The module: Molecules, Genes and Diseases (MGD)
Session 6
Lecture 12
Duration: 1 hour

Inheritance of Genes

Genetic linkage and pedigree analysis

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Human Heredity Chapters 2, 3, 4, 5
Lippincott's Illustrated Reviews: Cell and Molecular Biology Chapter 20
Complete and review questions started in work session 6.

For more detailed instruction, any question, cases need help please post to the group of session.

Intended learning outcomes of Lecture 8

At the end of this lecture you should be able to:

- Describe the different patterns of inheritance and be familiar with examples. **(LO.1)**
- Explain dominance, recessiveness, co-dominance and complementation. **(LO.2)**
- Describe the basis of the co-inheritance of certain traits. **(LO.3)**
- Draw a family pedigree according to convention from a given family history. **(LO.4)**
- Relate genetic information from a pedigree and describe the family concerned. **(LO.5)**
- Use genetic data to calculate probability of inheritance and recombination frequency **(LO.6)**.

(LO.1)

Describe the different patterns of inheritance and be familiar with examples.

Inheritance: is a process of transmission of characters from generation to next (parents to children).

patterns of inheritance for traits controlled by single genes can be classified into **five** basic patterns, **according to** whether gene responsible to genetic disorder resides on an **autosome** or a **sex chromosome**, and also whether that gene is expressed in its **homozygous** or **heterozygous** state, which are represented in the following:

Autosomal inheritance:

- Autosomal recessive inheritance.
- Autosomal dominant inheritance.

Sex-linked inheritance:

- X-linked inheritance (X-linked recessive inheritance & X-linked dominant inheritance).
- Y-linked inheritance (rare pattern of inheritance)

1. Autosomal Recessive Inheritance (AR)

(LO.1)

It results from defect gene located on an **autosome** and expressed in **homozygous** state, having several distinguishing characteristics:

- Heterozygotes unaffected while homozygotes affected.
- Mating between two heterozygotes individuals having:

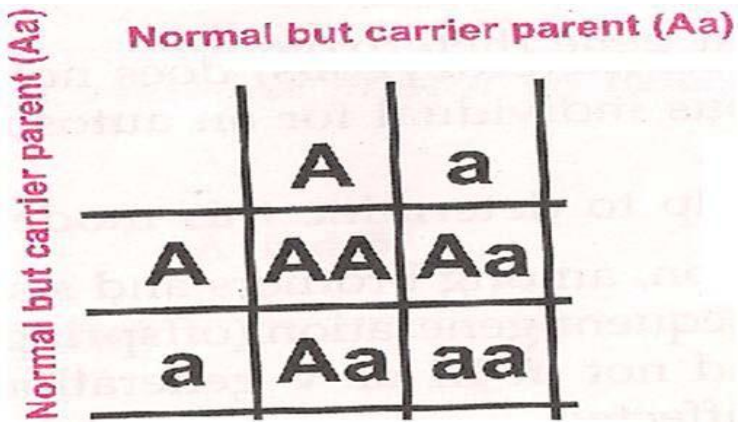
1. Risk of affected child = 25%.
2. Phenotypically unaffected carrier child= 50%.
3. Normal child = 25 %.

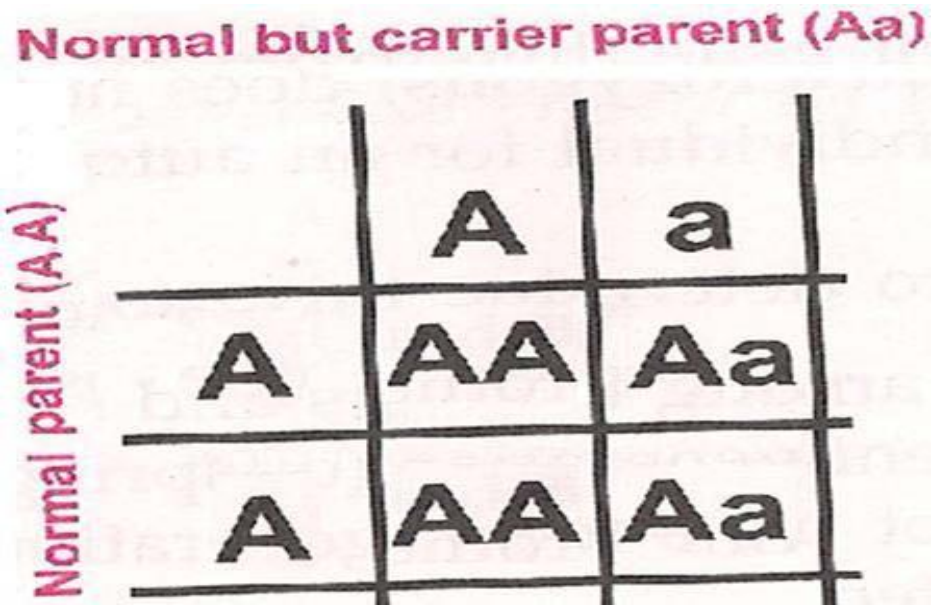
- If the **two** individuals are affected (homozygous), **all** offspring usually affected.
- Males and females are at **equal** risk.
- Affected individual usually in **one** single generation (**horizontal**).
- **Consanguineous** marriage (relatives) plays important role.

Genotype, Phenotype and Recurrence Risk:

(LO.1)

Assume **normal** allele= A Assume **mutant** allele= a





Genotype

aa = 1(25%) affected

Aa = 2(50%) normal but carrier

AA = 1(25%) normal

Phenotype

¼ affected

¾ normal

Genotype

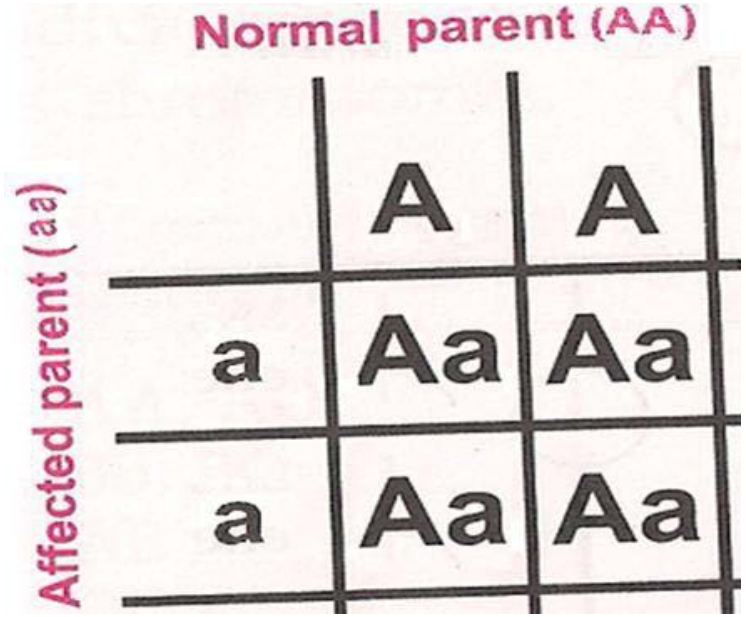
Aa = 2(50%) normal but carrier

AA = 2(50%) normal

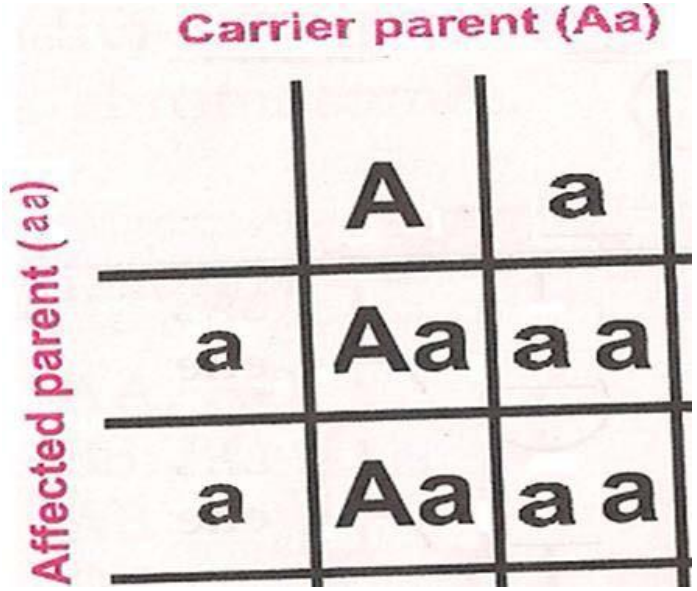
Phenotype

100% normal

(LO.1)

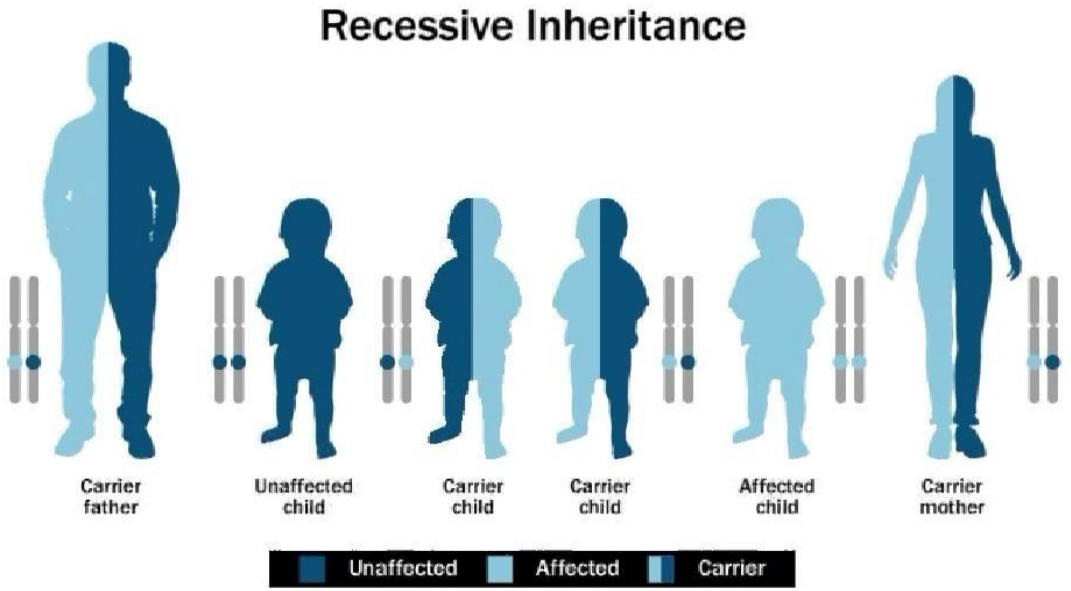


Genotype	Phenotype
Aa=100% normal but carrier	100% normal



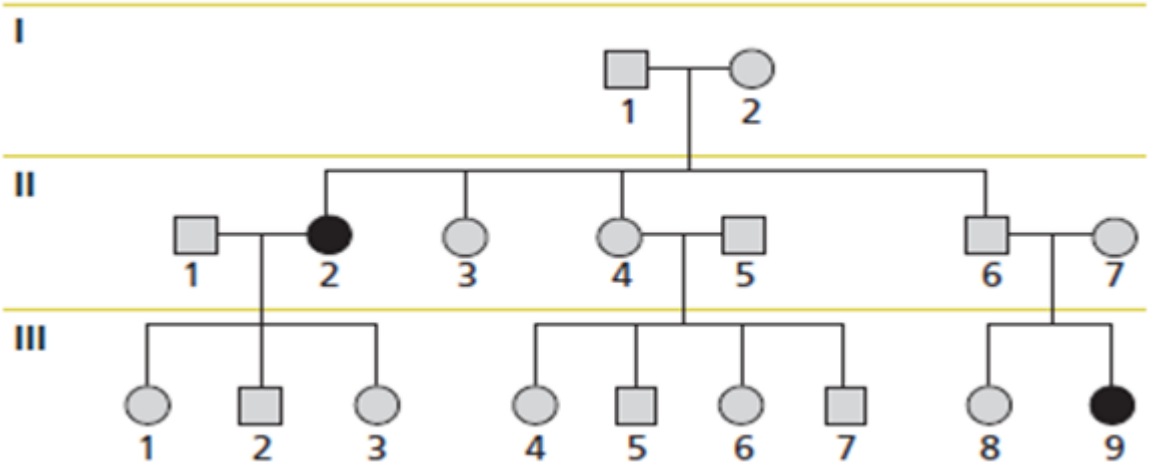
Genotype	Phenotype
Aa=50% normal but carrier	½ normal
aa=50% affected	½ affected

(LO.1)



Galactosemia	Accumulation of galactose in liver; mental retardation

Sickle cell anemia	Abnormal hemoglobin, blood vessel blockage; early death
Thalassemia	Improper hemoglobin production; symptoms range from mild to fatal



Cystic fibrosis is a genetic disorder that leads to early death.

(Metabolism Module) is caused by a functional defect in a membrane protein.

(CPS Module) Affected individuals have thick, sticky mucus secretions in their pancreas and lungs. Diagnosis is often made by finding elevated levels of chloride ions in sweat.

the risk of an affected child with heterozygous parents is 25%.

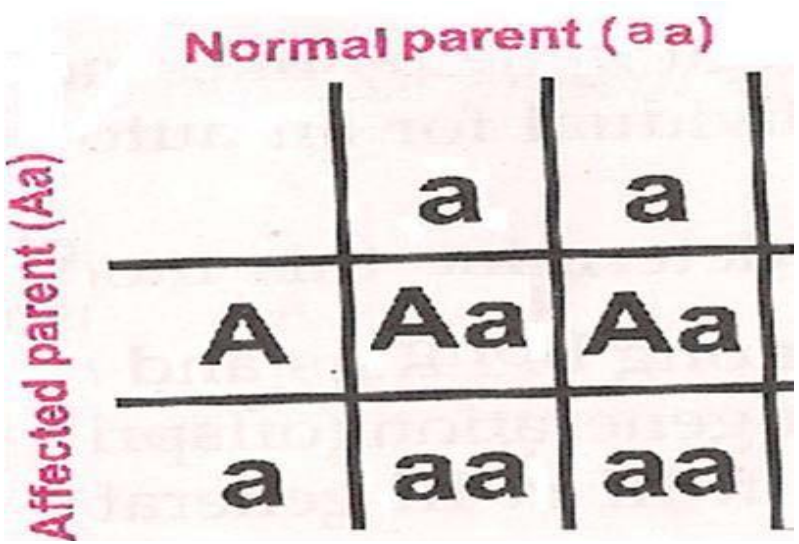
Autosomal Dominant Inheritance (AD)

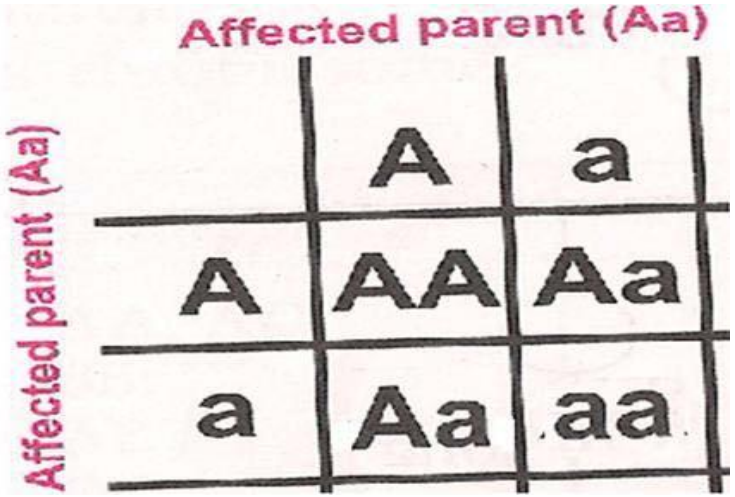
It results from defected gene located on an **autosome** and expressed in **heterozygous** state, having several distinguishing characteristics:

- **Heterozygotes** affected.
- Very **rare** that found in homozygous state.
- Affected person (Heterozygote) has 50% chance of transmitting the trait
- Males and females are at **equal** risk.
- Every affected individual usually has an affected parent, meaning the disease seen in every generation (**vertical**).

Genotype, Phenotype and Recurrence Risk:

Assume normal allele= A Assume mutant allele= a





Genotype

Aa=1(50%) heterozygous affected
aa=1(50%) homozygous normal

Phenotype

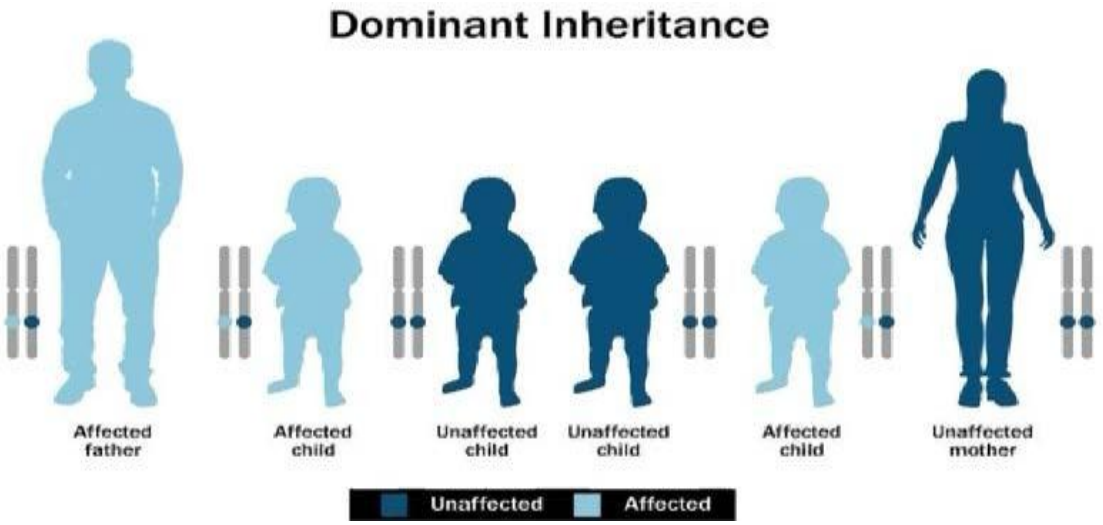
½ affected
½ normal

Genotype

AA=1(25%) severe affected
Aa=2(50%) heterozygous affected
aa=1(25%) homozygous normal

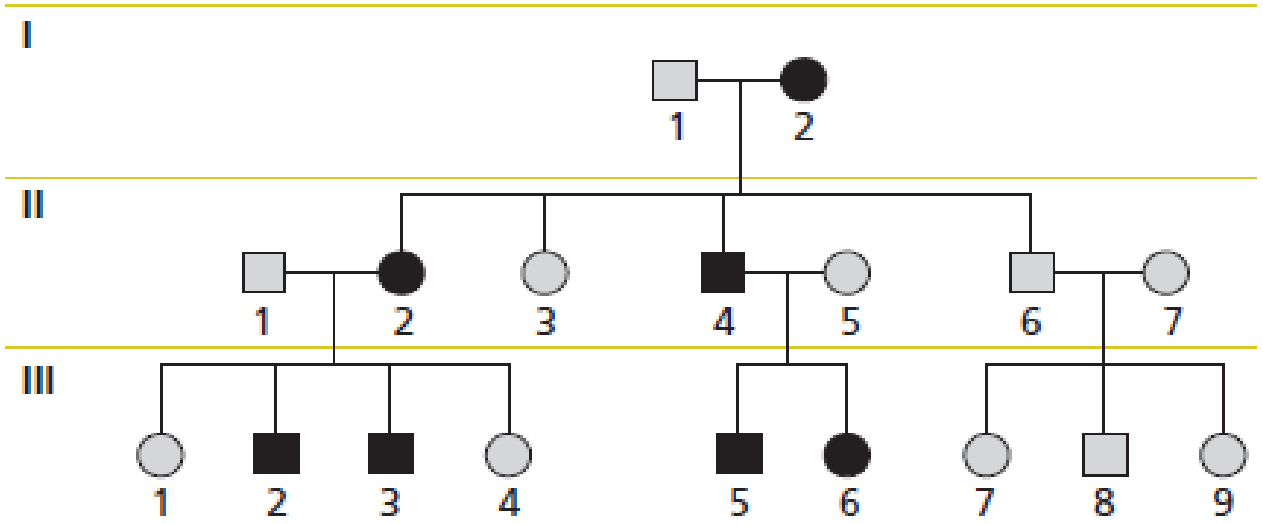
Phenotype

¼ severe affected
½ affected
¼ normal



(LO.1)

Adult polycystic kidney disease	Formation of cysts in kidneys; leads to hypertension, kidney failure
Huntington disease	Progressive degeneration of nervous system; dementia; early death
Marfan syndrome	Connective tissue defect; death by aortic rupture



Examples: Juvenile cataract, Achondroplasia, Ehlers-Danlos Syndrome, familial hypercholesterolemia, Marfan syndrome & myotonic dystrophy.

X-linked Recessive Inheritance (XLR)

(LO.1)

It results from defect gene located on **X chromosome** and expressed in **hemizygous** or **homozygous** state, having several distinguishing characteristics:

- **Only** Hemizygous males usually affected.
- Homozygous females for recessive alleles are affected (**rare**).
- Unaffected **carrier** females(heterozygous) will transmit the trait as follows:

1. Risk of affected son= 25% (50% of males).
2. Normal son = 25 % (50% of males).
3. Unaffected carrier daughter= 25% (50% of females)
4. Normal daughter = 25 % (50% of females)

- Affected males transmit the disorder to daughters (all be carriers 100%) but **not** to sons (100% normal).

Genotype, Phenotype and Recurrence Risk:

(LO.1)

Assume normal allele= XA Assume mutant allele= Xa

Genotype **Phenotype**

XAXA=1(25%) homozygous normal female ½ normal female XAXa=1(25%)

heterozygous normal carrier female

XaY=1(25%) affected male ¼ affected male

XAY=1(25%) normal male ¼ normal male

Therefore

Daughters (100%):

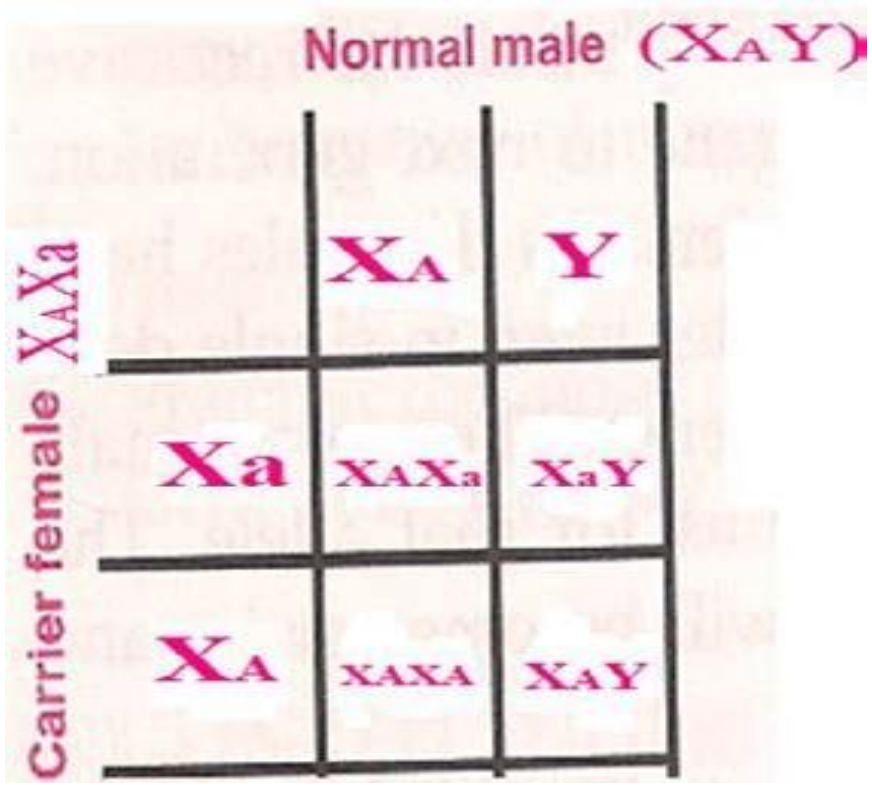
XAXA=1(50%) homozygous normal

XAXa=1(50%) heterozygous normal carrier 100% normal

Sons (100%):

XaY=1(50%) affected ½ affected

XAY=1(50%) normal ½ normal



(LO.1)

Genotype **Phenotype**

XAXa=1(50%) heterozygous normal carrier female ½ normal female

XAY=1(50%) normal male ½ normal male

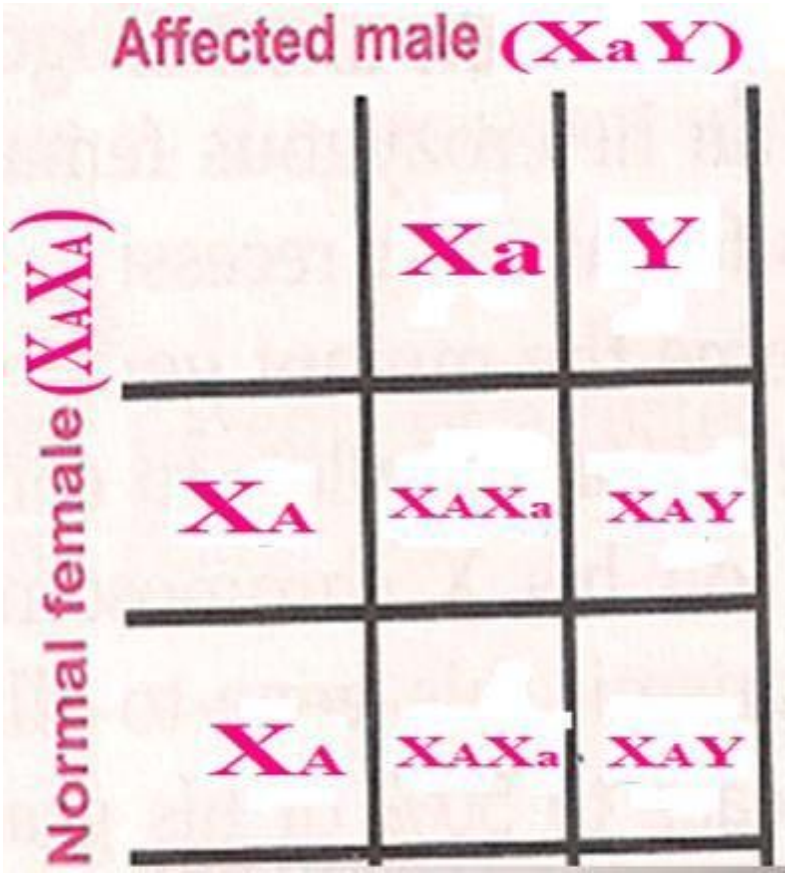
Therefore

Daughters (100%):

XAXa=100% heterozygous normal carrier 100% normal

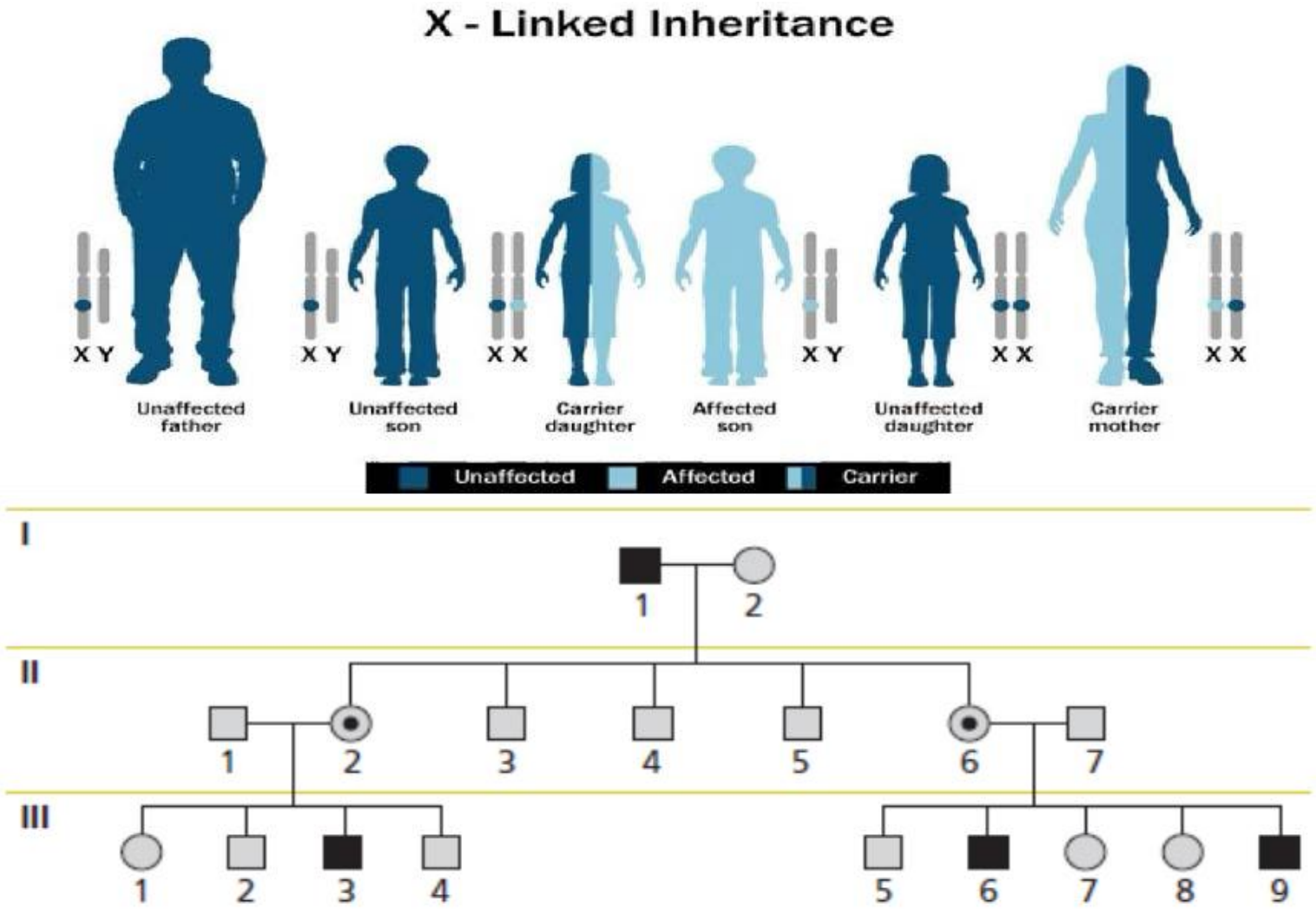
Sons (100%):

XAY=100% normal 100% normal



(LO.1)

Muscular dystrophy **A group of genetic diseases associated with progressive degeneration of muscles. Two of these, Duchenne and Becker muscular dystrophy, are inherited as X-linked allelic recessive traits.**



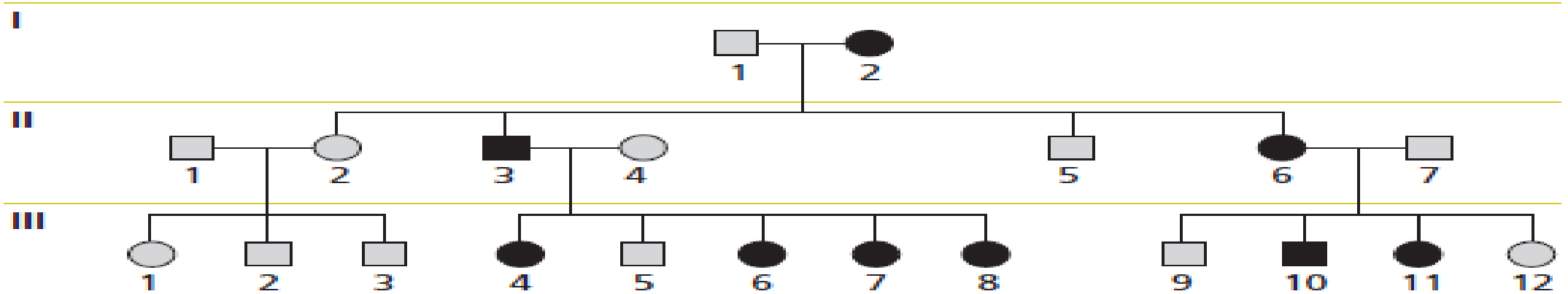
Examples: **Color blindness, glucose-6-phosphate dehydrogenase deficiency, hemophilia & muscular dystrophy.**

X-linked Dominant Inheritance (XLD)

It is result from defect gene located on **X chromosome** and expressed in **heterozygous** state, having several distinguishing characteristics: (LO.1)

- Males and females affected.
- Females **less** severely affected than males.
- Affected males can transmit the disorder to **all** their daughter (all be affected 100%), but **not** to sons (100% normal).
- Affected females have a 50% affected children, **irrespective** of sex.
- On average, **twice** as many females are affected as males (females can be heterozygous or homozygous).

Examples: X-linked dominant retinitis pigmentosa, Rett syndrome, and hypophosphatemia.



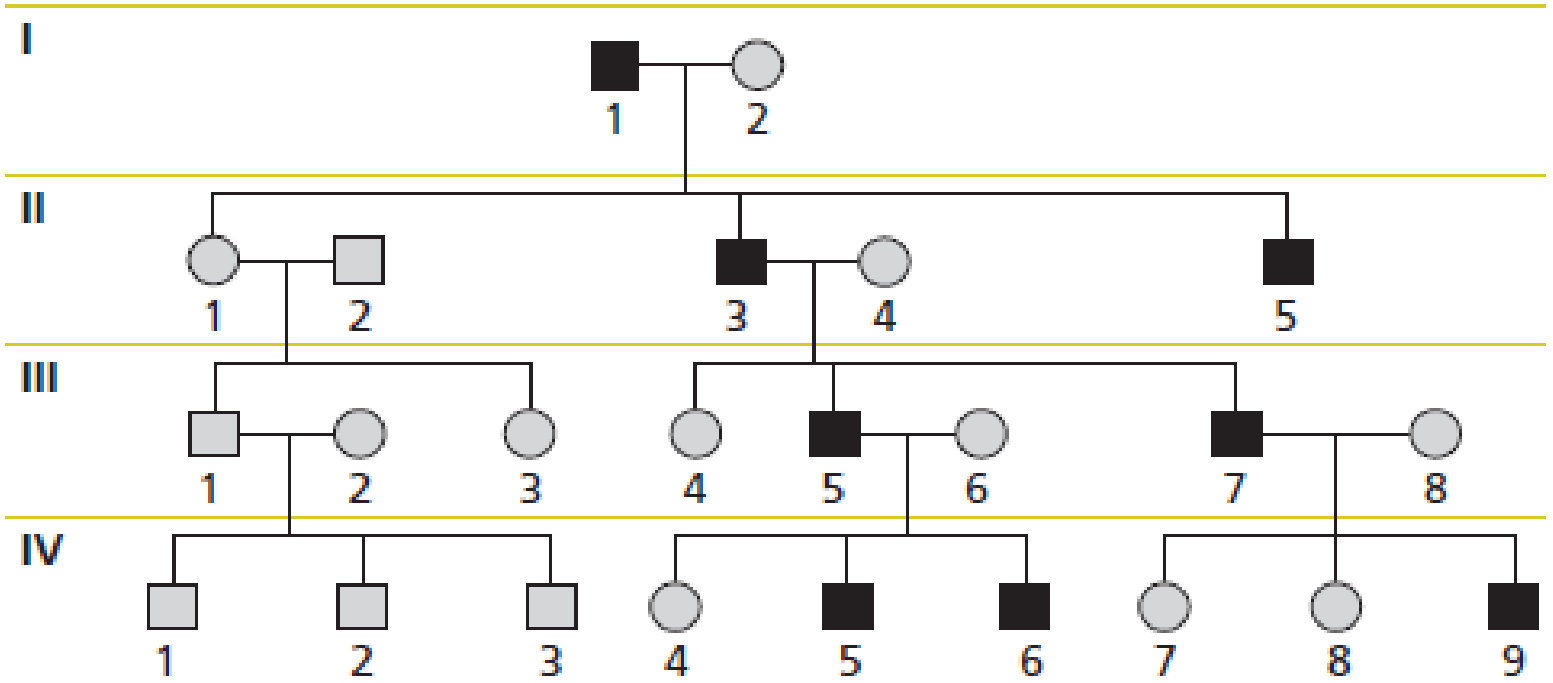
Y-linked Inheritance

(LO.1)

It is **rare** and result from defect gene located on **Y chromosome** and is inherited directly from father to son.

- Only males are affected.
- Affected males must transmit a disorder to their sons who are also be affected as shown in a pedigree below:

Examples: Infertility and Hairy pinna.



Explain dominance, recessiveness, co-dominance and complementation.

(LO.2)

There are only two possible traits for an allele: dominant or recessive.

- **Dominant allele:** those that mask the presence of other corresponding allele.
- **Recessive allele:** those whose physical expression (phenotype) is masked when in the presence of a dominant allele.

Dominance: a phenotypic trait is dominant when it occurs in **both** homozygotes and heterozygotes.

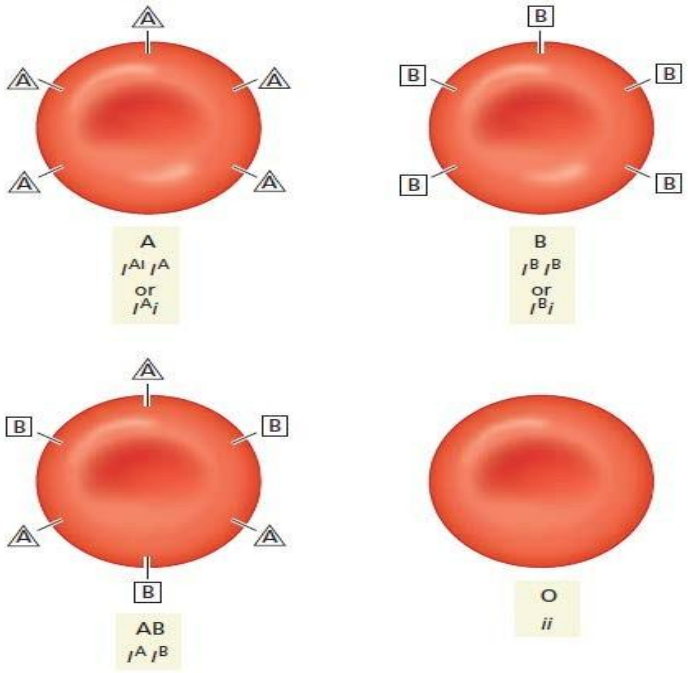
Recessive: a phenotypic trait is recessive when it occurs in homozygotes **only**.

Co-dominance:

It is full phenotypic expression of both members of a gene pair in the heterozygous condition. **Example** is ABO blood types.

Isoglutamin gene (I) codes for proteins (glycoproteins) on the surface of red blood cells. Co-dominant alleles are fully expressed in heterozygotes. There are three alleles, IA, IB, and i.

Genotypes	Phenotypes
I^AI^A, I^Ai	Type A
I^BI^B, I^Bi	Type B
I^AI^B	Type AB
ii	Type O

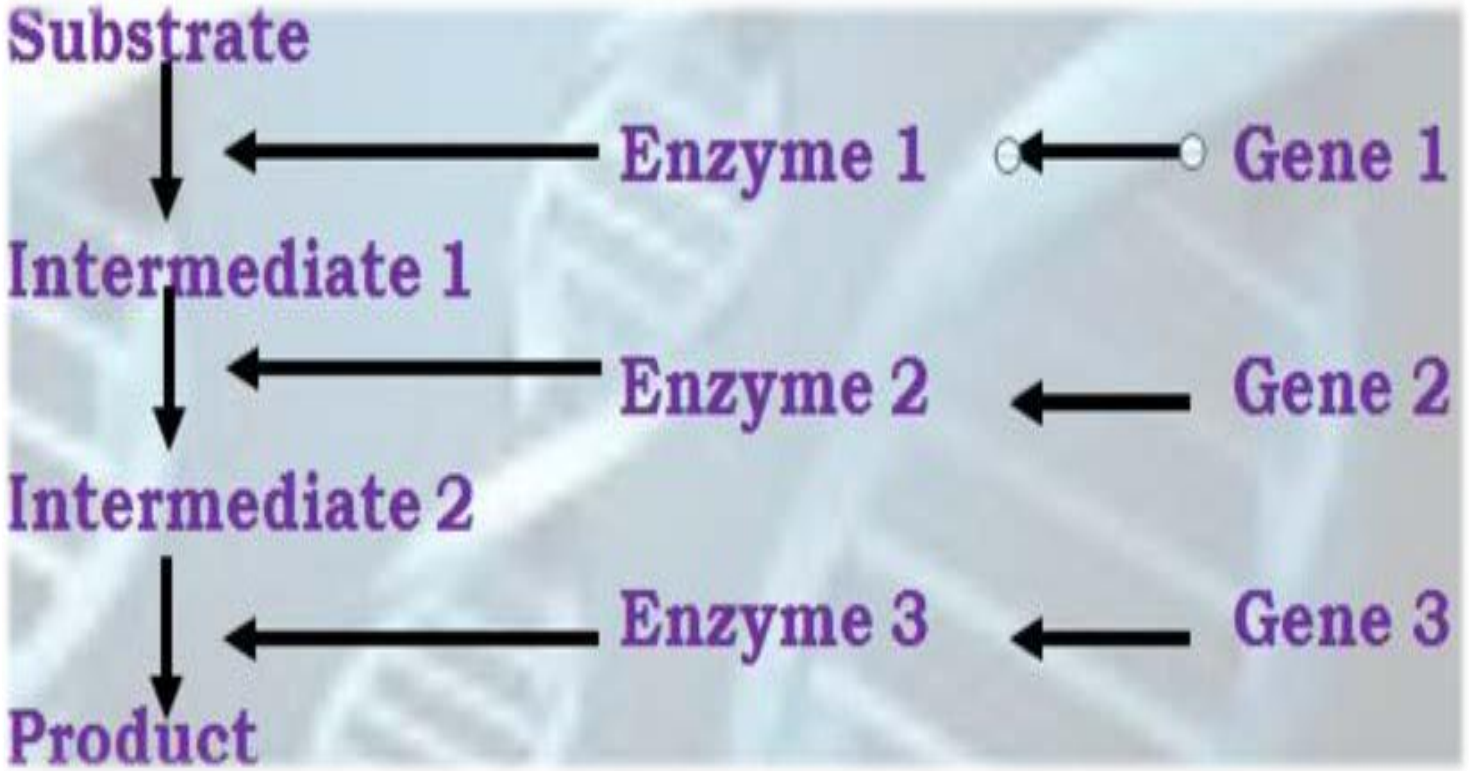


- **Type A blood has A antigens on the cell surface, and type B has B antigens on the surface. The i allele is recessive to both the A and the B alleles.**
- **In type AB blood, both the A and theB antigen are present on the cell surface. Thus, the A and the B alleles of the I gene are codominant.**
- **In type O blood, no antigen is present.**

Complementation:

(LO.2)

More than one gene can be involved in producing a phenotype

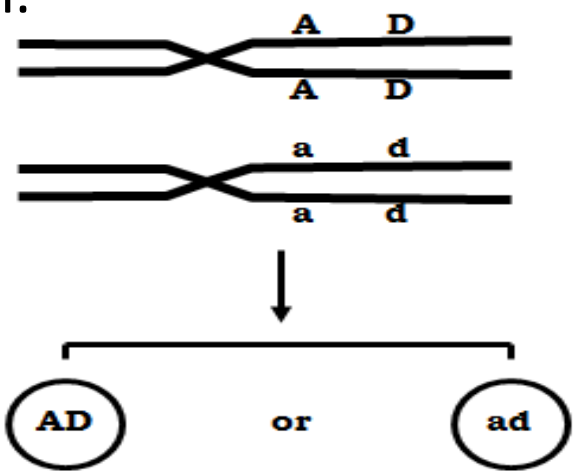


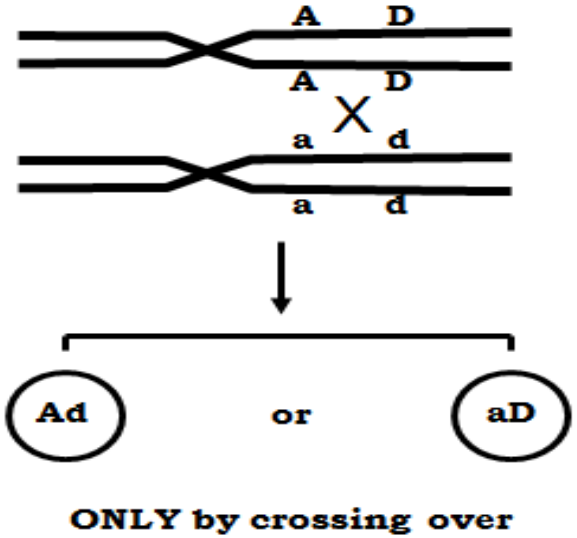
Describe the basis of the co-inheritance of certain traits

(LO.3)

Linkage and co-inheritance

- Genes on the same chromosome said to be **linked**, when these genes are close together.
- Linked genes do **not** show independent assortment at meiosis but tend to be **co- inherited.**
- The **frequency** of recombination between linked genes gives an indication of distance between them.
- The co-inheritance of two genes is **inversely** proportional to the distance between them.





ONLY by crossing over

Draw a family pedigree according to convention from a given family history.

Pedigree construction: is the fundamental method of genetic analysis in humans using family history to determine how a trait is inherited and to estimate risk factors for family members.

Pedigree: A diagram listing the members and ancestral relationships in a family; used in the study of human heredity.

Pedigrees use a standardized set of symbols, some of which are shown in following figure:

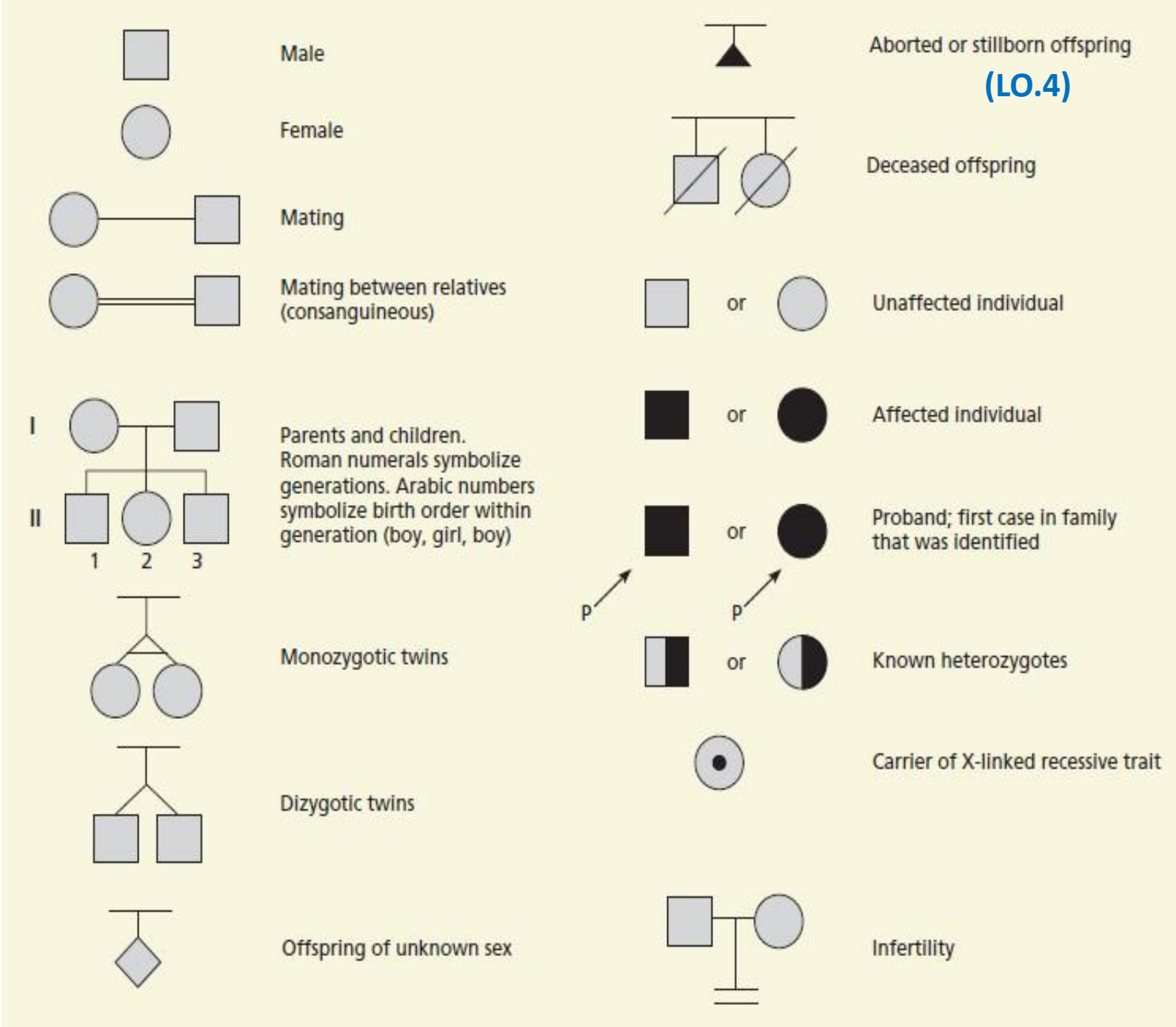
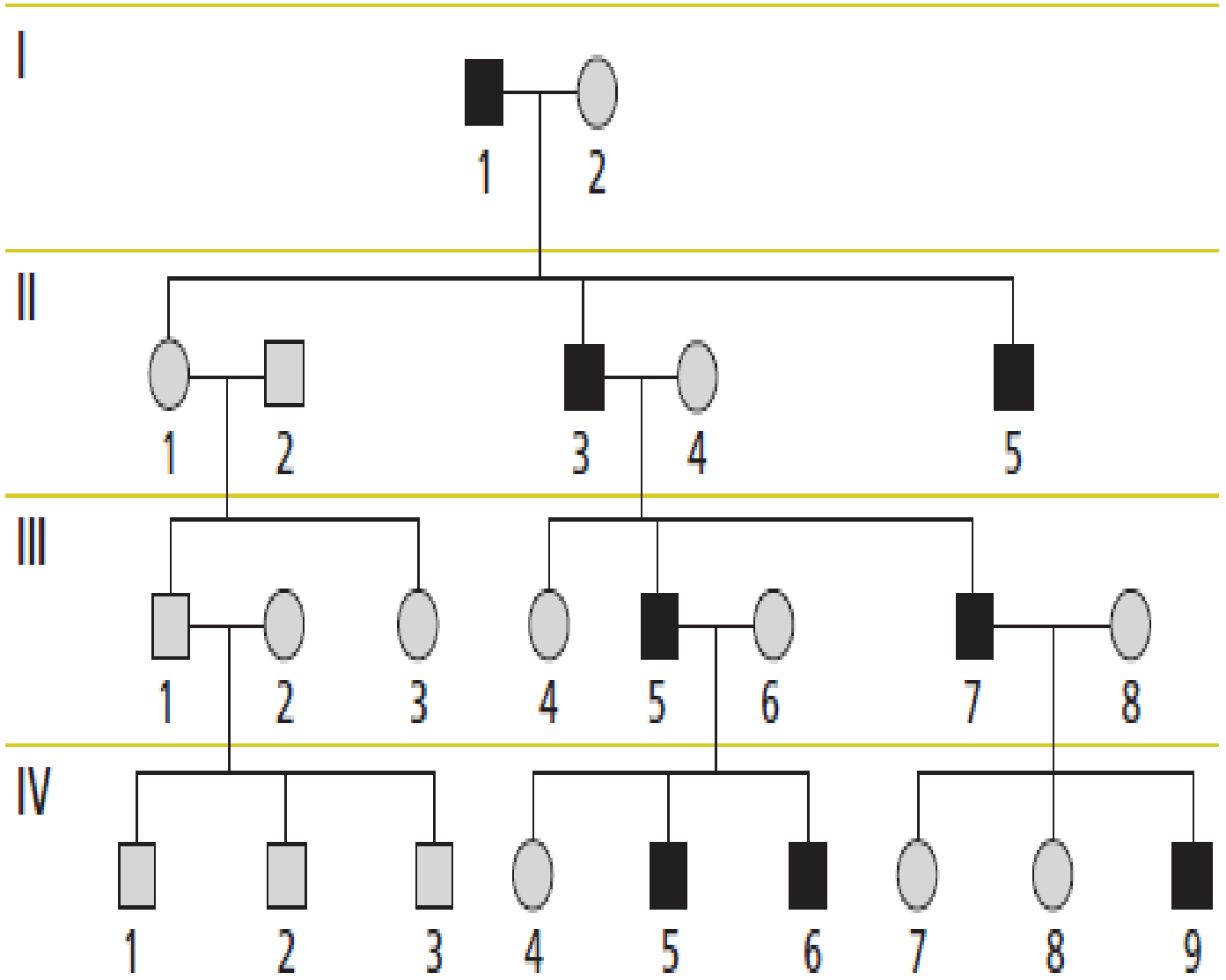


FIGURE 4.18 A pedigree for a Y-linked trait. These traits are transmitted from males to all male offspring in each generation.



KEEP IN MIND AS YOU READ

- Many human diseases are controlled by the actions of several genes.
- Environmental factors interact with genes to produce variations in phenotype.
- The genetic contribution to phenotypic variation can be estimated.
- Twin studies provide an insight into the genetic contribution to phenotypic variance.
- Many multifactorial traits have social and cultural impacts.

A numbering system is used in pedigree construction. Each generation is identified by a Roman numeral (I, II, III, and so on), and each individual within a generation is identified by an Arabic number (1, 2, 3, and so on): (LO.4)

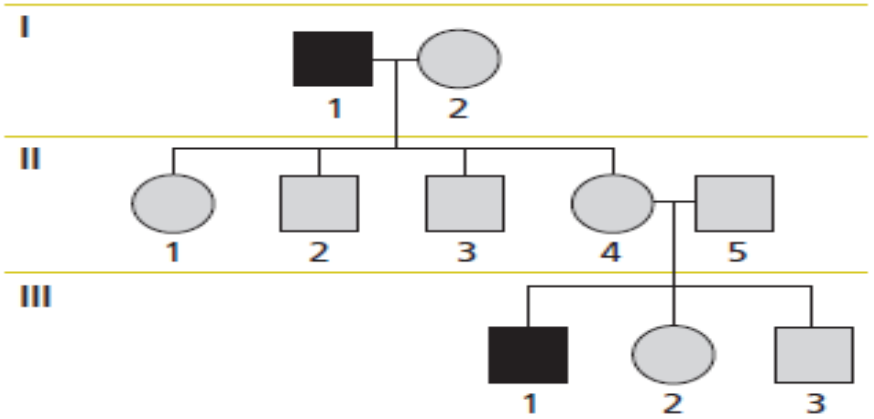
Pedigrees are often constructed after a family member afflicted with a genetic disorder has been identified. This individual, known as the proband, is indicated on the pedigree by an arrow and the letter P:

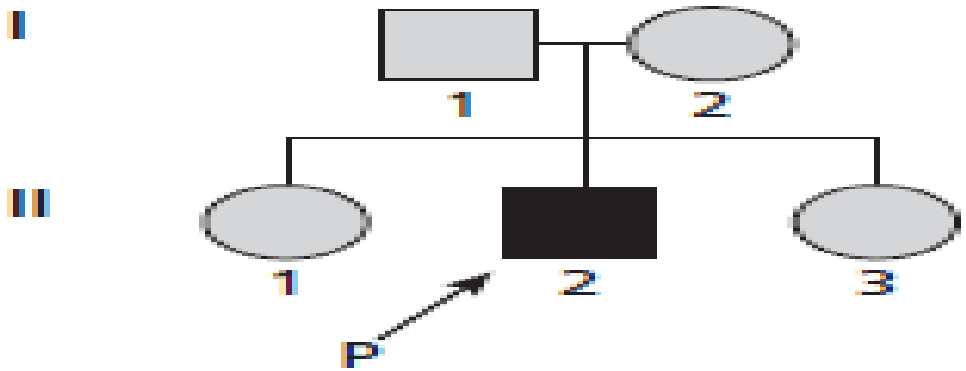
Analysis of pedigrees has two initial goals:

1. To determine whether the trait has a dominant or a recessive pattern of inheritance.
2. To discover whether the gene in question is located on an X or a Y chromosome or on an autosome (chromosomes 1 to 22).

If the pattern of inheritance can be established, it can be used to predict genetic risk in several situations, including:

1. Pregnancy outcomes.
2. Adult-onset disorders.
3. Recurrence risks in future offspring.





(LO.5)

(LO 6.10) Relate genetic information from a pedigree and describe the family concerned.

Small group session

(LO.6)

Use genetic data to calculate probability of inheritance and recombination frequency

Genetic Map

A graphic representation of the arrangement of genes or DNA sequences on a chromosome. Arrangement and distance between genes on a chromosome deduced from studies of recombination:

1 map unit = 1% recombination

Map unit or centimorgan (cM): is a measure of the genetic (or linkage) distance between two loci. If two loci are 1 cM apart, a crossover occurs between them on average only **once** in every **100** meiosis. Mapping more accurate when genes are close together.