# Modes of Heredity

autosomal recessive
autosomal dominant
X-linked recessive
X-linked dominant (very rare)
Y-linked

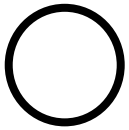
# Goals of Pedigree Analysis

1. Determine the mode of inheritance

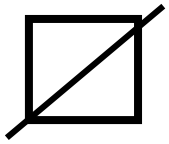
2. Determine the probability of an affected offspring for a given cross.

# Standard pedigree symbols

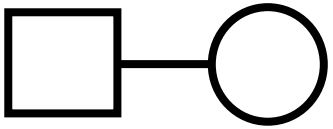
Male, affected



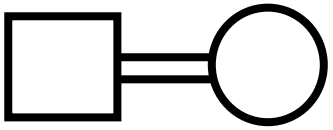
Female, unaffected



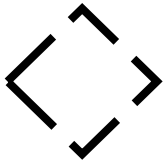
Male, deceased



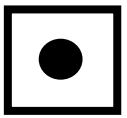
Mating



Consanguineous mating

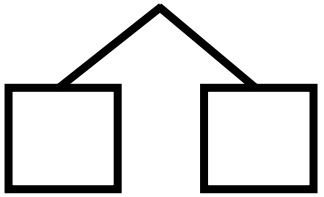


Pregnancy

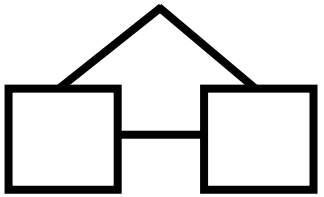


Male, heterozygous for autosomal recessive trait

Female, heterozygous for Autosomal or X-linked recessive trait



Dizygotic (non-identical) twins



Monozygotic (identical) twins

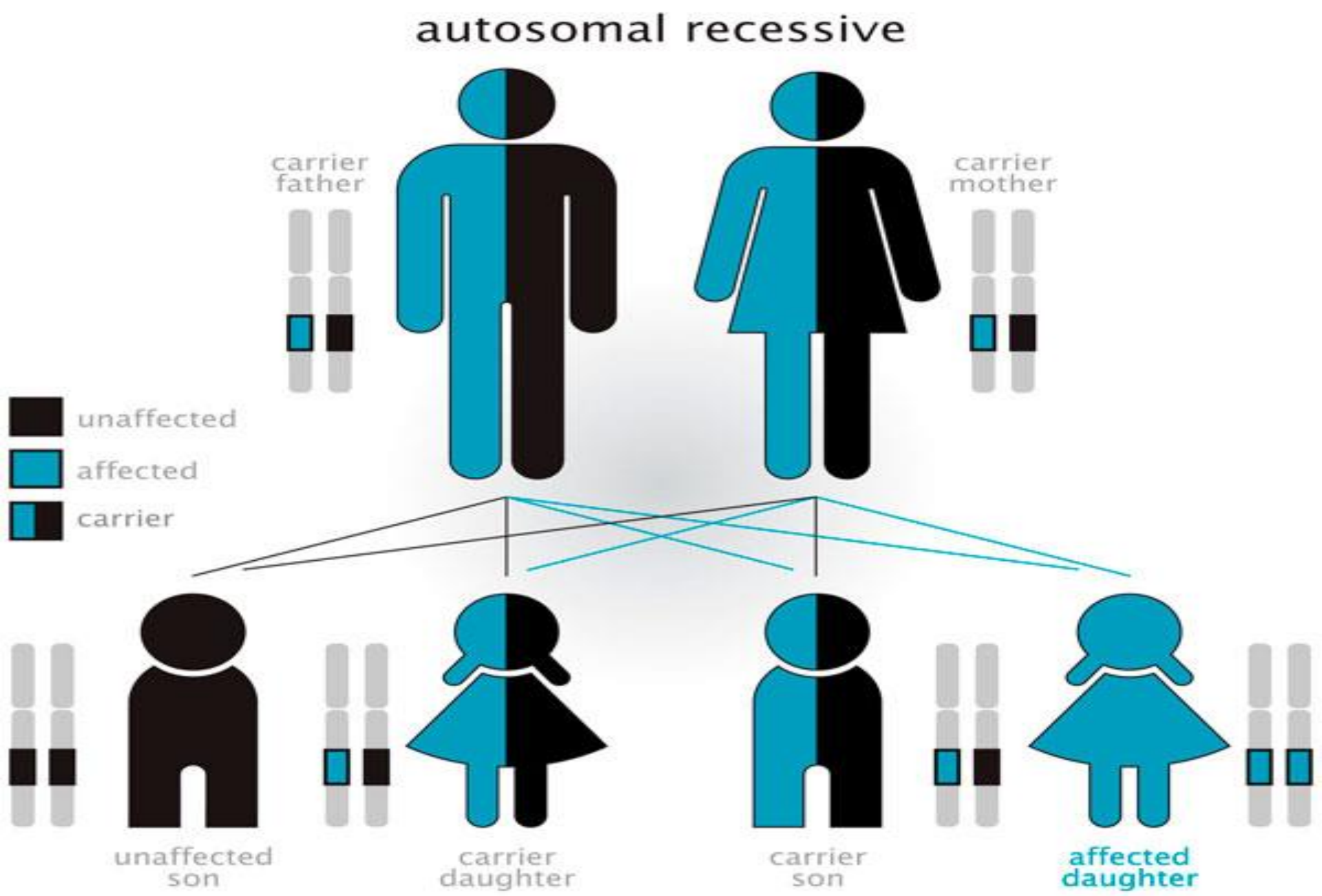
Spontaneous abortion or still birth

# Autosomal recessive

Affected persons must be homozygous for the disease allele

Thus, the usual mating is:

Aa x Aa




**autosomal recessive disorders, in which a person needs to inherit two copies of a mutant gene to be affected by the disorder.**

# Features of recessive pedigrees:

**Usually see “skipped” generations.**

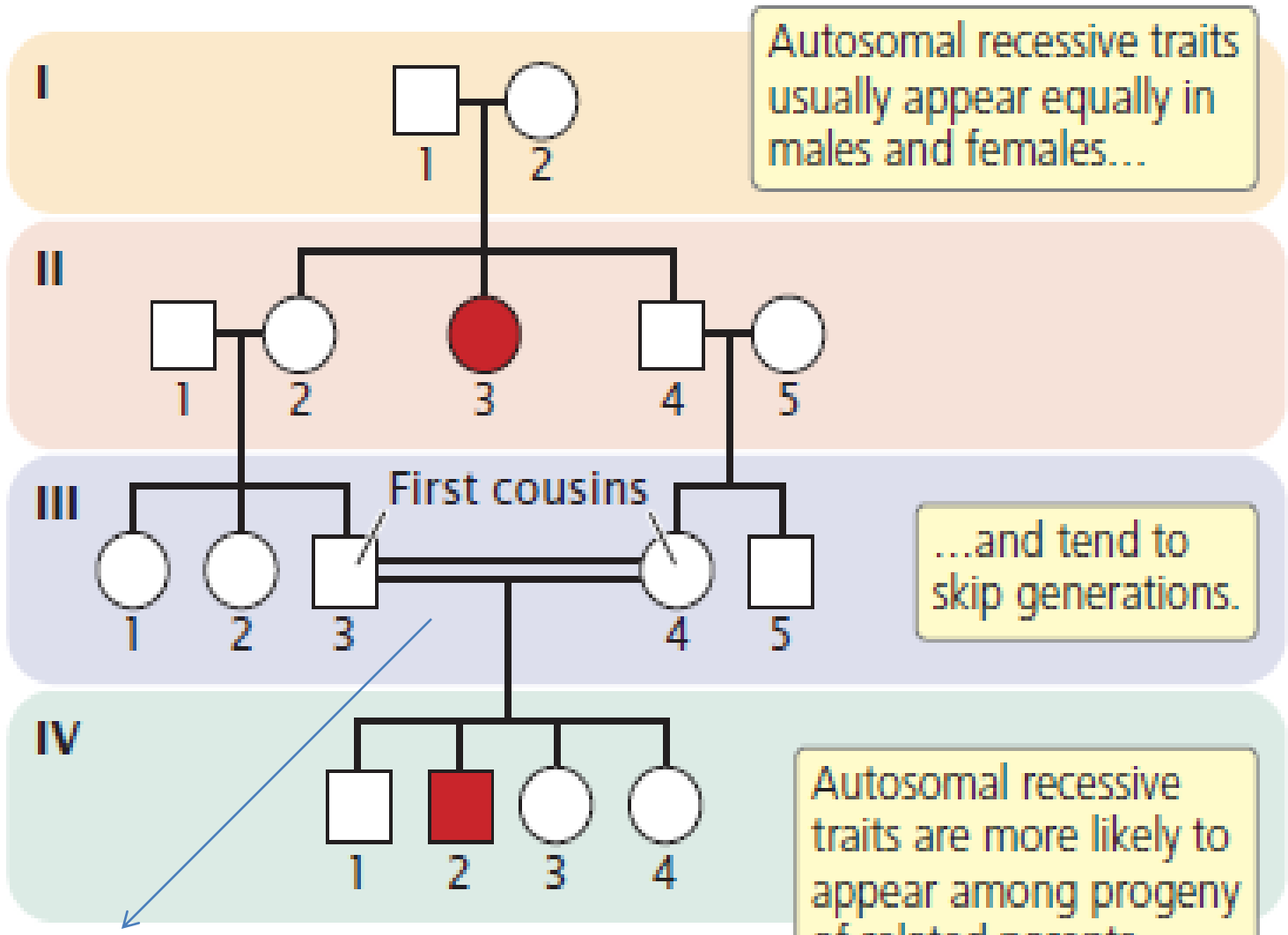
**Both males and females are affected.**

**Diseased offspring from normal parents**

**Expect increased consanguinity between the parents.**

**That is, the parents are more likely to be relatives**

**.**

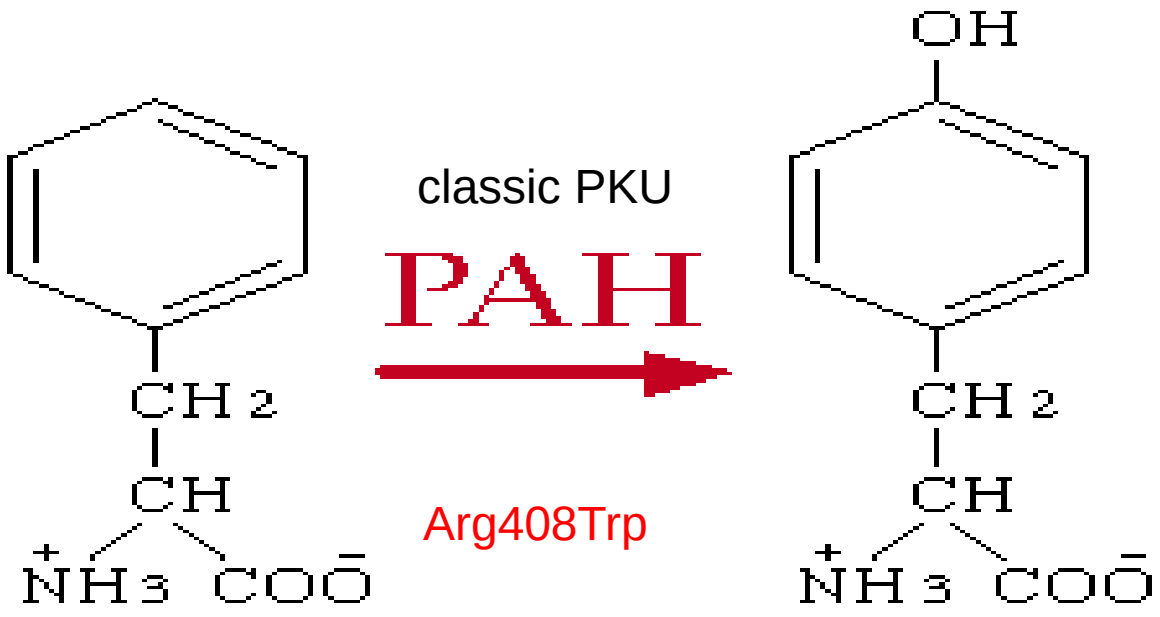

I
1
2
II
1
2
3
4
5
III
First cousins
1
2
3
4
5
IV
1
2
3
4
Autosomal recessive traits usually appear equally in males and females…
…and tend to skip generations.
Autosomal recessive traits are more likely to appear among progeny of related parents.
1/4 of their children are expected to have the recessive trait.

# Examples of autosomal recessive diseases

Sickle-cell anemia
Cystic fibrosis
Phenylketunuria(PKU).
Albinism
Thalassemia

Example:

PKU is a metabolic disorder caused by a deficiency of the liver enzyme **phenylalanine hydroxylase**. It prevents normal metabolization of phenylalanine. Phenylalanine builds up in the body to toxic levels, causing mental retardation




L-Phenylalanine

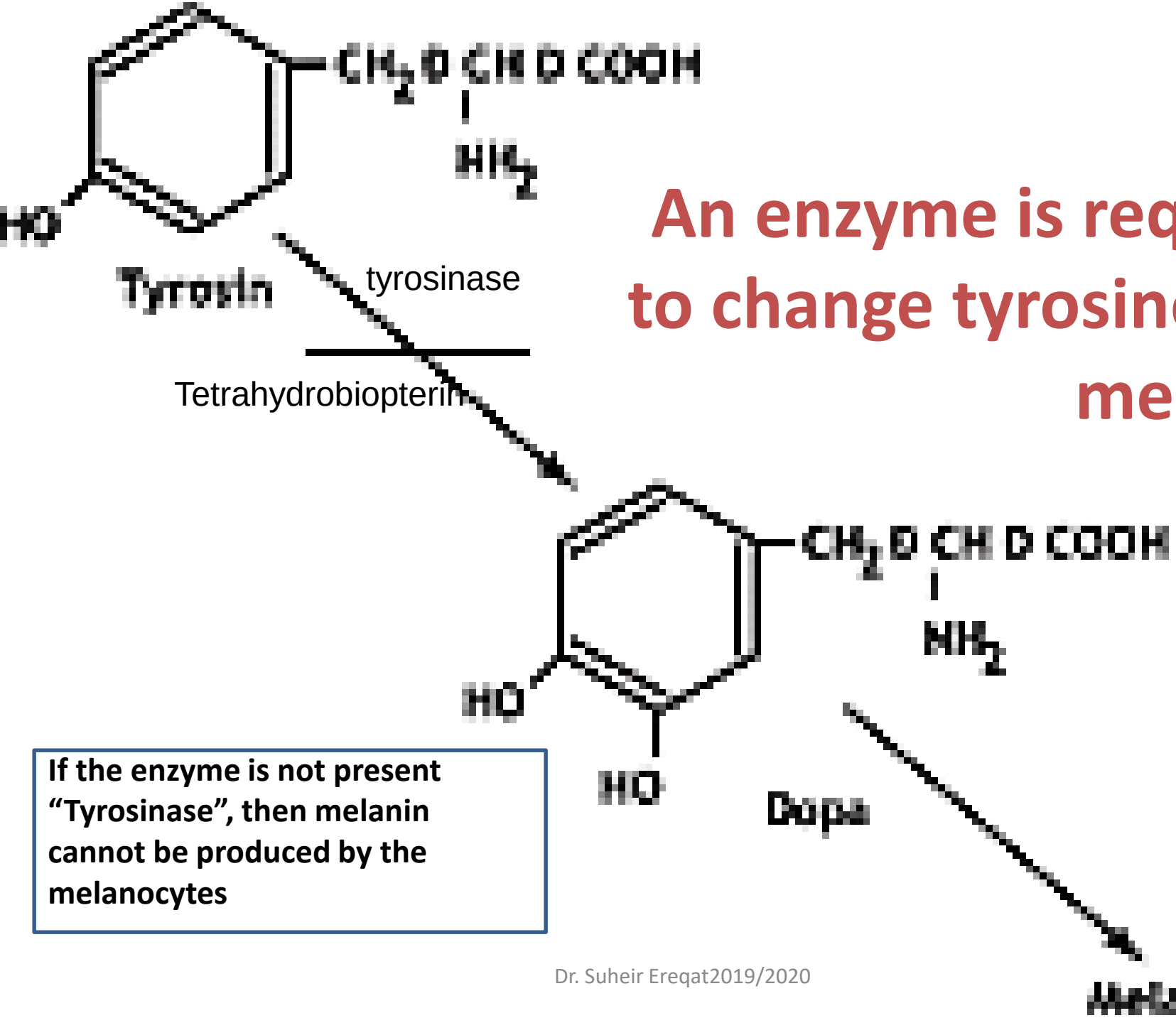
L-Tyrosine

Phe to Tyr Conversion =newborn screening program

# Albinism

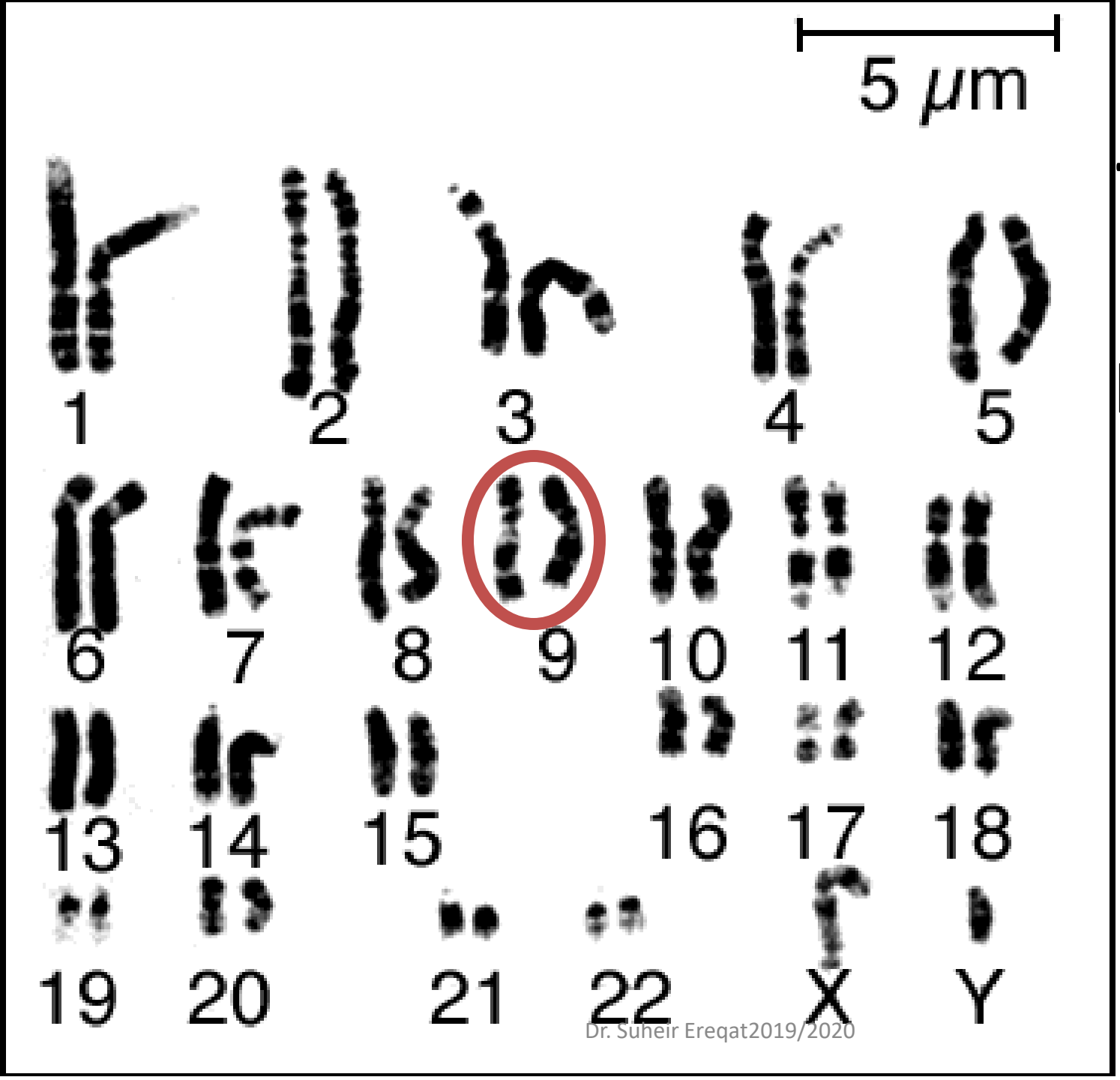
**To be albino, both genes must be albino genes**

photophobia, nystagmus,
ultraviolet radiation > the risk of melanomas

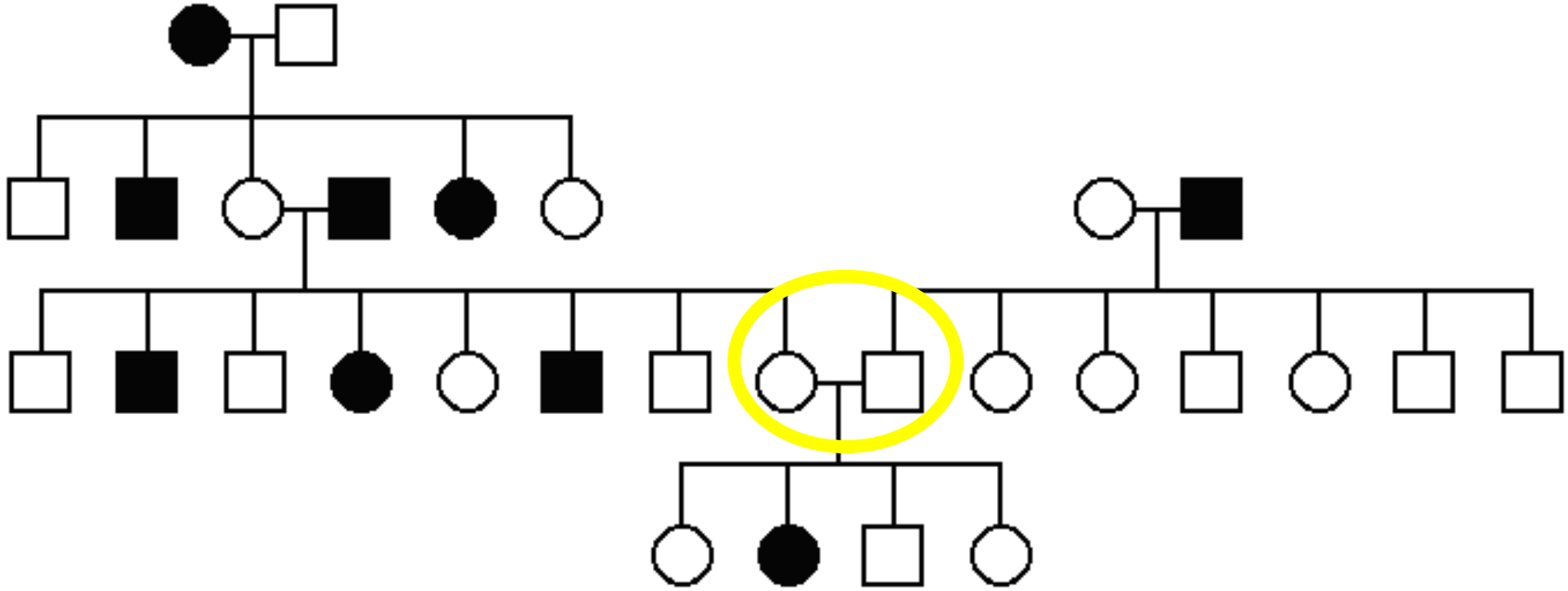



# An enzyme is required to change tyrosine into melanin.

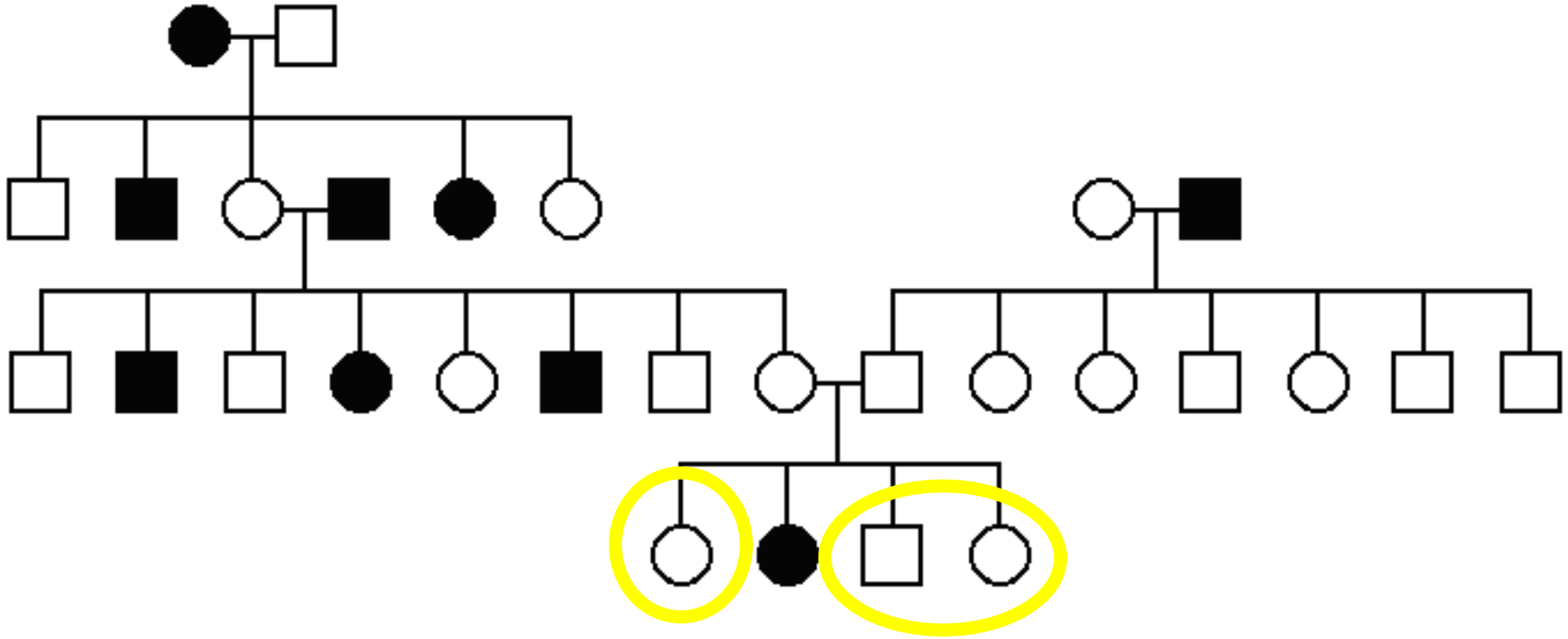
**If the enzyme is not present "Tyrosinase", then melanin cannot be produced by the melanocytes**




**The gene that produces this enzyme is on chromo-some 9**



**The parents in the circle have normal pigment.**



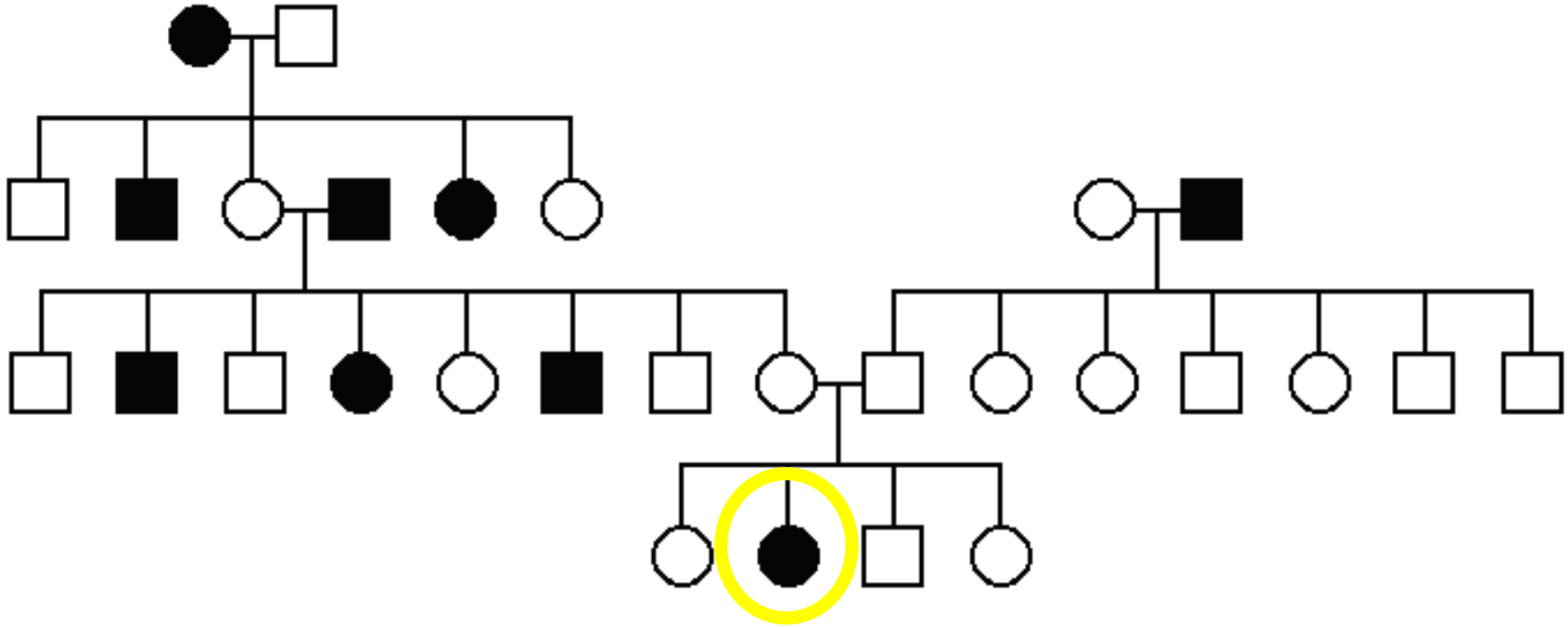
# Most of the offspring received at least one normal gene from a parent.

What is the probability of having a child with normal pigmentation (AA or Aa)= 1/4+2/4=3/4

What is the probability of a normal child to be a carrier= 2/3

# II. Probability methods

**Addition Rule: “either ,or”**
**Multiplication Rule: “And”**



**But one female offspring received an albino gene from both the mother and the father.**

What is the probability of having a child with albinism=1/4

What is the probability of having three children ,all with albinism
1/4x1/4x1/4=1/64

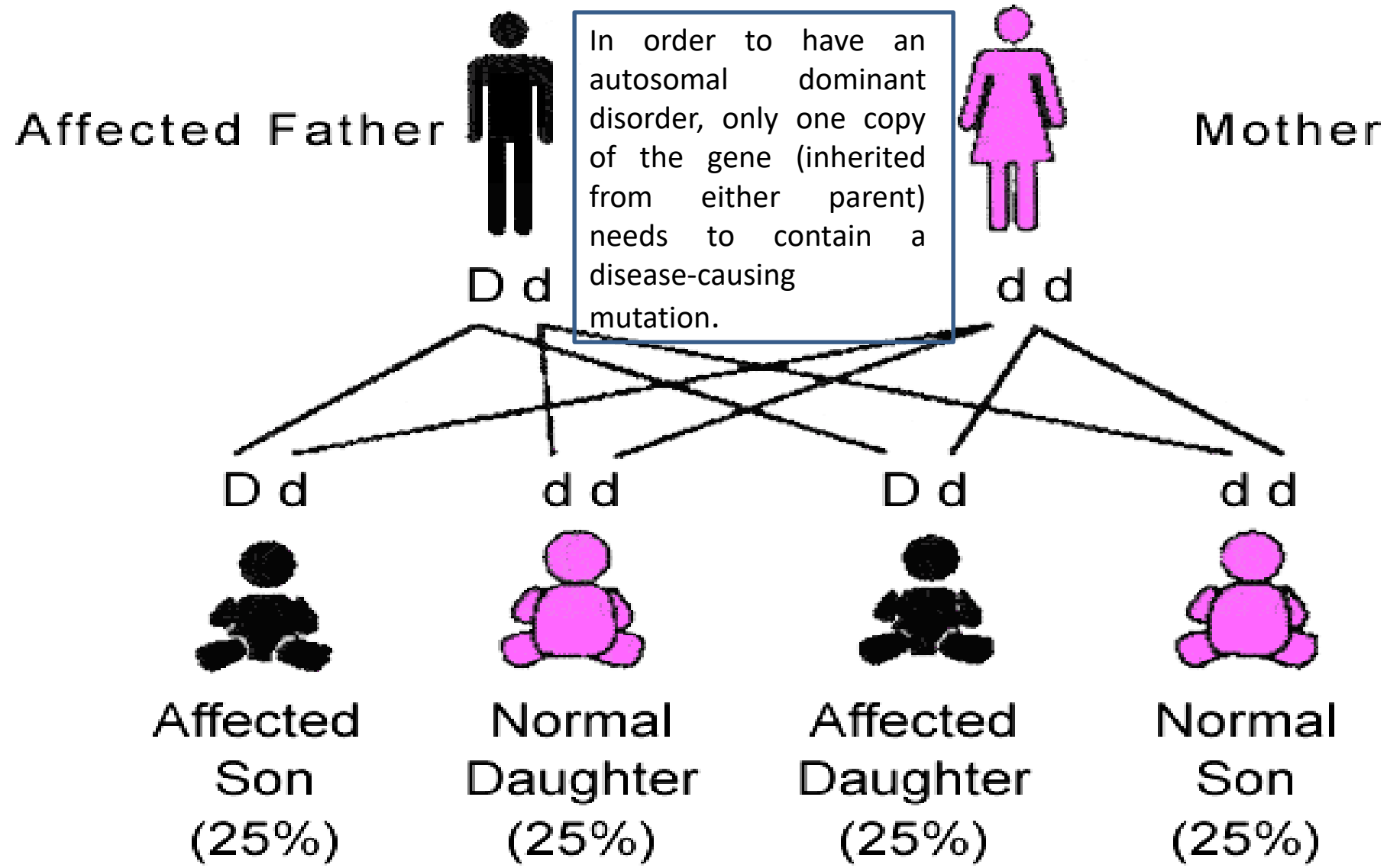
# Autosomal Dominant

the autosomal dominant allele is rare,

Affected individual more likely heterozygous.
Homozygous most likely fail to survive

# Autosomal Dominant Inheritance

## (One Parent Affected)



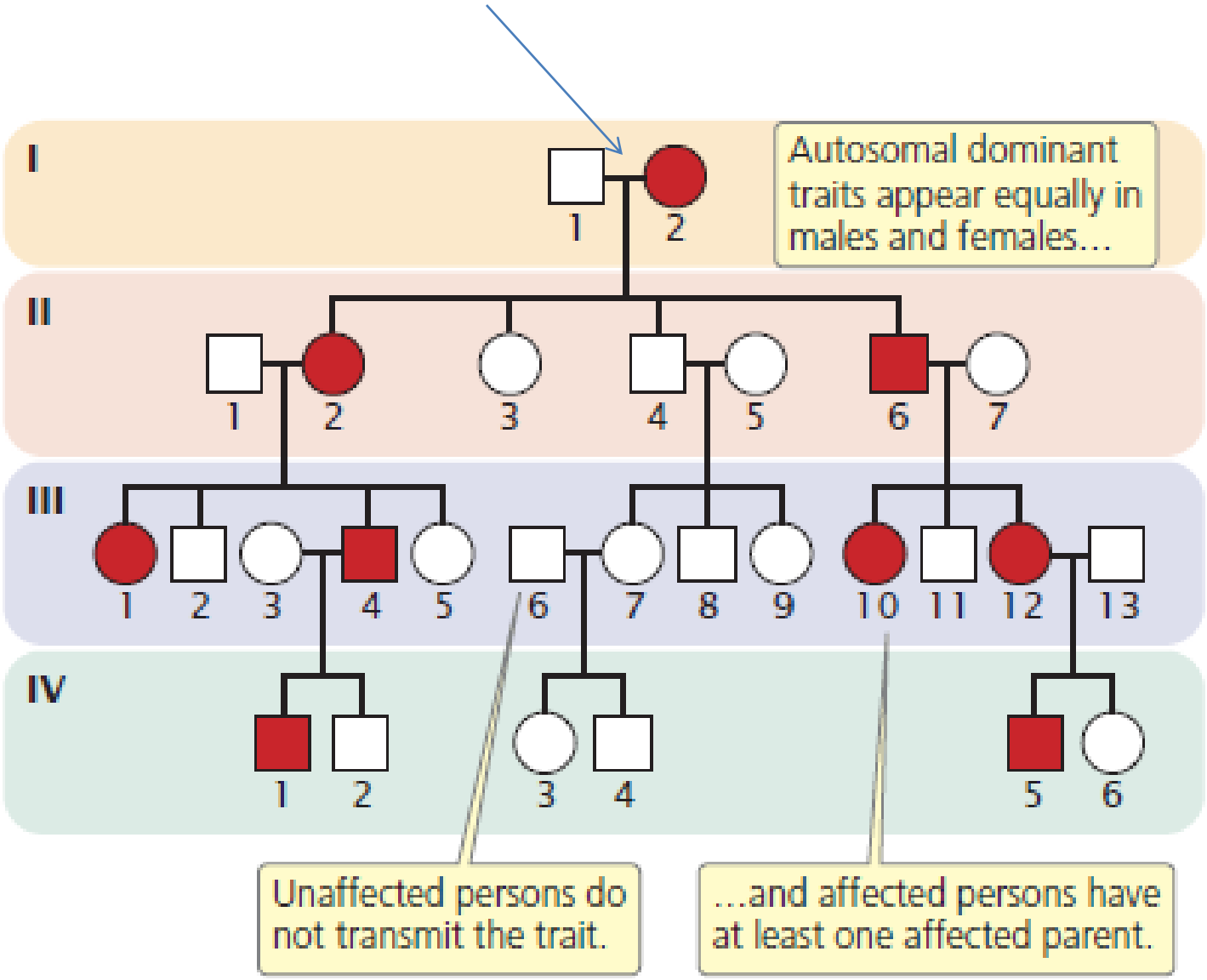
# Features of dominant pedigrees:

Males and females are equally affected.

**Phenotype tend to appear in every generation.**

**Affected offspring have at least affected parent**.

1/2 of the offspring will be affected.



# Autosomal dominant disorders

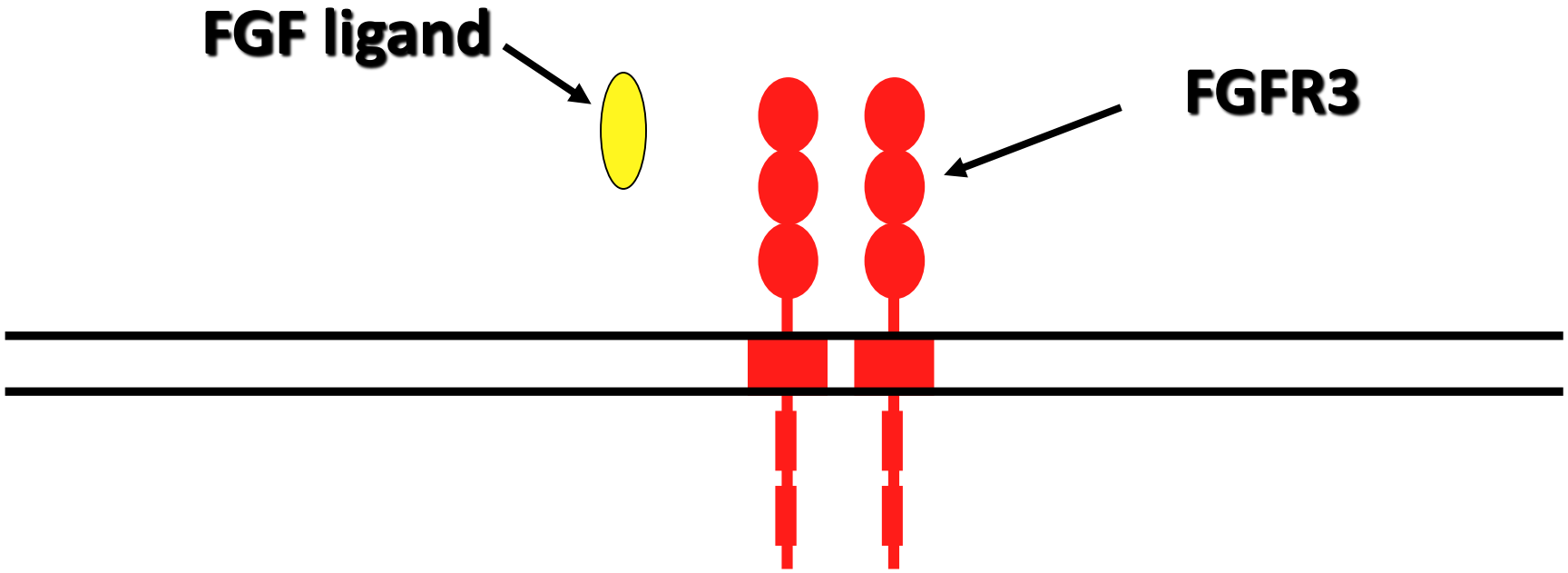
Huntigton disease.
Familial hypercholesterolemia.
Achondroplasia

# Example: Achondroplasia

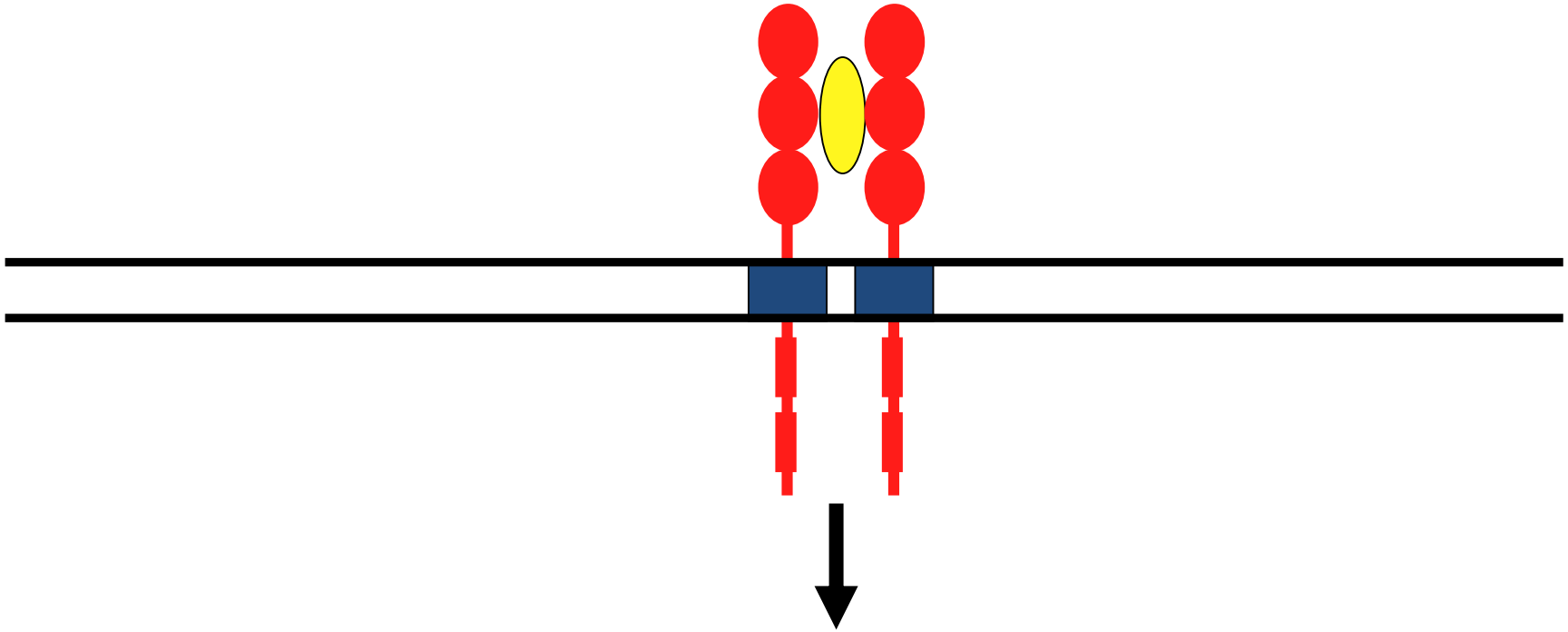
- Short limbs, a normal-sized head and body, normal intelligence

100% penetrance.
caused by Gly380Arg mutation in the Fibroblast growth factor receptor 3(**FGFR3**) gene

# Normal FGFR3 signaling



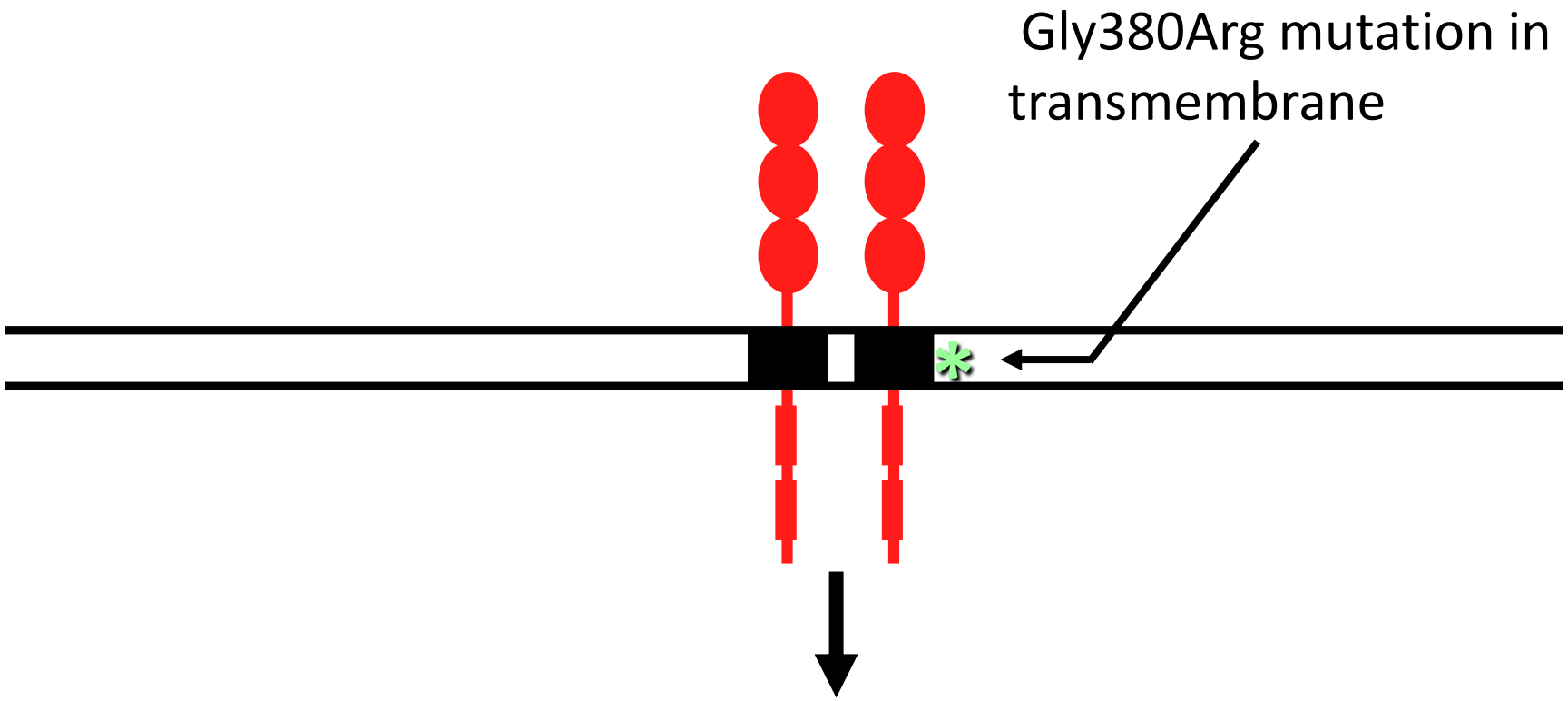
# Normal FGFR3 signaling



## Inhibition of cartilage growth

limiting the formation of bone from cartilage(ossification)

# Achondroplasia




- Receptor signals in absence of ligand
- Bone growth attenuated

# X-linked traits:

X-linked recessive

X-linked dominant

# Mammalian Sex Determination

- Sex determination depends on the presence or absence of a single gene, *SRY*, found on the Y chromosome

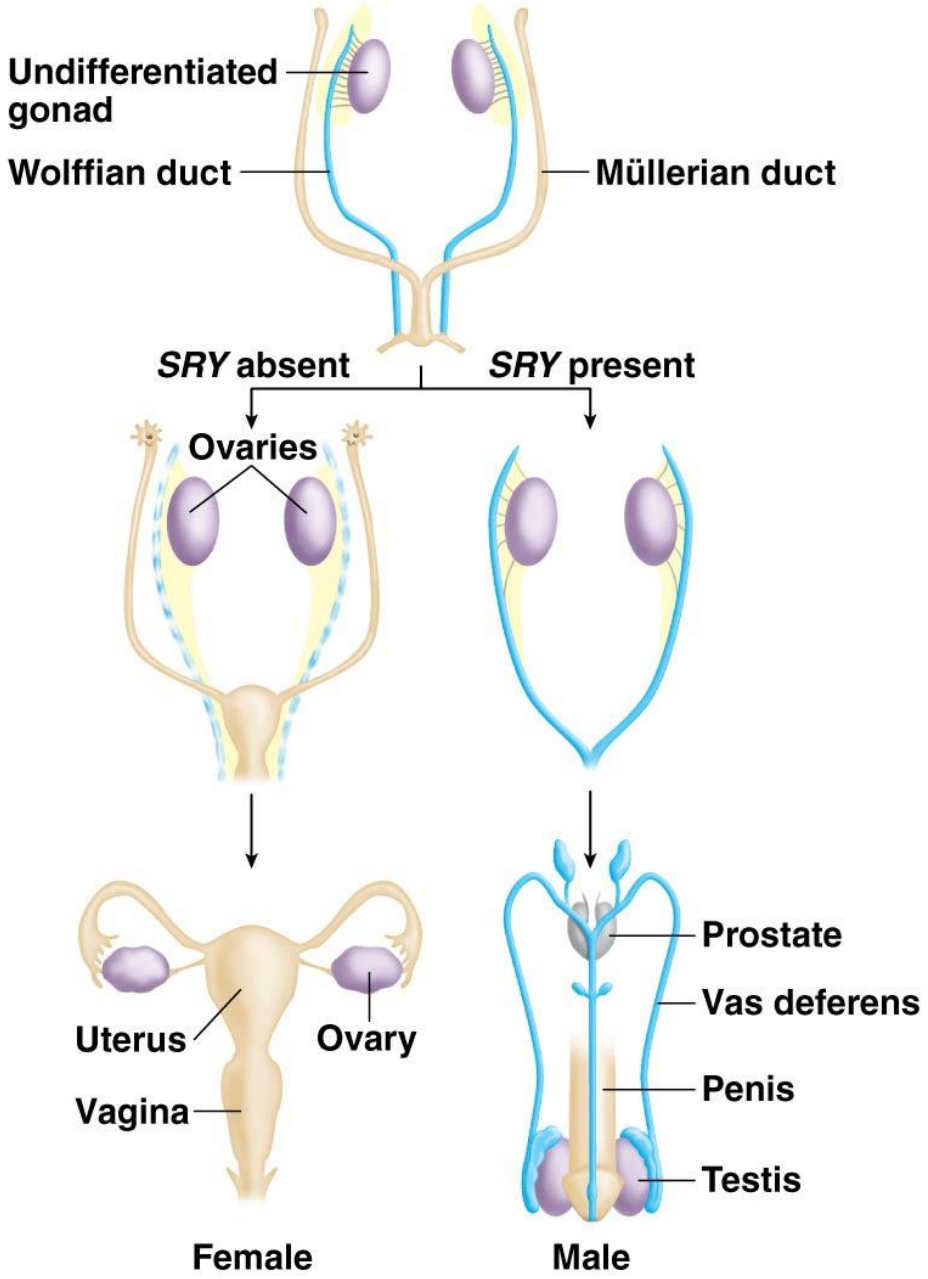
- *SRY* is a transcription factor needed for male-specific gene expression

# the primary determinant of sex in human embryos :*SRY*

- Early mammalian embryos have clusters of tissue called undifferentiated gonads, which can develop as ovaries or testes

- Expression of *SRY* initiates testicular development of the undifferentiated gonads

- The absence of *SRY* expression allows the default, female state, to develop

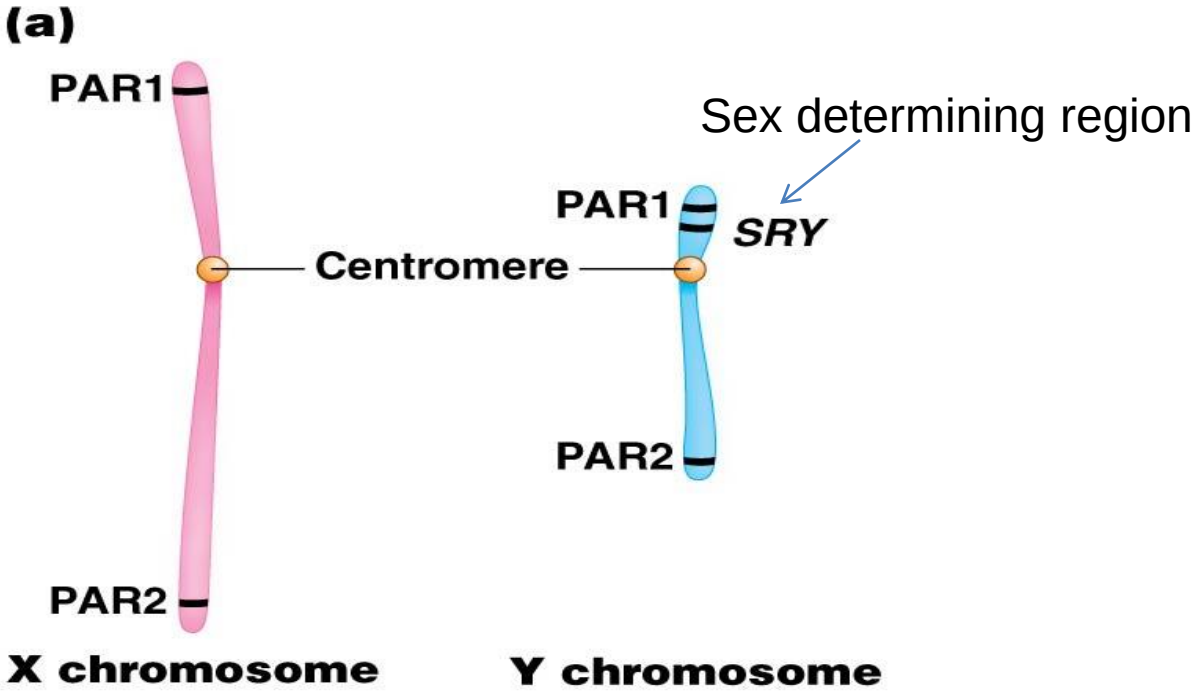

Undifferentiated gonad
Wolffian duct
Müllerian duct
SRY absent
SRY present
Ovaries
Uterus
Ovary
Vagina
Prostate
Vas deferens
Penis
Testis
Female
Male

# The Pseudoautosomal Region

- Two small regions of homology, the **pseudoautosomal regions** (PAR1 and PAR2), exist between the X and Y chromosomes

- These allow homologous pairing between the X and Y at meiosis

- There is evidence that crossing over occurs within these regions during meiosis


(a)
PAR1
PAR2
X chromosome
Centromere
PAR1
SRY
PAR2
Y chromosome
Sex determining region

# X-linked recessive

**more frequently in males than in females, WHY?**

Males have only one X chromosome. A single recessive gene on that X chromosome will cause the disease

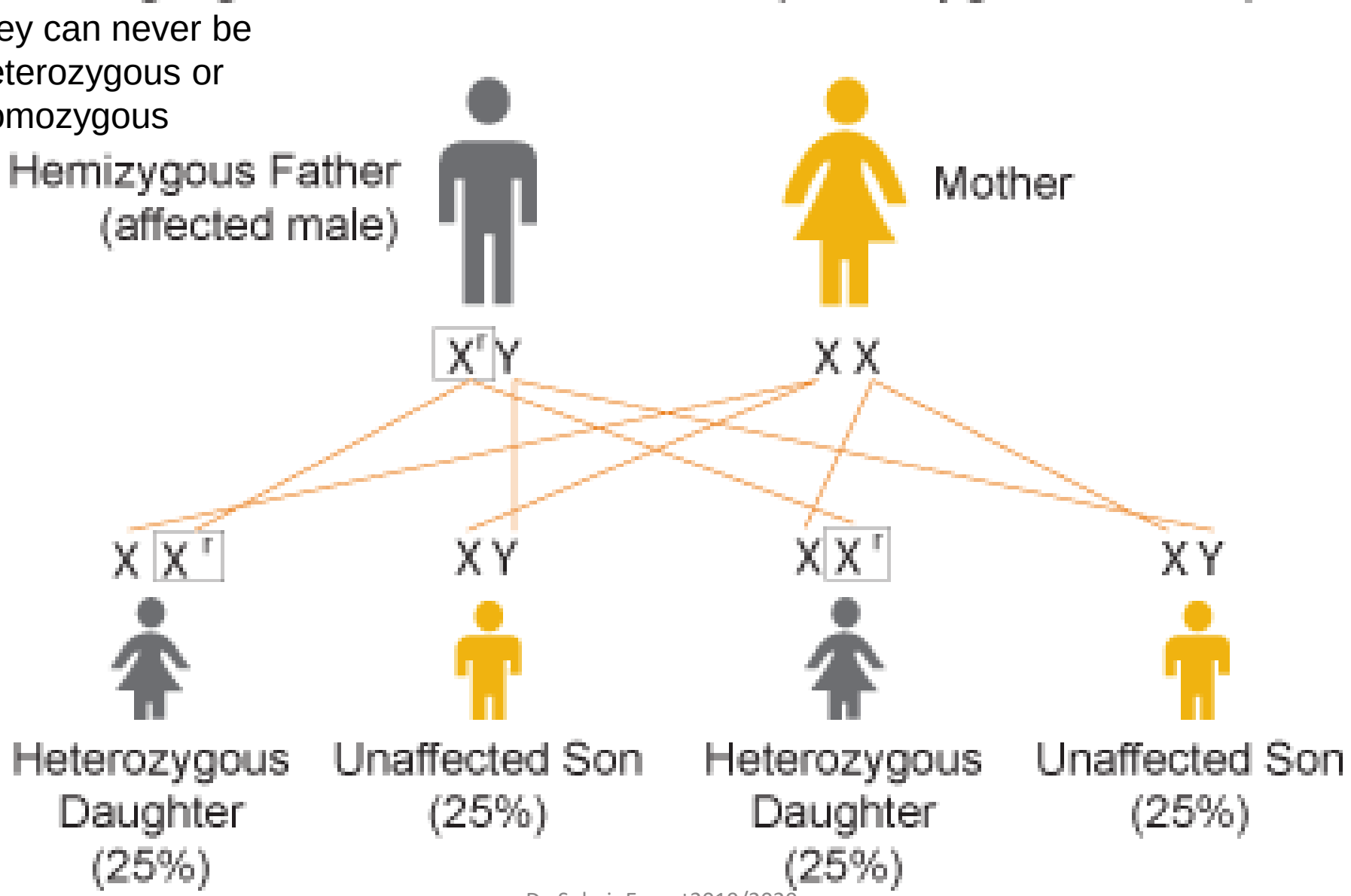
**affected males are usually born to unaffected mothers who are carriers, the trait skips generations.**

**not passed from father to son, WHY?**

Males take only one y chromosome from their father

# X-linked recessive

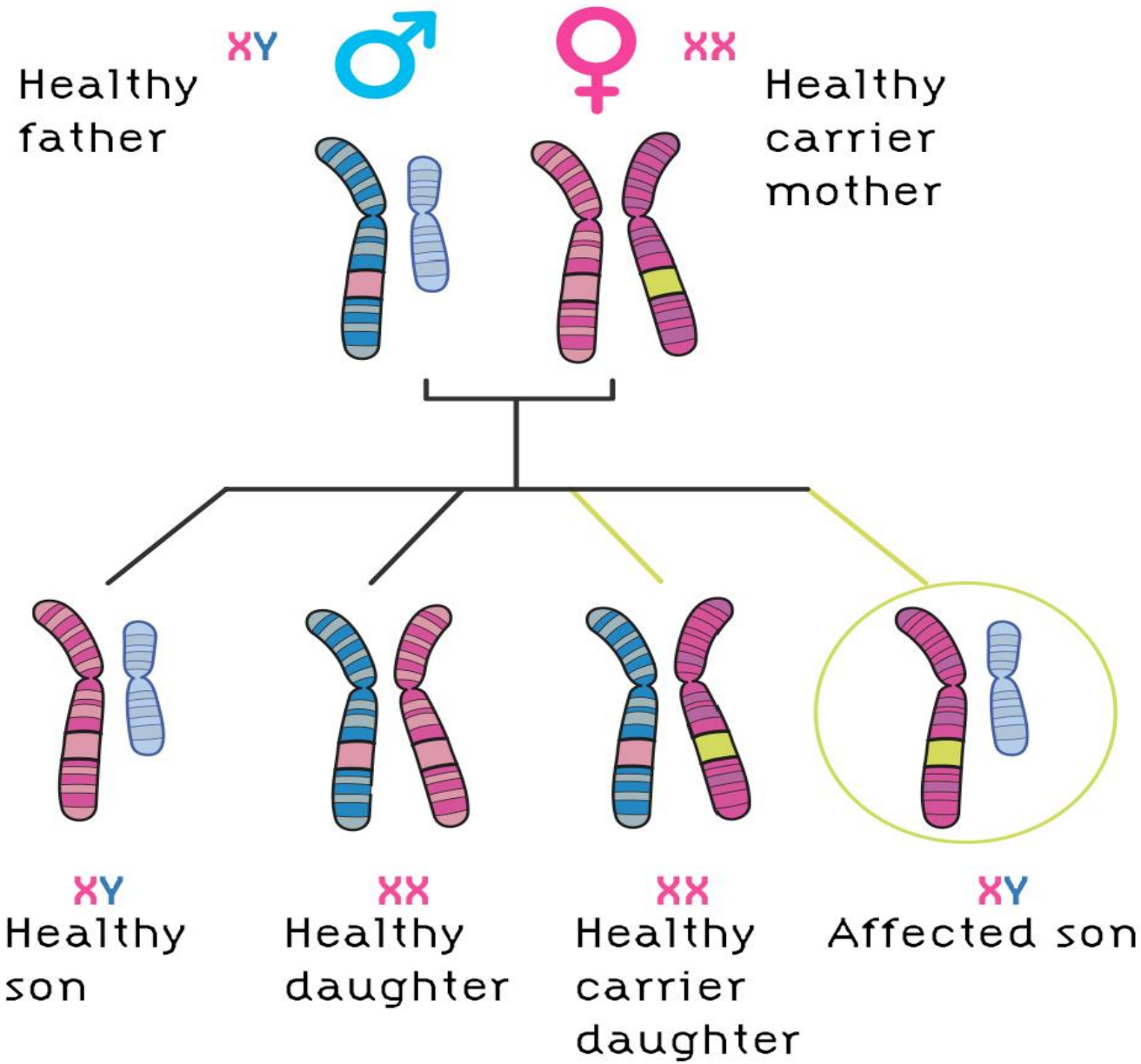
they can never be heterozygous or homozygous



3

# X-linked recessive

| | X | X |
|---|---|---|
| X | XX | XX |
| Y | XY | XY |
| | | |



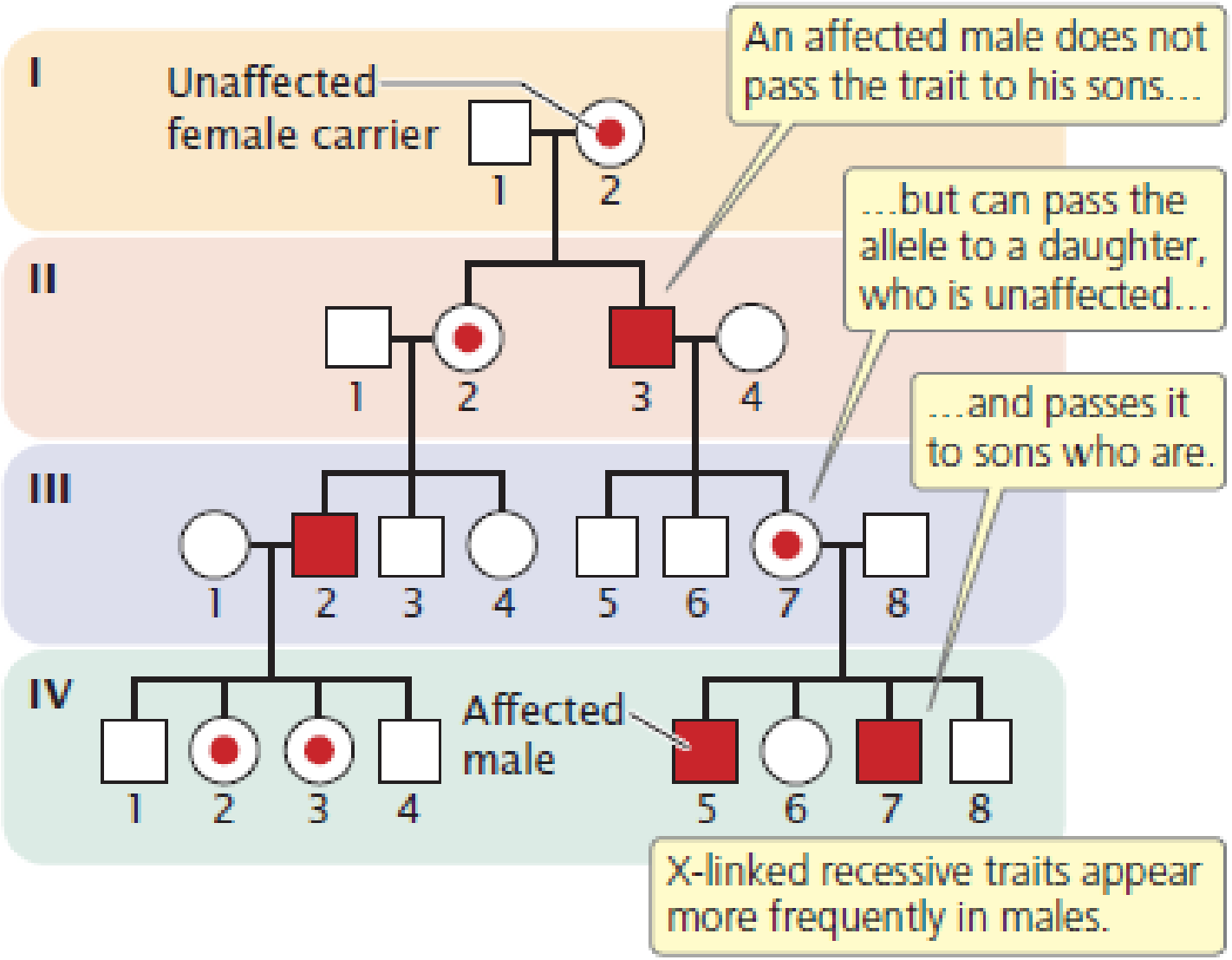

Ex : myopathie de Duchenne, hémophilie A

# Keep in Mind

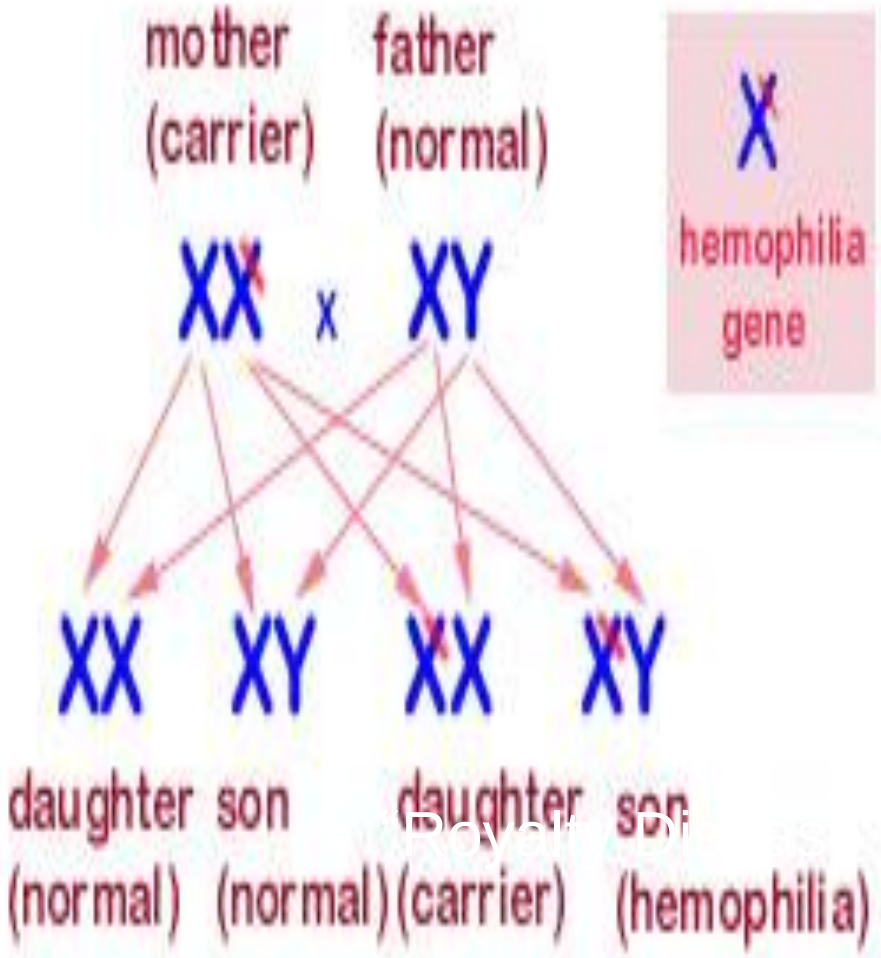
**X-linked traits in males=They are never carriers. A single dose of a mutant allele will produce a mutant phenotype in the male, whether the mutation is dominant or recessive.**

# Examples:

- Hemophilia A,
- Duchenne muscular dystrophy,
- color blindness


I
II
III
IV
Unaffected female carrier
Affected male
An affected male does not pass the trait to his sons...
...but can pass the allele to a daughter, who is unaffected...
...and passes it to sons who are.
X-linked recessive traits appear more frequently in males.

# Hemophilia




**Hemophilia A** is caused by a mutation in the factor VIII gene on the X chromosome

The mutant allele produces a nonfunctional blood-clotting protein

Normal plasma levels of FVIII range from 50% to 150%. Levels below 50%, or half of what is needed to form a clot, determine a person's symptoms.

•**Mild hemophilia A- 6% up to 49% of FVIII in the blood.** People with mild hemophilia Agenerally experience bleeding only after serious injury, trauma or surgery. In many cases, mild hemophilia is not diagnosed until an injury, surgery or tooth extraction results in prolonged bleeding. The first episode may not occur until adulthood. Women with mild hemophilia often experience menorrhagia, heavy menstrual periods, and can hemorrhage after childbirth.

•**Moderate hemophilia A. 1% up to 5% of FVIII in the blood.** People with moderate hemophilia A tend to have bleeding episodes after injuries. Bleeds that occur without obvious cause are called spontaneous bleeding episodes.

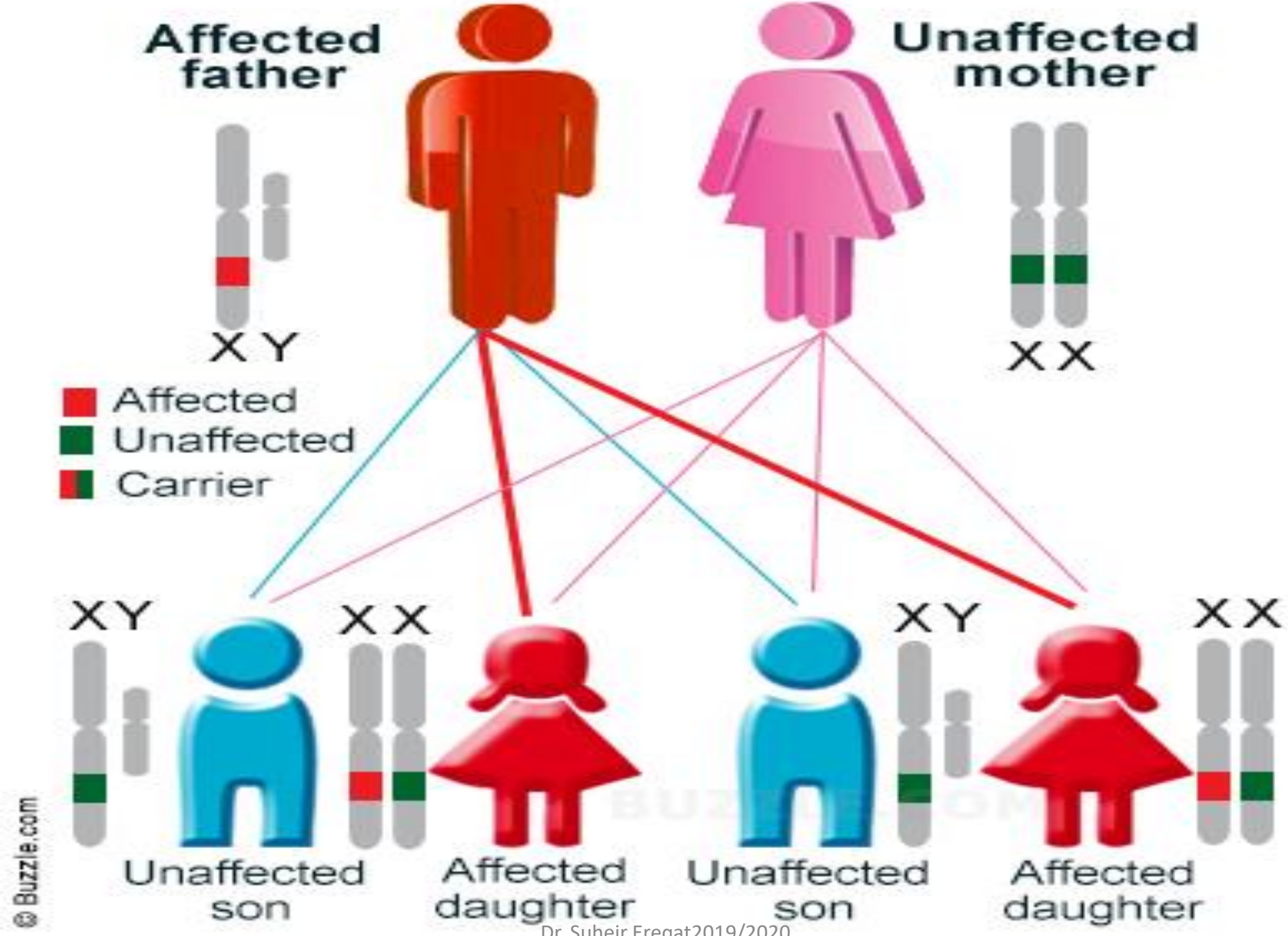
•**Severe hemophilia A. <1% of FVIII in the blood.** People with severe hemophilia A experience bleeding following an injury and may have frequent spontaneous bleeding episodes, often into their joints and muscles.

# X-linked dominant

If male is transmitting the disease then all of his daughter show the disease.

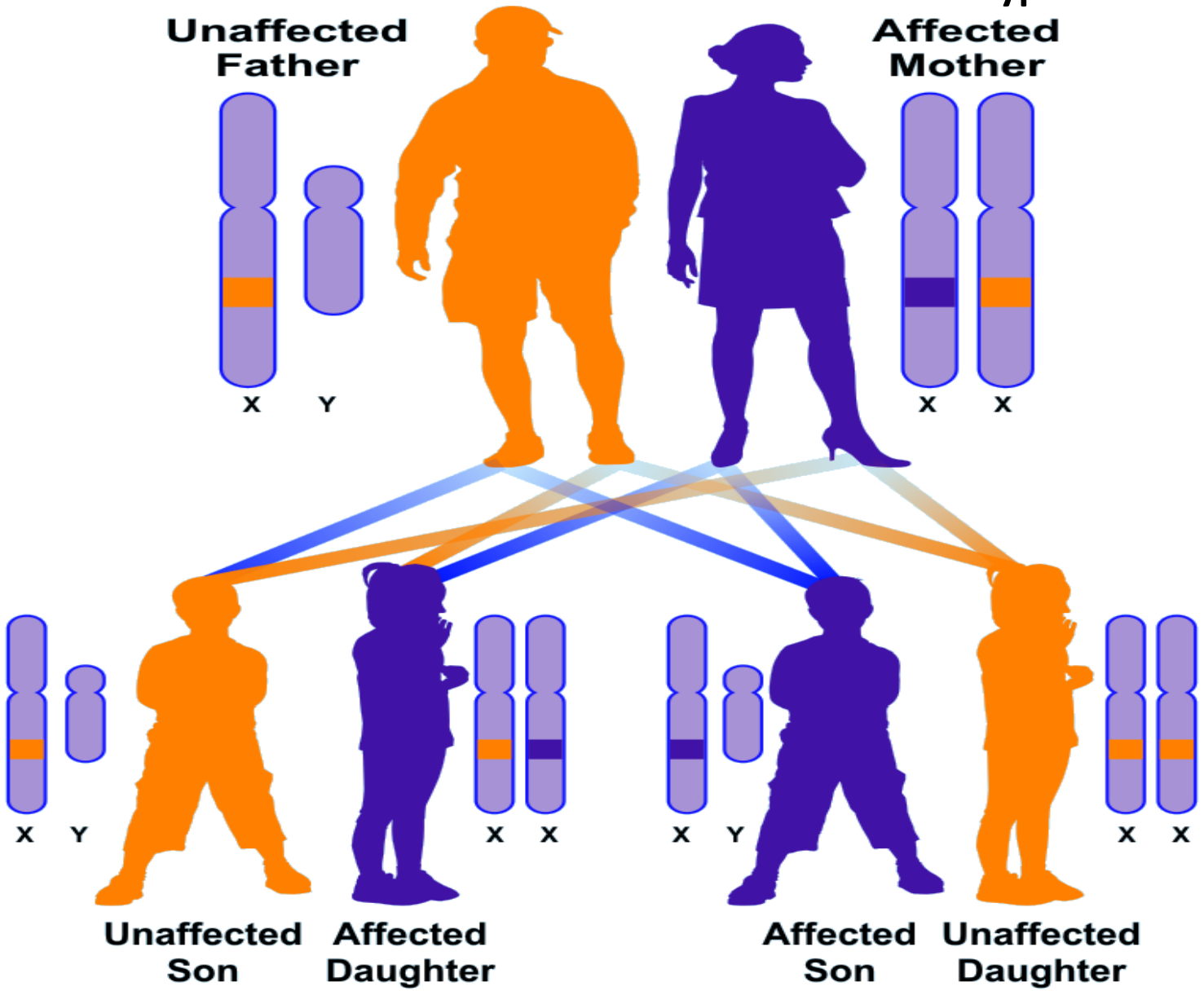
If female is transmitting the disease then half of her progeny (males and females show the disease. (if she is heterozygous)
OR all of her progeny show the disease if she is homozygous.

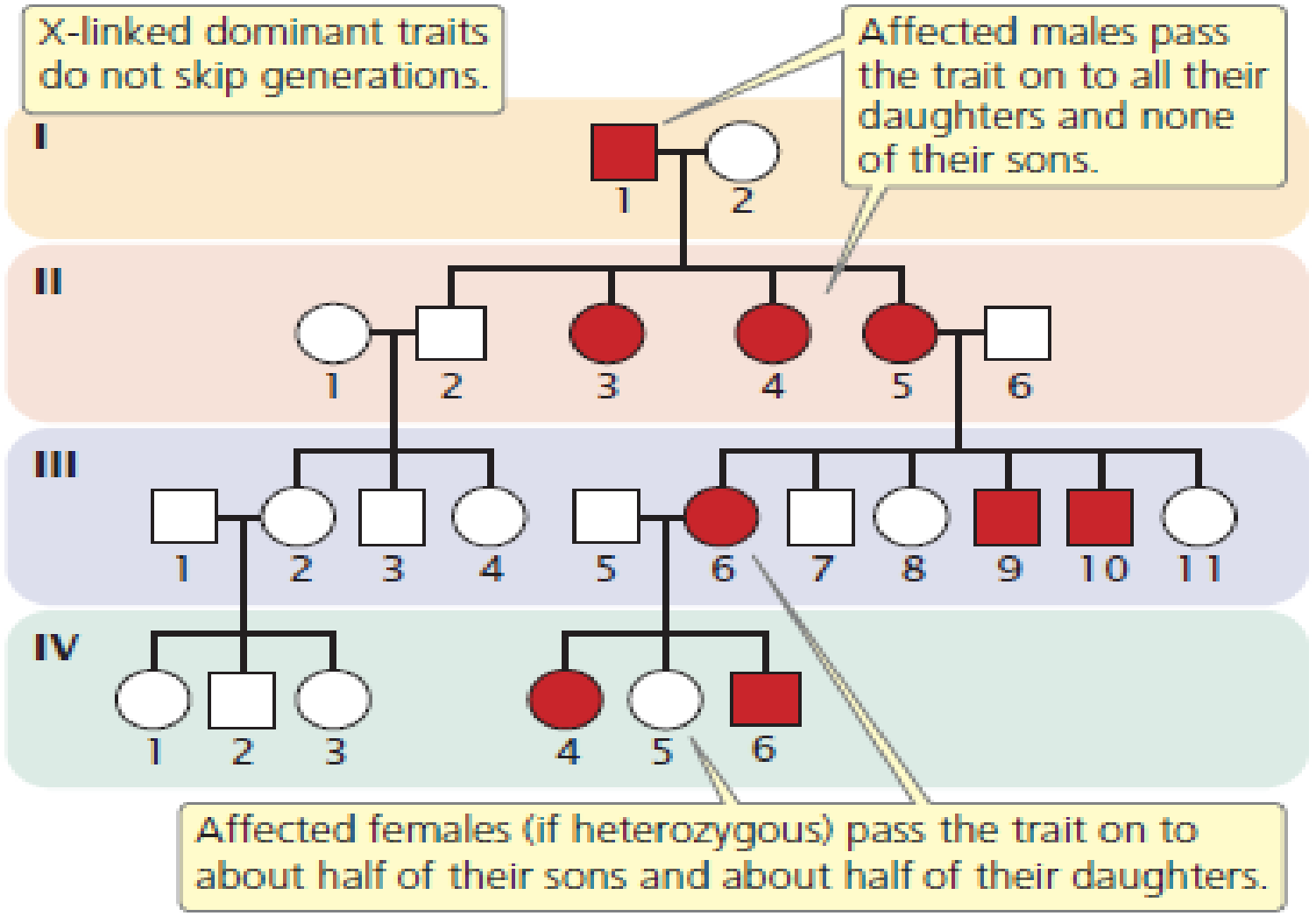
# X-linked dominant



# X-linked Dominant, Affected Mother

**it is less common than the X-linked recessive type.**



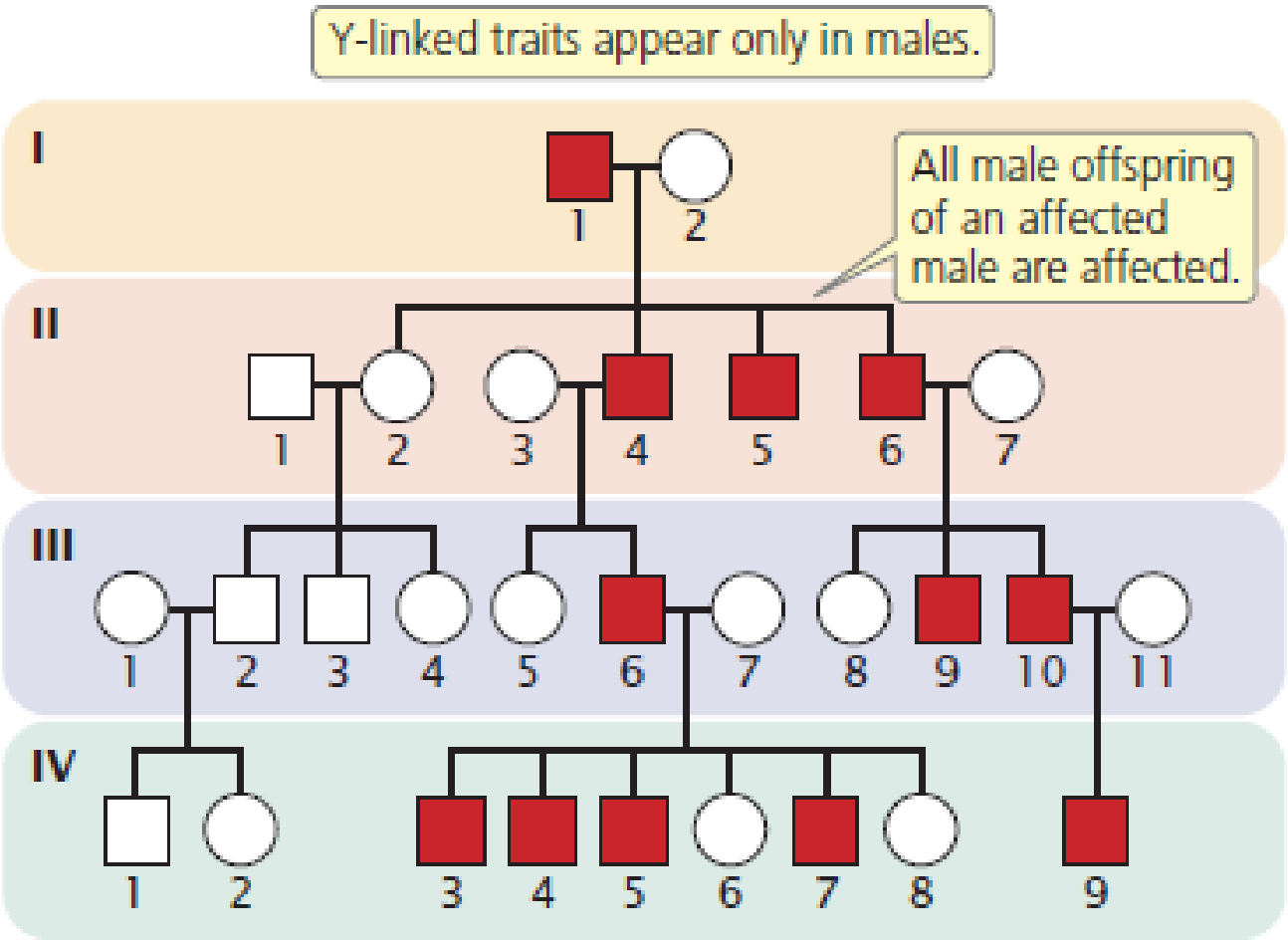



**6.9 X-linked dominant traits affect both males and females.** An affected male must have an affected mother.

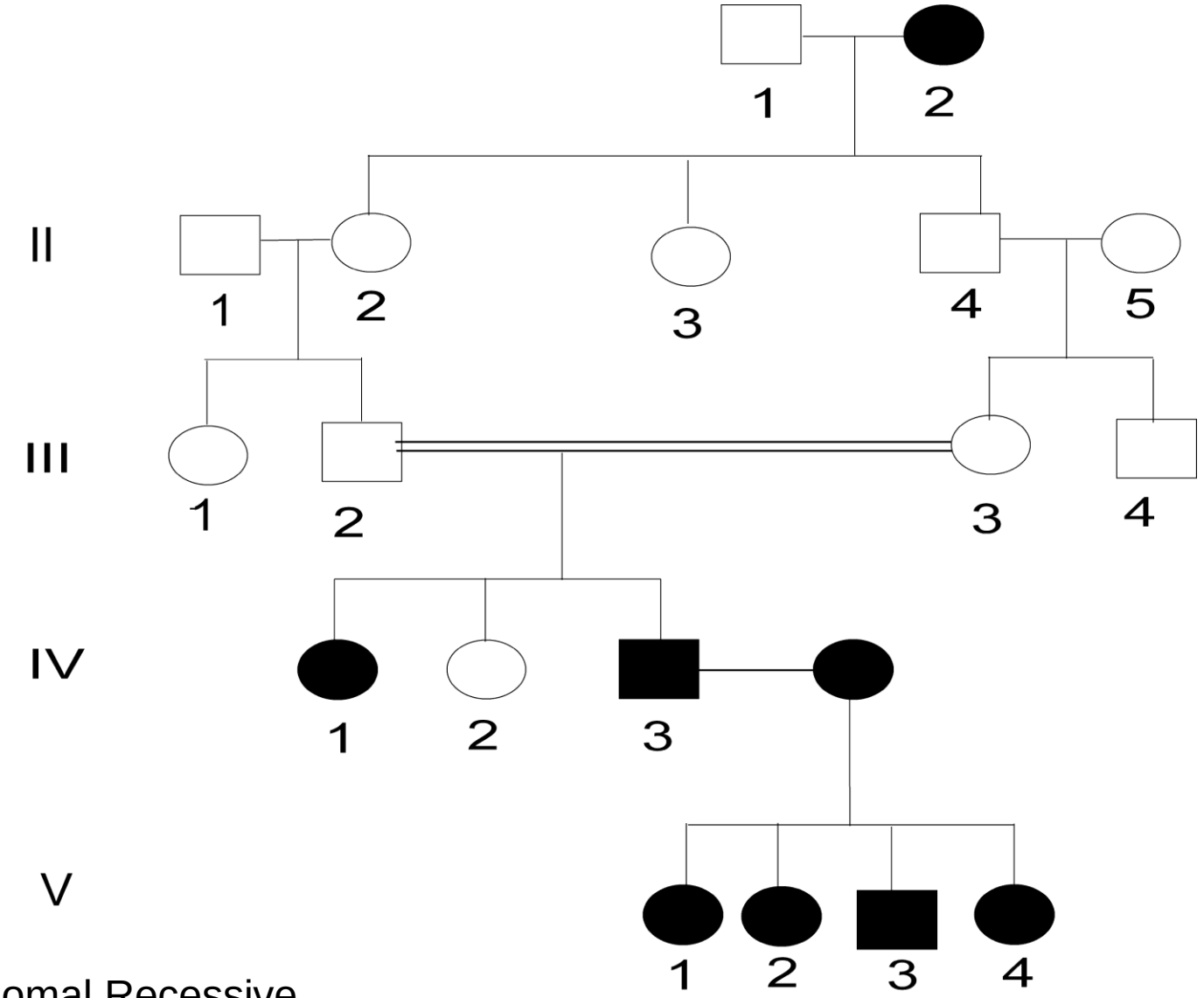
# Examples

Fragile-X Syndrome: with variable expressivity and possibly reduced penetrance

# Y-linked traits

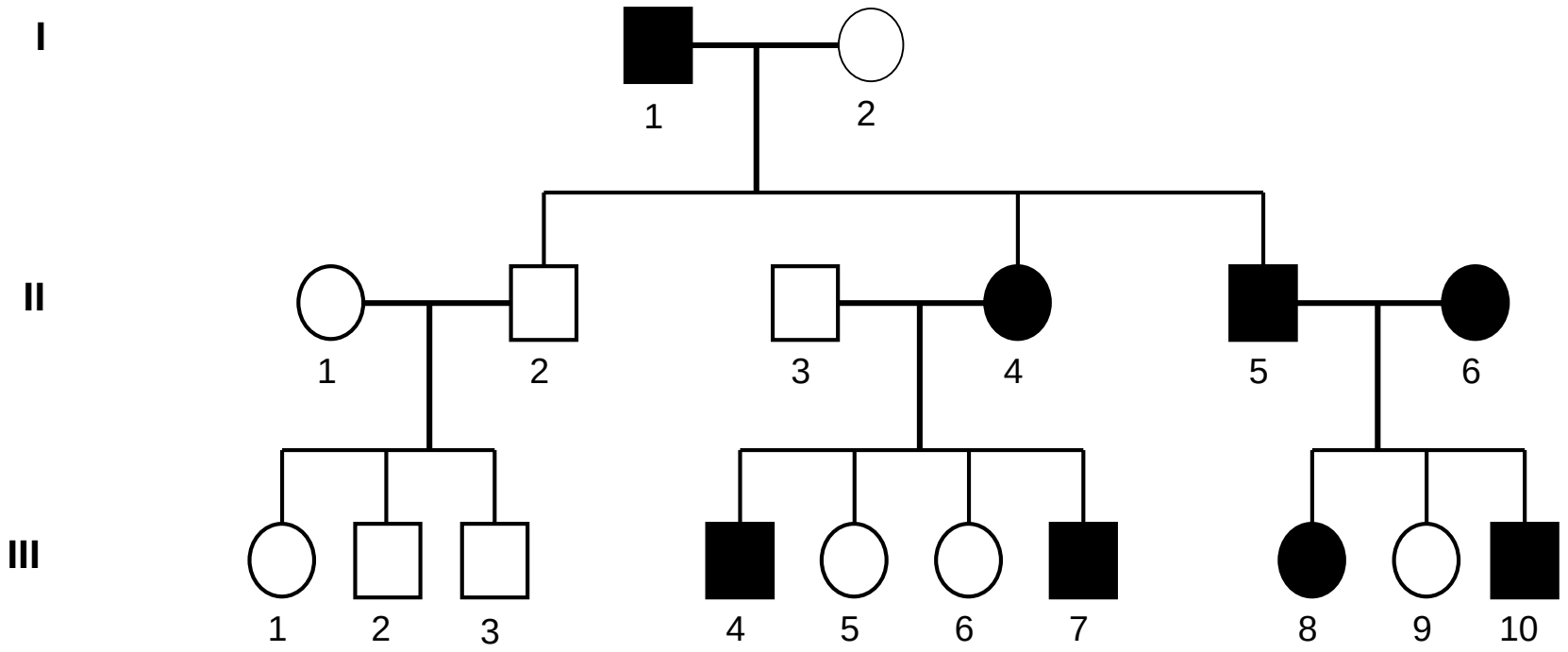


# What is the inheritance pattern?



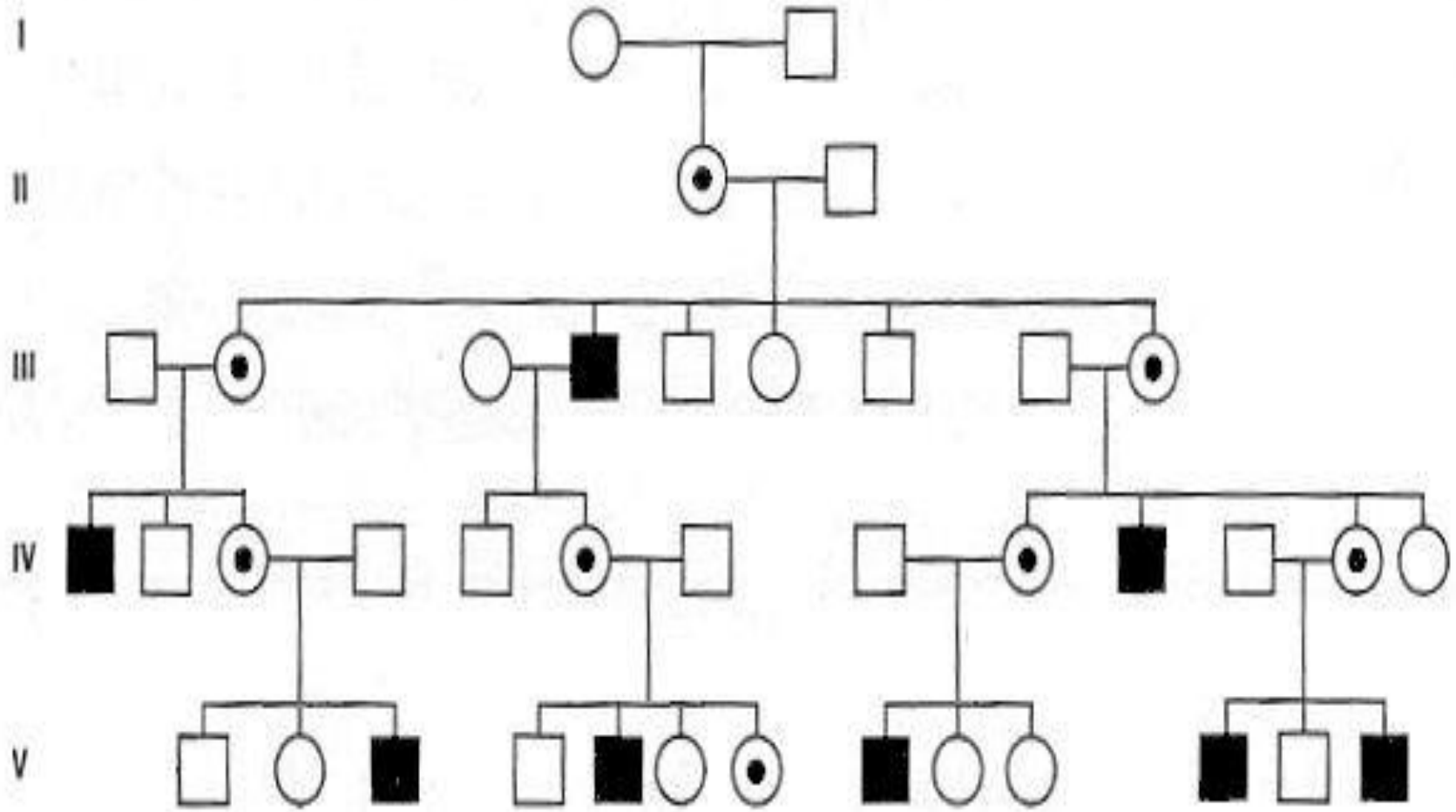

Autosomal Recessive

# What is the inheritance pattern?




**Autosomal dominant**

# What is the inheritance pattern?




X linked recessive

# Think about

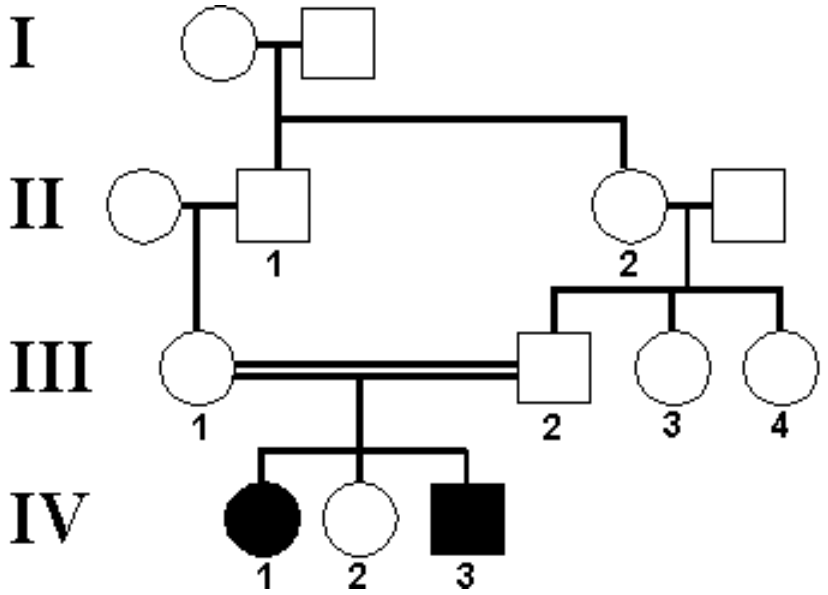
>>If two affected people have an unaffected child, it must be a dominant/Recessive pedigree?

>>If two unaffected people have an affected child, it is a recessive/ dominant pedigree?

>>If every affected person has an affected parent it is a dominant/recessive pedigree

# Assignment

**What is the pattern of inheritance?**
**What is IV-2's chance of being a carrier?**



What is the inheritance pattern?
What is the genotype of III-1, III-2, and II-1?