Genetics
& Cell biology

◉ Sheet ○ Slides

Number

7

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***RECAP**

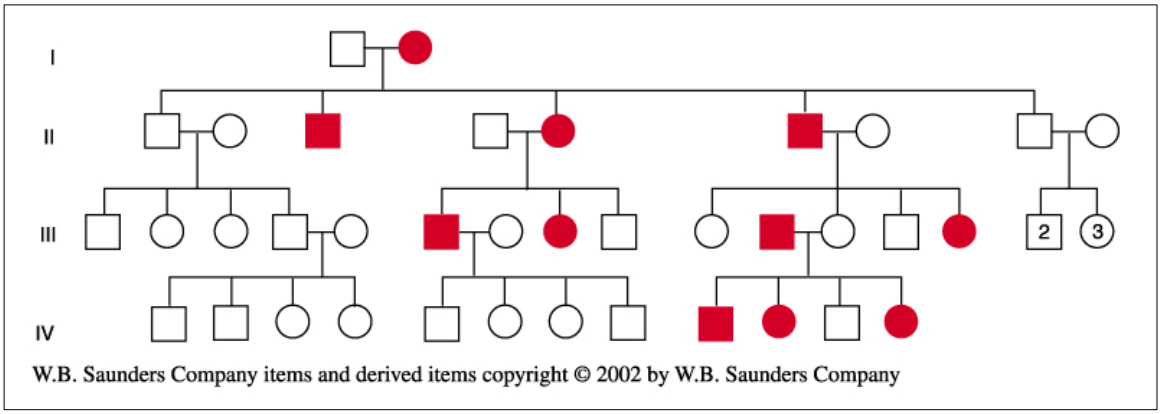
Autosomal dominant disorders:

1. Familial hypercholesterolemia
2. Huntington disease
3. Neurofibromatosis (NF1)
4. Myotonic dystrophy
5. Achondroplasia

Each of these disorders has specified characters, for example, NF1 has variable expressivity (variable severity), between different individuals the cafe au tait spots are varying.

Features of autosomal dominant disorders:

1. Vertical transmission (not skipping generations)
2. Male to female 1:1
3. Both parents transmit the disorder equally to offspring
4. Most genes that are mutated code for structural proteins
5.



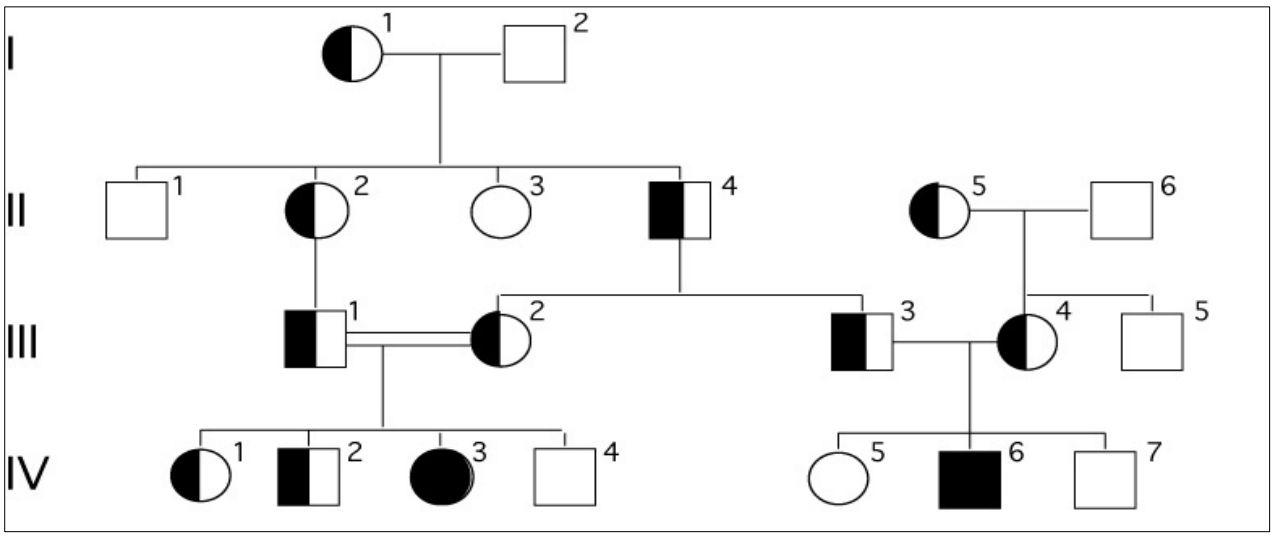
Autosomal recessive disorders:

1. Cystic fibrosis
2. Sickle cell anemia
3. Tay-Sachs disease
4. Phenylketonuria (PKU) and most inborn errors of metabolism.

Cystic fibrosis is an example of a phenomenon called **Pleiotropy**, where one gene affects more than one tissue. Autosomal recessive disorders are usually the result of consanguineous mating.

Features of autosomal recessive disorders:

1. Not every generation is affected, but only the third or fourth generations are affected.(skipping generation)
2. (Horizontal transmission) : In the same generation there is more than one affected individual
3. Male to female 1:1
4. Both sexes may equally transmit the disease
5. Most genes that are mutated code for enzymes
6. May observe consanguinity (زواج اقارب)



Sex Linked Disorders:

There are differences between sex linked and sex influenced or sex limited disorders.

If a gene is sex linked then it is physically located on the sex chromosomes.

X-linked → on the X chromosome.
Y-linked → on the Y chromosome.

And because the X chromosome is way bigger than the Y chromosome, it has 10 times more genes. So if the allele is only on the X chromosome and does not exist on the Y chromosome it is hemizygous in males and in females it is either homozygous or heterozygous.

Dosage Compensation:

Not all genetic disorders result from mutations that change the sequence, because you can have a normal DNA sequence but the amount of expression is not correct.

For autosomal traits, two doses lead to a normal phenotype, because proteins of the two genes will interact with each other to function, while one dose or more than two doses often have clinical significance.

For X-linked traits two doses in females (XX) and one dose in males (XY) both lead to a normal phenotype, this is because of **X-inactivation** (**Lyon Hypothesis)**

In early embryonic life (3-7 days after fertilization), there is a significant number of cells, at that time each cell, individually and randomly, will decide to inactivate one of the two X chromosomes in females only. This inactivation happens by condensation into Heterochromatin and it is called a **Barr body**.

One cell may decide to inactivate the paternal X chromosome while the neighboring cell may decide to inactivate the maternal X chromosome (because it is a random process). But once it occurs, all the daughter cells will have the same inactive chromosome as the original cell. This inactivation occurs to compensate for the dose between males and females.

Some genes on the inactive X chromosome will 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.

If a female is heterozygous for a particular gene located on the X chromosome, she will be a mosaic for that character (composed of cells of two genetically different types

(Some cells will have the mutated allele inactivated and other group of cells the mutated allele will be active this will give us mosaic)

The X chromosome has genes for many characters unrelated to sex, whereas the Y chromosome mainly encodes genes related to sex determination.

e.g : Duchenne muscular dystrophy , hemophilia (blood will not clot), red-green color blindness

X-Linked Recessive Disorders:

- 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**)

    So in male one allele in enough to have the disease but a heterozygote female might shoe mild features of the disease because the X-inactivation
- X-Linked recessive disorders are much more common in males than in females

They are some disorders caused by recessive alleles on X chromosome in humans.

Examples: - Color blindness (Red-green color blindness)
- Duchenne Muscle Dystrophy (DMD)
- Hemophilia

Duchenne Muscle Dystrophy:

- Peripheral muscle weakness and loss of muscle tissue, patients are wheelchair bound.
- Progressive muscle weakness (muscle will deteriorate further and further with the patient's life)
- 30% of cases due to new mutations (not inherited, spontaneous mutations, de novo)
- Allele heterogeneity (Becker muscle dystrophy) same gene on the X chromosome but the type of mutation is different leading to a less severe disorder than Duchenne.
- Death typically in 2^{nd} or 3^{rd} decade

Hemophilia:

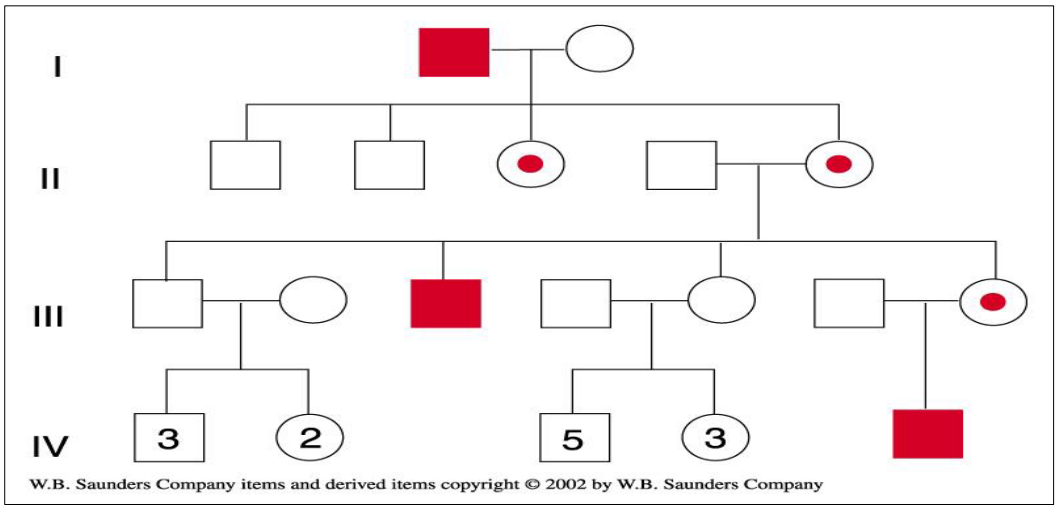
- Coagulation disorder, patients have prolonged bleeding and they bruise easily
- Hemorrhage
- Various mutations of the same gene have been reported between different individuals, so we have different severities of this disorder.

Features of X-linked recessive disorders:

1. Diagonal(قطري) inheritance: affected males are related to females of the maternal line, because the X chromosome in males comes from the mother, so an affected

female will definitely have affected sons, and sons of carrier females have a 50% chance of inheriting the disorder.

2. A son never inherits the disorder from his affected father (Absence of male-to-male transmission), but an affected father will have carrier daughters.
3. Male to female 2:1
4. No or mild expression in carrier females (heterozygous females) due to X-inactivation.
5. Full expression in hemizygous males



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**

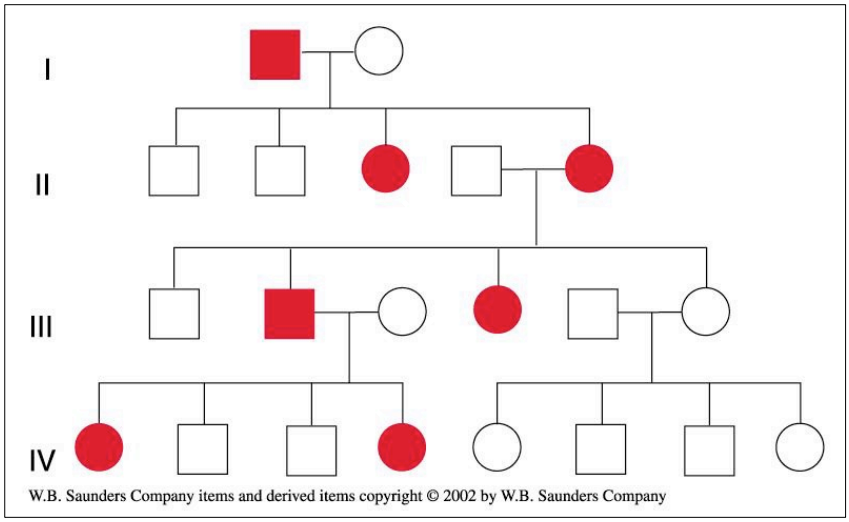
X-Linked Dominant Disorders:

Example, Vitamin D Resistant Rickets, which is characterized by short stature, low serum phosphate, and is less severe in heterozygous females; due to X-inactivation.

Features of X-linked recessive disorders:

1. Most of the time the female affected is heterozygous.
2. Every generation is affected with the disorder (dominant)
3. Male to female 1:2 (because females have a higher chance of having the X chromosome)

4. No male-to-male transmission
5. Females usually have more mild and variable expression due to X-inactivation.
6. Sons and daughters of affected females have a 50% chance of inheriting the disorder.
7. All daughters of male with the disorder will also have the disorder.
8. You can distinguish between autosomal and X-linked dominant by looking at offspring of affected males.

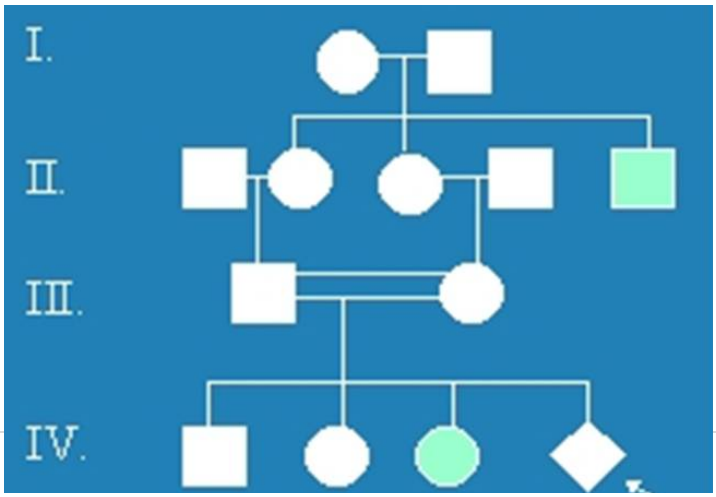


**In the exam the doctor will give us a pedigree, and he will ask us what the mode of inheritance is like in the examples in the following pages.

Question: What is the mod of inheritance for each of these pedigrees?

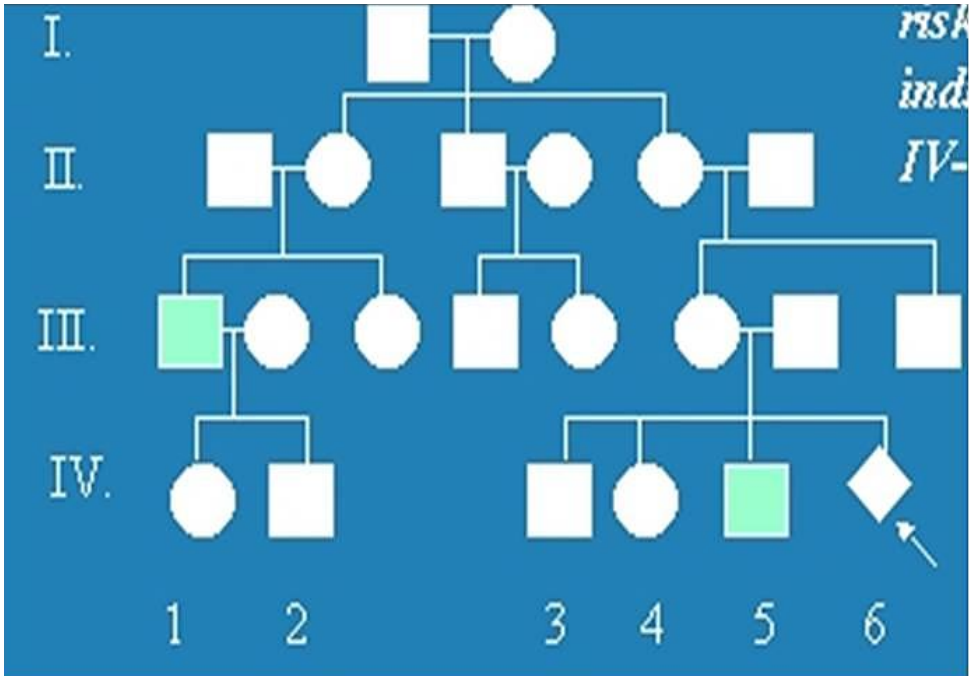
(This is mostly estimation of what the disorder is, it might have more than one possible mode of inheritance but we choose the most probable one)

1.



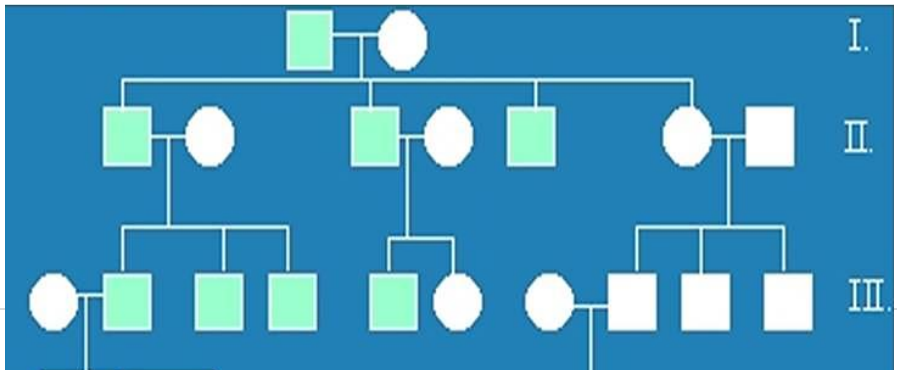
A: Autosomal recessive, because it is skipping generations, male to female 1:1, also there is consanguinity which is mostly the cause of autosomal recessive disorders.

2.



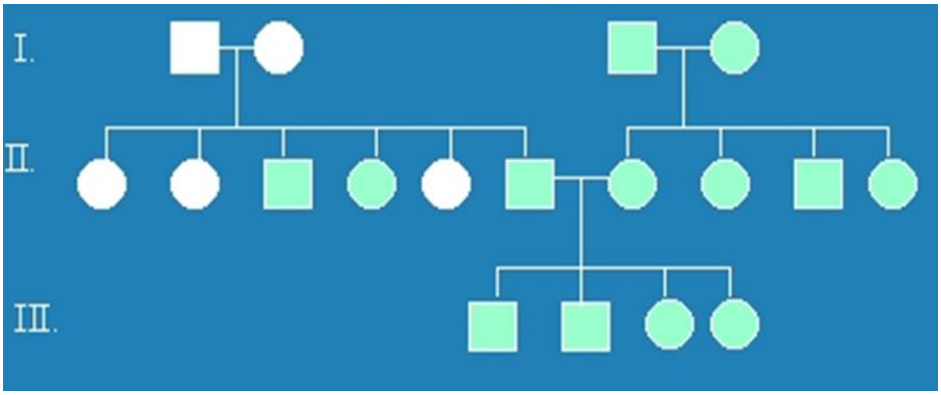
A: X-linked recessive, because there are no affected females, not every generation is affected (recessive). It could be autosomal recessive but there is a higher chance it is X-linked.

3.



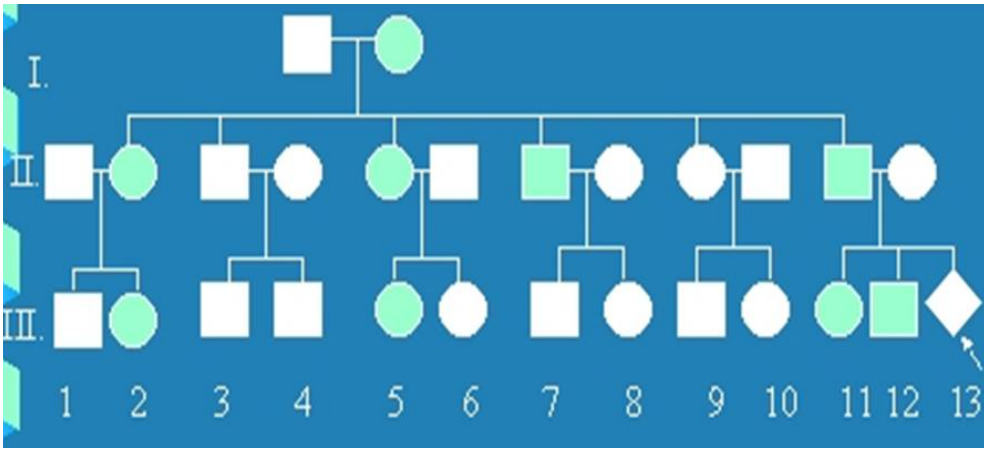
A: Y-linked is the most probable mode of inheritance, because there are no affected females, and because the affected male transmits the disease to all of his sons, if there was at least one male that is not affected it won't be Y-linked.

4.



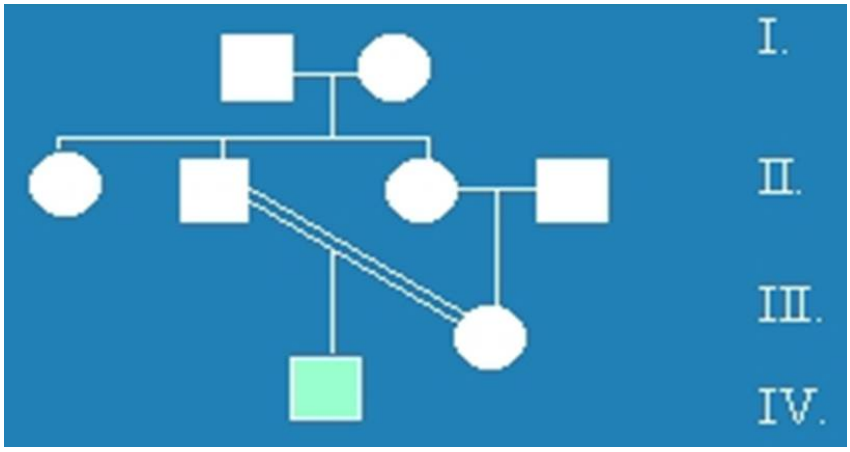
A: It is not autosomal dominant, because the affected children on the left none of their parents is affected, that's why it can't be autosomal dominant but is autosomal recessive.

5.



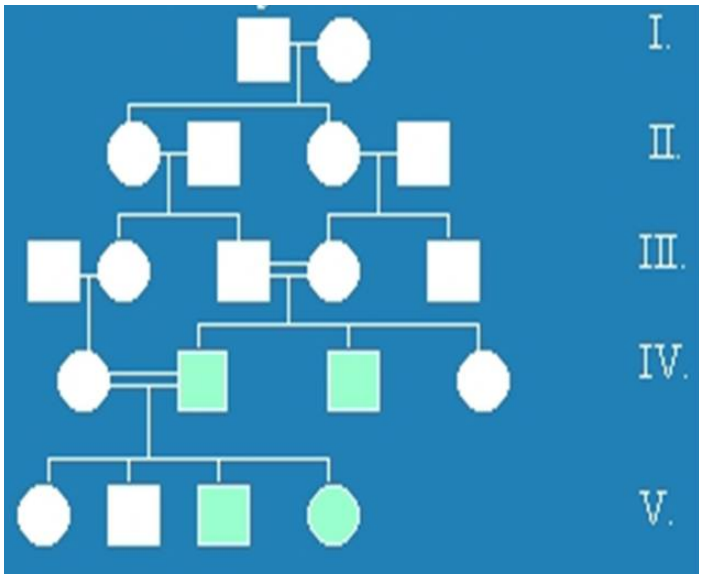
A: It is not X-linked dominant although it is not skipping generations and affected females are more than affected males, but there is a catch, male II,7 → his daughter is not affected, this excludes it from being X-linked dominant. That is why it is autosomal dominant.

6.



A: Autosomal recessive, because it appeared in the fourth generation, and because of consanguinity.

7.



A: X-linked recessive, it appeared in the fourth generation, more affected males than affected females, and because of consanguinity.

Good Luck