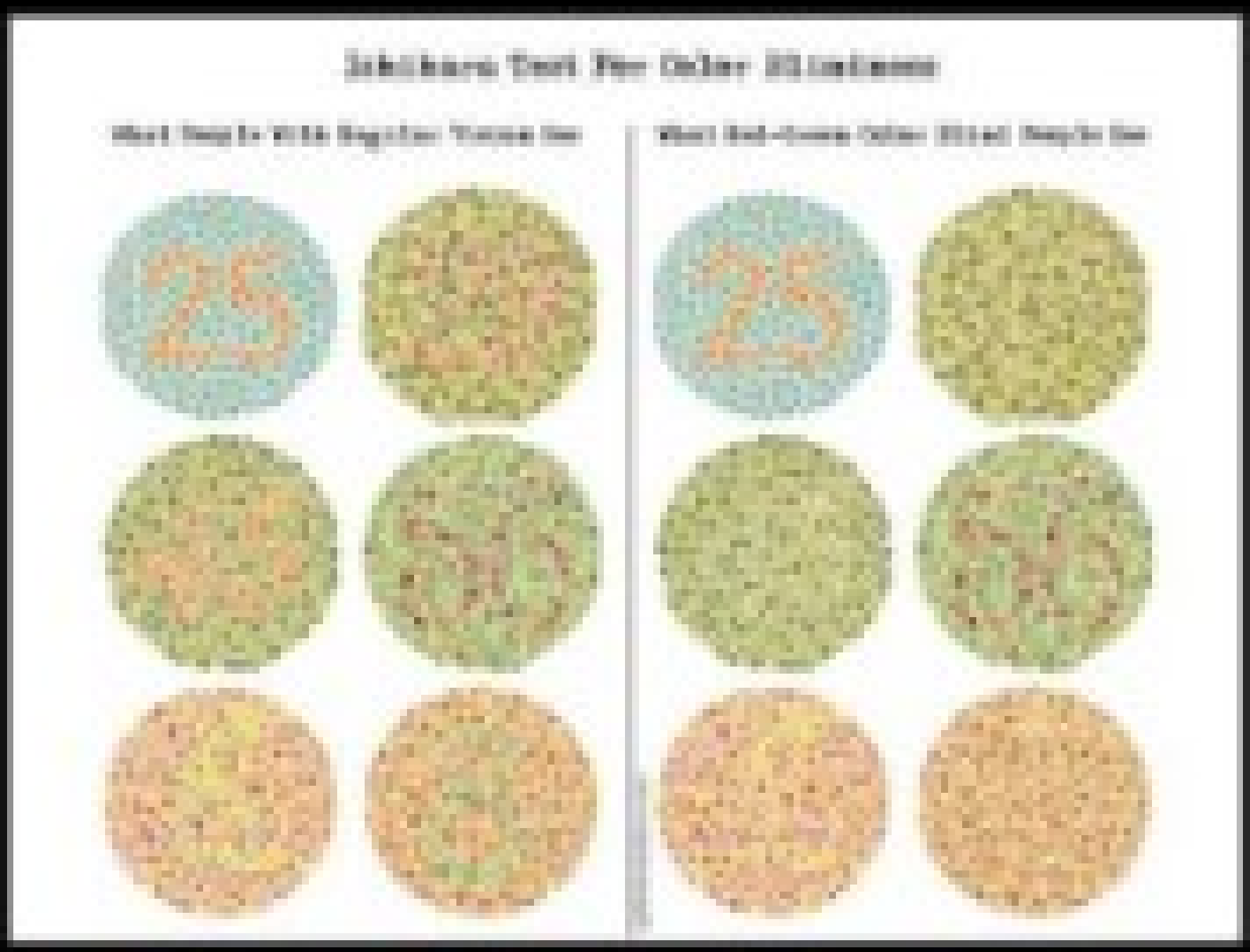
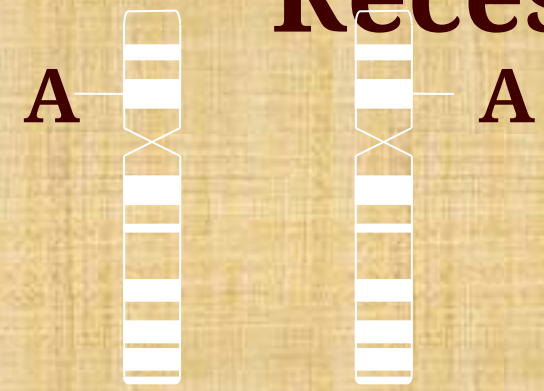
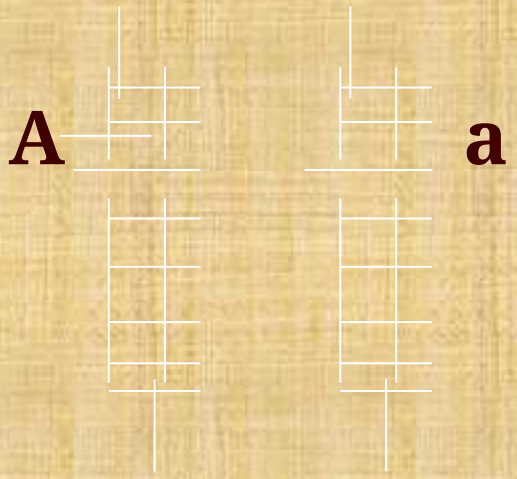


Autosomal Recessive

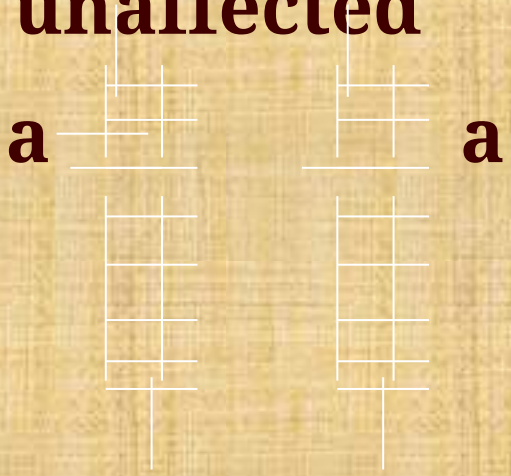


Unaffected, not a carrier

A=normal allele
a=mutant allele

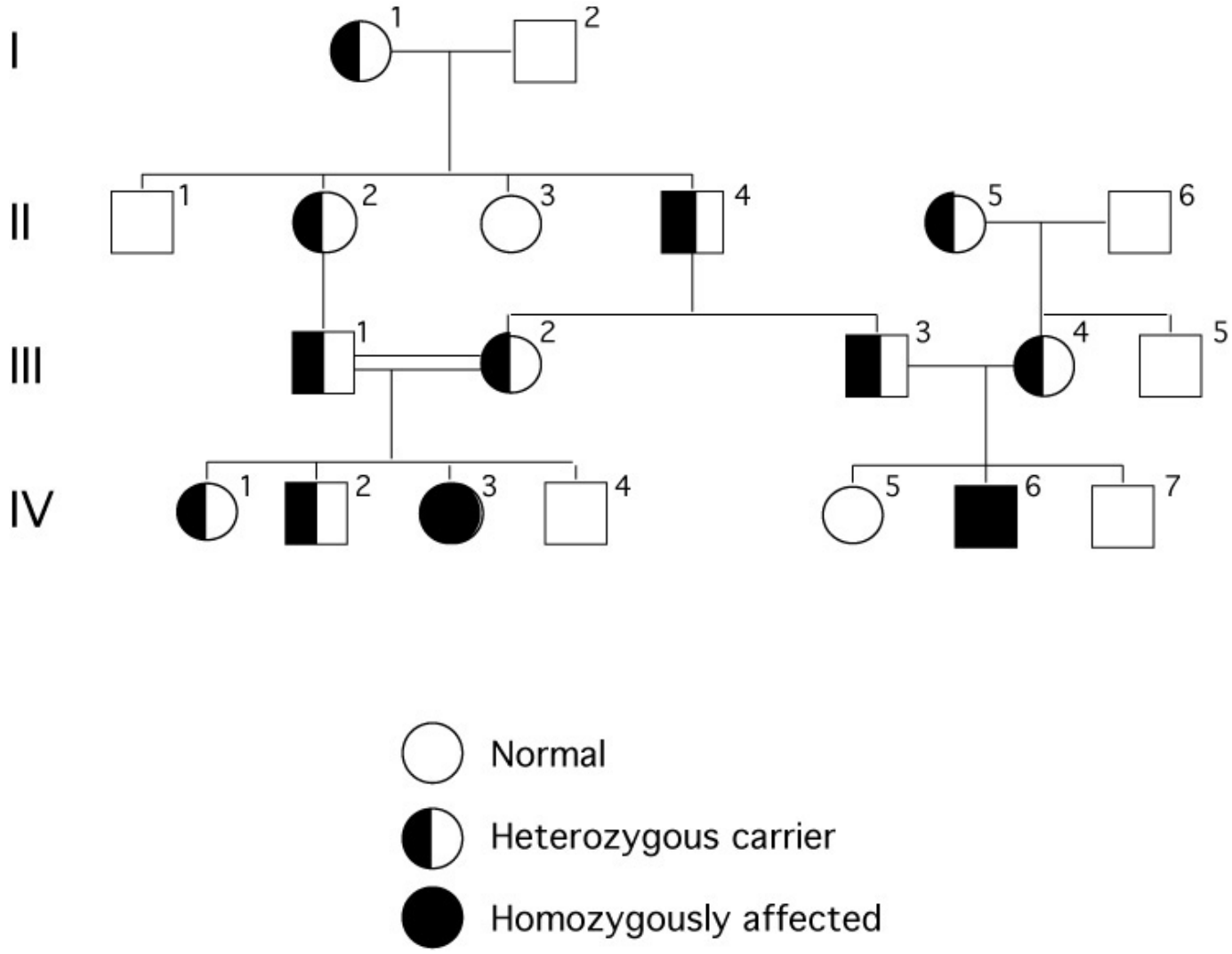


Carrier, unaffected

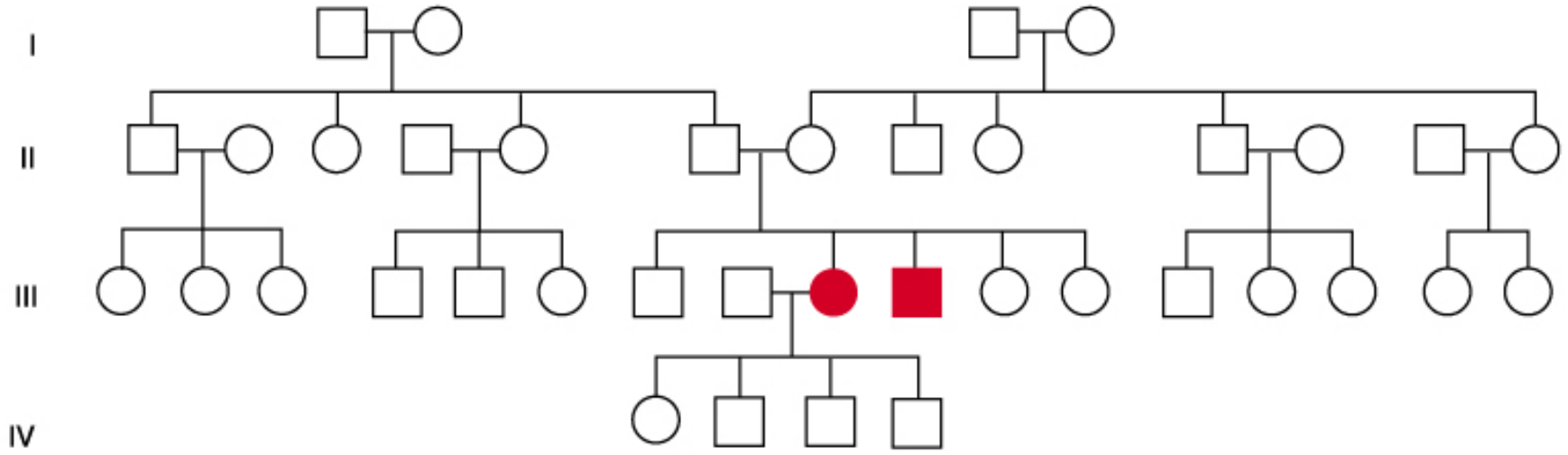


Affected

Autosomal Recessive Pedigree



Autosomal Recessive Pedigree



Features of Autosomal Recessive Inheritance

1. Horizontal transmission – affected individuals usually within the same sibship or generation
2. Both sexes affected in 1:1 ratio
3. Both sexes may equally transmit the mutant allele
4. May observe consanguinity
5. Gene product is usually an enzymatic protein

Transmission probabilities and use of the Punnett square

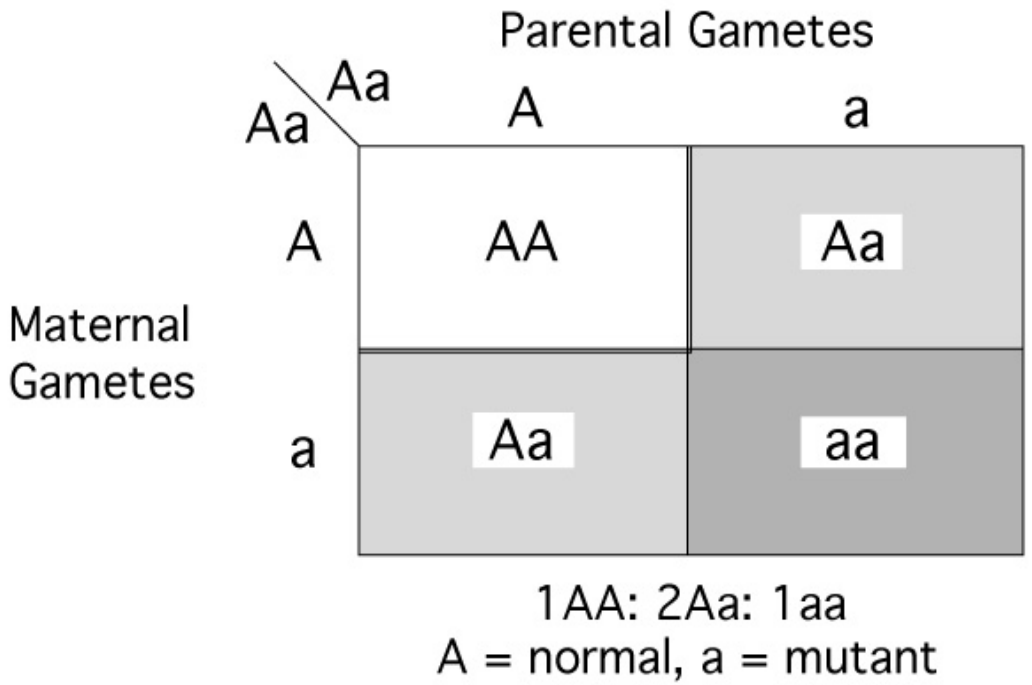
If both parents are carriers (Aa x Aa) then there is

- 25% chance that the child will have the disorder (aa)
- 50% chance that the child will be a carrier (Aa), and
- 25% chance that the child will be neither affected nor a carrier (AA).

Thus the chance that an unaffected child of carrier parents is also a carrier is two in three.

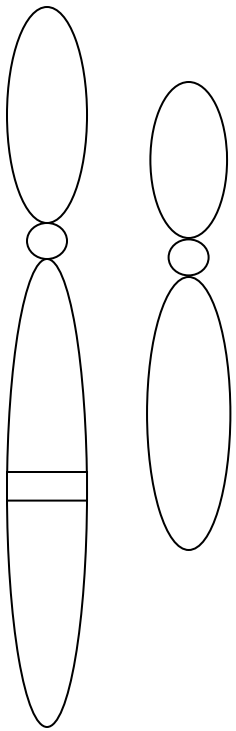
Autosomal Recessive Inheritance

(Both Parents Carriers)

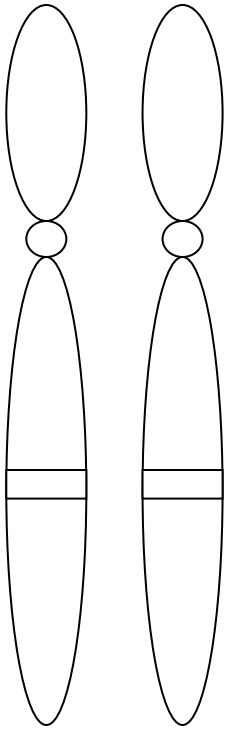


Affected homozygotes are commonly the offspring of two heterozygote carriers.

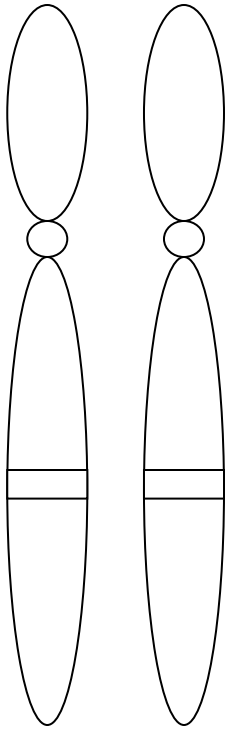
Sex Linkage and X-Inactivation



X^A Y



$X^A X^a$



$X^a X^a$

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

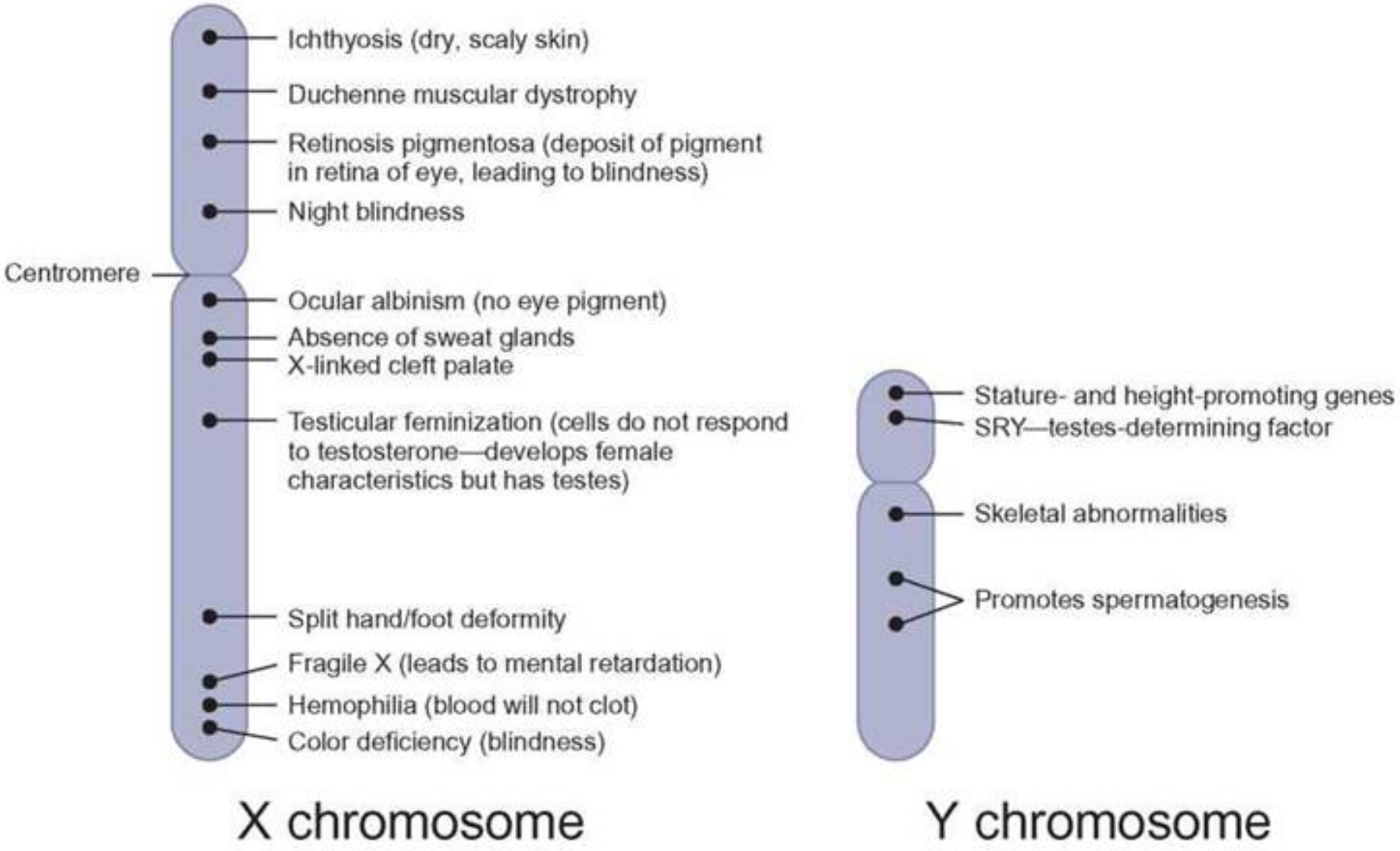
2. For X-linked traits two doses in females and one dose in males both lead to a normal phenotype

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 pseudoautosomal region 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


Ichthyosis (dry, scaly skin)
Duchenne muscular dystrophy
Retinosis pigmentosa (deposit of pigment in retina of eye, leading to blindness)
Night blindness
Centromere
Ocular albinism (no eye pigment)
Absence of sweat glands
X-linked cleft palate
Testicular feminization (cells do not respond to testosterone—develops female characteristics but has testes)
Split hand/foot deformity
Fragile X (leads to mental retardation)
Hemophilia (blood will not clot)
Color deficiency (blindness)
Stature- and height-promoting genes
SRY—testes-determining factor
Skeletal abnormalities
Promotes spermatogenesis
X chromosome
Y chromosome

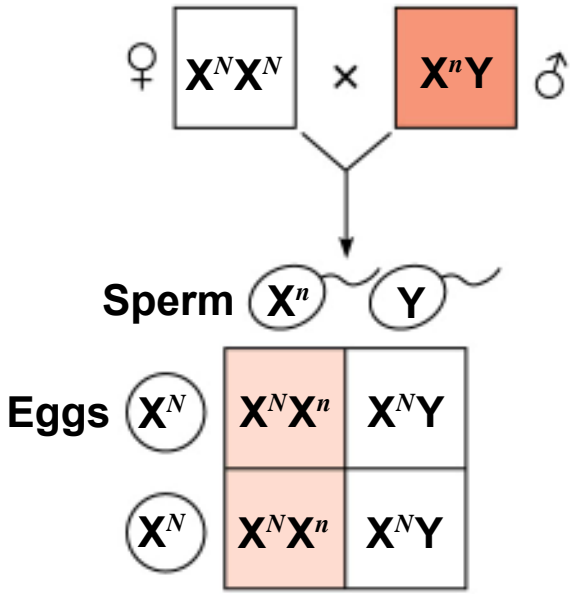
- A gene that is located on either sex chromosome is called a **sex-linked gene**
- Genes on the Y chromosome are called Y-linked genes; there are **few** of these
- Genes on the X chromosome are called **X-linked genes**

Inheritance of X-Linked Genes

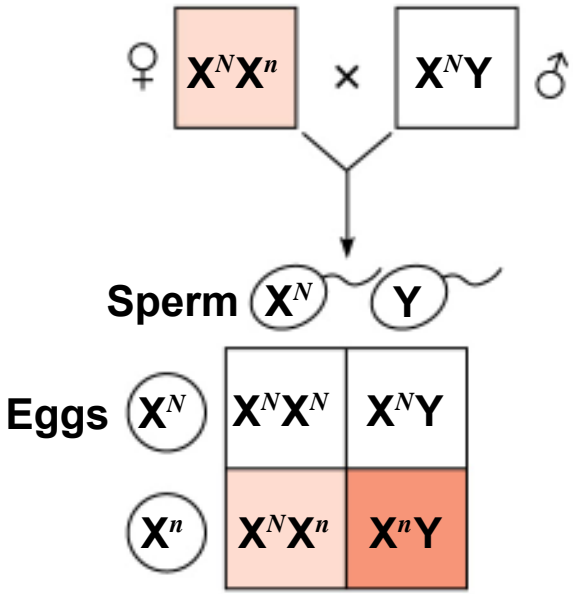
- X chromosome have genes for many characters **unrelated** to sex, whereas the Y chromosome mainly encodes genes **related** to sex determination

- 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

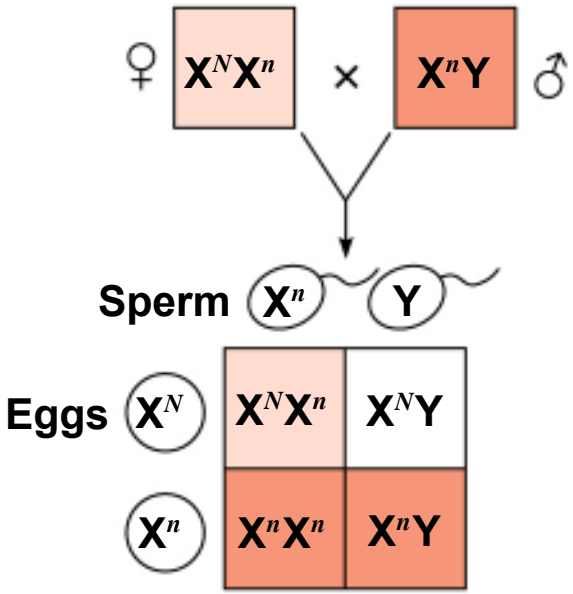
Figure 15.7



(a)



(b)

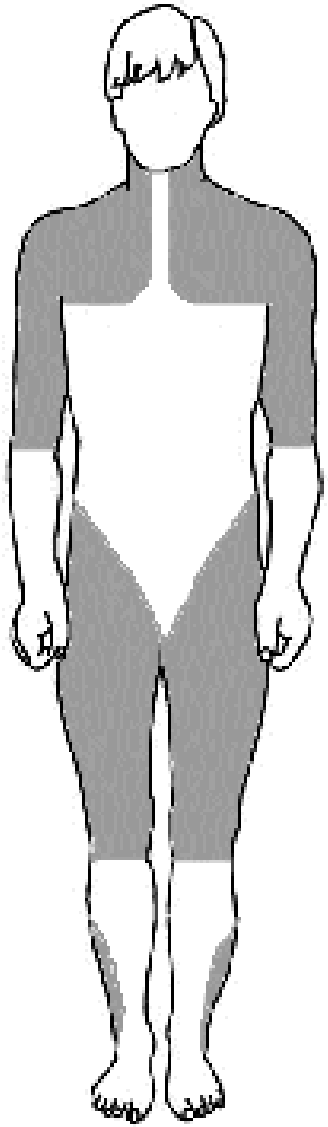


(c)

- 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)

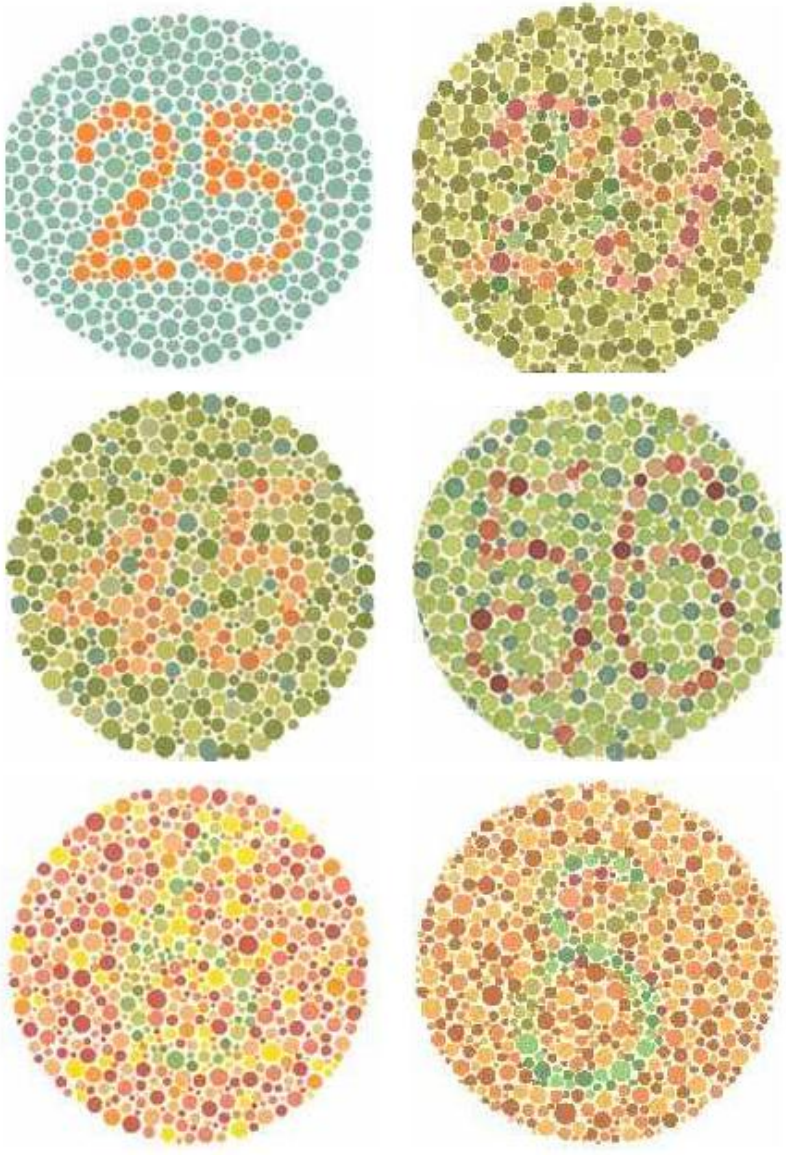
  - **Hemophilia**



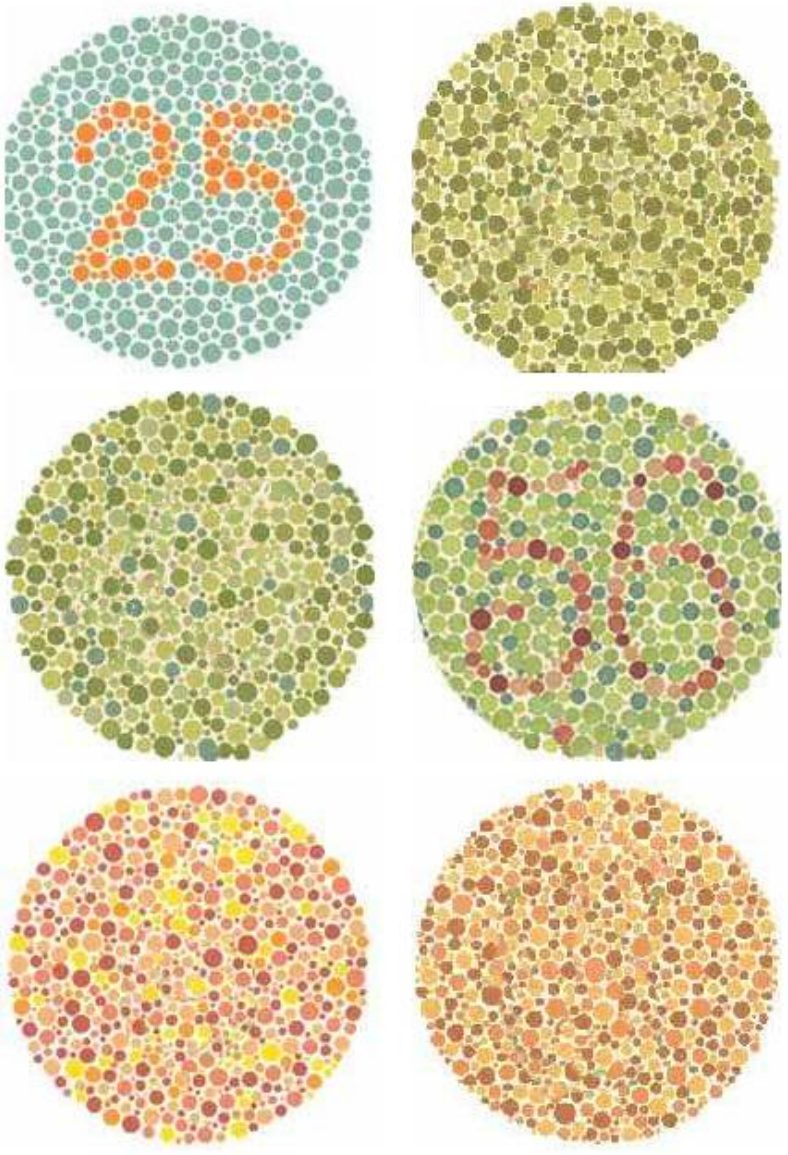
Duchenne and Becker Types

Ishihara Test For Color Blindness

What People With Regular Vision See



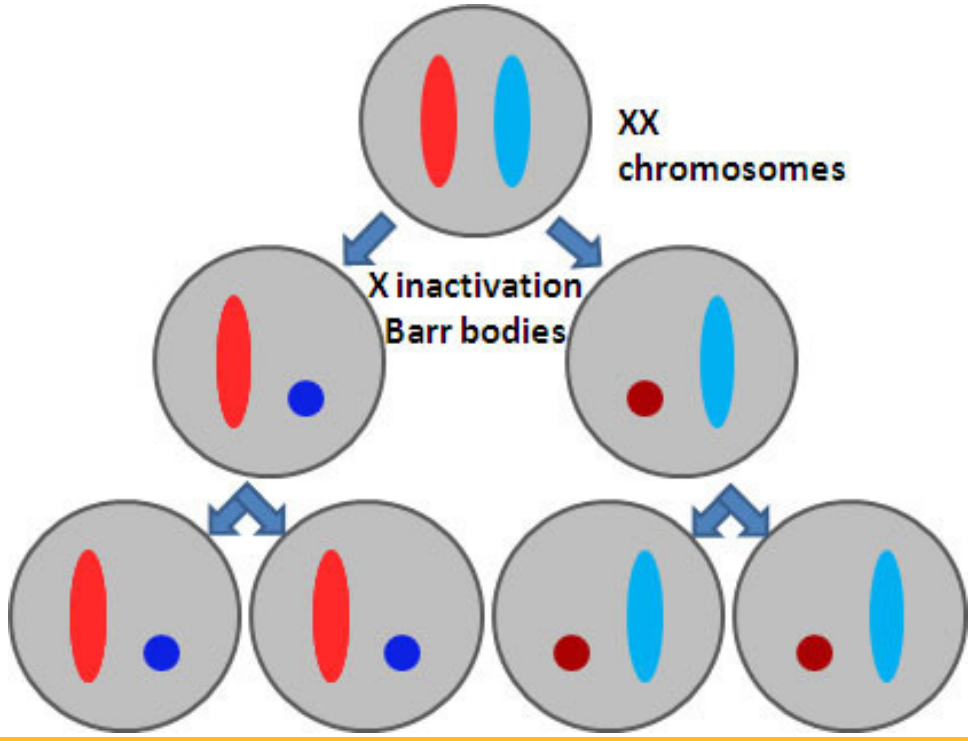
What Red-Green Color Blind People See



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)**

Duchenne muscular dystrophy

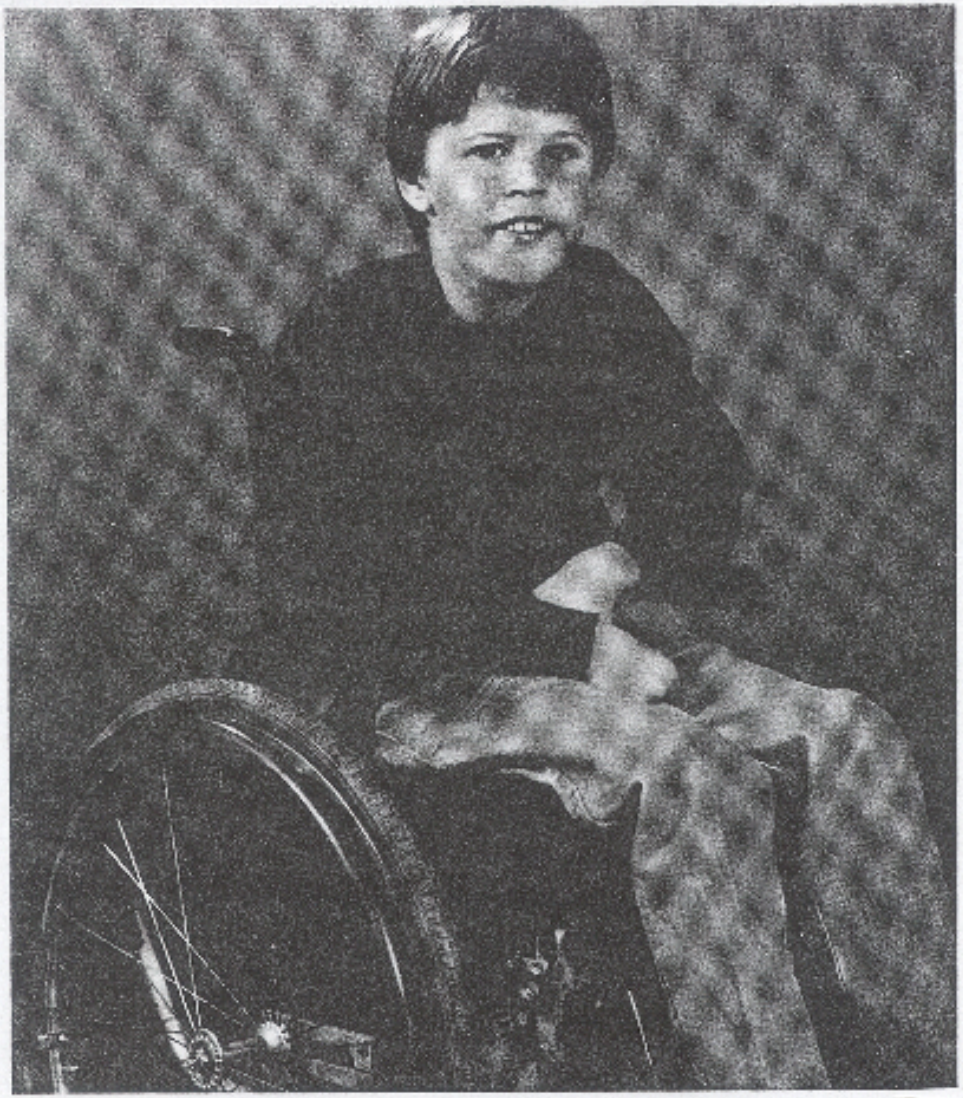
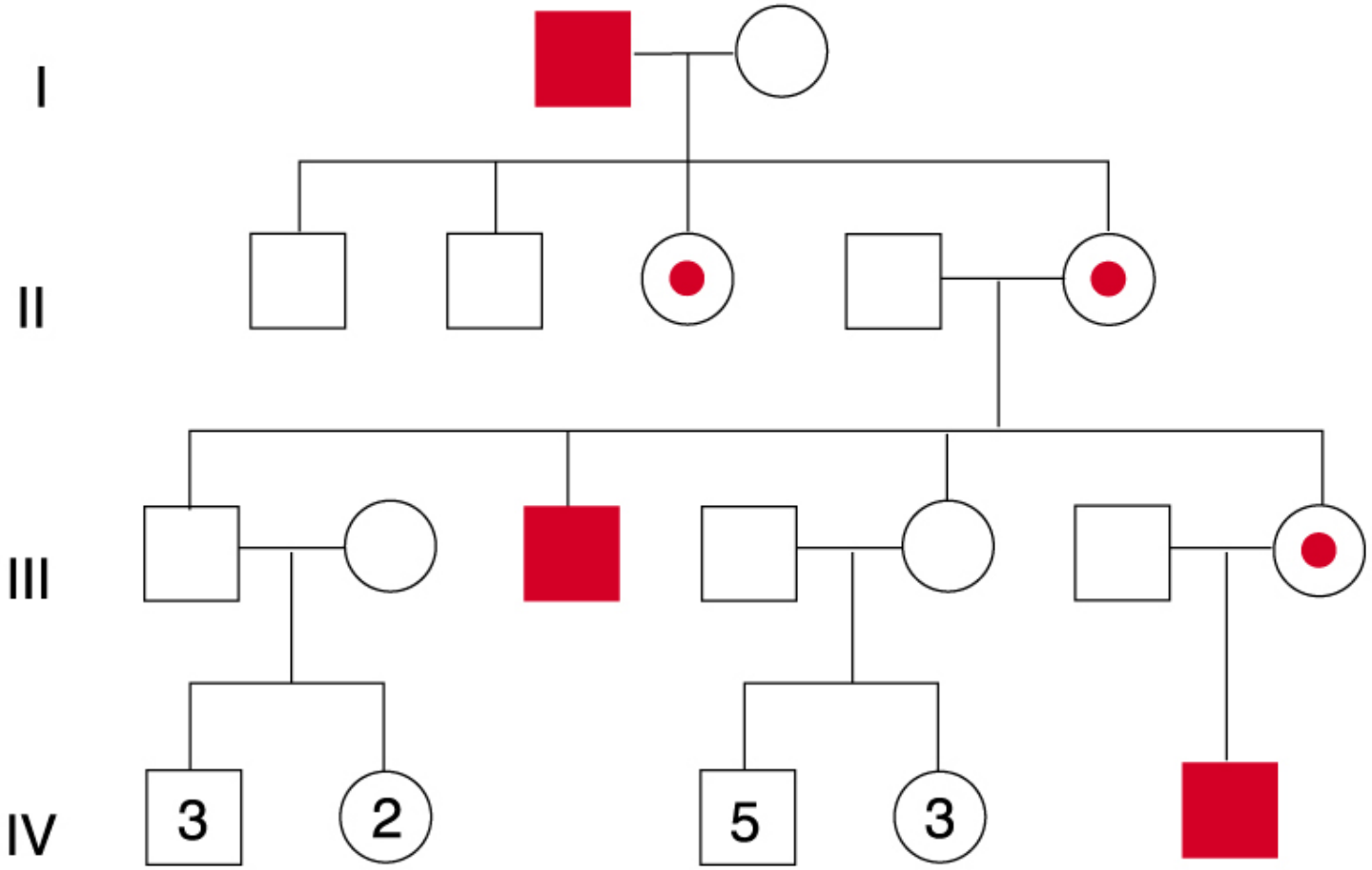


Figure 1.4. A 15-year-old boy with Duchenne muscular dystrophy

X-Linked Recessive Pedigree



Features of X-Linked Recessive Inheritance

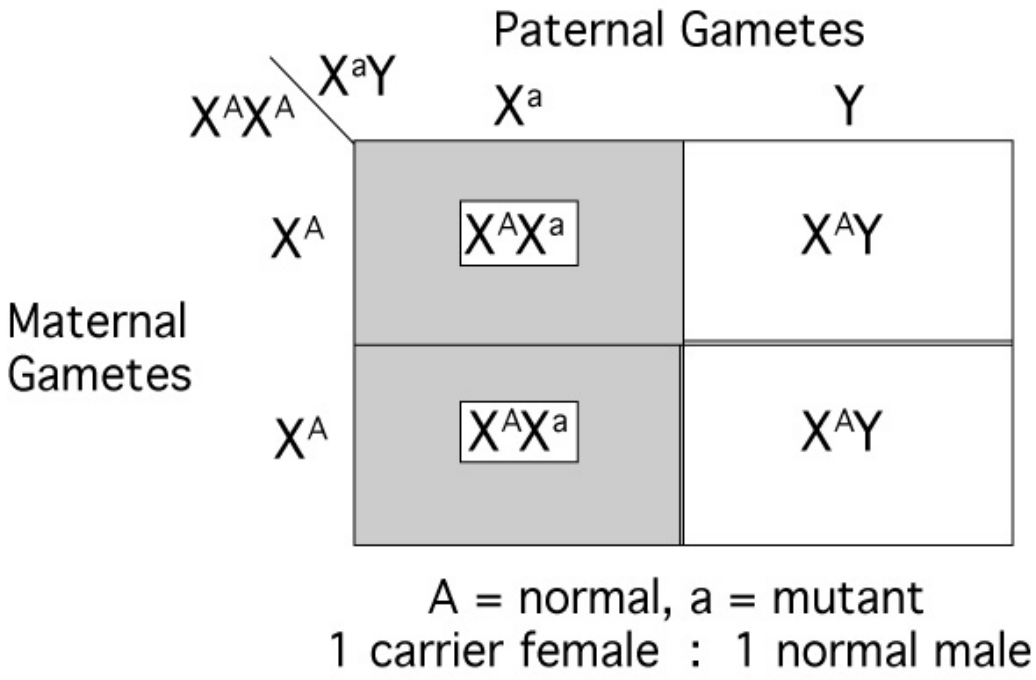
1. Diagonal inheritance – affected males related through females of the maternal line
2. Absence of male-to-male transmission
3. Incidence of trait much higher in males than females
4. Full expression in hemizygous males
5. No or mild expression in carrier females due to X-inactivation

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)

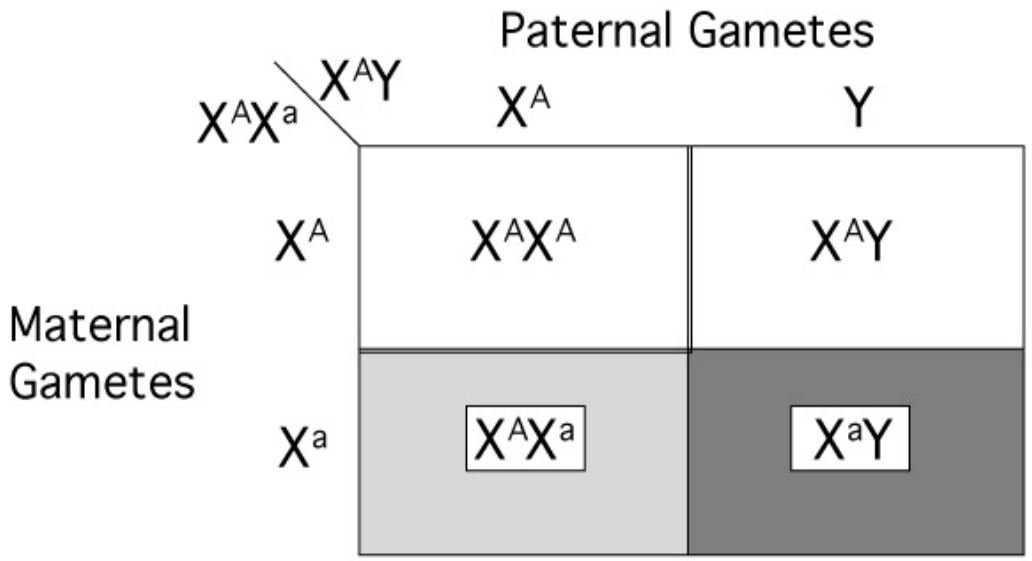


A = normal, a = mutant

1 carrier female : 1 normal male

X-Linked Recessive Inheritance

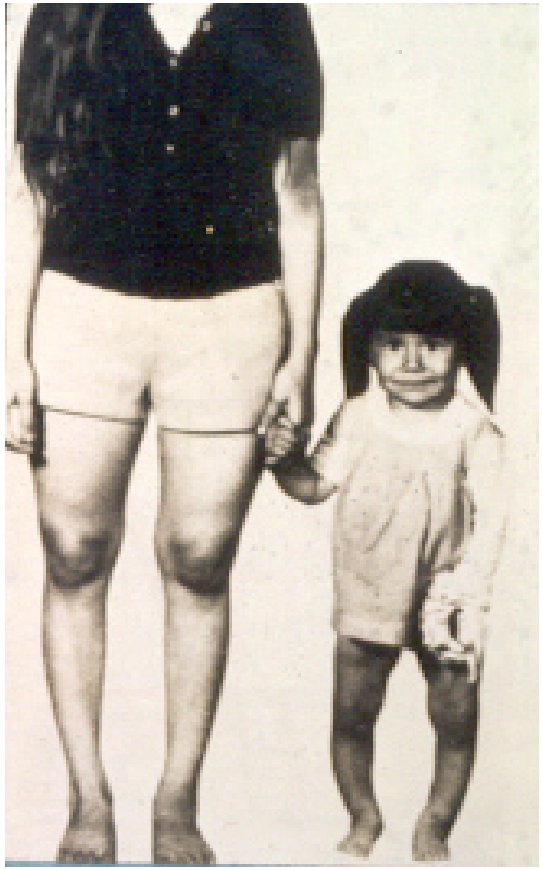
(Carrier Mother)



A = normal, a = mutant

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

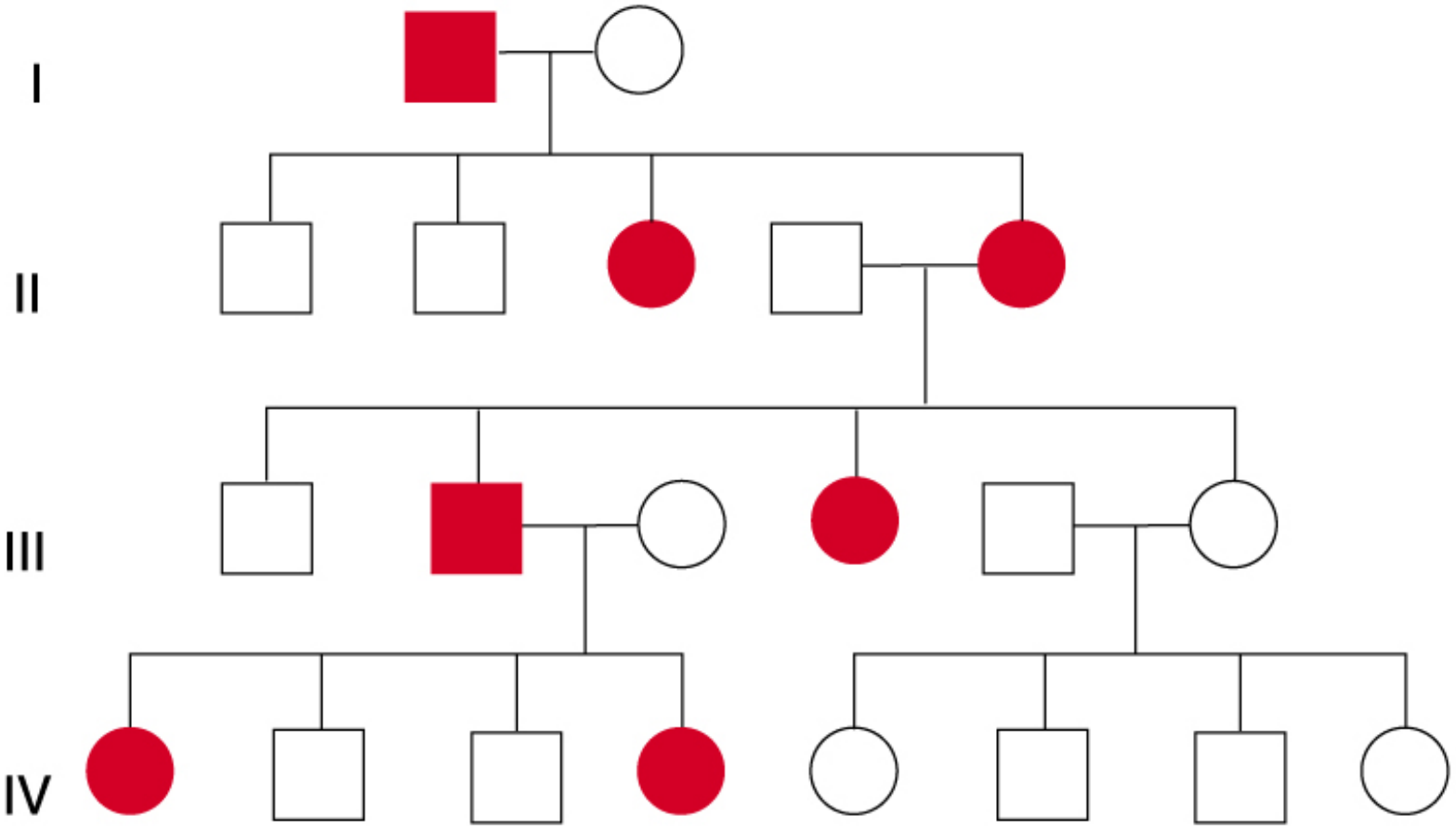
Examples and Features of X-Linked Dominant Inheritance



X-linked Dominant

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

X-Linked Dominant Pedigree



Features of X-Linked Dominant Inheritance

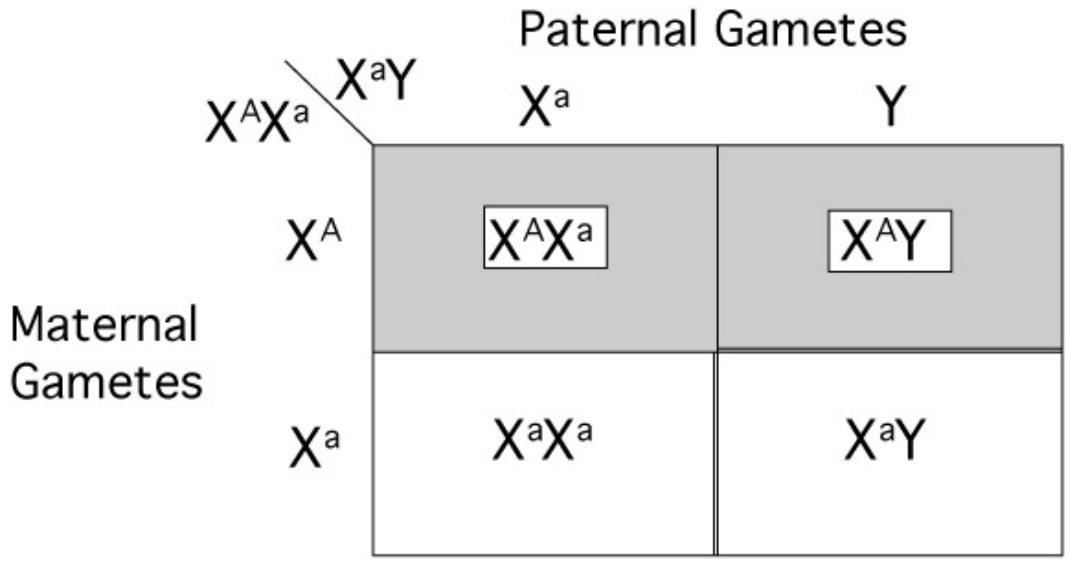
1. Twice as many females with the disorder as males
2. Absence of male-to-male transmission
3. Males with the disorder transmit it to all daughters and no sons
4. Females usually have more mild and variable expression due to X-inactivation
5. Few disorders classified as X-linked dominant

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

X-Linked Dominant Inheritance

(Affected Mother)



A = mutant, a = normal

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