Sex-linked and Mitochondrial Inheritance

- The human X chromosome is **a large** chromosome, containing **about 5% of the nuclear genome's DNA** (approximately 155 million base pairs, or **155Mb**).
- Almost **1,100 genes** have been localized to the X chromosome.

- The **Y chromosome is quite small (60Mb**) and contains only a **few dozen genes**.

- More than a dozen diseases are now known to be caused by mutations in mitochondrial DNA.

X INACTIVATION

- Females have two X chromosomes while males have only one.
- X chromosome contains many important protein-coding genes.
- Females have two copies of each X-linked gene, while males have only one copy!! Yet males and females do not differ in terms of the products.
- **Lyon hypothesis: one X chromosome in each somatic cell of the female is inactivated**

→ **dosage compensation**: an equalization of X-linked gene products in males and females

X INACTIVATION

- The **Lyon hypothesis** stated that **X inactivation occurs early in female embryonic development and that the X chromosome contributed by the father is inactivated in some cells, whereas in other cells the X chromosome contributed by the mother is inactivated.**

- **Each cell chooses one of the two X chromosomes at random** to be inactivated, so the maternally and paternally derived X chromosomes will **each be inactivated in about half of the embryo's cells**.

X INACTIVATION

- X inactivation is therefore said to be randomly determined, but fixed
- All normal females have two distinct populations of cells: one population has an active paternally derived X chromosome, and the other has an active maternally derived X chromosome.

- Females are mosaics for the X chromosome
- Males are Hemizygous for X chromosome

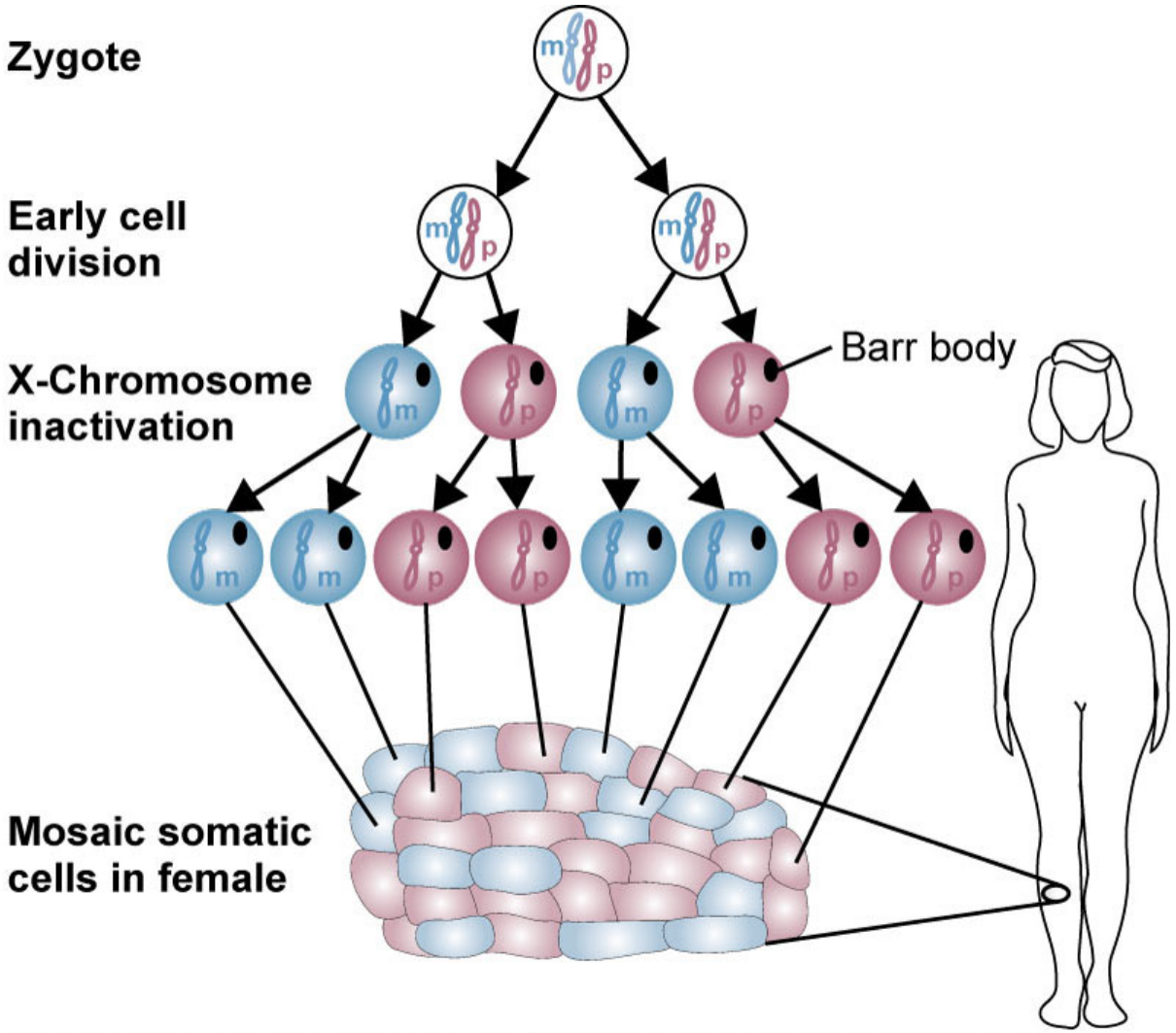


Fig. 5-1. The X inactivation process. The maternal (*m*) and paternal (*p*) X chromosomes are both active in the zygote and in early embryonic cells. X inactivation then takes place, resulting in cells having either an active paternal X or an active maternal X chromosome. Females are thus X chromosome mosaics, as shown in the tissue sample at the bottom of the figure.

X INACTIVATION

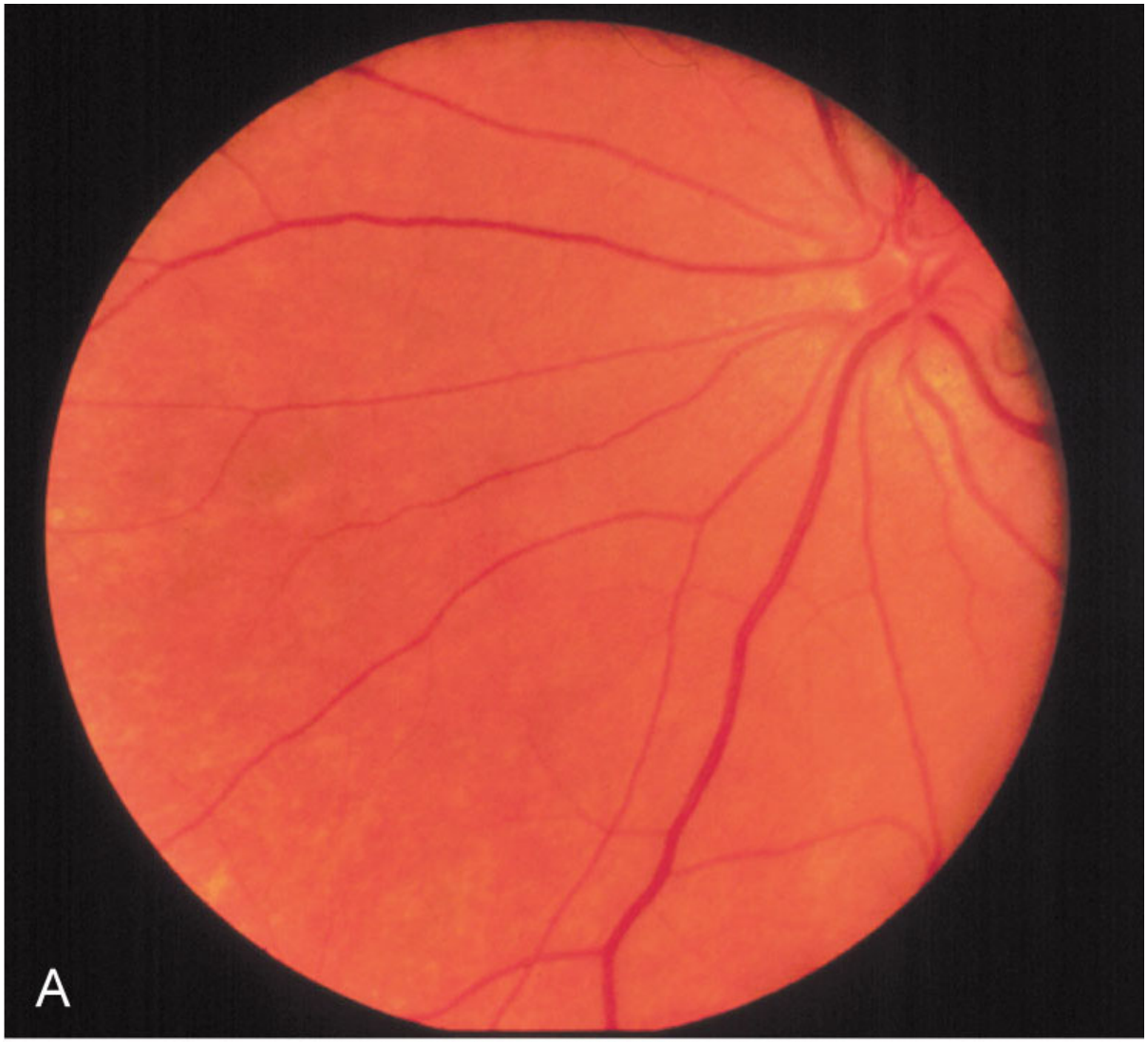
- The Lyon hypothesis relied on **several pieces of evidence:**

- It was known that females are typically mosaics for some X-linked traits while males are not.

→ For example, **female mice that are heterozygous for certain X-linked coat-color genes exhibit a dappled coloring of their fur, whereas male mice do not**.

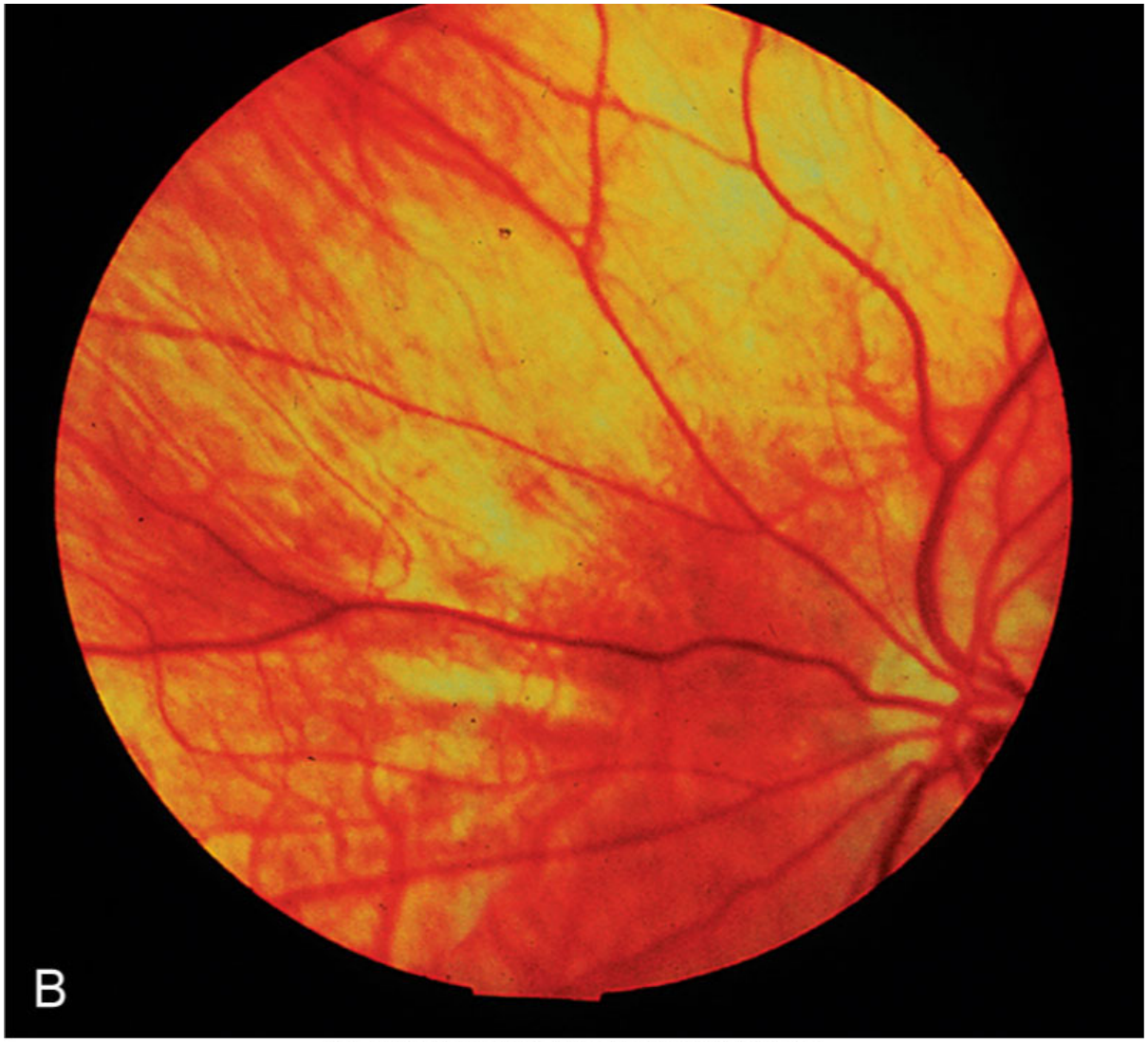
→ A similar example is given by the "calico cat." These female cats **have alternating black and orange patches of fur that correspond to two populations of cells: one that contains X chromosomes in which the "orange" allele is active and one that contains X chromosomes in which the "black" allele is active**. **Male cats of this breed do not exhibit alternating: colors**.

→ A final example, seen in humans, **is X-linked ocular albinism**. This is an X-linked recessive condition characterized by a **lack of melanin production in the retina** and by ocular problems such as nystagmus (rapid involuntary eye movements) and decreased visual acuity. **Males who inherit the mutation show a uniform lack of melanin** in their retinas, while **female heterozygotes exhibit alternating patches of pigmented and non pigmented tissue**.



(Courtesy of Dr. Donnell J. Creel, University of Utah Health Sciences Center.)

Fig. 5-2. Fundus photos of X-linked ocular albinism. **A,** Fundus photograph of a female heterozygous carrier for X-linked ocular albinism. The pigmented and nonpigmented patches demonstrate mosaicism of the X chromosome as a result of random X inactivation.



(Courtesy of Dr. Donnell J. Creel, University of Utah Health Sciences Center.)

Fig. 5-2. Fundus photos of X-linked ocular albinism. **B,** Fundus photograph of the heterozygous carrier's son, showing a much greater lack of melanin pigment.

X INACTIVATION

- Biochemical Evidence:

- enzyme glucose-6-phosphate dehydrogenase (G6PD) is encoded by a gene on the X chromosome and is present in equal quantities in males and females (dosage compensation)

→ In females who are heterozygous for two common G6PD alleles (labeled A and B), some skin cells produce only the A variant of the enzyme and others produce only the B variant.

- Cytogenetic studies in the 1940s showed that interphase cells of female cats often contained a densely staining chromatin mass in their nuclei. Barr Bodies.

→ the **inactive X chromosome is observable as a Barr body in the somatic cells of normal females.**

X INACTIVATION

- Messenger RNA (mRNA) is transcribed from only one X chromosome in each somatic cell of a normal female.

- Inactivation **is** initiated in a single 1-Mb region on the X chromosome long arm, termed **the X inactivation center**.

- Inactivation is random among cells that make up the embryo itself, only the paternally derived X chromosome is inactivated in cells that will become extraembryonic tissue (e.g., the placenta).
- inactive X chromosome must become reactivated in the female's germ line

X INACTIVATION

- The number of Barr bodies in somatic cells is always one less than the number of X chromosomes.
- Normal females have one Barr body in each somatic cell, while normal males have none.
- Turner Syndrome, Kleinfelter syndrome, XXX females
- If the extra X chromosomes are inactivated, why aren't people with extra (or missing) X chromosomes phenotypically normal?

X INACTIVATION

- **X inactivation is *incomplete,* *some regions of the X chromosome remain active in all copies....***
- Tips of the short and long arms of the X chromosome do not undergo inactivation
- The tip of the short arm of the X chromosome is highly homologous to the distal short arm of the Y chromosome.
- About 15% of the genes on the X chromosome may escape inactivation
- Some of the X-linked genes that escape inactivation have homologs on the Y chromosome, preserving equal gene dosage in males and females

X INACTIVATION

- The X inactivation center contains at least one gene required for inactivation, XIST
- Transcribed only on the inactive X chromosome, and its 17-kb mRNA transcripts are detected in normal females but not in normal males
- Is not translated into a protein → it remains in the nucleus and coats the inactive X chromosome
- Methylation and histone deacetylation are additional features of the inactive X chromosome
- CG dinucleotides in the 5' regions of genes on the inactive X are heavily methylated

X-Linked Recessive Inheritance

- Hemophilia A, Duchenne muscular dystrophy, and red-green color blindness.

- Females inherit two copies of the X chromosome: Homozygous for the disease allele, Heterozygous or Homozygous for the normal.
- In females, an X-linked recessive trait behaves much like an autosomal recessive trait.

- Males are hemizygous for the X chromosome: If a male inherits a recessive disease gene on the X chromosome, he will be affected.

X-Linked Recessive Inheritance

- An X-linked recessive disease with gene frequency q will be seen in a proportion q of males
- Females, needing two copies of the mutant allele to express the disease, will have a disease frequency of only q^2

- **Males are more frequently affected with X-linked recessive** diseases than are females

X-Linked Recessive Inheritance

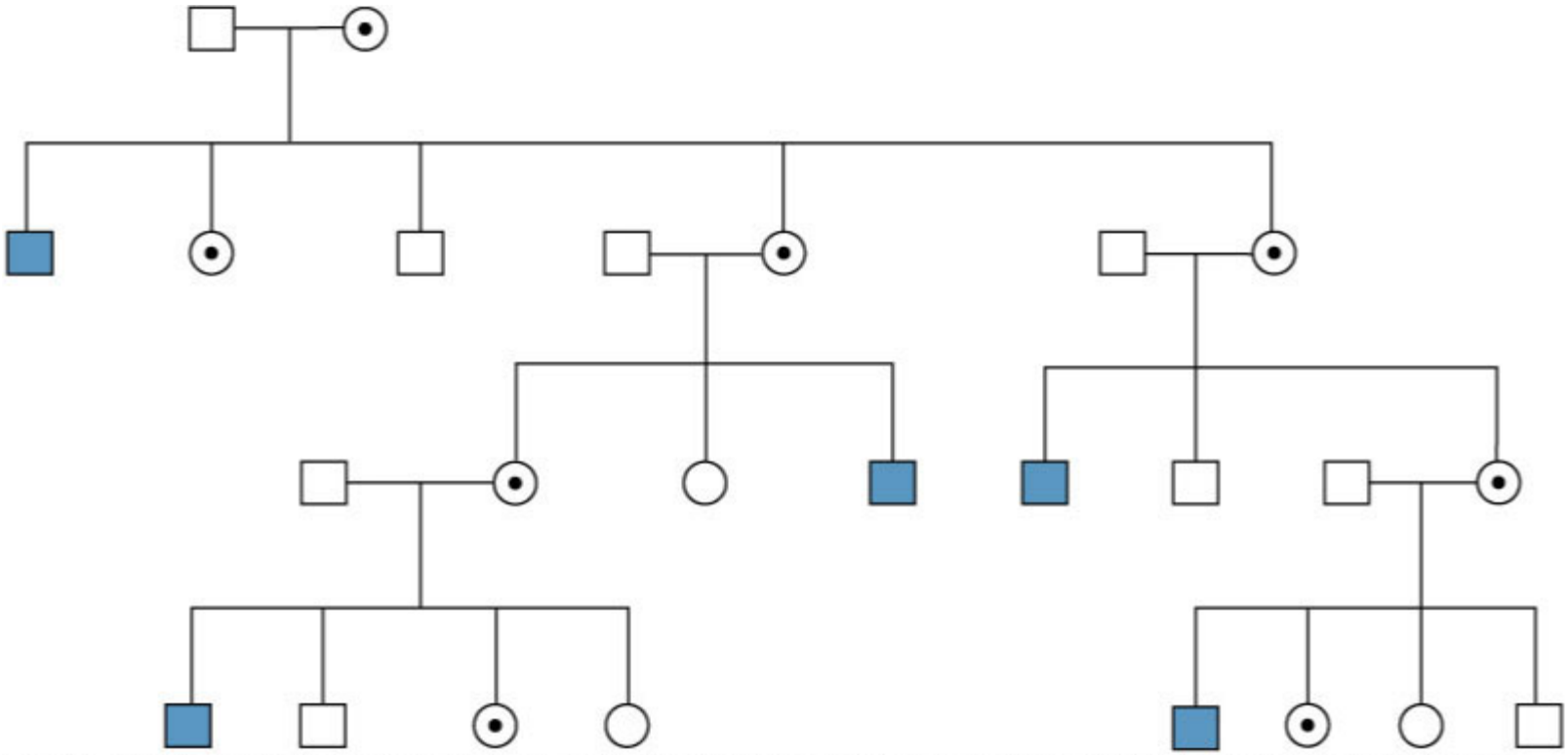


Fig. 5-3. A pedigree showing the inheritance of an X-linked recessive trait. *Solid symbols* represent affected individuals, and *dotted symbols* represent heterozygous carriers.

- Since a father can transmit only a Y chromosome to his son, X-linked genes are not passed from father to son.

X-Linked Recessive Inheritance

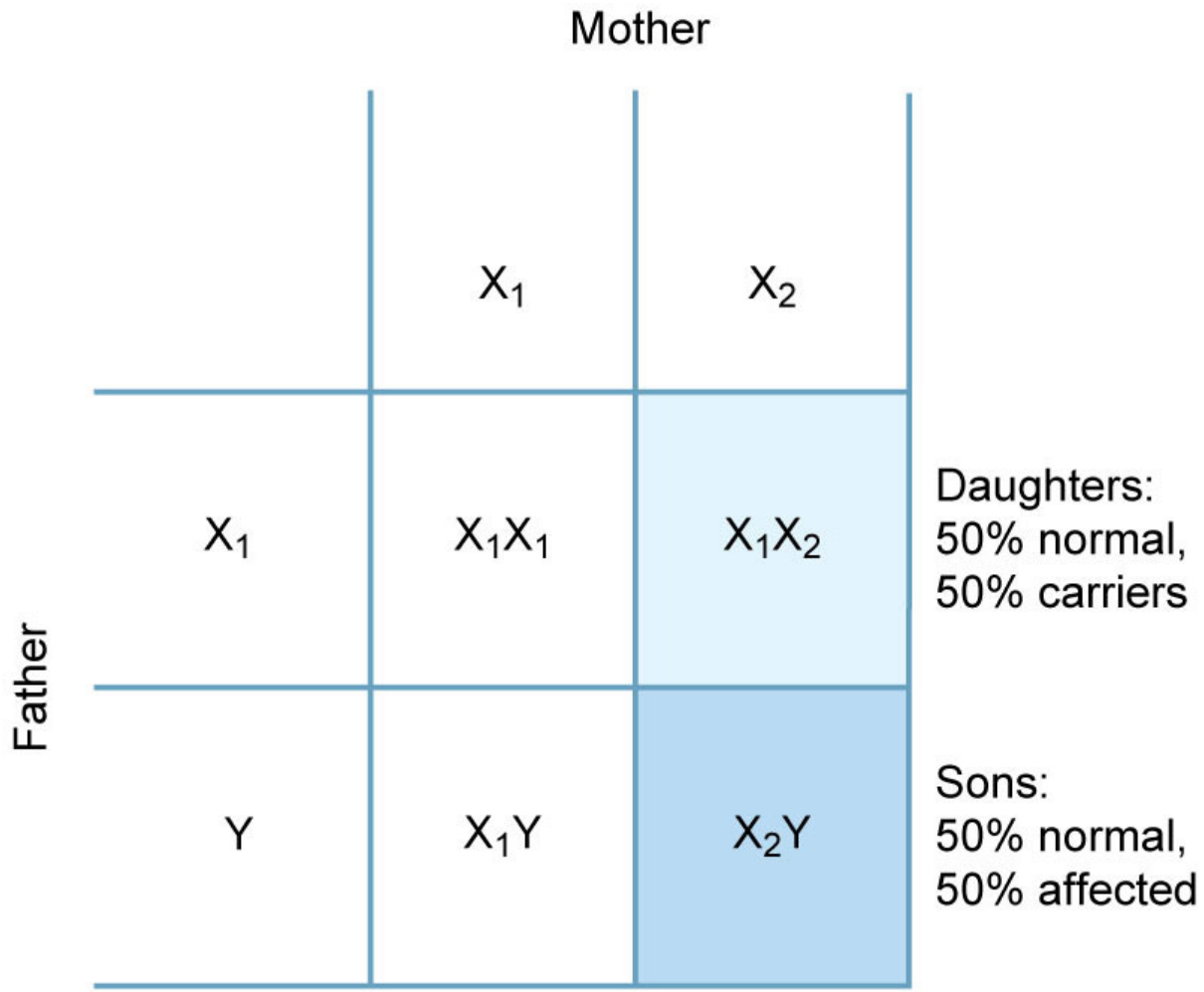


Fig. 5-4. Punnett square representation of the mating of a heterozygous female who carries an X-linked recessive disease gene with a normal male. X_1, chromosome with normal allele; X_2, chromosome with disease allele.

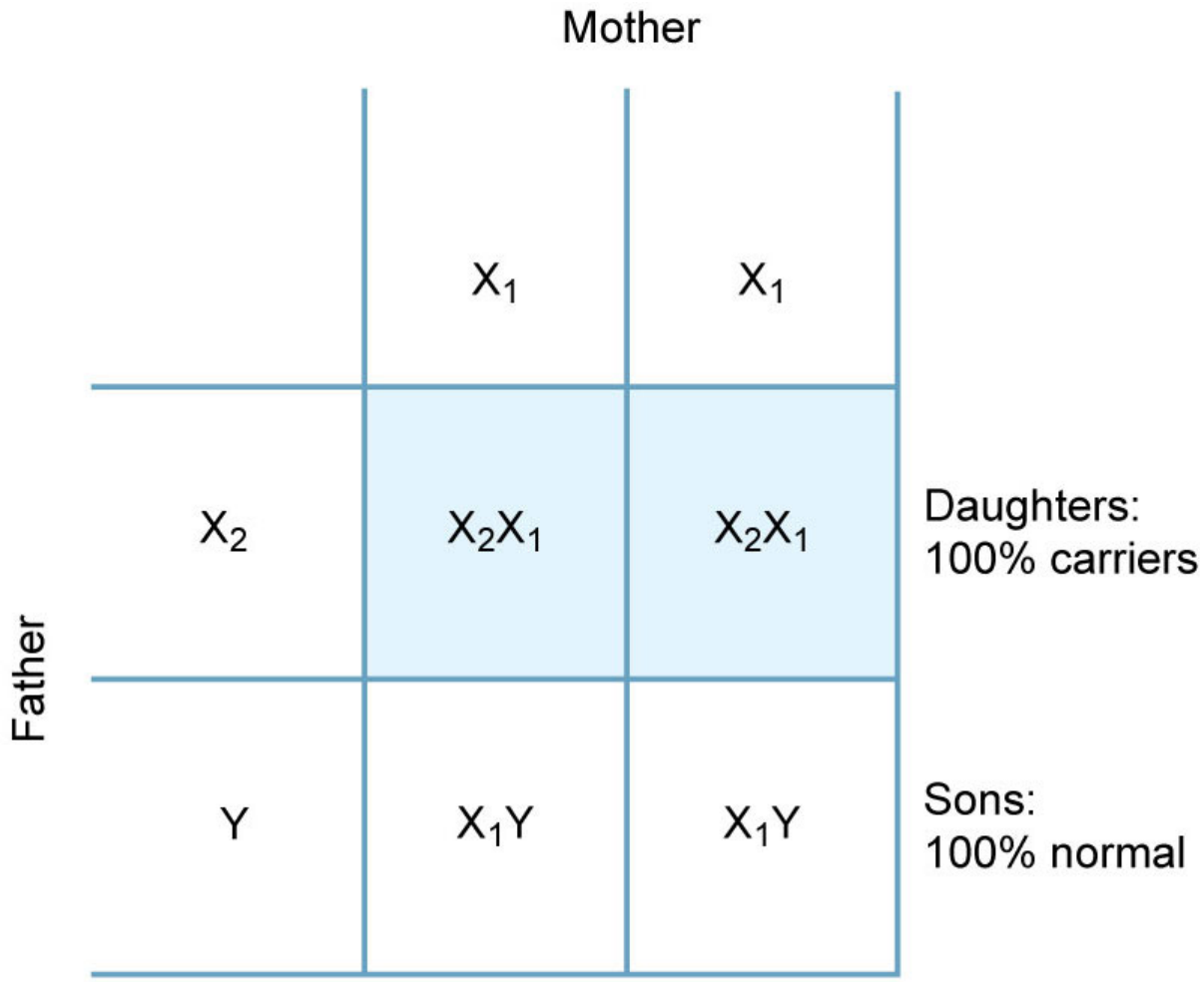


Fig. 5-5. Punnett square representation of the mating of a normal female with a male who is affected by an X-linked recessive disease. X_1, chromosome with normal allele; X_2, chromosome with disease allele.

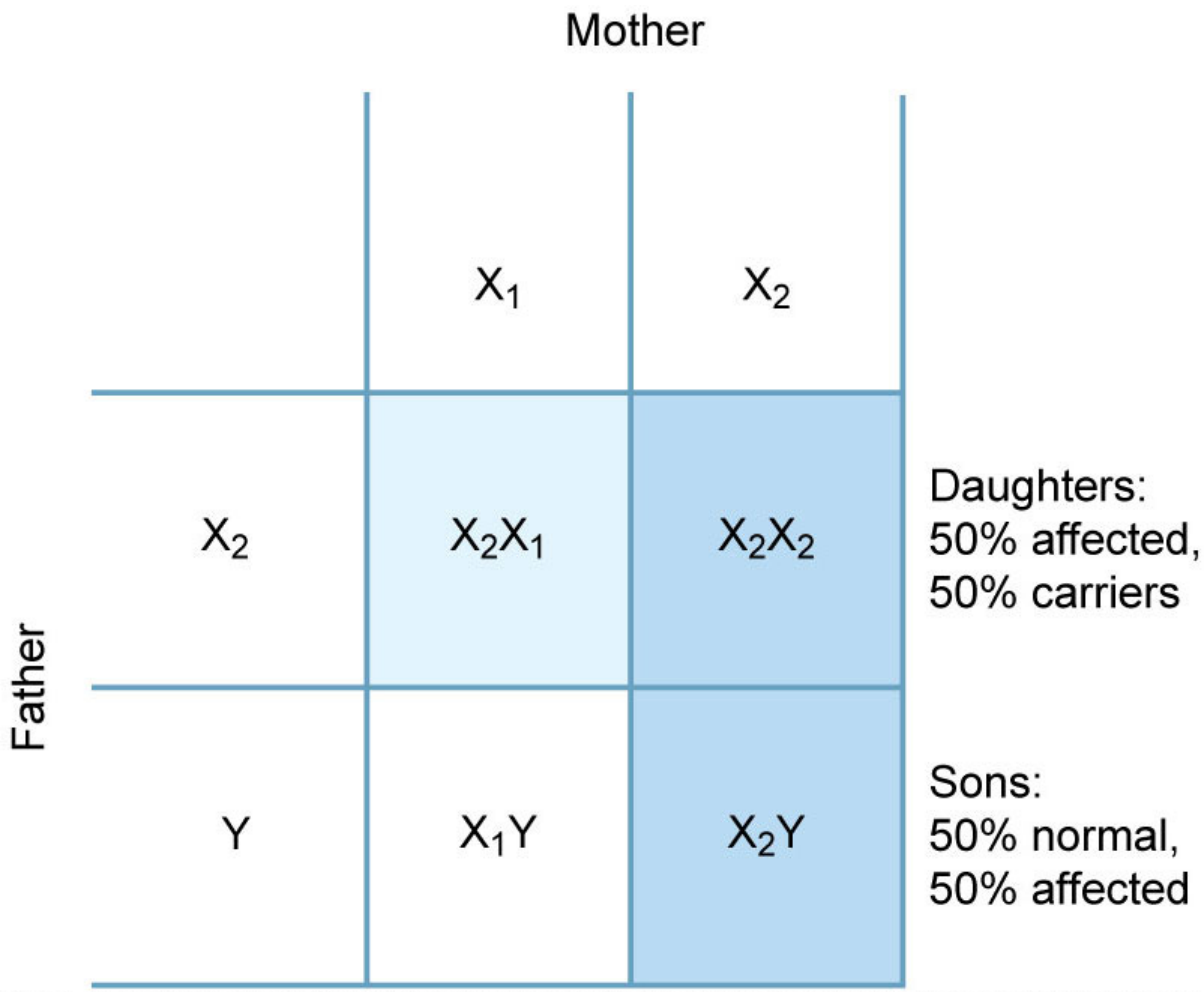


Fig. 5-6. Punnett square representation of the mating of a carrier female with a male affected with an X-linked recessive disease. X_1, chromosome with normal allele; X_2, chromosome with disease allele.

X-Linked Recessive Inheritance

- Occasionally, females who inherit only a single copy of an X-linked recessive disease gene can be affected with the disease: **manifesting heterozygotes**
- For example, approximately 5% of females who are heterozygous for hemophilia A have factor VIII levels low enough to be classified as mild hemophiliacs.

- Less commonly, females having only a single X chromosome (Turner syndrome) have been seen with X- linked recessive diseases such as hemophilia A

X-Linked Dominant Inheritance

- Are fewer in number and prevalence than are X-linked recessive
- **Hypophosphatemic rickets**, a disease in which the kidneys are impaired in their ability to reabsorb phosphate.
- **Incontinentia pigmenti type 1**, a disorder characterized by abnormal skin pigmentation, conical or missing teeth, and ocular and neurological abnormalities.

→ seen **only in females**

→ **Heterozygous females**, having one normal X chromosome, tend generally to have **milder expression of X- linked dominant traits.**

X-Linked Dominant Inheritance

- **Rett syndrome**, a **neurodevelopmental disorder** seen in **1/10,000 to 1/15,000** females and in a smaller proportion of males.

→ mutations in a gene, MECP2, whose protein product binds to methylated CG sequences

→ the protein helps to bring about repression of the transcription of the downstream genes

X-Linked Dominant Inheritance

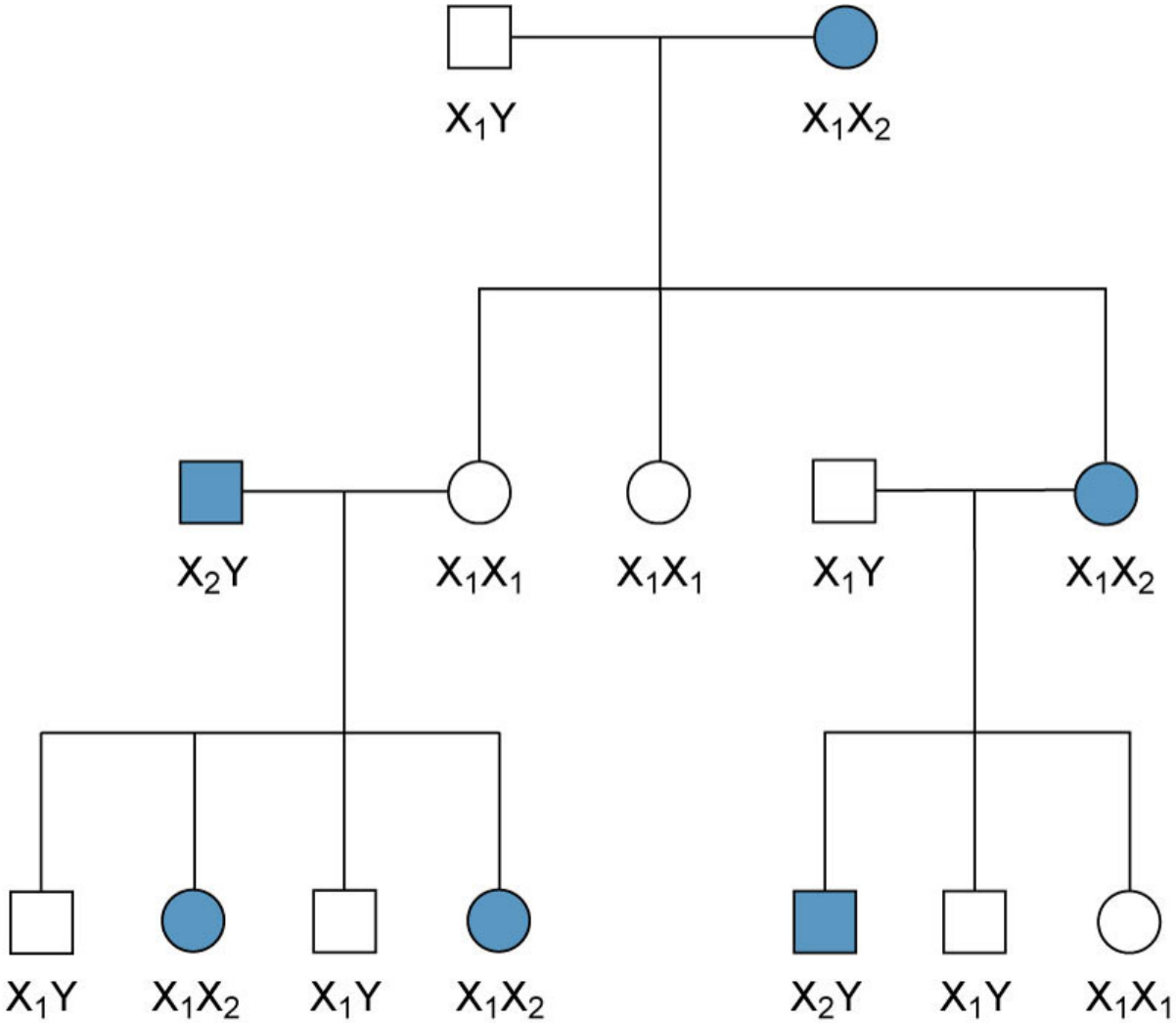


Fig. 5-7. Pedigree demonstrating the inheritance of an X-linked dominant trait. X_1, chromosome with normal allele; X_2, chromosome with disease allele.

TABLE 5-2 Comparison of the Major Attributes of X-Linked Dominant and X-Linked Recessive Inheritance Patterns*

ATTRIBUTE	X-LINKED DOMINANT	X-LINKED RECESSIVE
Recurrence risk for heterozygous female × normal male mating	50% of sons affected; 50% of daughters affected	50% of sons affected; 50% of daughters heterozygous carriers
Recurrence risk for affected male × normal female mating	0% of sons affected; 100% of daughters affected	0% of sons affected; 100% of daughters heterozygous carriers
Transmission pattern	Vertical; disease phenotype seen in generation after generation	Skipped generations may be seen, representing transmission through carrier females
Sex ratio	Twice as many affected females as affected males (unless disease is lethal in males)	Much greater prevalence of affected males; affected homozygous females are rare
Other	Male-to-male transmission is not seen; expression is less severe in female heterozygotes than in affected males	Male-to-male transmission not seen; manifesting heterozygotes may be seen in females

*Compare with the inheritance patterns for autosomal diseases shown in Table 4-1.

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

- 40% of all cases of X-linked mental retardation
- Distinctive facial appearance, with large ears and long face, hypermobile joints, and macroorchidism.
- Mental retardation tends to be milder and more variable in females

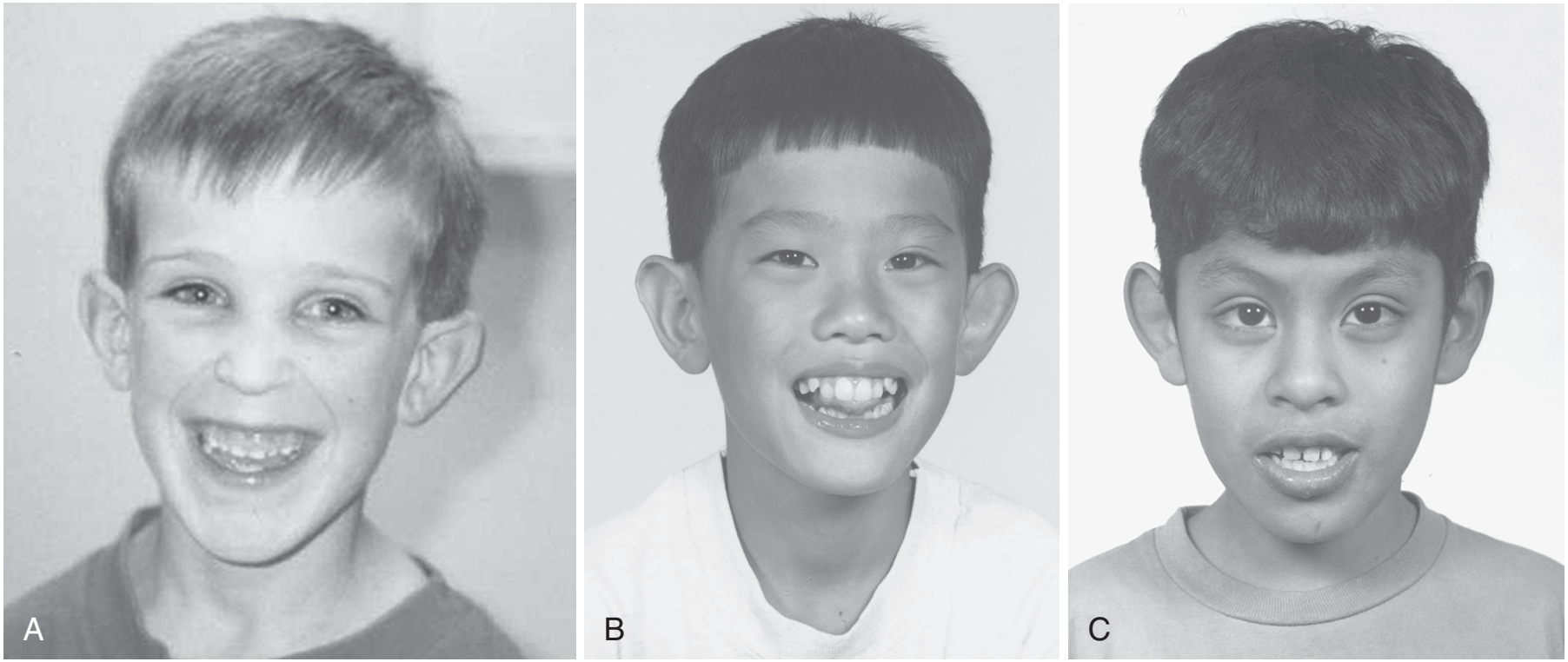


FIG 5-20 Boys with fragile X syndrome. Note the long faces, prominent jaws, and large ears and the similar characteristics of children from different ethnic groups: European **(A),** Asian **(B),** and Latin American **(C).**

FIG 5-21 An X chromosome from a male with fragile X syndrome, showing an elongated, condensed region near the tip of the long arm. (From Stein CK. Applications of cytogenetics in modern pathology. In: McPherson RA, Pincus MR, eds. *Henrys Clinical Diagnosis and Management by Laboratory Methods.* 21st ed. Philadelphia: Saunders; 2006.)

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

- Although the presence of a single fragile X mutation is sufficient to cause disease in either males or females, the prevalence of this condition is higher in males (1/4,000) than in females (1/8,000)

- Males who have affected descendants but are not affected themselves are termed "normal transmitting males''

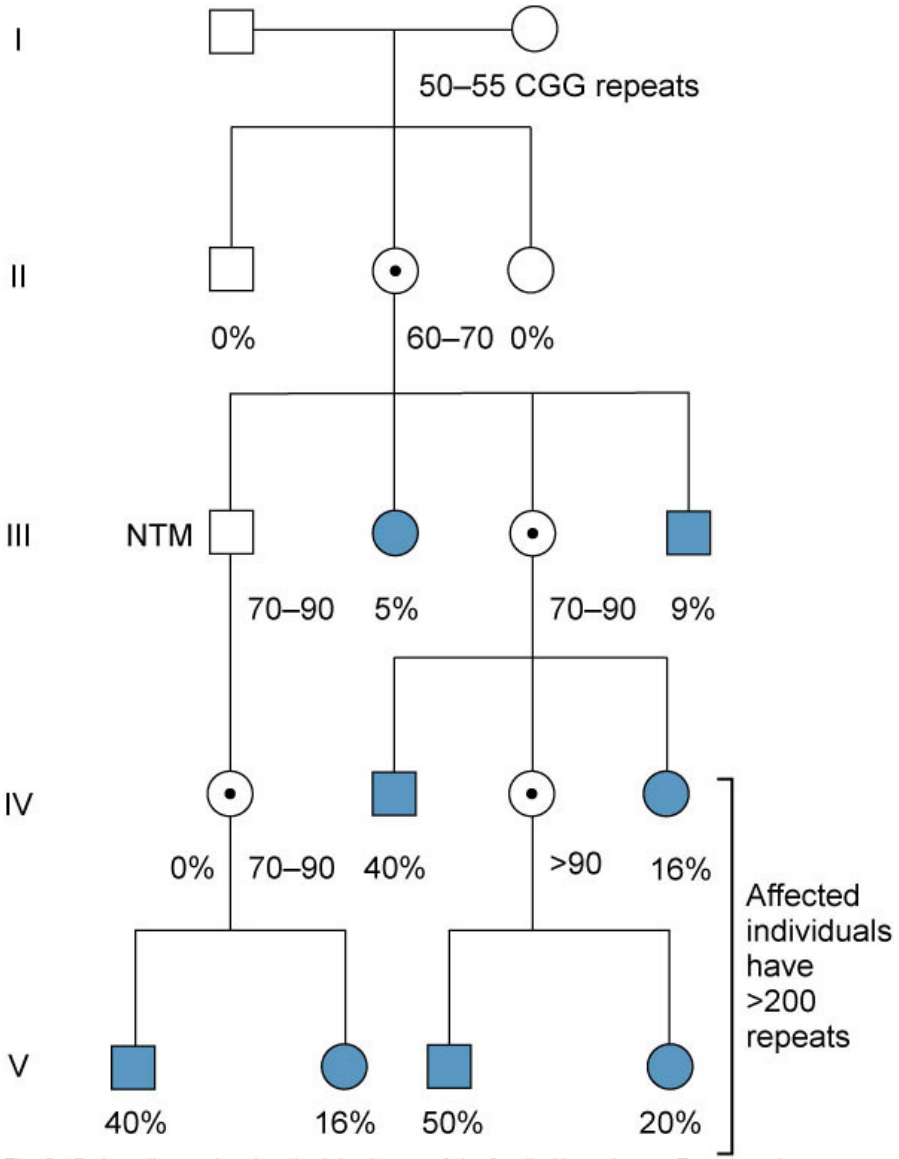


Fig. 5-17. A pedigree showing the inheritance of the fragile X syndrome. Females who carry a premutation (50 to 230 CGG repeats) are shown by *dotted* lines. Affected individuals are represented by *solid* symbols. A normal transmitting male, who carries a premutation of 70 to 90 repeat units, is designated NTM. Note that the number of repeats increases each time the mutation is passed through another female. Also, only 5% of the NTM's sisters are affected, and only 9% of his brothers are affected, but 40% of his grandsons and 16% of his granddaughters are affected. This is the Sherman paradox.

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

- ***FMR1***
- the 5' untranslated region of the gene contains a CGG repeat unit that is present in 6 to 50 copies in normal individuals

- Those **with fragile X syndrome have 230 to 1,000 or more** CGG repeats (a **"full mutation"**)

- An intermediate number of repeats, ranging approximately from 50 to 230 copies, is seen in normal transmitting males and their female offspring.

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

- Those with full mutations have no FMR1 mRNA in their cells
- The degree of methylation is correlated with severity of expression of the disorder

The Fragile X Story: Molecular Genetics Explains a Puzzling Pattern of Inheritance

- Another fragile site distal to the fragile X site
- ***FRAXE***
- associated with an **expansion of a CGG trinucleotide** repeat in the 5' region of a **gene labeled *FMR2***
- subsequent **hypermethylation, and a phenotype that includes mental retardation**
- **the CGG repeat at this locus can expand when transmitted through either males or females**.

- **advances have also improved diagnostic accuracy**

Y-Linked Inheritance

Although it consists of approximately 60 Mb of DNA, the Y chromosome contains relatively few genes.

Only a few dozen Y-linked, or holandric, genes have been identified. These include the gene that initiates differentiation of the embryo into a male, several genes that encode testis-specific spermatogenesis factors, and a minor histocompatibility antigen (termed HY).

Several housekeeping genes are located on the Y chromosome, and they all have inactivation-escaping homologs on the X chromosome.

Transmission of Y-linked traits is strictly from father to son.

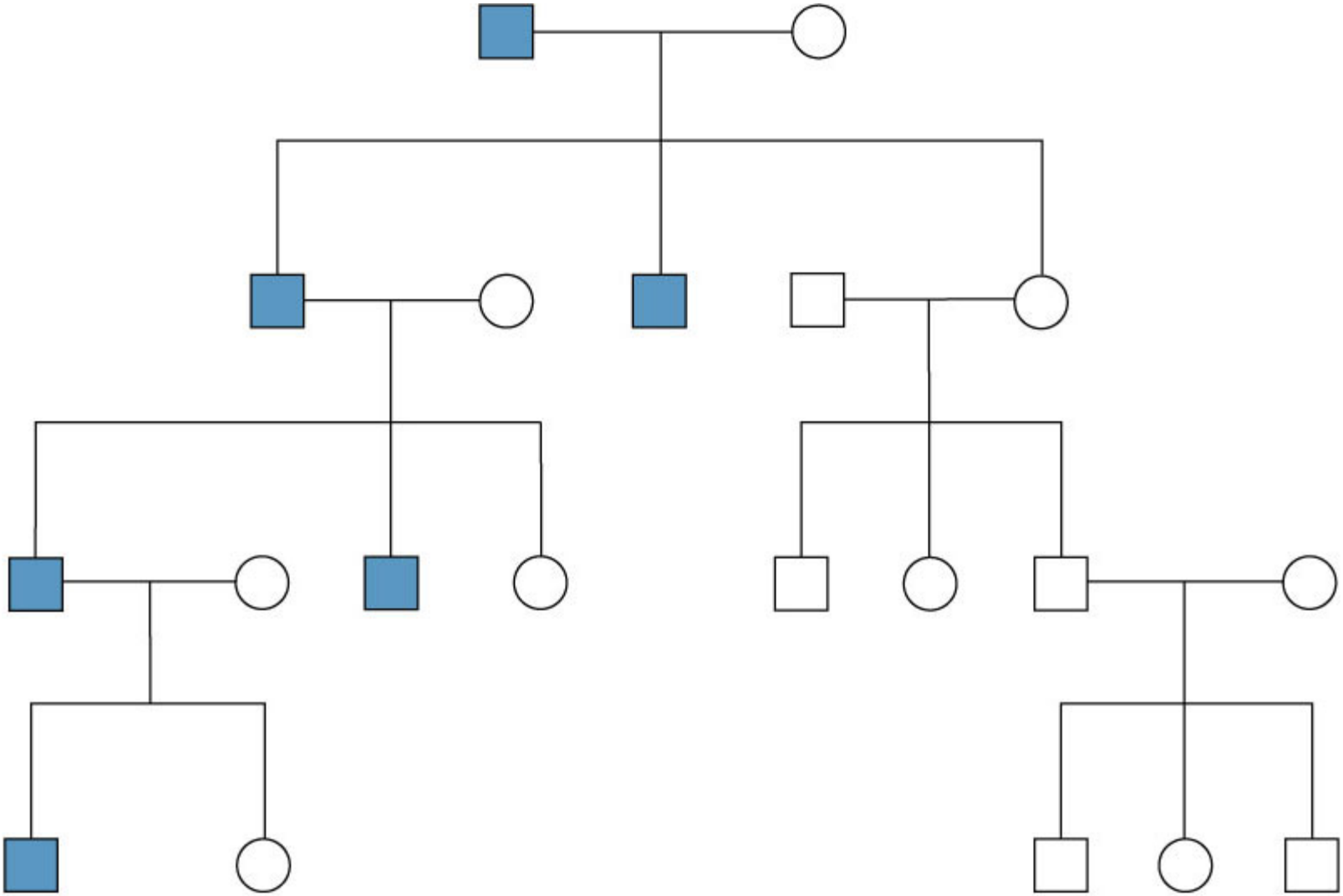


Fig. 5-8. Pedigree demonstrating the inheritance of a Y-linked trait. Transmission is exclusively male to male.

SEX-LIMITED AND SEX-INFLUENCED TRAITS

A sex-limited trait occurs in only one of the sexes-due, for instance, to anatomical differences. Inherited uterine or testicular defects would be examples.

An example of a sex-influenced trait is male-pattern baldness, which occurs in both males and females but much more commonly in males.

Contrary to oft-stated belief, male-pattern baldness is not X-linked; It is thought to be inherited as an autosomal dominant trait in males, whereas in females it is inherited as an autosomal recessive trait.

Female heterozygotes can transmit the trait to their off-spring but do not manifest it.

Females display the trait only if they inherit two copies of the gene. Even then, they are more likely to display marked thinning of the hair, rather than complete baldness.

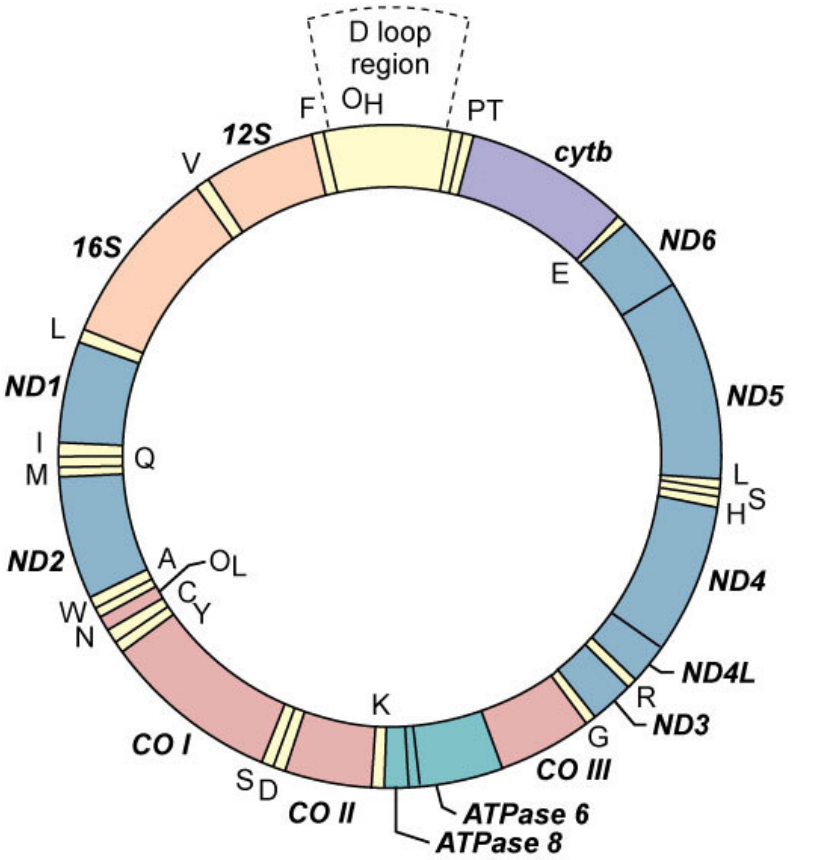
MITOCHONDRIAL INHERITANCE

- A small but significant number of diseases are the result of mitochondrial mutations
- Each human cell contains several hundred or more mitochondria in its cytoplasm
- Oxidative phosphorylation: ATP: cell survival

MITOCHONDRIAL INHERITANCE

- several copies per organelle
- 16,569 base pairs arranged on a double-stranded circular molecule
- Encodes two ribosomal RNAs, 22 transfer RNAs (tRNAs), and 13 polypeptides involved in oxidative phosphorylation.

- Transcription of mitochondrial DNA (mtDNA) takes place in the mitochondrion
- mtDNA contains no introns
- mtDNA is inherited exclusively through the maternal line



(Modified from MITOMAP: A Human Mitochondrial Genome Database.http://www.mitomap.org, 2008.)

Fig. 5-9. The circular mitochondrial DNA genome. Locations of protein-encoding genes (for reduced nicotinamide adenine dinucleotide [NADH] dehydrogenase, cytochrome c oxidase, cytochrome c oxidoreductase, and adenosine triphosphate [ATP] synthase) are shown, as are the locations of the two ribosomal RNA genes and 22 transfer RNA genes (designated by single letters). The replication origins of the heavy (OH) and light (OL) chains and the noncoding D loop (also known as the control region) are shown.

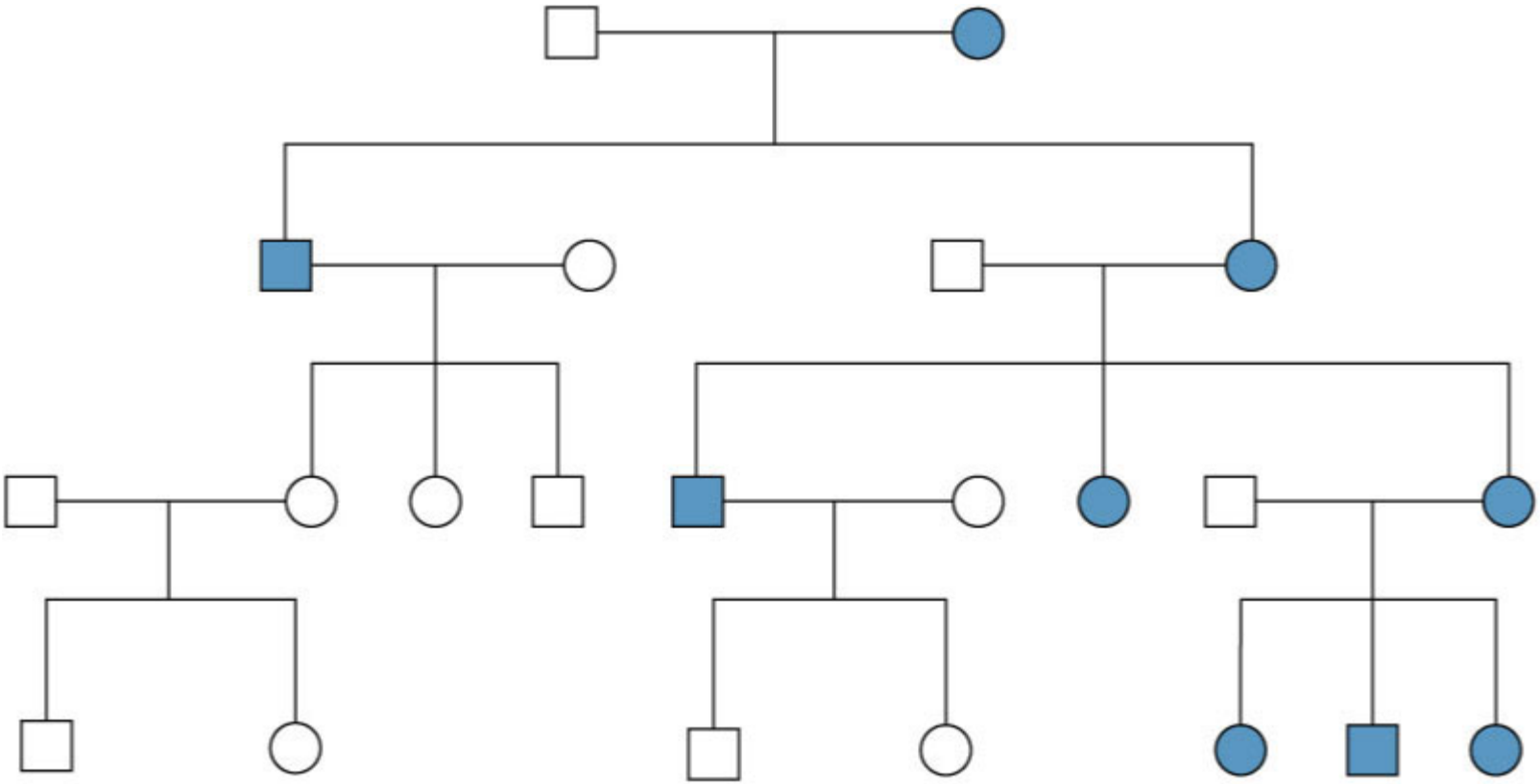


Fig. 5-10. A pedigree showing the inheritance of a disease caused by a mitochondrial DNA mutation. Only females can transmit the disease mutation to their offspring. Complete penetrance of the disease-causing mutation is shown in this pedigree, but heteroplasmy often results in incomplete penetrance for mitochondrial diseases.

MITOCHONDRIAL INHERITANCE

- 10 times higher mutation rate

- Heteroplasmy: a single cell can harbor some molecules that have an mtDNA mutation and other molecules that do not.
- The larger the proportion of mutant mtDNA molecules, the more severe the expression of the disease.

- As cells divide, changes in the proportion of mutant alleles can occur through chance variation or because of a selective advantage.

MITOCHONDRIAL INHERITANCE

- Each tissue type requires a certain amount of mitochondrially produced ATP for normal function.
- The central nervous system consumes about 20% of the body's ATP production and therefore is often affected by mtDNA mutations.

- Mitochondrial disorders can be classified according to the type of mutation that causes them.

- Missense mutations in protein-coding mtDNA genes cause one of the best-known mtDNA diseases, Leber hereditary optic neuropathy (LHON).

MITOCHONDRIAL INHERITANCE

- Single-base mutations in a tRNA gene can result in myoclonic epilepsy with ragged-red fiber syndrome (MERRF)
- MERRF is heteroplasmic and thus highly variable in its expression.

- Another example of a mitochondrial disease caused by a single-base tRNA mutation is mitochondrial encephalomyopathy and stroke-like episodes (MELAS).

- Duplications and deletions: Keams-Sayre disease (muscle weakness, cerebellar damage, and heart failure), Pearson syndrome (infantile pancreatic insufficiency, pancytopenia, and lactic acidosis), and chronic progressive external ophthalmoplegia (CPEO).

Hemophilia A

- Hemophilia A, or "classical" hemophilia, affects approximately 1 in 5,000 to 1 in 10,000 males worldwide. It is the most common of the severe bleeding disorders and has been recognized as a familial disorder for centuries.

- Hemophilia A is caused by deficient or defective factor VIII, a key component of the clotting cascade. Fibrin formation is affected, resulting in prolonged and often severe bleeding from wounds and hemorrhages in the joints and muscles.

- Hemophilia A varies considerably in its severity, and this variation is correlated directly with the level of factor VIII.

Hemophilia A

- Until the early 1960s, hemophilia A was often fatal by about 20 years of age. Then it became possible to purify factor VIII from donor plasma. Factor VIII is usually administered at the first sign of a bleeding episode and is a highly effective treatment.

- The factor VIII gene has been mapped to the distal long arm of the X chromosome and cloned: It contains 186 kb of DNA and 26 exons. The 9-kb mRNA transcript encodes a mature protein consisting of 2,332 amino acids.

- Patients with nonsense mutations usually develop severe hemophilia, while those with missense mutations usually have relatively mild disease.

Hemophilia A

- About 45% of severe cases of hemophilia A are caused by a chromosome inversion that disrupts the factor VIII gene. An additional 5% of patients have deletions, which usually lead to relatively severe disease.

- There are two other major bleeding disorders, hemophilia B and von Willebrand disease.

Hemophilia B

- Hemophilia B, sometimes called "Christmas disease," is also an X-linked recessive disorder and is caused by a deficiency of clotting factor IX.
- It is less severe than hemophilia A, and it is only about one fifth as common.
- The factor IX gene has also been cloned, and it consists of 34 kb of DNA and eight exons.
- The disorder can be treated with donor-derived factor IX.

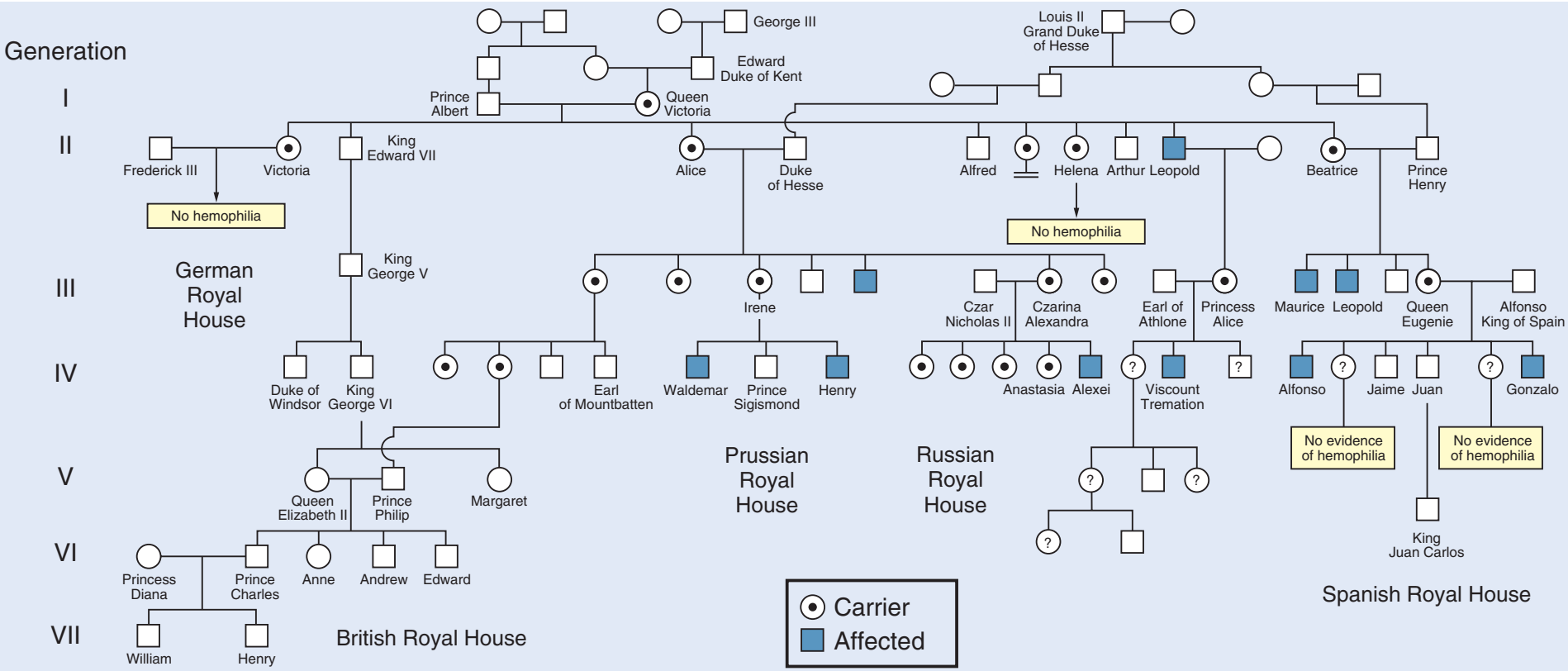


FIG 5-4 A pedigree showing the inheritance of hemophilia B in the European royal families. The first known carrier in the family was Queen Victoria. Note that all of the affected individuals are male. (Modified from McCance K, Huether S. *Pathophysiology: The Biologic Basis for Disease in Adults and Children.* 5th ed. St. Louis: Mosby; 2005.)

Von Willebrand Disease

- von Willebrand disease is an autosomal dominant disorder that is highly variable in expression.
- While it may affect as many as 1% of Caucasians, it reaches severe expression in fewer than 1 in 10,000.
- The von Willebrand factor, which is encoded by a gene on chromosome 12, acts as a carrier protein for factor VIII.
- In addition, it binds to platelets and to damaged blood vessel endothelium, thus promoting adhesion of platelets to damaged vessel walls.