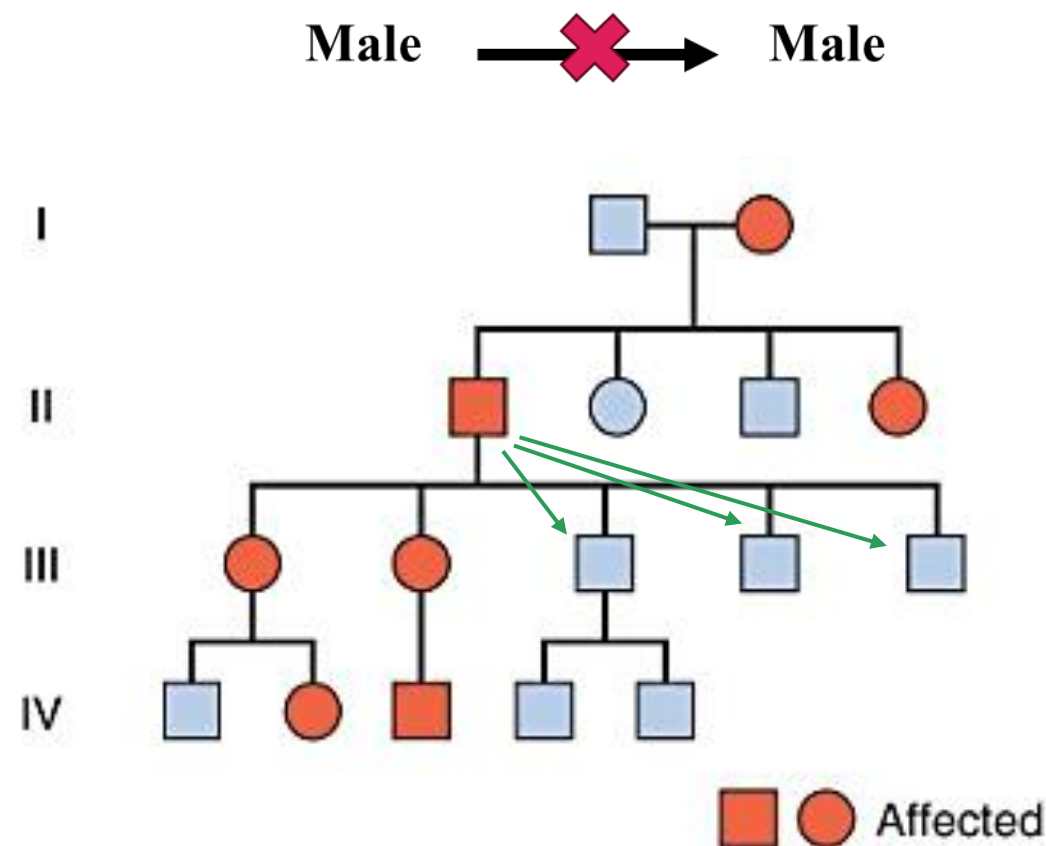


FIG. 6.17 Family tree of an X-linked dominant trait.

X-Linked **Dominant** Inheritance

- ❑ X-linked **Hypophosphatemia/ Vitamin D-resistant rickets** (**PHEX: Phosphate-regulating endopeptidase homolog X-linked**)
 - ❑ Both males and females have **short stature** because of short, and often bowed, long bones, although the females usually have less severe skeletal changes than males.
- ❑ The X-linked form of **Charcot-Marie-Tooth disease** (hereditary motor and sensory neuropathy)
- ❑ A **mosaic pattern** of involvement may be apparent in **females heterozygous** for some X-linked dominant disorders.
 - ❑ **Abnormal skin pigmentation in incontinentia pigmenti**
 - ❑ Usually **lethal for male embryos**
- ❑ Others include the neurological conditions **Rett syndrome** (MECP2 gene) and **periventricular nodular heterotopia** (FLNA: filamin A).



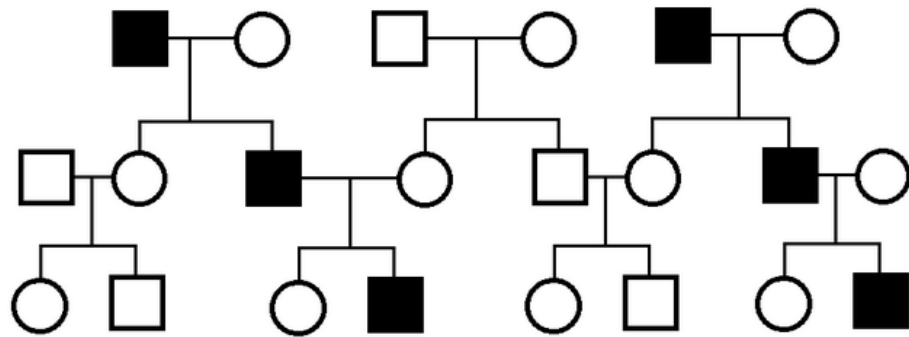
FIG. 6.18 **Mosaic pattern** of skin pigmentation in a female with the X linked dominant disorder, **incontinentia pigmenti**. The patient has a variant in a gene on one of her X chromosomes; the pigmented areas indicate tissue in which the normal X chromosome has been inactivated. This developmental pattern follows **Blaschko's lines**.

Paradoxical X-Linked Inheritance

- Recently it has been observed that patients who are **hemizygous** for variants in the **X-linked gene PCDH19 (protocadherin-19)** demonstrate the complete reversal of what is expected: **males are unaffected** and **females are severely affected** with a form of **early infantile epileptic encephalopathy (EIEE-type 9)**.
- The theory that the **heterozygous** state produces a **harmful effect** because of “**metabolic interference**” between the protein product of the mutated allele and that of the normal allele, whereas the mutated allele **alone is benign**.
- Another possibility is that **X-inactivation is disturbed** by the **variant allele**, giving rise in females to “**functional disomy**” for genes **not inactivated**. This parallels the situation in **learning-disabled and dysmorphic females** with a **ring X-chromosome**, because there is **no functional X-inactivation center**.



Y-Linked Inheritance/ Holandric Inheritance



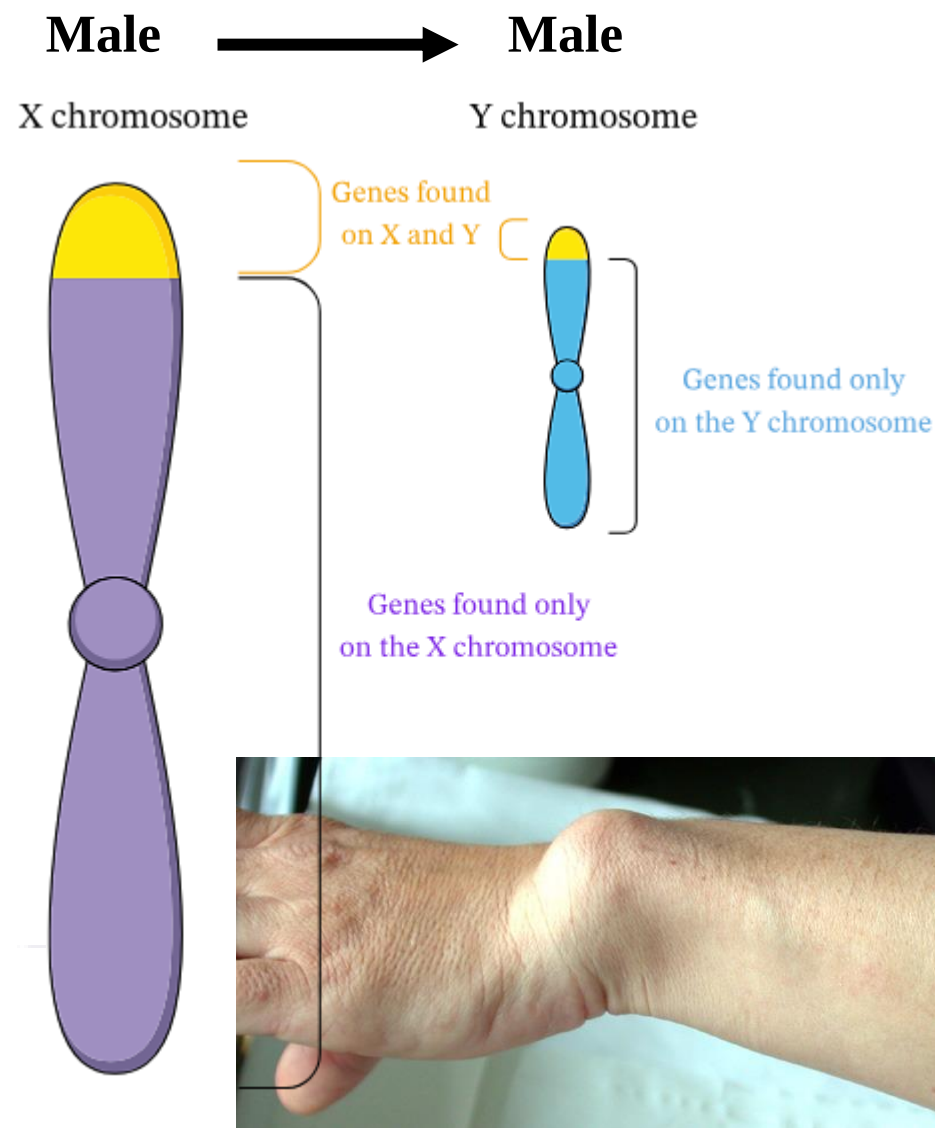
Female  Female

- ☐ Porcupine skin
- ☐ Hairy ears
- ☐ Webbed toes
- ☐ Azoospermia
- ☐ The H-Y antigen: Causing rejection of male-derived tissue grafts by female recipients, even when they share the same MHC: *SMCY (Selected Mouse cDNA on Y) / KDM5D (Lysine Demethylase 5D)*



Partial Sex-Linkage

- **Autosomal dominant** inheritance in **some** families and **X-linked inheritance** in others.
- In fact, this is because of genes present **on the tip of Xp**, which share homology with the Y chromosome (which **escapes X-inactivation**).
- During **meiosis**, pairing occurs between the homologous **Xp and Yp chromosomal regions**, the so-called pseudoautosomal regions
- As a result of a **meiotic crossover**, a gene could be **transferred from the X to the Y chromosome, or vice versa**, allowing the possibility of **male to-male transmission**.
- **Leri-Weill dyschondrosteosis** with short stature (**SHOX gene**)



Sex Influence

- More frequently in *one sex than in another*
- *In males*, gout and presenile baldness are examples of sex-influenced autosomal dominant traits, probably through the effect of male hormones.
 - *Gout* is *very rare in women* before the menopause but more frequent later
 - *Baldness* does not occur in males who have been castrated.
- *Hemochromatosis*: The most common autosomal recessive disorder in Western society, homozygous females are much less likely than homozygous males to develop iron overload and associated symptoms: the usual explanation being that women lose blood naturally through menstruation.



Sex Limitation

Sex limitation refers to the appearance of certain features **only** in individuals of a particular **sex**.

Examples include:

- **Congenital adrenal hyperplasia (CAH):** virilization of **female infants** affected with the **autosomal recessive endocrine** disorder
- **Breast** development in females
- **Beard** growth in males



Box 6.1

Features that support the single-gene or mendelian patterns of inheritance

Autosomal Dominant

- Males and females affected in equal proportions
- Affected individuals in multiple generations
- Transmission by individuals of both sexes (i.e., male to male, female to female, male to female, and female to male)

Autosomal Recessive

- Males and females affected in equal proportions
- Affected individuals usually in only a single generation
- Parents can be related (i.e., consanguineous)

X-Linked Recessive

- Only males usually affected
- Transmitted through unaffected females
- Males cannot transmit the disorder to their sons (i.e., no male-to-male transmission)

X-Linked Dominant

- Males and females affected, but often an excess of females
- Females less severely affected than males
- Affected males can transmit the disorder to their daughters but not to sons

Y-Linked Inheritance

- Only males affected
- Affected males must transmit it to their sons

Multiple Alleles and Complex Traits

- Some *traits* and *diseases* are *neither monogenic nor polygenic*.
- Some genes have *more than two allelic forms* (i.e., *multiple alleles*).
- Multiple alleles are the result of *a normal gene having variants* that produce different alleles, some of which determine *dominant* inheritance and others *recessive*.
- In the *ABO blood group system*, there are at least four alleles (A₁, A₂, B, and O).

Table 6.1 Possible genotypes, phenotypes, and gametes formed from the four alleles A₁, A₂, B, and O at the ABO locus

Genotype	Phenotype	Gametes
A ₁ A ₁	A ₁	A ₁
A ₂ A ₂	A ₂	A ₂
BB	B	B
OO	O	O
A ₁ A ₂	A ₁	A ₁ or A ₂
A ₁ B	A ₁ B	A ₁ or B
A ₁ O	A ₁	A ₁ or O
A ₂ B	A ₂ B	A ₂ or B
A ₂ O	A ₂	A ₂ or O
BO	B	B or O

Digenic Inheritance

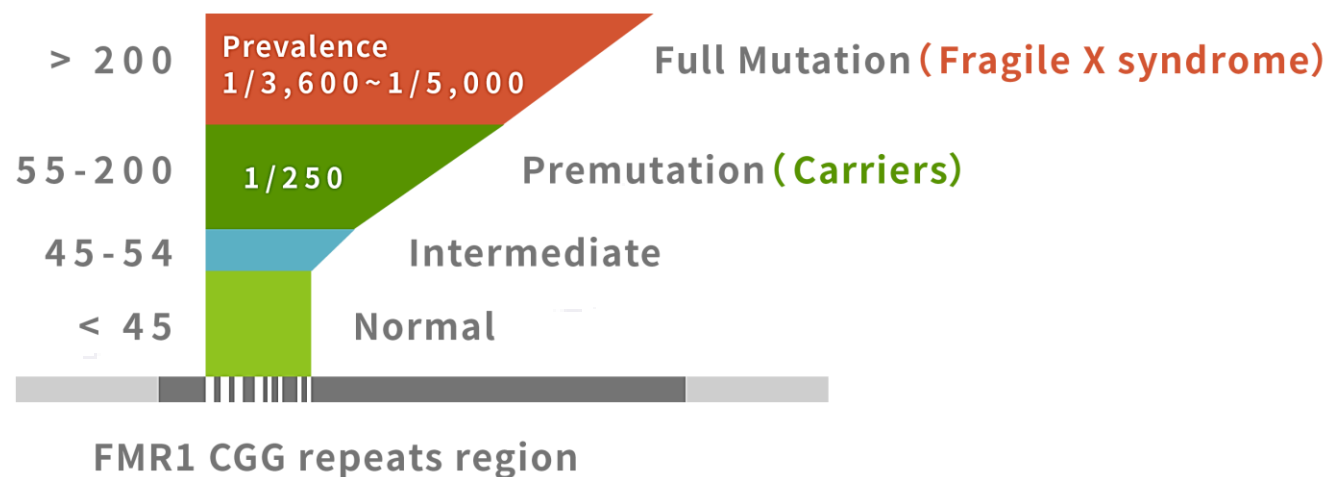
- ❑ The additive effects of heterozygous variants at two different gene loci.
- ❑ *Vertebral defects in* mice that are *double heterozygotes* for *rv* and *Dll1*.
- ❑ *Retinitis pigmentosa (RP)* is caused by *double heterozygosity* for variants in two unlinked genes, *ROM1* and *PRPH2 (Peripherin)*, which both encode proteins present in *photoreceptors*. Individuals with *only one* of these variants *are not affected*.
- ❑ Usher syndrome, in which RP occurs with sensorineural deafness
- ❑ Inherited cardiac arrhythmias and cardiomyopathies
- ❑ Inherited deafness
- ❑ Bardet-Biedl syndrome
- ❑ Joubert syndrome

Anticipation

In some *autosomal dominant* traits or disorders, such as *myotonic dystrophy*, the onset of the disease occurs at an *earlier age* in the offspring than in the parents, or the disease occurs with *increasing severity* in subsequent generations.

- *The severe neonatal form of myotonic dystrophy*: An expansion of the CTG triplet repeat in the 3' untranslated end of the myotonic dystrophy gene, occurring predominantly in maternal meiosis
- *Fragile X syndrome*: major instability in the expansion CGG repeats occurring during maternal meiosis
- *Huntington disease*: A similar expansion of CAG repeats in the 5' end of the gene in paternal meiosis
- *Inherited spinocerebellar ataxia*

CGG REPEATS



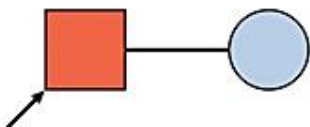
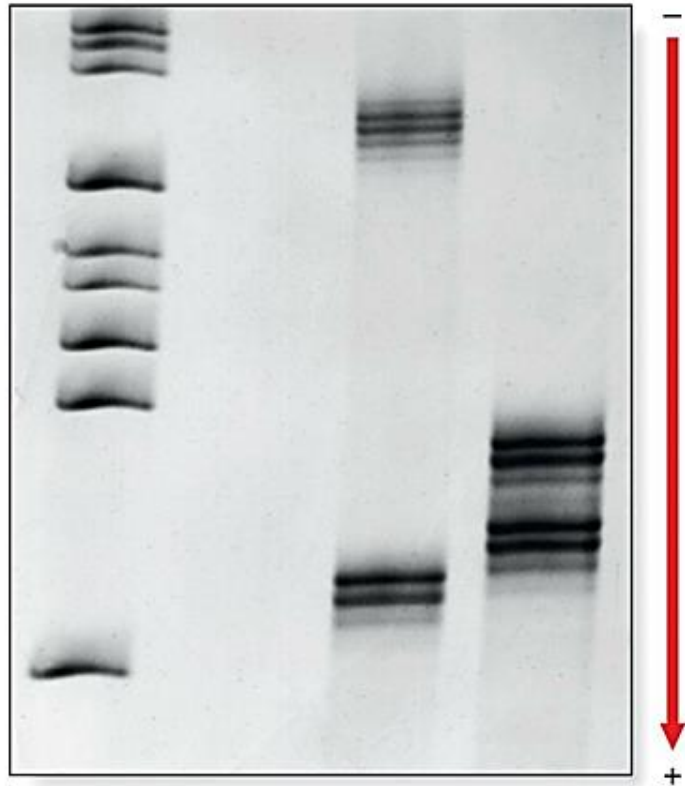


FIG. 6.20 Silver staining of a 5% denaturing gel of the polymerase chain reaction products of the **CAG triplet in the coding sequence of the huntingtin gene** from an affected male and his wife, showing her to have two similar-sized repeats in the normal range (20 and 24 copies) and him to have one normal-sized triplet repeat (18 copies) and an expanded triplet repeat (44 copies). The bands in the left lane are standard markers to allow sizing of the CAG repeat.



FIG. 6.19 Newborn baby with severe hypotonia requiring ventilation as a result of having inherited **myotonic dystrophy** from his **mother**.

Mosaicism

- An **individual**, or a particular **tissue** of the body, can consist of more than one cell type or line, through an error occurring during **mitosis** at **any stage after conception**.
- Mosaicism of either **somatic tissues** or **germ cells**

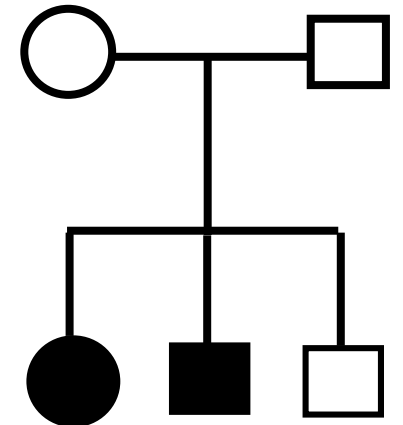
❑ Somatic Mosaicism

- **Neurofibromatosis type I**

❑ **Gonadal Mosaicism:** *The timing of the variant arising in early development* may determine whether it is **transmitted** to the next generation with full expression—this will depend on the variant being present in **gonadal tissue**, and hence **germline cells**. **De novo** autosomal dominant and X-linked recessive variants in:

- Achondroplasia
- Osteogenesis imperfecta
- Duchenne muscular dystrophy
- Hemophilia

The **parents** are phenotypically normal, and the results of genetic tests also normal, but in which **more than one of their children has been affected**.

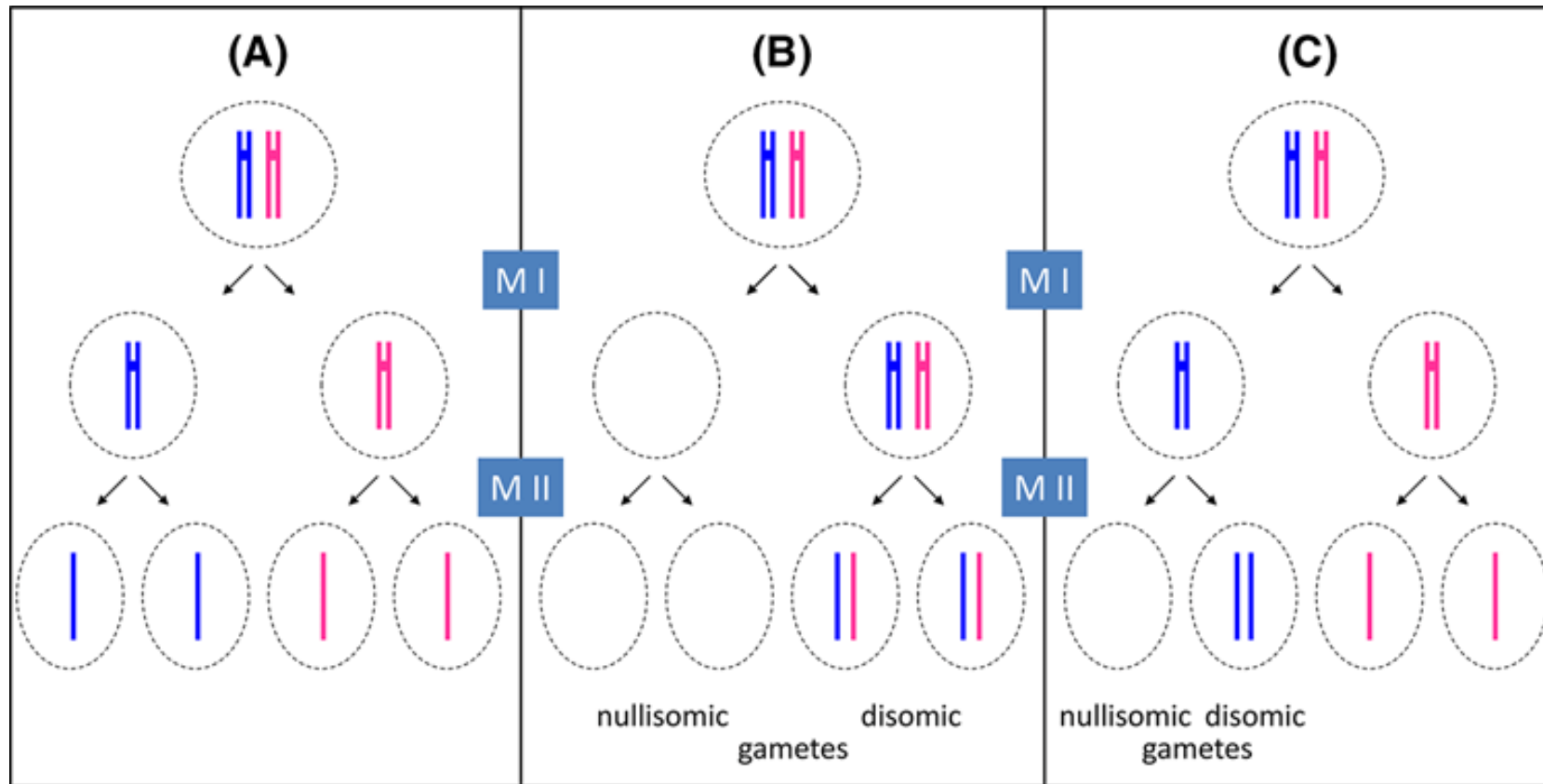


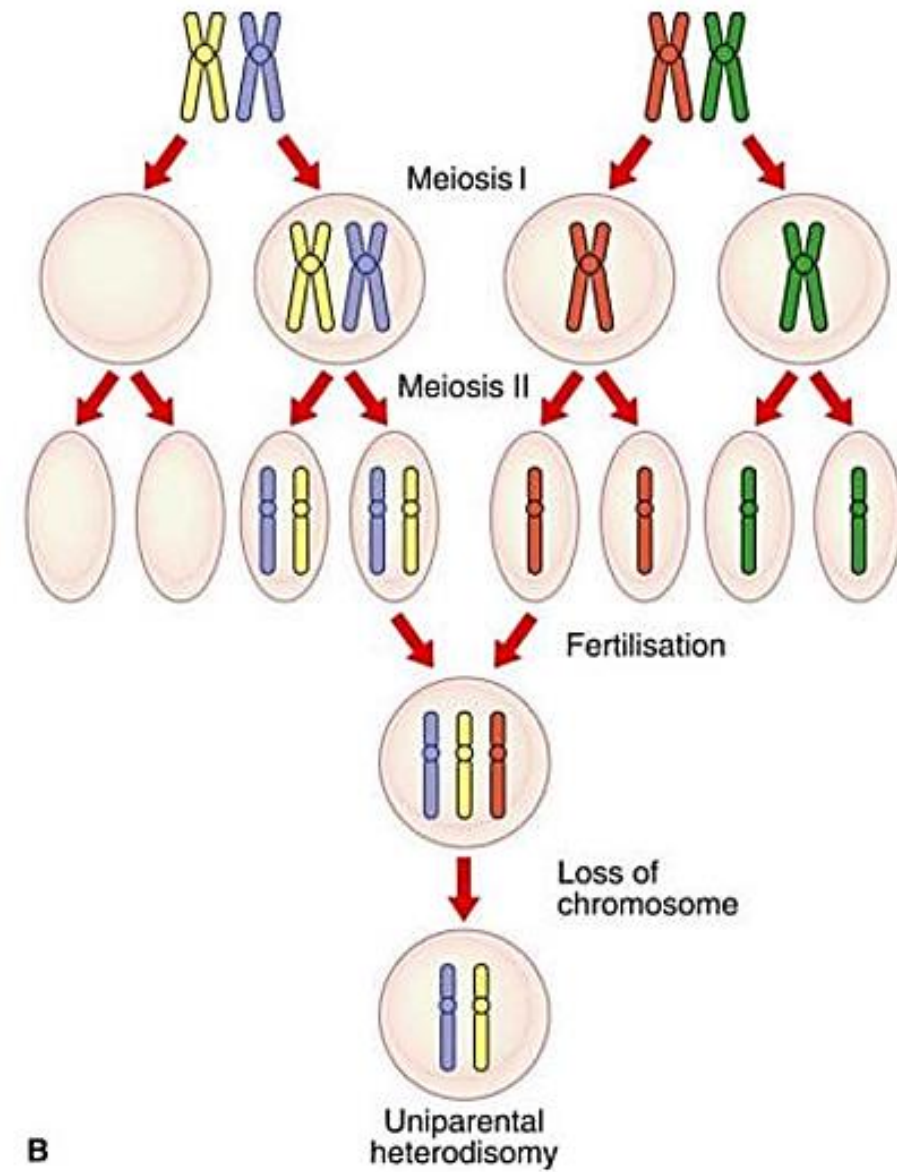
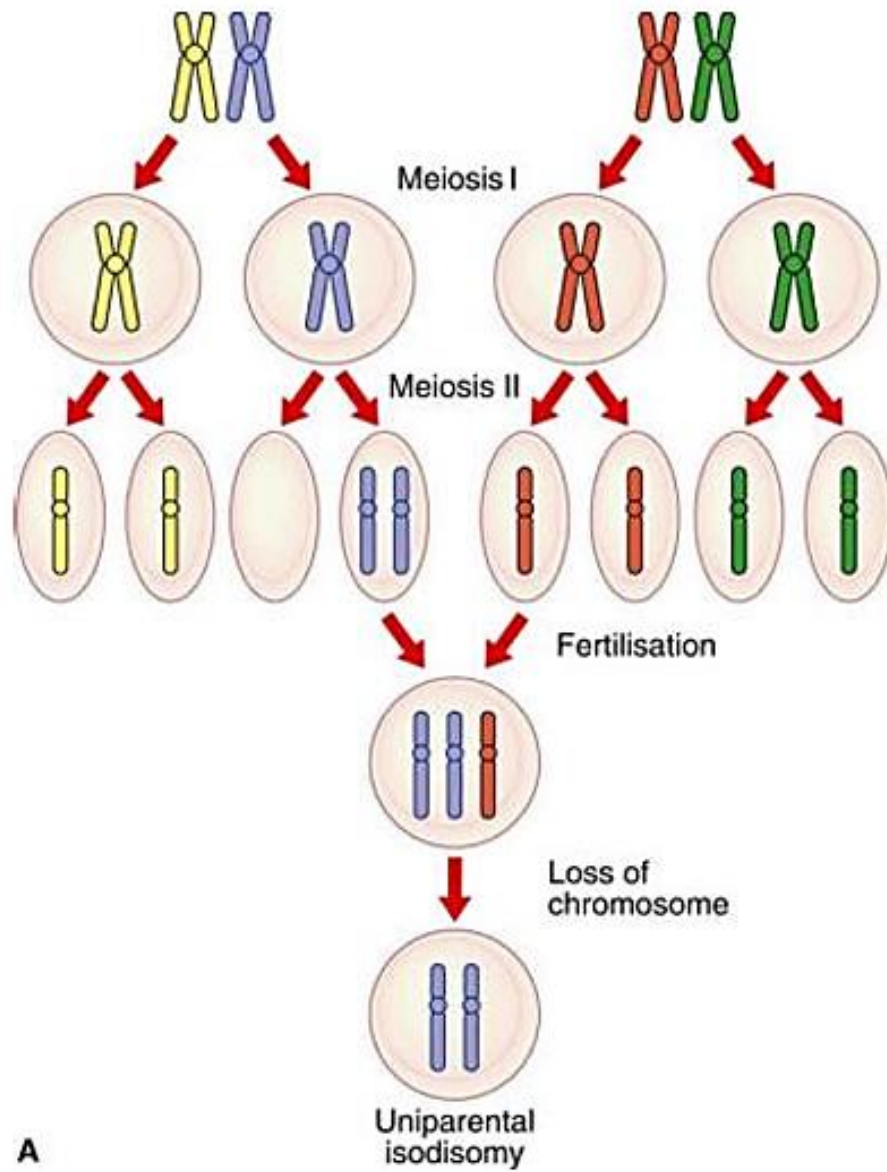
Uniparental Disomy (UPD)

- Individuals inherit one of *a pair of homologous chromosomes from only one parent.*
 - **Uniparental isodisomy:** two copies *of the same homologue* from one parent through an error in *meiosis II*
 - **Uniparental heterodisomy:** two different homologues from one parent through an error in *meiosis I*
- ❑ It is presumed that the *conceptus* would *originally* be *trisomic*, with early *loss of a chromosome* leading to the “normal” *disomic state*.
 - *One-third of such chromosome losses*, if they occurred with equal frequency, would result in *UPD*.
- ❑ A *nullisomic* gamete is “rescued” by fertilization with a *disomic* gamete.

B) Uniparental heterodisomy occurring through a disomic gamete arising from nondisjunction in meiosis I fertilizing a monosomic gamete with loss of the chromosome from the parent contributing the single homologue.

C) Uniparental isodisomy occurring through a disomic gamete arising from nondisjunction in meiosis II fertilizing a monosomic gamete with loss of the chromosome from the parent contributing the single homolog.





UPD Examples:

- A father with hemophilia having an affected son
- A child with cystic fibrosis being born to a couple in which only the mother was a carrier
- UPD for chromosome 15q gives rise to either Prader-Willi syndrome (PWS; maternal UPD) or Angelman syndrome (AS; paternal UPD)
- Paternal UPD for chromosome 11p is one of the causes of the overgrowth condition known as the Beckwith Wiedemann syndrome (BWS) and Maternal UPD in Silver-Russell syndrome (SRS) with growth restriction.

Genomic Imprinting

- Although it was **originally** thought that genes on **homologous** chromosomes were **expressed equally**, it is now recognized that different clinical features can result depending on **whether a gene is inherited from the father or from the mother**.
- This “parent of origin” effect is referred to as genomic imprinting, and DNA methylation, occurring mostly at **a CpG site**, is **the main mechanism** by which **expression is modified**.
- Methylation is the imprint applied to certain DNA sequences in ***their passage through gametogenesis***
- The differential allele expression (i.e., ***maternal or paternal***) may occur in all somatic cells, or in specific tissues or stages of development. Thus far, **at least 80 human genes** are known to be imprinted, and the regions involved are known as ***differentially methylated regions (DMRs)***.
 - These DMRs include ***imprinting control regions (ICRs)*** that control gene expression across imprinted domains.

Prader-Willi Syndrome (PWS)

- ❑ 1 in 20,000 births
- ❑ Short stature, obesity, hypogonadism, and learning difficulty
- ❑ 50% to 60% of individuals with PWS can be shown to have an approximately 2-megabase (Mb) interstitial deletion of the proximal region of chromosome 15q11-q13, visible by conventional cytogenetic means
- ❑ 15% a submicroscopic deletion can be demonstrated by fluorescence in situ hybridization (pp. 55, 259) or molecular means.
- ❑ Almost always the paternally derived homologue.
- ❑ 25% to 30% have maternal UPD



Prader-Willi Syndrome (PWS)

- Critical region of 15q11-q13
- PWS is a **multigene disorder**, and in the normal situation the gene encoding
- Small nuclear ribonucleoprotein polypeptide N (**SNRPN**) and adjacent genes (**MKRN3**, etc.) are **paternally** expressed.
- Expression is under the control of a specific **ICR**.
- **The 3' end of the ICR** is required for expression of the **paternally** expressed genes and also the origin of the long SNURF/SNRPN transcript.
- **The maternally expressed genes** are not differentially methylated, but they are **silenced on the paternal allele**, probably by an **antisense RNA generated from SNURF/SNRPN**.
- In normal cells, **the 5' end of the ICR**, needed for maternal expression and involved in **AS** that is **methylated on the maternal allele**.

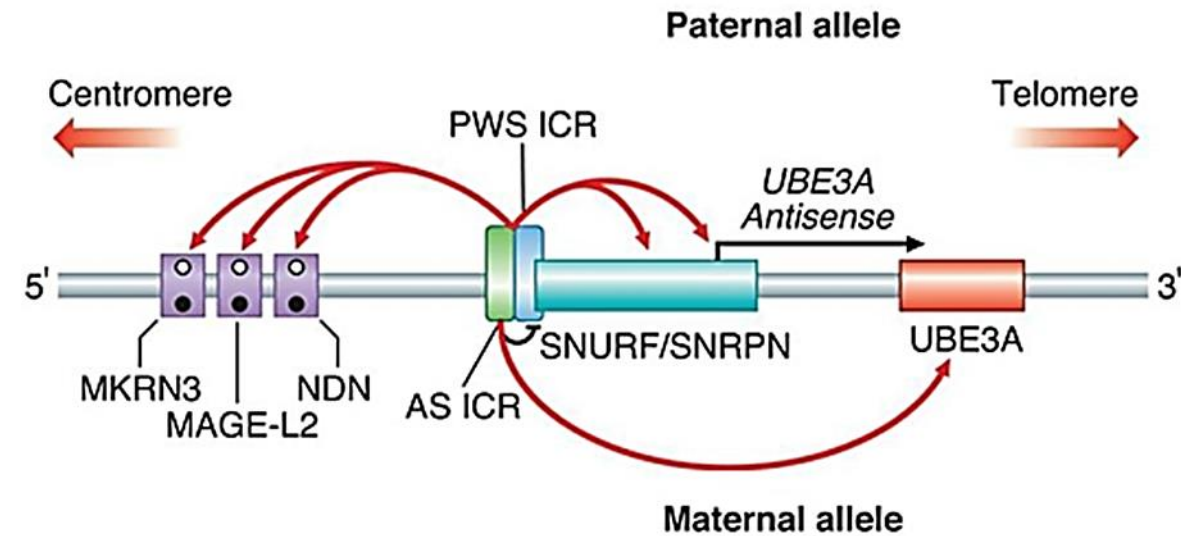
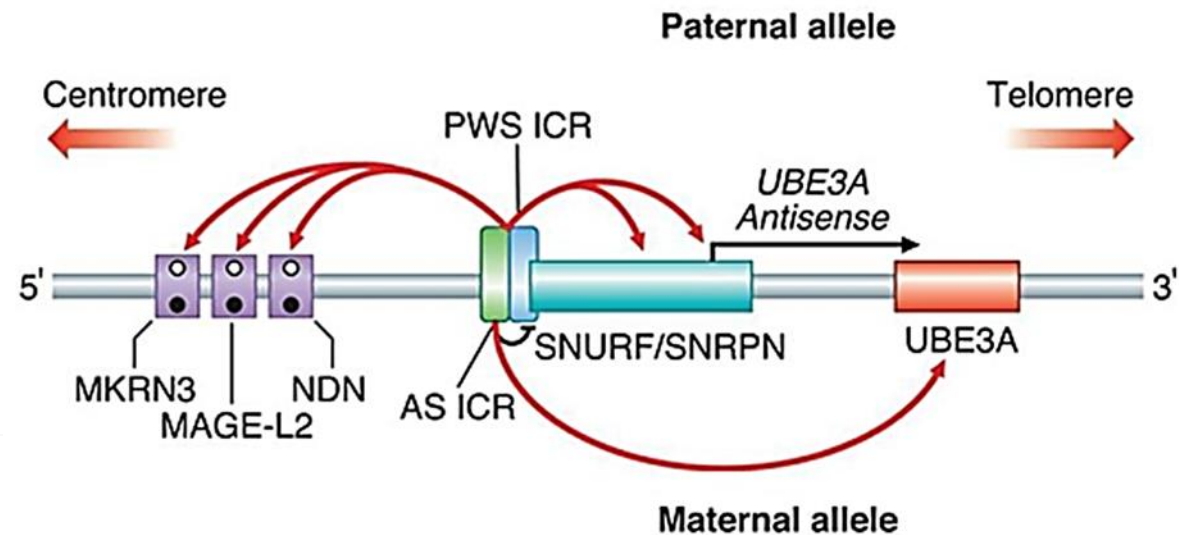


FIG. 6.23 Molecular organization (simplified) at 15q11-q13: Prader-Willi syndrome (PWS) and Angelman syndrome (AS). The imprinting control region (ICR) for this locus has two components. The more telomeric acts as the PWS ICR and contains the promoter of SNURF/SNRPN. SNURF/SNRPN produces several long and complex transcripts, one of which is believed to be an RNA antisense inhibitor of UBE3A. The more centromeric ICR acts as the AS ICR on UBE3A, which is the only gene whose maternal expression is lost in AS. The AS ICR also inhibits the PWS ICR on the maternal allele. The PWS ICR also acts on the upstream genes MKRN3, MAGE-L2 and NDN, which are unmethylated (○) on the paternal allele but methylated (●) on the maternal allele.

Angelman Syndrome (AS)

- 1 in 15,000 births
- Epilepsy, severe learning difficulties, an unsteady or ataxic gait, and a happy demeanor
- 70% have an **interstitial deletion** of the same **15q11 q13 region** on the **maternally** derived homologue.
- 5% have arisen through **paternal UPD**
- Up to **10%** variants have been identified in loss of **a single gene UBE3A**, a ubiquitin ligase gene, which appears to be **preferentially or exclusively** expressed from the **maternally** derived chromosome 15 in the **brain**.
- Ubiquitin-mediated destruction of proteins in the CNS in development, particularly where UBE3A is expressed most strongly, namely the hippocampus and Purkinje cells of the cerebellum.
- UBE3A is under control of the **AS ICR**, which was mapped slightly upstream of SNURF/SNRPN through analysis of patients with AS who had **various different microdeletions**.



Angelman Syndrome (AS)



FIG. 6.24 (A) and (B) Two young girls with Angelman syndrome. (C) Adult male with Angelman syndrome.

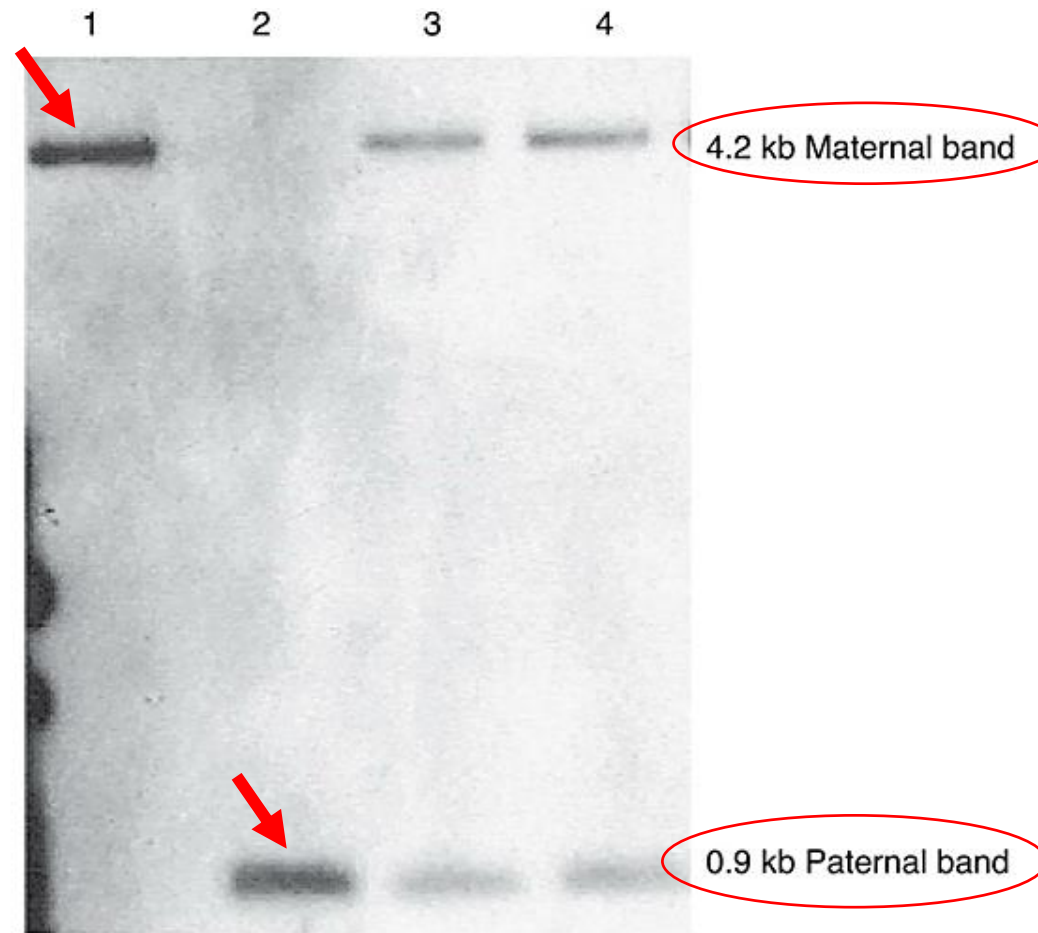


FIG. 6.25 Southern blot to detect methylations of SNRPN. DNA digested with XbaI and NotI was probed with KB17, which hybridises to a CpG island within exon 1 of SNRPN. Patient 1 has Prader-Willi syndrome, patient 2 has Angelman syndrome, and patients 3 and 4 are unaffected. (Courtesy A. Gardner, Department of Molecular Genetics,

Beckwith-Wiedemann (BWS)

- Paternally derived duplications of 11p15
- A well-known “**overgrowth**” condition:
- Macrosomia (prenatal and/or postnatal overgrowth), macroglossia (large tongue), abdominal wall defect (omphalocele, umbilical hernia, diastasis recti), and neonatal hypoglycemia
- Hemihyperplasia may be present, as well as visceromegaly, renal abnormalities, ear anomalies (anterior earlobe creases, posterior helical pits), and cleft palate, and there may be embryonal tumors (particularly **Wilms tumor**).

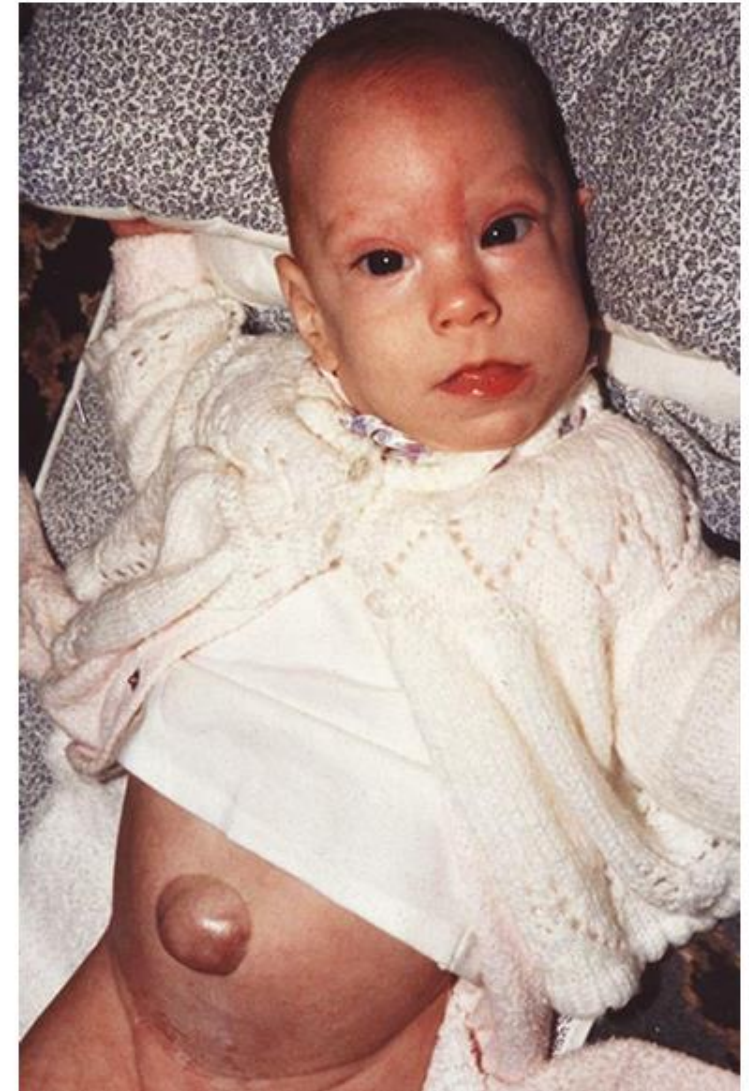


FIG. 6.26 Baby girl with Beckwith-Wiedemann syndrome. Note the **large tongue** and **umbilical hernia**.

Russell-Silver Syndrome (RSS)

- “**Opposite**” characteristics to BWS by virtue of marked prenatal and postnatal **growth retardation**.
- The head circumference is relatively normal, **the face rather small and triangular**, giving rise to a “**pseudohydrocephalic**” appearance, **body asymmetry**
- **10%** of cases appear to be as a result of **maternal UPD**
- **Maternally derived duplications** of 11p15 region are associated with **growth retardation**.
- Up to **50%** of RSS cases are as a result of abnormalities of **imprinting** at the **11p15.5 locus**. Whereas **hypermethylation** of **DMR1** leads to **upregulated IGF2** and **overgrowth**, **hypomethylation** of **H19** leads to **downregulated IGF2** and **RSS**.
- Interestingly, in contrast to BWS, there are **no** cases of **RSS** with **altered methylation** of the more centromeric **DMR2** region.



FIG. 6.28 Girl with Russell-Silver syndrome. Note the bossed forehead, triangular face, and “pseudohydrocephalic” appearance.

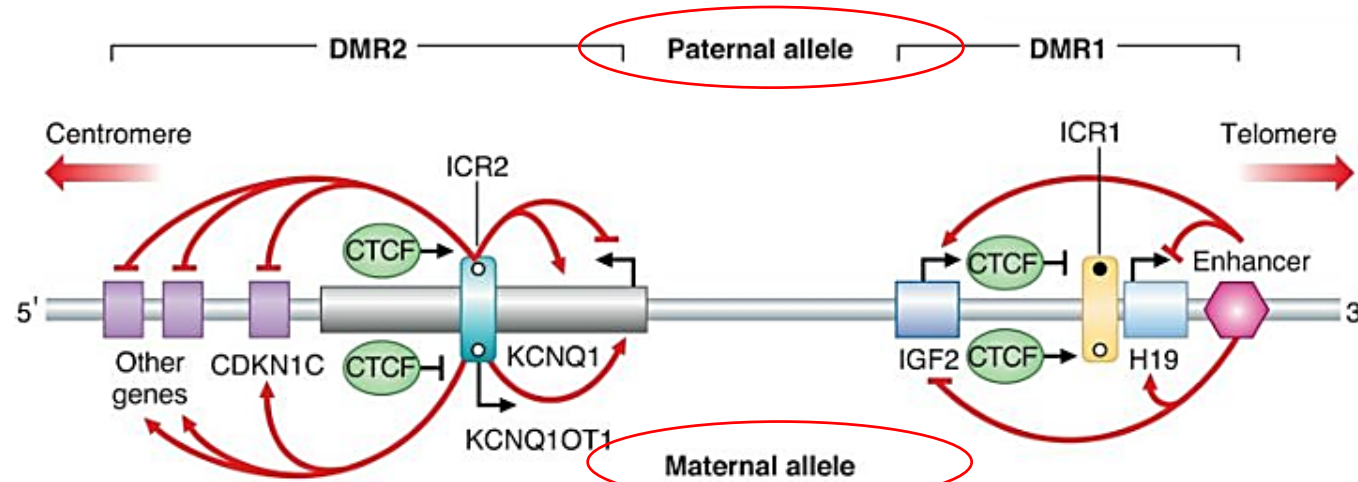


FIG. 6.27 Molecular organization (simplified) at 11p15.5: Beckwith-Wiedemann and Russell-Silver syndromes. The region contains two imprinted domains (DMR1 and DMR2) that are regulated independently. The imprinting control regions (ICRs) are differentially methylated (● methylated; ○ unmethylated). CCCTC-binding factor (CTCF) binds to the unmethylated alleles of both ICRs. In DMR1, coordinated regulation leads to expression of IGF2 only on the paternal allele and H19 expression only on the maternal allele. In DMR2, coordinated regulation leads to maternal expression of KCNQ1 and CDKN1C (plus other genes) and paternal expression of KCNQ1OT1 (a non-coding RNA with antisense transcription to KCNQ1). Angled black arrows show the direction of the transcripts.

Mitochondrial /Cytoplasmic Inheritance

Maternal or Matrilinear Inheritance

- ❑ Each cell contains thousands of copies of mitochondrial DNA, with more being found in cells that have high energy requirements, such as **brain** and **muscle**.
- ❑ Mitochondria, and therefore their DNA, are inherited almost exclusively from the **mother through the oocyte**
- ❑ Mitochondrial DNA has **a higher rate of spontaneous variation** than nuclear DNA, and the accumulation of variants in mitochondrial DNA has been proposed as being responsible for some of the somatic effects seen with **aging**.
- ❑ In humans, **mitochondrial inheritance** explains the pattern of inheritance observed in some rare disorders that affect **both males and females** but are transmitted **only through females**, so-called **maternal or matrilinear inheritance**

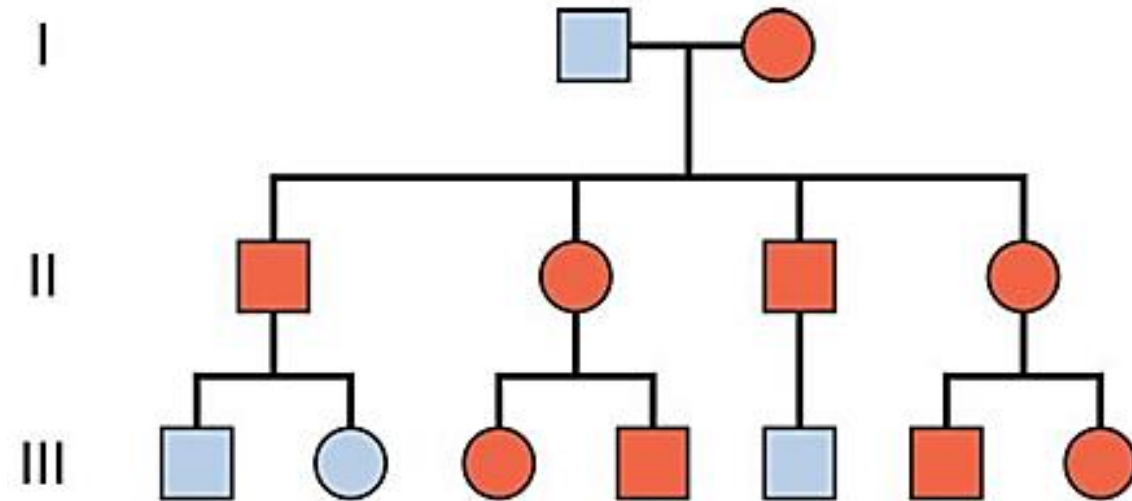


FIG. 6.29 Family tree consistent with mitochondrial inheritance.

Mitochondrial Inheritance

- ❑ Unusual combinations of neurological and myopathic features, sometimes occurring in association with other conditions such as cardiomyopathy and conduction defects, diabetes, or deafness
- ❑ Because mitochondria are crucial to cellular metabolism through oxidative phosphorylation, it is not surprising that the organs most susceptible to mitochondrial variants are the central nervous system, skeletal muscle, and heart.
- ❑ In most persons, the mitochondrial DNA across different mitochondria is identical, or shows what is termed homoplasmy.
- ❑ If a variant occurs in the mitochondrial DNA of an individual, there will initially be two populations of mitochondrial DNA, so-called heteroplasmy: phenotypic severity in affected persons with mitochondrial disorders.

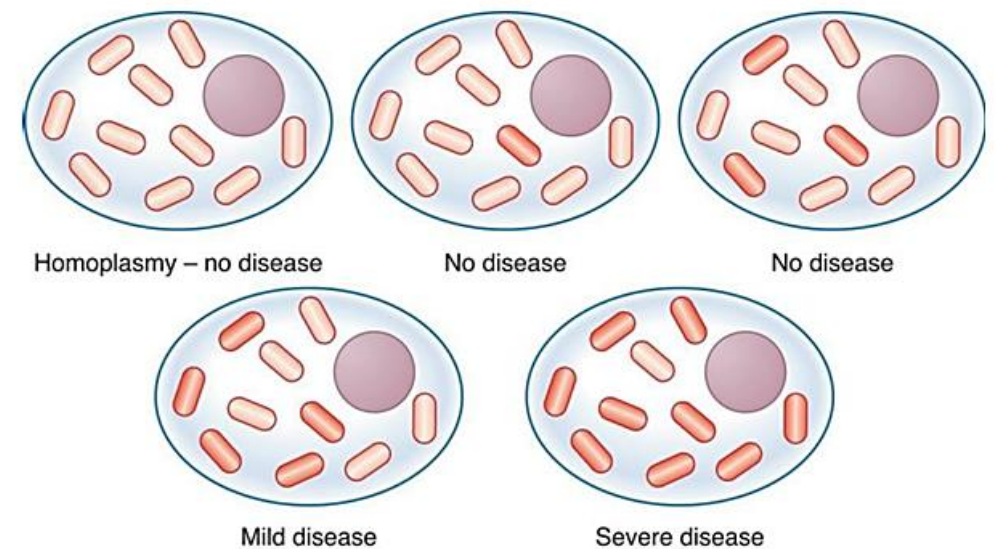
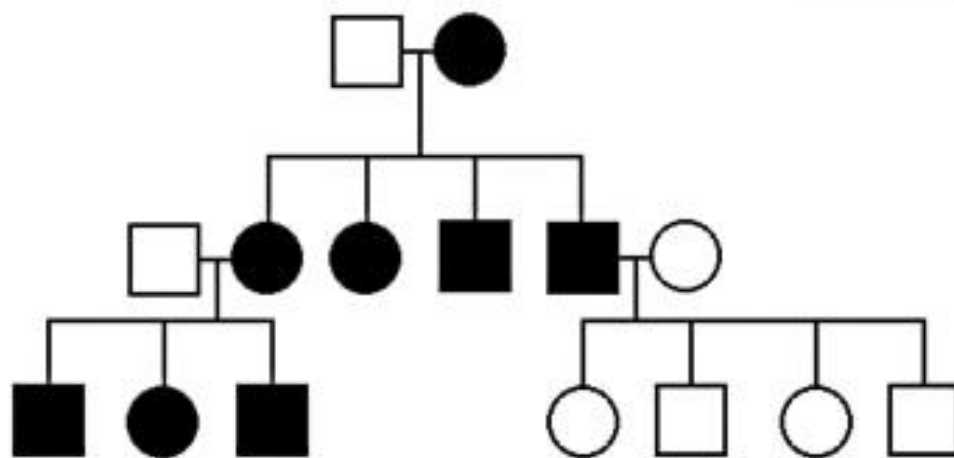


FIG. 6.30 Progressive effects of heteroplasmy on the clinical severity of disease from variants in the mitochondrial genome. Low proportions of variant mitochondria are tolerated well, but as the proportion increases, different thresholds for cellular, and hence tissue, dysfunction are breached (mauve circle represents the cell nucleus).

Mitochondrial inheritance



Leber Hereditary Optic Neuropathy (LHON)



Kearns-Sayre syndrome

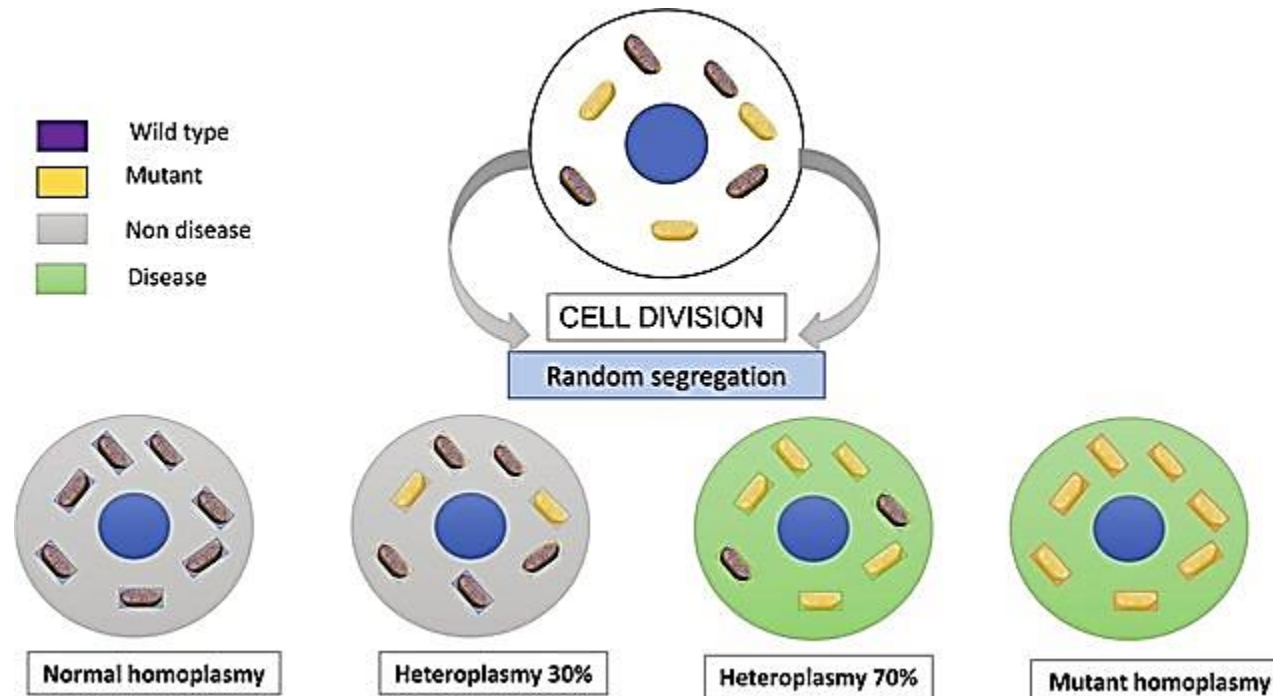
Female  **Male**
Female

 **Affected female**
 **Affected male**

Heteroplasmy

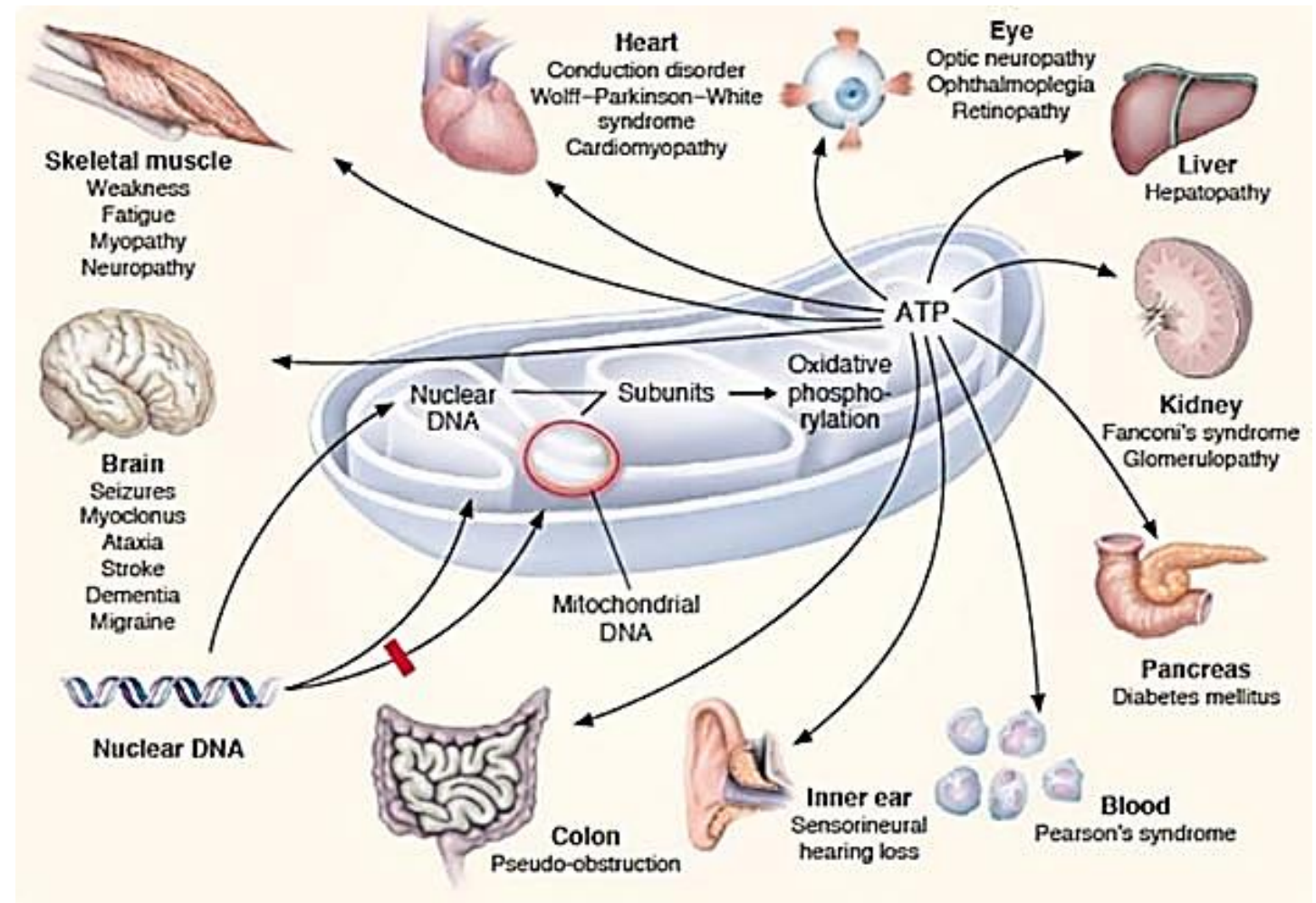
Describes the situation in which **two or more mtDNA variants** exist within **the same cell**.

Heteroplasmies are often caused by **de novo mutations** occurring either in the **germline** or in the **somatic tissues**.



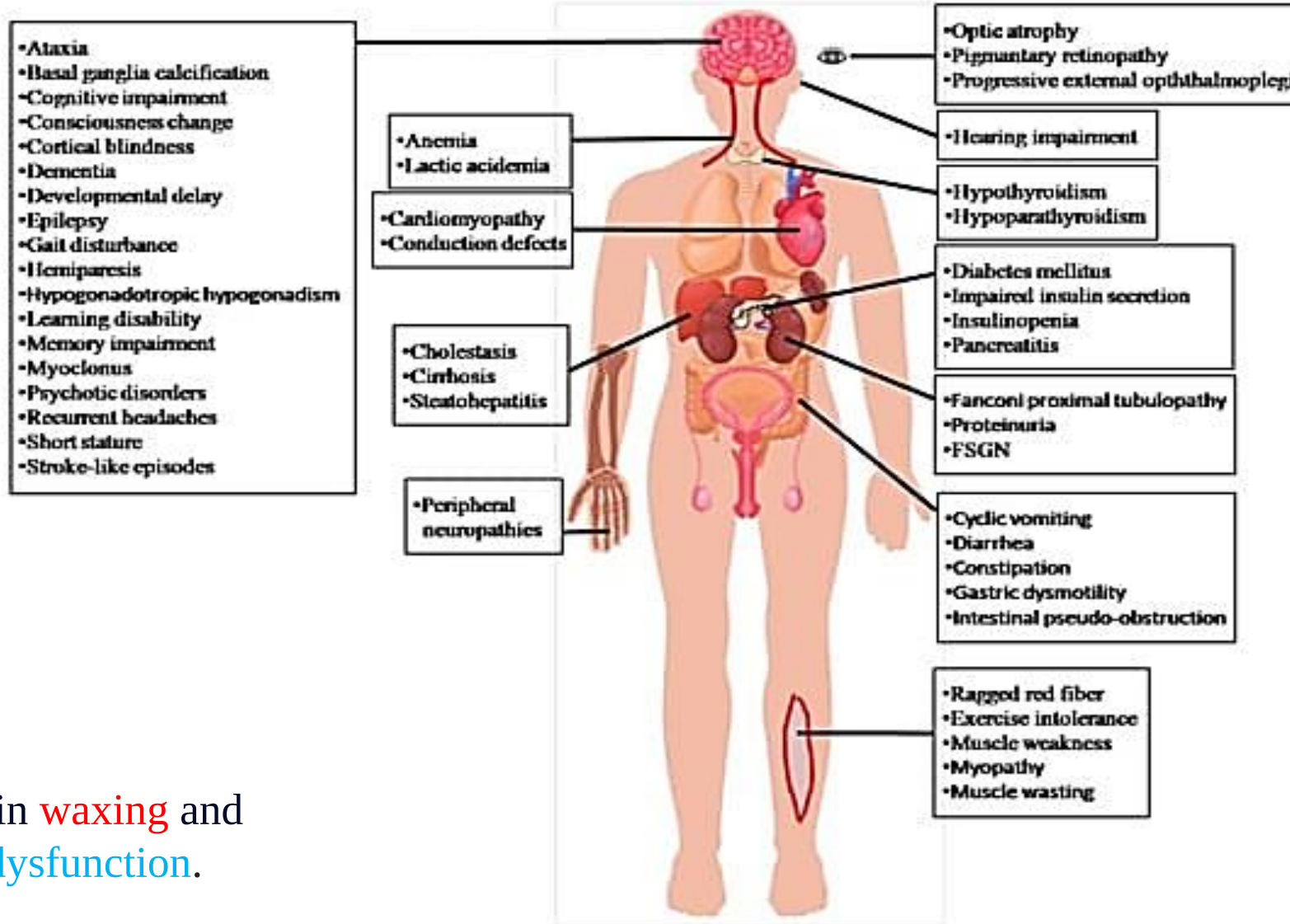
What are common mitochondrial diseases?

- Mitochondrial **E**ncephalopathy, Lactic **A**cidosis and **S**troke-like episodes (**MELAS**) syndrome.
- Myoclonic **E**pilepsy with Ragged **R**ed **F**ibers (**MERRF**)
- **N**euroathy, **A**taxia and **R**etinitis **P**igmentosa (**NARP**) syndrome
- Leber **H**ereditary **O**ptic **N**euroathy (**LHON**)



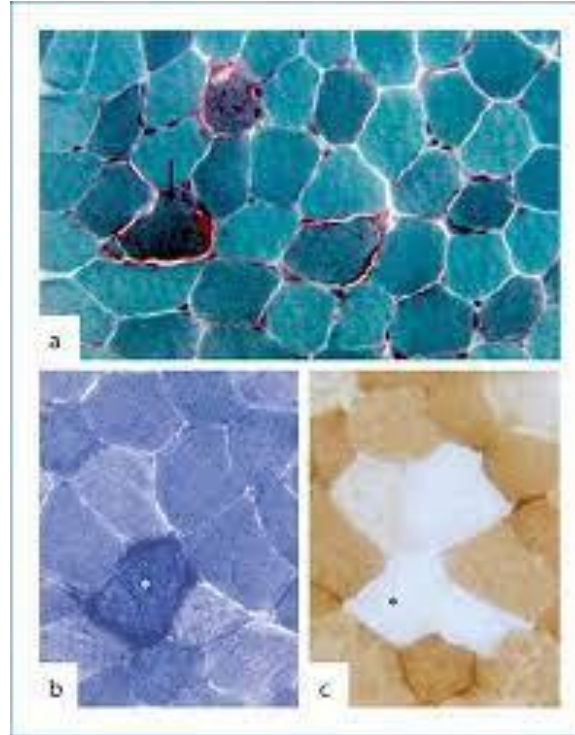
MELAS

A rare **inherited** disorder that results in **waxing** and **waning** nervous system and **muscle dysfunction**.



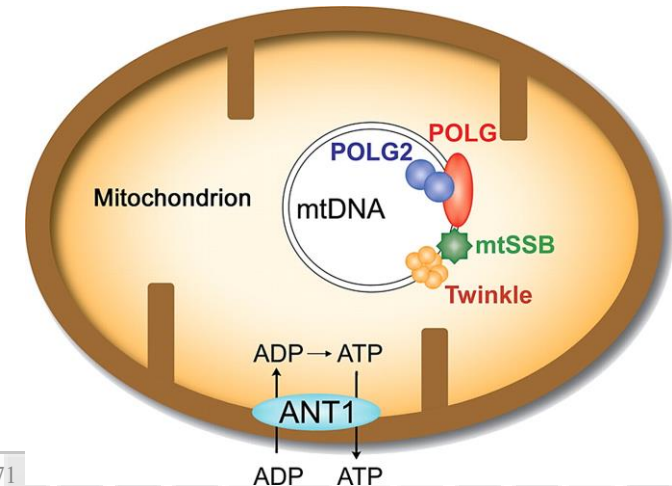
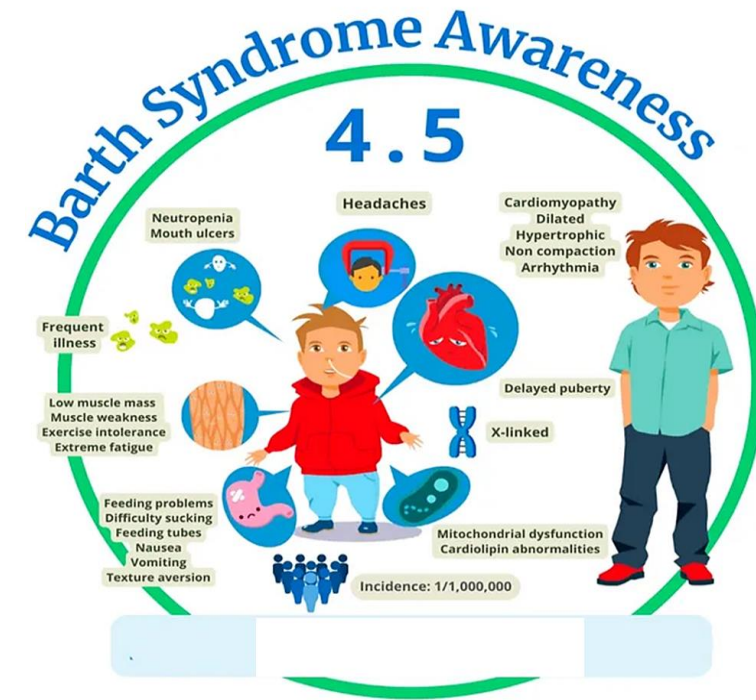
MERRF

A **multisystem** mitochondrial syndrome characterized by **progressive myoclonus** and **seizures**. cerebellar ataxia, myopathy, cardiac arrhythmia, sensorineural hearing loss, optic atrophy, lipoma, and dementia.



Other Mitochondrial Diseases

- Whereas matrilinear inheritance applies to disorders that are **directly** attributed to variants in **mitochondrial DNA**:
- Mitochondrial proteins are encoded mainly by **nuclear genes**. Variants in these genes can have a devastating impact on **respiratory chain functions within mitochondria**:
 - **Autosomal recessive**: The **Cytochrome C Oxidase (COX)** system, for example **SURF1**.
 - **X-linked**: The **G4.5 (TFAZZIN: TAZ)** gene that causes (endocardial fibroelastosis/ Barth syndrome) in males.
 - **Autosomal dominant**: Mitochondrial **myopathy**, in which multiple **mitochondrial DNA deletions** can be detected, may be caused by variants in **POLG** genes.
POLG gene: Making the catalytic subunit of **DNA polymerase gamma**, an enzyme essential for **replicating and repairing** mitochondrial DNA (**mtDNA**). Mutations in **POLG** can lead to a variety of mitochondrial disorders, often with **neurological** symptoms, due to impaired mtDNA maintenance.



More power to you

