- There are three important terms: sex-linked, sex-influenced, and sex-limited.

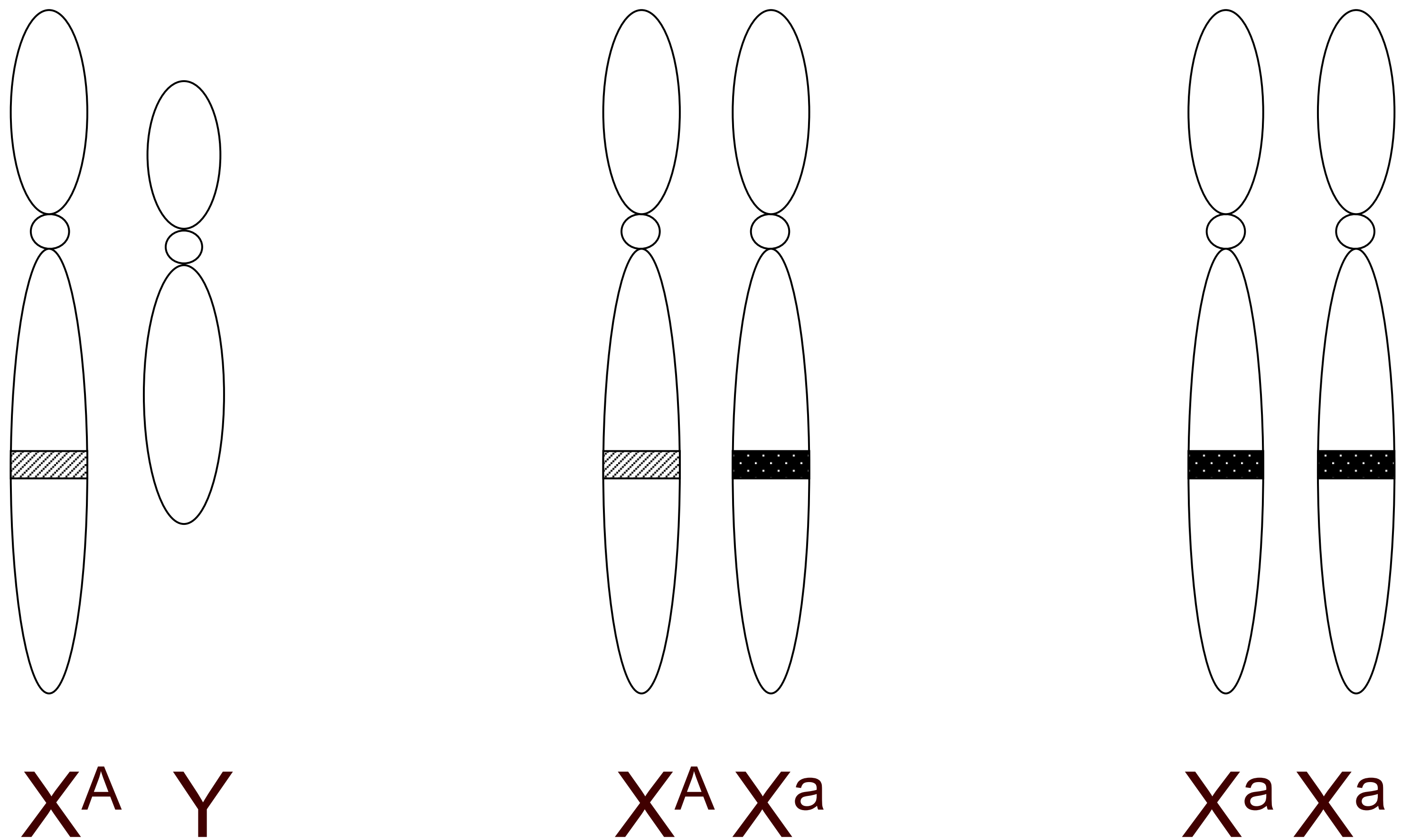
- A ***sex-linked*** gene or disease refers to a gene that is physically **located on a sex chromosome.**

- ✓ If the gene is located on the X chromosome, it is called X-linked; if it is located on the Y chromosome, it is called Y-linked.
- Females have two X chromosomes and therefore may be homozygous or heterozygous for X-linked genes.
- Males have only one X chromosome, and most genes on the X chromosome do not have corresponding alleles on the Y chromosome.

- Whereas ***Sex-limited*** or ***sex-influenced*** traits do not necessarily involve genes located on sex chromosomes. Instead, **the clinical expression is either limited to one sex or influenced by biological sex.**

- ✓ For example, **hemochromatosis** is a sex-influenced disease. The gene is located on an autosomal chromosome, but **disease severity** varies depending on the **biological sex** of the affected individual.

Sex Linkage and X-Inactivation



- ➢ There are many genes located on the X chromosome.
- ○ Males possess one X chromosome; therefore, they have one physical allele for X-linked genes, while females possess two X chromosomes and therefore have two alleles for the same X-linked gene.

- ○ Gene expression occurs when transcription factors together with RNA polymerase bind to DNA regulatory regions and initiate transcription, leading to synthesis of RNA, and subsequently protein (or sometimes functional RNA only).

- ✓ In females, because two alleles are present, transcription factors and RNA polymerase can bind to both maternal and paternal alleles, allowing **expression from both copies of the gene.**
- ✓ In males, only a single allele is present; therefore, transcription factors and RNA polymerase bind to one allele only, resulting in **gene expression from a single copy.**

- ○ Consequently, females theoretically possess one additional gene template compared with males, which could lead to a **higher expression level of X-linked genes in *females*** relative to males.

- ✓ This creates a potential biological problem:
- ❑ Genes located on **autosomal chromosomes** are present in two copies in both males and females and are expressed at an optimal level required for normal cellular and tissue function.

- The gene products derived from autosomal chromosomes must interact with gene products encoded by genes on the sex chromosomes. Therefore, unequal expression of X-linked genes between males and females would disrupt the balanced level of proteins and RNA required for normal cellular function.

- Thus, the question arises:
- **How are comparable overall gene expression levels maintained between males and females despite the difference in the number of X-chromosome alleles?**

- Male and female individuals have sex chromosomes and autosomal chromosomes whose gene products, including enzymes and structural proteins, function together within biological pathways regardless of whether they are produced from autosomal chromosomes or sex chromosomes.

- If differential gene expression existed between males and females, this imbalance in expression levels would be abnormal. Therefore, the potential difference in gene expression from the sex chromosomes, particularly the X chromosome, is compensated.

- Because the X chromosome contains many more genes than the Y chromosome, gene expression imbalance is corrected through a mechanism known as **dosage compensation,** also referred to as the ***Lyon hypothesis***. This hypothesis is now established as a biological fact.

Dosage compensation

1. For autosomal traits, two doses lead to a normal phenotype, while one dose or more than two doses often have clinical significance

2. For X-linked traits two doses in females and one dose in males both lead to a normal phenotype

X-inactivation in females allows compensation for this difference in dosage for X-linked traits

- Lyon hypothesis

- In early embryonic life (3-7 days after fertilization) one X chromosome is inactivated. The inactive X chromosome is condensed in a **Barr body**.

- Inactivation of the maternal or paternal X chromosome is **random**, but once it occurs, the same X will be inactive in all descendants of a particular cell.

- Some genes on the inactive X chromosome remain active, i.e., **escape inactivation**. These include the genes in the <u>pseudoautosomal region</u> that have matching genes on the Y chromosome, genes outside the pseudoautosomal region that have related copies on the Y chromosomes, and others.

X-Inactivation

- Allows dosage compensation between males and females for genes on the X chromosome
- In females, early in embryonic life, one of the X chromosomes is inactivated
- The process is random and clonal
- Some genes escape X-inactivation

- Following fertilization, the zygote undergoes **extensive rounds of mitotic cell divisions**. During the nine-month period of embryonic and fetal development, this single cell progressively differentiates and gives rise to a **multicellular** organism consisting of specialized tissues, organs, and integrated organ systems.

- A few days after fertilization, during early embryonic development in females, one of the two X chromosomes undergoes **random inactivation regardless of the parent of origin.**

- This process occurs through chromosomal condensation. The inactivated X chromosome becomes **highly condensed**, making its genes **inaccessible** to RNA polymerase and transcription factors. Consequently, **gene expression occurs only from the remaining active homologous X chromosome.**

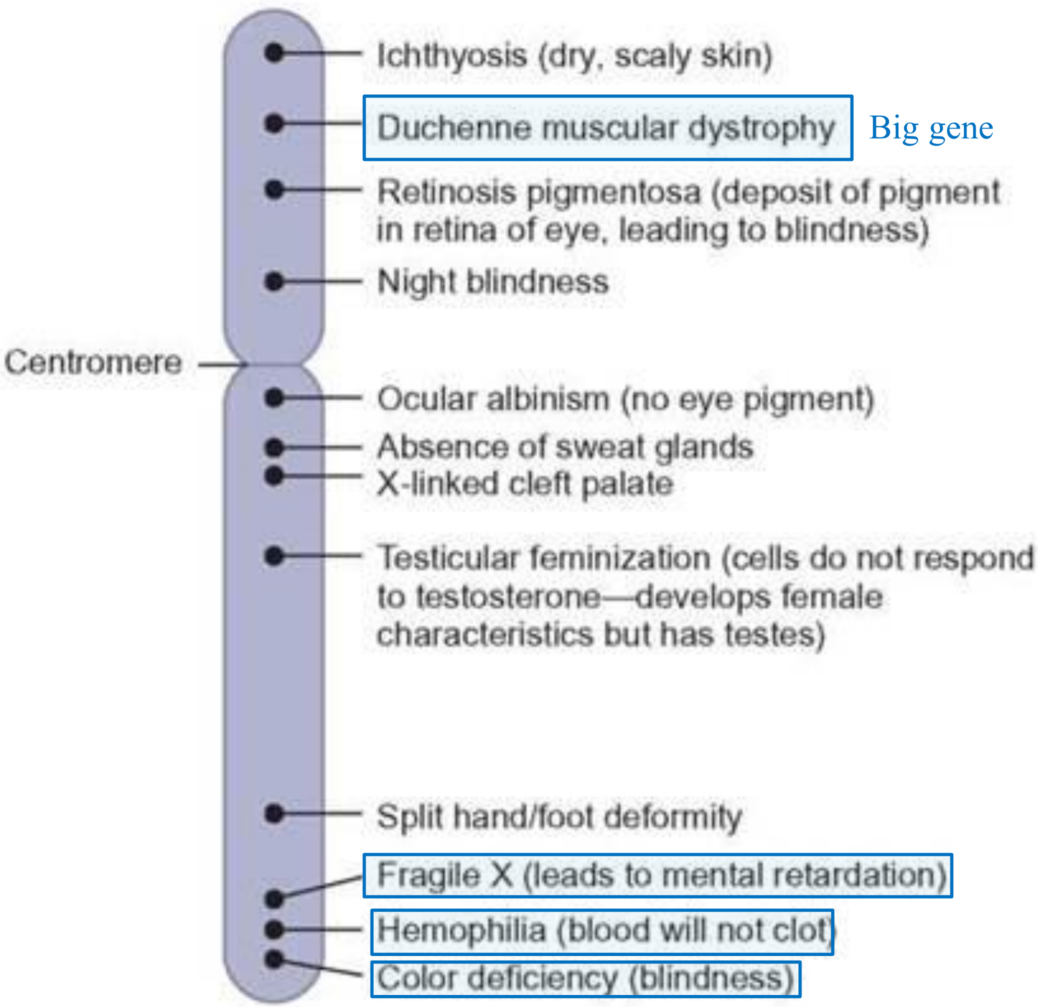
✓ This mechanism is known as *X-chromosome inactivation or dosage compensation.*

- Normally, during interphase of the cell cycle (G1, S, and G2 phases), chromosomes are decondensed to allow transcription. However, in female cells during interphase, one X chromosome remains condensed and transcriptionally inactive.

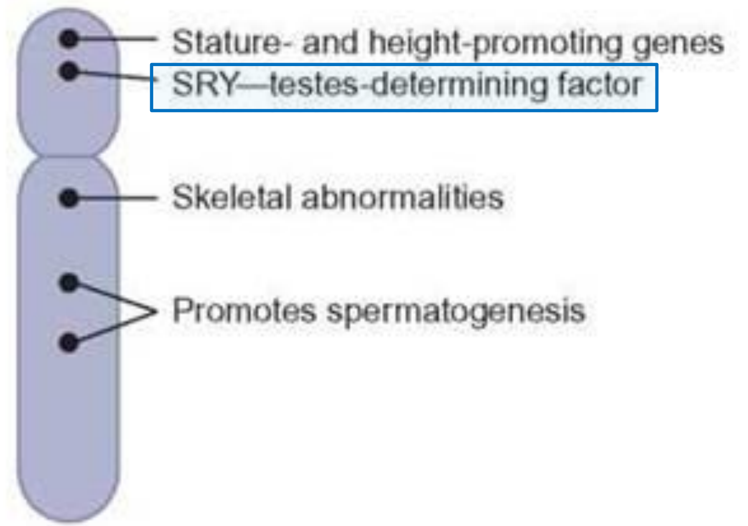
❖ **As a result, females express levels of X-linked gene products comparable to males, despite possessing two X chromosomes.**

- Once a cell establishes which X chromosome is inactivated, this pattern is permanently maintained in all descendant cells produced through mitosis. Therefore, all daughter cells derived from that original cell retain **the same inactive X chromosome.**

- Genes located on the sex chromosomes encode proteins that are not necessarily related to sexual development or sex determination. However, most of the genes on Y chromosome are related to sex determination and male reproductive function.



X chromosome



Y chromosome

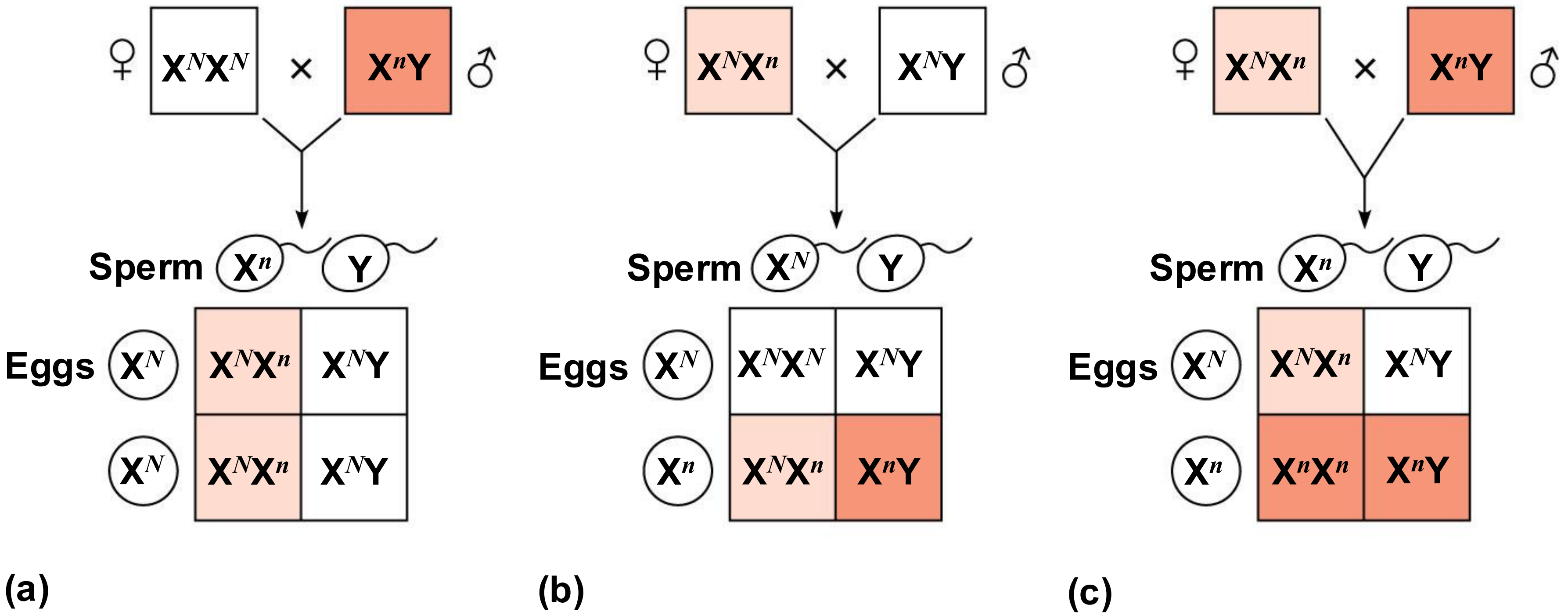
- A gene that is located on either sex chromosome is called a **sex-linked gene**
- Genes on the Y chromosome are called Y-linked genes; there are **few** of these
- Genes on the X chromosome are called **X-linked genes**

Inheritance of X-Linked Genes

- X chromosome have genes for many characters **unrelated** to sex, whereas the Y chromosome mainly encodes genes **related** to sex determination

- X-linked genes follow specific patterns of inheritance
- For a recessive X-linked trait to be expressed
  - A female needs two copies of the allele (**homozygous**)
  - A male needs only one copy of the allele (**hemizygous**)
- X-linked recessive disorders are much **more** common in males than in females

Figure 15.7

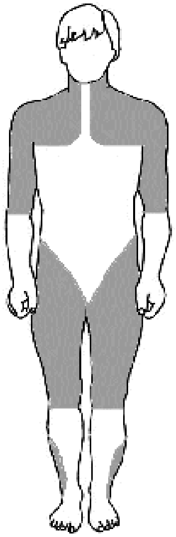


♀
X^NX^N
×
X^nY
♂
Sperm
X^n
Y
Eggs
X^N
X^NX^n
X^NY
X^N
X^NX^n
X^NY
(a)
♀
X^NX^n
×
X^NY
♂
Sperm
X^N
Y
Eggs
X^N
X^NX^N
X^NY
X^n
X^NX^n
X^nY
(b)
♀
X^NX^n
×
X^nY
♂
Sperm
X^n
Y
Eggs
X^N
X^NX^n
X^NY
X^n
X^nX^n
X^nY
(c)

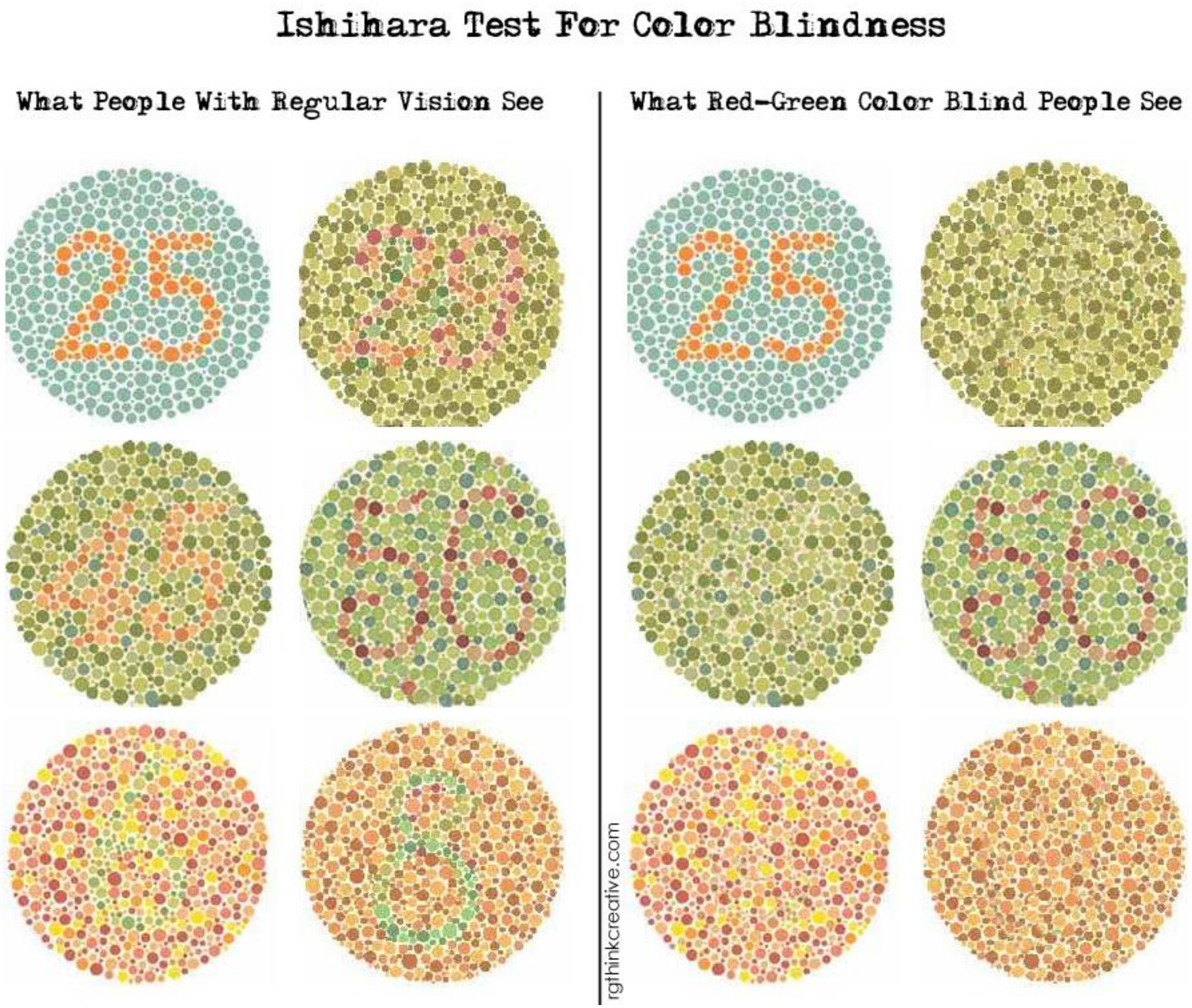
- Some disorders caused by recessive alleles on the X chromosome in humans
  - Color blindness (mostly X-linked) (**Red-green color blindness)**
  - **Duchenne muscular dystrophy** (**dystrophy** muscle weakness and loss of muscle tissue)

✓ Depending on the type of mutation, the disease severity can vary. Clinically, this variability results in two muscle diseases: Duchenne muscular dystrophy (severe damage) and Becker muscular dystrophy (milder), which **differ in their degree of severity.**

  - **Hemophilia**



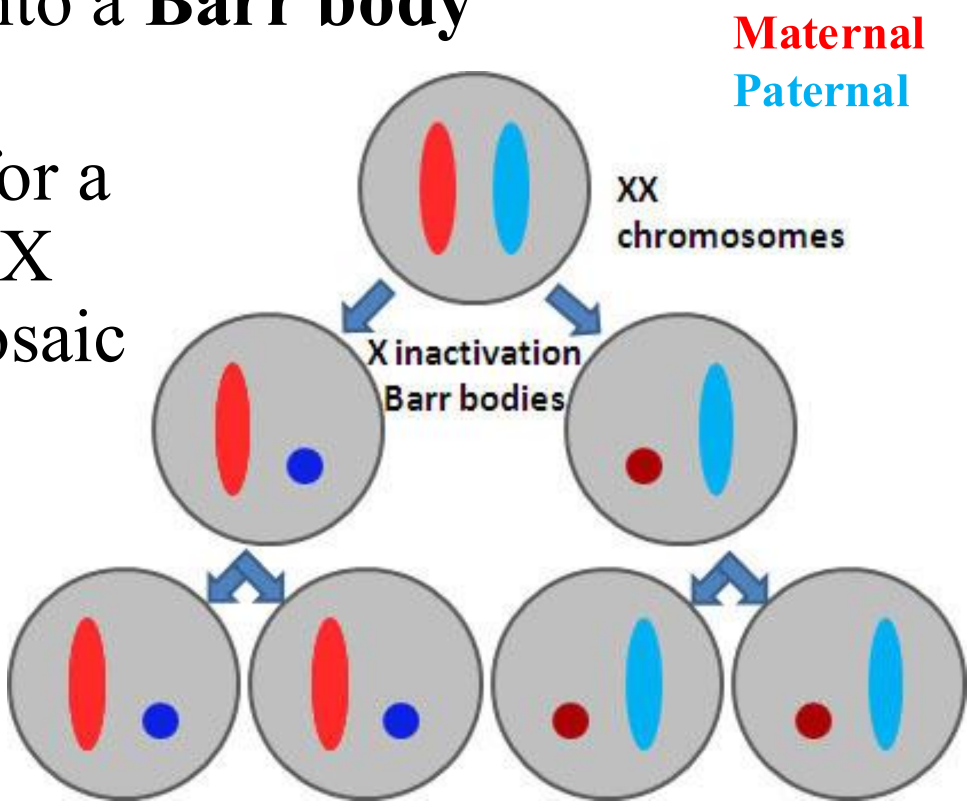
Duchenne and Becker Types



✓ Color blindness is more common in **males** because it is an **X-linked** disorder. Since males possess only one X chromosome (hemizygous), the presence of a single mutated allele is sufficient to cause the disease.

X Inactivation in Female Mammals

- In mammalian females, one of the two X chromosomes in each cell is randomly inactivated during embryonic development
- The inactive X condenses into a **Barr body**



- If a female is heterozygous for a particular gene located on the X chromosome, she will be a mosaic for that character

Examples and Features of X-Linked Recessive Inheritance

Examples:

X-Linked Recessive	
HEMOPHILIA A	Coagulation disorder Prolonged bleeding Easy bruising Hemorrhage Various mutations & very heterogeneous
DUCHENNE MUSCULAR DYSTROPHY	Progressive muscle weakness Death typically in 2nd or 3rd decade 30% cases due to new mutation **Allelic heterogeneity (Becker MD)**

The severity of the disease

- A new mutation refers to a genetic mutation present in the affected individual but **absent in both parents.** Such mutations are also called **spontaneous mutations or de novo mutations**. These mutations usually arise during gametogenesis, either during spermatogenesis or oogenesis, as a result of an error occurring during DNA replication.

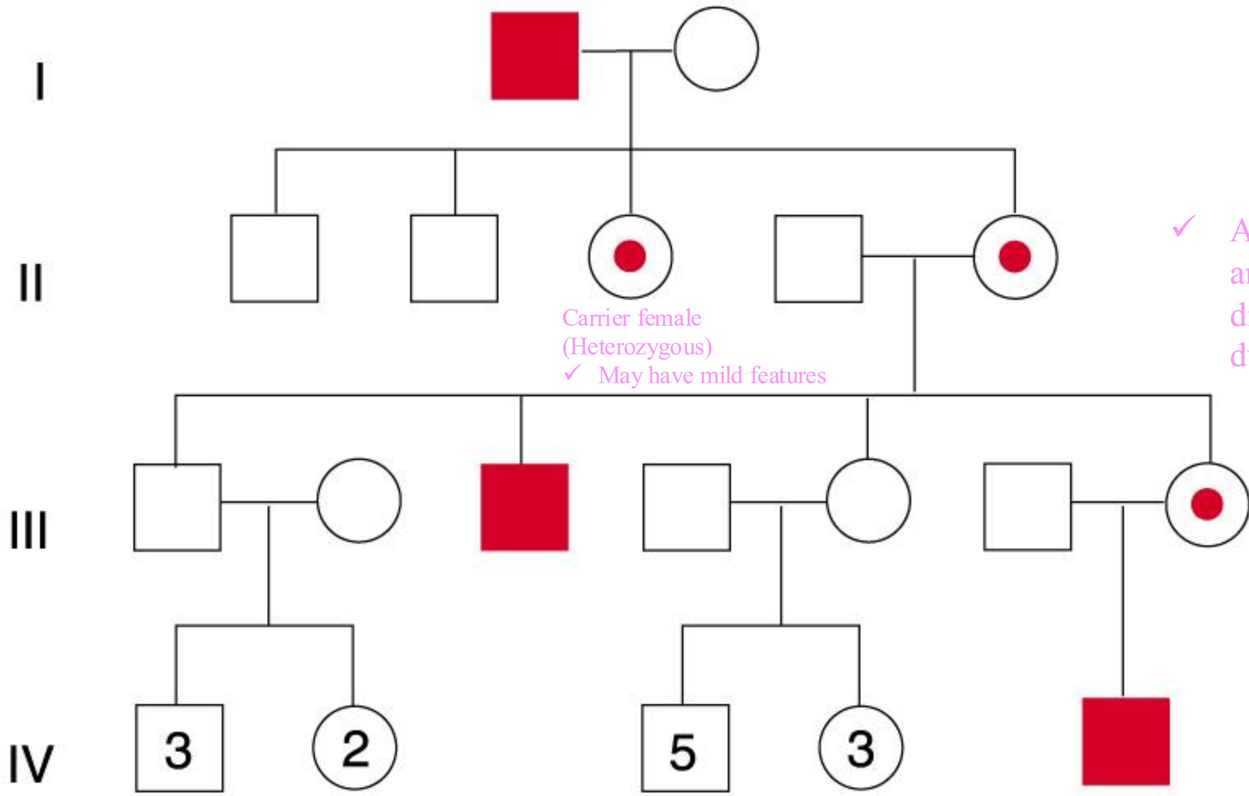
More affected males

Duchenne muscular dystrophy

Figure 1.4. A 15-year-old boy with Duchenne muscular dystrophy

X-Linked Recessive Pedigree

- ✓ There is no male-to-male transmission in X-linked inheritance.



- ✓ A mild expression of an X-linked recessive disease in females is due to X inactivation

- In X-linked recessive inheritance, the pattern is referred to as diagonal inheritance. This means that affected males are connected through females in the maternal lineage. Males inherit their X chromosome from their mothers and the Y chromosome from their fathers. Therefore, when a mother is a heterozygous carrier, there is a 50% probability that her son will be hemizygous for the mutation and thus affected.

Features of X-Linked Recessive Inheritance

1. Diagonal inheritance – affected males related through females of the maternal line
2. Absence of male-to-male transmission
3. Incidence of trait much higher in males than females
4. Full expression in hemizygous males
5. No or mild expression in carrier females due to X-inactivation

Transmission probabilities and use of the Punnett square

1. A son never inherits the disorder from his father.
2. All daughters of a male with the disorder are obligate carriers.
3. Sons of carrier females have a 50% chance of inheriting the disorder.
4. Daughters of carrier females have a 50% chance of being carriers too.

X-Linked Recessive Inheritance

(Affected Father)

Paternal Gametes

X^AX^A \ X^aY	X^a Mutant allele	Y
X^A	X^AX^a	X^AY
X^A	X^AX^a	X^AY

Maternal Gametes

A = normal, a = mutant

1 carrier female : 1 normal male

- An affected hemizygous male will transmit the mutant X chromosome to all of his daughters, making them obligate carriers.
- All of his sons will inherit the Y chromosome and will therefore be normal and unaffected.

X-Linked Recessive Inheritance

(Carrier Mother)

Paternal Gametes

X^AX^a \ X^AY	X^A	Y
Maternal Gametes X^A	X^AX^A	X^AY
Maternal Gametes X^a	X^AX^a	X^aY

A = normal, a = mutant

1 normal female : 1 carrier female : 1 normal male : 1 affected male

- An unaffected mother who is heterozygous (carrier) has a 50% chance of transmitting the mutant allele to her offspring.
- Among her daughters, 50% will be carriers (heterozygous) and 50% will be homozygous wild type.
- Among her sons, 50% will be affected and 50% will be unaffected.

- Regardless of gender, the offspring distribution is: 25% homozygous wild type, 25% heterozygous unaffected carriers, 25% hemizygous wild type, and 25% hemizygous affected males.

Examples and Features of X-Linked Dominant Inheritance

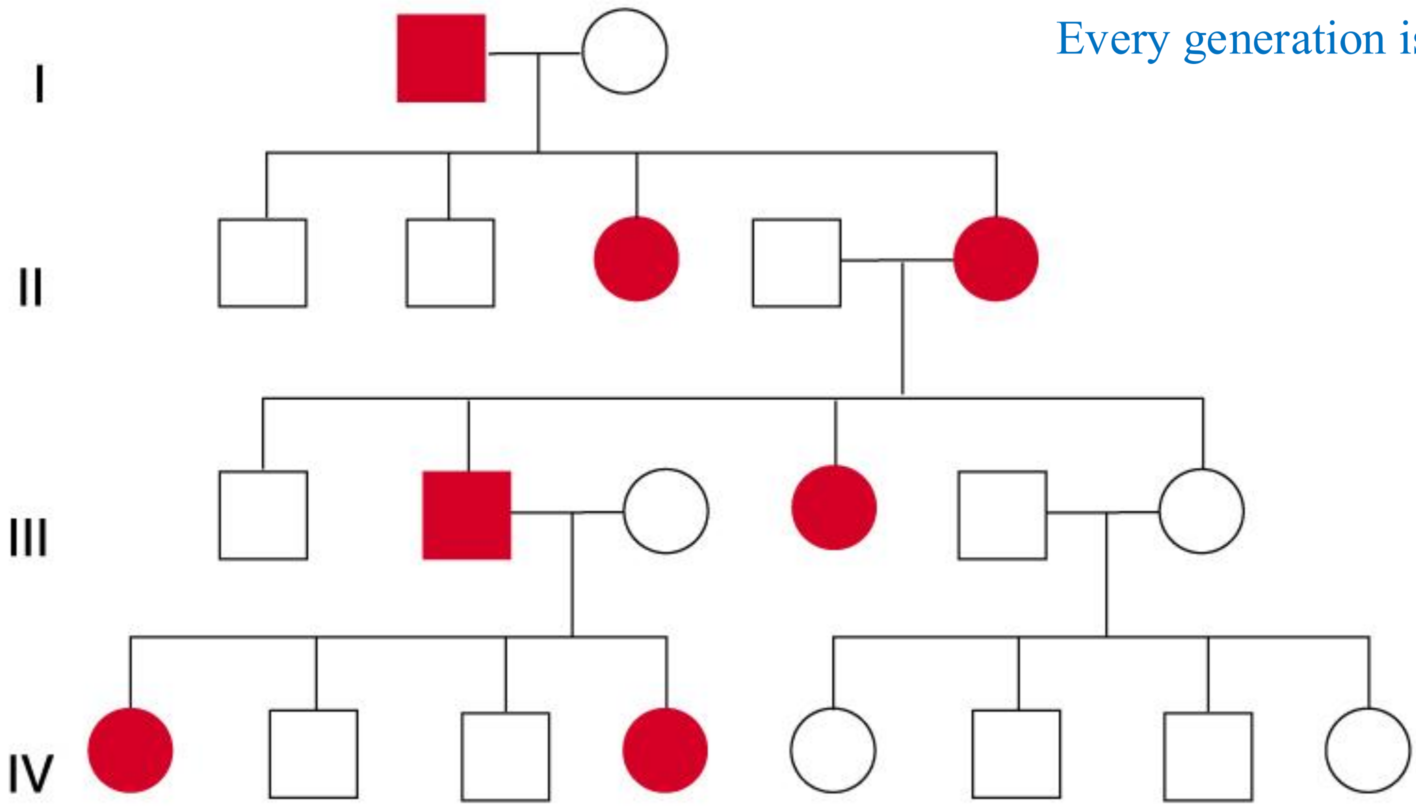
X-linked Dominant

VITAMIN D RESISTANT RICKETS	Rickets Short stature Low serum phosphate Less severe in heterozygous females

Rickets is a softening of bones in children due to deficiency or impaired metabolism of vitamin D

X-Linked Dominant Pedigree

Every generation is affected



✓ More females are affected than males in X-linked dominant disorders.

Features of X-Linked Dominant Inheritance

1. Twice as many females with the disorder as males
2. Absence of male-to-male transmission
3. Males with the disorder transmit it to all daughters and no sons
4. Females usually have more mild and variable expression due to X-inactivation
5. Few disorders classified as X-linked dominant

Transmission probabilities and use of the Punnett square

1. A son never inherits the disorder from his father
2. All daughters of male with the disorder will also have the disorder
3. Sons of affected females have a 50% chance of inheriting the disorder
4. Daughters of affected females also have a 50% chance of inheriting the disorder
5. Can distinguish between autosomal and X-linked dominant by looking at offspring of affected males
6. None of the sons of a healthy (unaffected) female will be affected.

❖ **REMEMBER :** In dominant diseases, whether X-linked or autosomal dominant, affected individuals are assumed to be heterozygous unless otherwise indicated.

X-Linked Dominant Inheritance

(Affected Mother)

Paternal Gametes

Maternal Gametes

X^AX^a \ X^aY	X^a	Y
X^A Mutant allele	X^AX^a	X^AY
X^a	X^aX^a	X^aY

A = mutant, a = normal

1 normal female : 1 normal male : 1 affected female : 1 affected male

✓ 50% of daughters will be affected.

The distribution of offspring in slide #23 has been corrected

Please click here and let me know if there's any mistake.

Good Luck ☺