Medical Genetics

Sheet: 8-Patterns of Inheritance& Pedigree Practice

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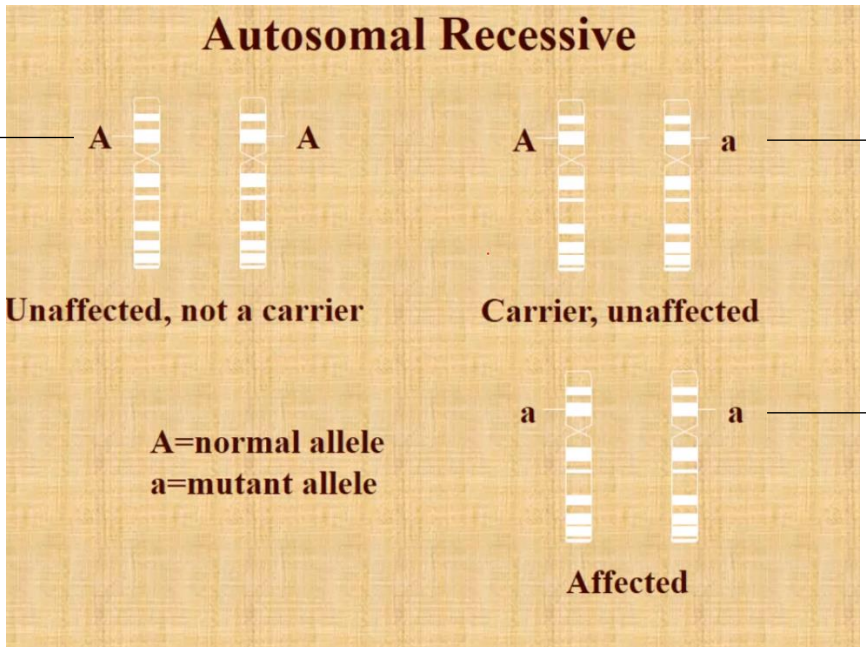
In the Name of Allah, The Most Gracious, The Most Merciful

In this sheet, we will talk about the mood of transmission.



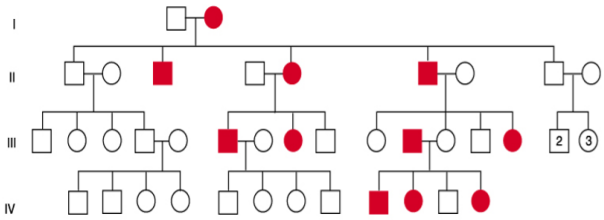
If both alleles are homozygous for the dominant allele which is the normal one → Normal

Here, there are both (the mutant and the normal allele) → normal carrier

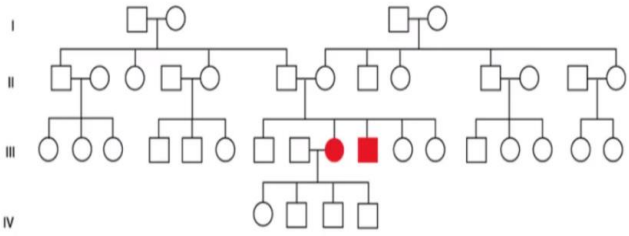
If both are disease causing alleles (which are recessive in this case) → affected individual

Now look at these pedigrees:

Remember: we said that in an autosomal dominant disorder, the transmission is vertical which means that every generation is affected.



In a recessive disorder, the transmission isn't vertical, instead, it's horizontal; there might be more than one affected individual in the same generation (in the 3rd generation here)



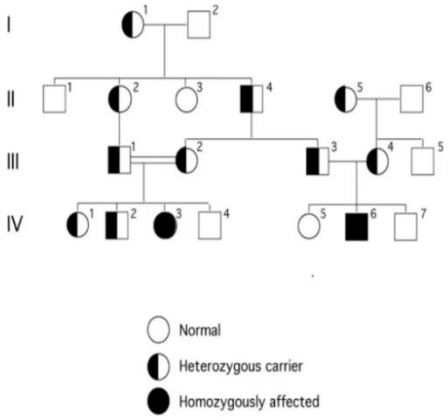
Some Notes:

The disease is skipping generations (focus on the affected individuals not the carries) → indicates that it is a recessive disease.

Also, the male to female ratio is 1:1 → which indicates an autosomal disease.

Let's continue our notes:

You might observe consanguinity "blood relation" (it is denoted in the pedigree by two lines between the couple), look at 1 & 2 in the 3rd generation here →



Genes that encode for autosomal recessive diseases are typically enzymes, while in autosomal dominant diseases they are structural proteins rather than enzymes.

Let's do a quick recap:

Here are the features of autosomal recessive inheritance:

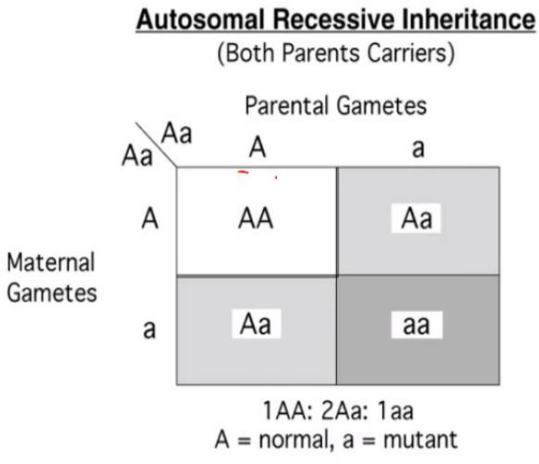
1. Horizontal transmission--- affected individuals usually within the same sibship or generation.
2. Both sexes are affected in 1:1 ratio.
3. Both sexes may equally transmit the mutant allele.
4. You may observe consanguinity.
5. Gene product is usually an enzymatic protein.

Transmission probabilities and use of 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).
- 25% chance that the child will be neither affected nor a carrier (AA).

So, 'If both parents are carriers of an autosomal recessive condition, an unaffected child has a 2 in 3 chance of being a carrier.'



Affected homozygotes are commonly the offspring of two heterozygote carriers.

Sex Linkage and X-Inactivation

Sex linked or linkage means that the gene is physically on one of the sex chromosomes;

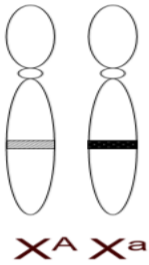
- if it is on the X chromosome → it is called X linked
- if it is on the Y chromosome → it is called Y linked (there are few of these).

Don't be confused with sex limited or sex influenced.

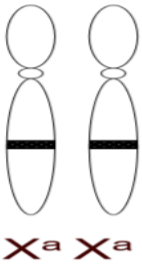
Is the male here homozygous or heterozygous?

Neither right? homozygous or heterozygous of what? He has a single copy of X chromosome and a single copy of Y chromosome.

So, he is hemizygous.



This female is heterozygous



This female is homozygous for the same gene.

Dosage Compensation

Take a quick idea: **'Dosage compensation** is the process by which organisms equalize the expression of genes between members of different biological sexes.' Wikipedia.

Both males and females carry 22 pairs of autosomal chromosomes and 1 pair of sex chromosomes in their cells.

let's talk about the autosomal chromosomes, shall we?
If you look at gene expression (quantitywise), each gene in these 22 pairs of chromosomes has 2 alleles, which means that the RNA polymerase will physically bind to the first and 2nd alleles of each gene, and it will make RNAs, which will be translated. and the same scenario in both sexes.

Now if you look at the genes on the X chromosome, physically or quantitatively speaking, would you expect to have more RNA and protein from the expression of X linked genes in males or females?
In females, there will be more expression of these genes, simply because each gene on the X chromosome in females is made of two alleles, so physically RNA polymerase binds to the first allele and the second one and makes RNA from both alleles.

In males, there is only one allele that is being transcribed into RNA.

So, quantitywise, the RNA is more in females than in males for genes on X chromosome.

Consequently, these genes and proteins, weather from the autosomal chromosomes or from the sex chromosomes, don't function individually, they interact with each other, and function together as a group, there is a network of interactions between different genes and their products.

Now because we have the same quantity of expression of autosomal chromosomes, and a difference in the quantity of sex chromosomes, so how can we make up for this difference? This is called **Dosage Compensation**.

The dosage compensation happens through X inactivation 'Lyon hypothesis'

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

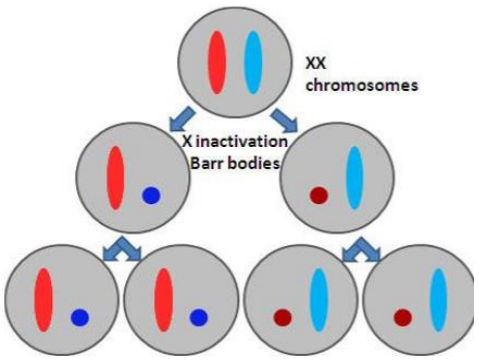
For X-linked traits, two doses in females and one dose in males, both lead to a normal phenotype.

X inactivation

After the egg is fertilized and the zygote is formed during the first week after fertilisation, you will have a group of cells (the zygote tries to do divide as fast as possible by mitosis).

At that time, each cell will randomly and individually decide whether it wants to condense and inactivate X chromosome that came from the father (sperm), or the X chromosome that came from the mother (egg).

One cell might inactivate the paternal X chromosome while the other inactivates the maternal one (it is random), but once the cell decides which X chromosomes it wants to inactivate, ALL the daughter cells from that cell will have the same inactive X chromosome (look at the picture)



So, if a female is heterozygous for a particular gene located on the X chromosome, she will be a mosaic for that character.

The inactivation happens through condensation of an X chromosome, which turn into heterochromatin (Barr body), and therefore, it is very condensed physically so the RNA polymerase cannot express its genes.

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 (they are accessible by the RNA polymerase)

> Extra info :
> The **pseudo autosomal regions** (PAR1 and PAR2) are short **regions** of homology between the mammalian X and Y chromosomes. The PAR behave like an autosome and recombine during meiosis. Thus, genes in this **region** are inherited in an autosomal rather than a strictly sex-linked fashion.

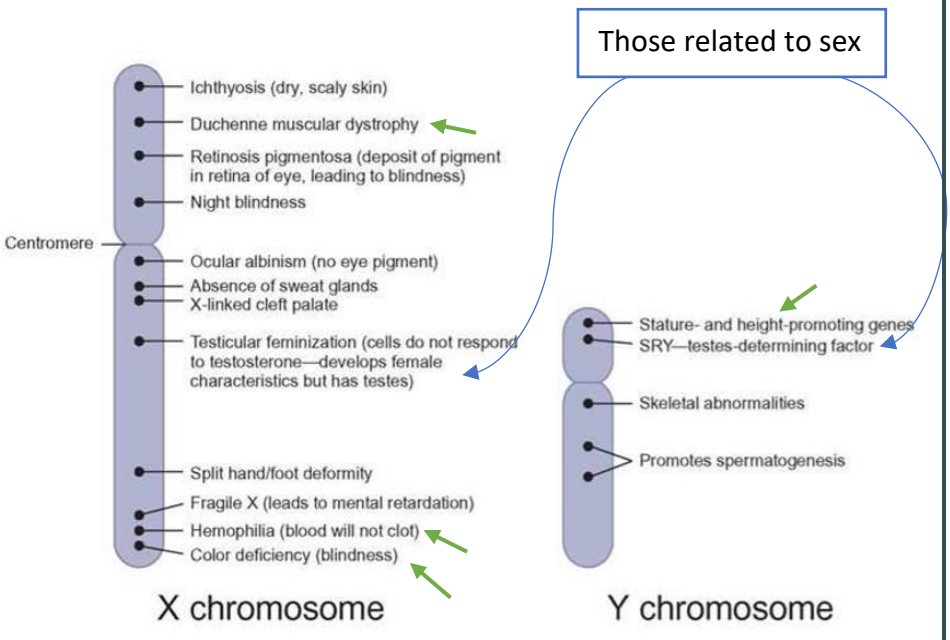
To sum up:

- In early embryonic life (3-7 days after fertilization), one X chromosome is inactivated (to allow compensation for the difference in dosage of X-linked traits).
- The inactive X chromosome is condensed in a Barr body.
- Inactivation of the maternal or paternal X chromosome is random.

Not all genes on the sex chromosomes are related to sex.

Examples on genes are not related to sex (the short green arrows) :

Color blindness (and it is on the tip of the q arm of the X chromosomes),
Duchenne muscular dystrophy (muscle weakness),
Hemophilia (blood clotting disorder),
the region on the Y chromosome right above the SRY (sex-determining region Y) is related to height and stature.



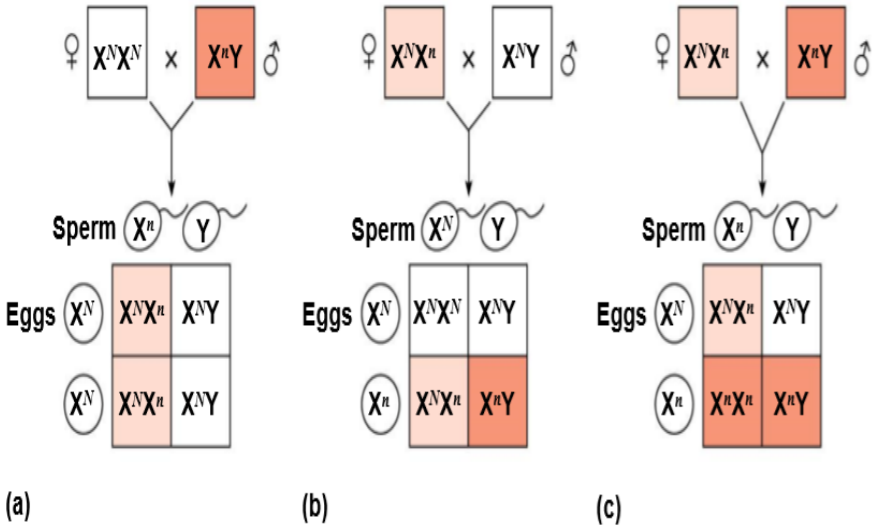
The X chromosome has genes for many characters unrelated to sex, whereas the Y chromosome mainly encodes genes related to sex determination.

X-linked 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)

X-linked recessive disorders are much **more common in males than in females**



We will start talking about some recessive X-linked disorders:

1. **Duchenne muscular dystrophy-DMD**
   weakness in the peripheral muscles, and consequently, the individuals will become wheelchair-bound, and those poor people typically die in the 2nd to 3rd decade of their life, (dystrophy muscle weakness and loss of muscle tissue).

   30% due to new mutations (not inherited; acquired), the parents don't carry the mutation, it might be during the formation of the gametes or when the zygote is formed. these new mutations called spontaneous mutations (not inherited) or de novo mutations.

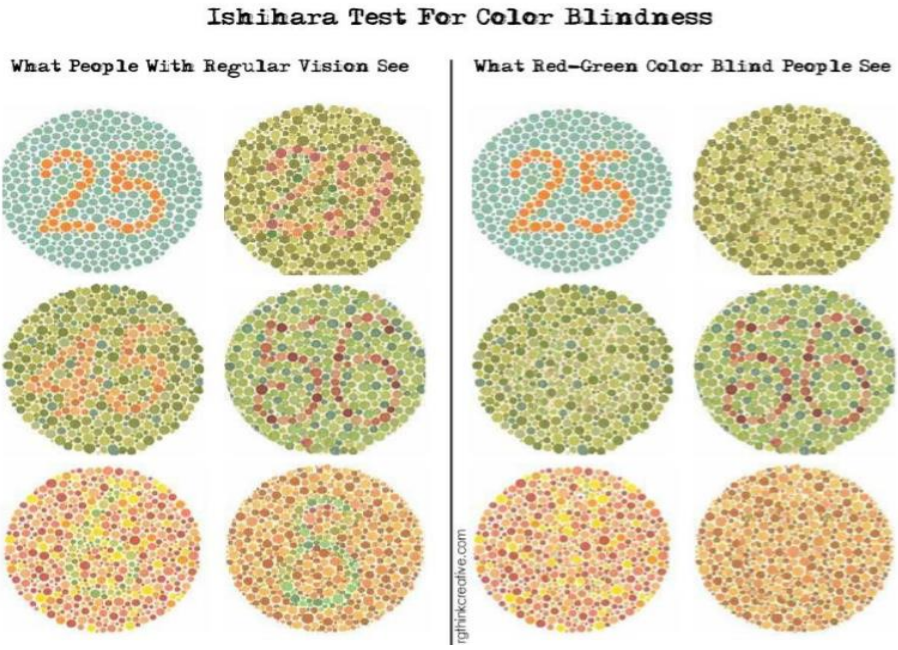
   There are multiple mutations, not all people carry the same mutations of the same gene.

   In Duchenne mutation, the clinical outcome is more severe than other mutations, if the clinical outcome is less severe, we call it Becker MD (muscular dystrophy) rather than DMD.

2. **Hemophilia**
   X-linked disorder, deletion disorder that leads to prolonged bleeding.
   Those people are easily bruised, they might suffer from hemorrhage (internal bleeding).
   Various mutations & very heterogenous.

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)**

3. **Color blindness**
   Mostly X-linked; Red-green color blindness.

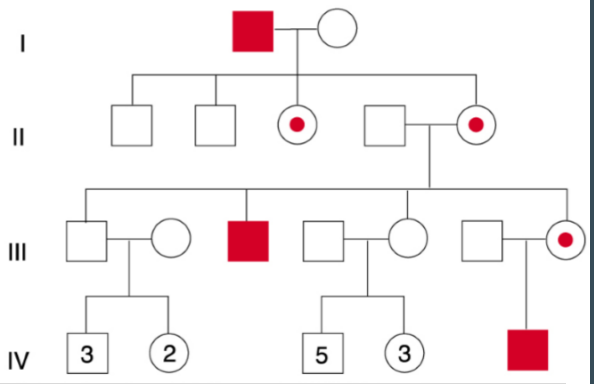


Features of X-Linked Recessive - (11:00) lecture 8-1

As you can see the mode of transmission isn't vertical (as in the dominant) or horizontal (as in the recessive).

It is *Diagonal* because the transmission of the mutation depends on the sex.

Let's talk about this pedigree.



As you know the male is XY and only his daughters will get the X chromosome, and his Y will go to his sons, right?

This means that the mutations on the X from the male is transmitted to the females but not to the males, so for an affected male, all of his daughters are obligate carriers assuming that the mother is not a carrier.

For carrier female, the chance to have an affected male is 50% (she might give her son the normal X or the mutant X, so it is fifty-fifty chance).

For females to get affected, both alleles should be mutated, whereas for males, one is enough (they just have 1 X).

That is why in the pedigree you will see that the affected males are more than the affected females **(it is not 1:1 ratio**).

Those heterozygous females might show mild to moderate clinical features **due to X inactivation,** but still classified normal. for example, in DMD, the affected children can't walk, and they will pass away in their twenties.

While heterozygous females are normal, but they have a kind of weakness in their muscles, they will not be wheelchaired bound. They will have mild disease features (they drop stuff sometimes), but still you can't clinically classify them as affected.

Most genetic disorders are untreatable. If there is a treatment, it is usually biochemical, such as avoiding consuming certain amino acids (like in phenylketonuria).

Read these 2 slides quickly to make sure everything is covered ☺✌

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

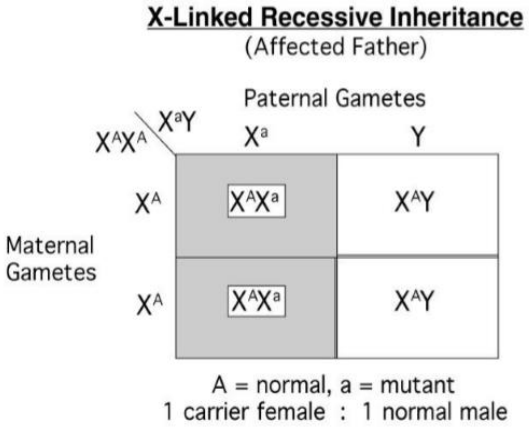
1. A son never inherits the disorder from his father.
2. All daughters of a male with the disorder are obligate carriers.
3. Sons of carrier females have a 50% chance of inheriting the disorder.
4. Daughters of carrier females have a 50% chance of being carriers too.

Here we have an affected male has children with an unaffected female, what is the percentage of the children who will be affected? Zero

What is the percentage of the children who will be carriers? 50%

What is the percentage of the females who will be carriers? 100%

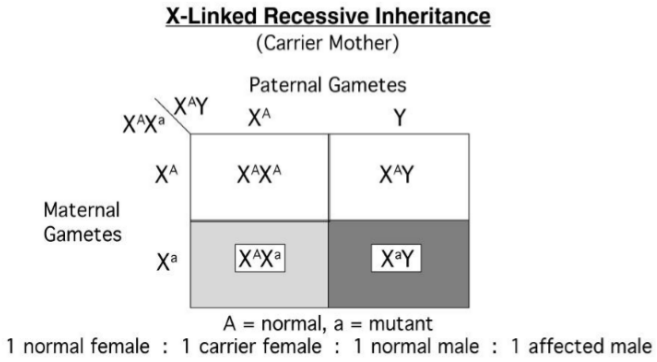
Pay Attention if the question determines the sex of the children or not.



Now we have a heterozygous female, who has children with a hemizygous normal male.

What is the percentage of the affected children? 25%

What is the percentage of affected males? 50%



X-linked Dominant inheritance

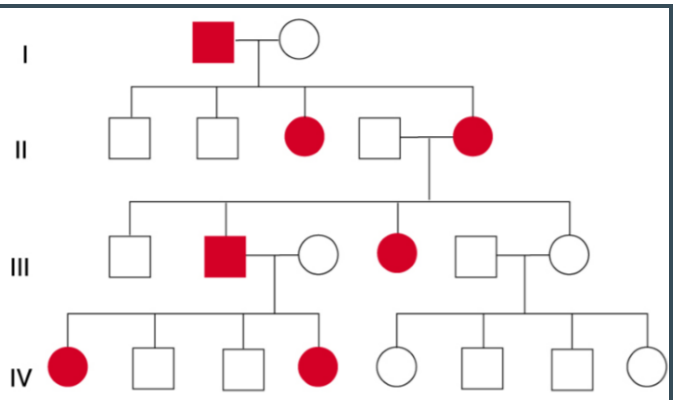
They are very rare conditions.

Vitamin D Resistant Rickets is an example of this type of disorders. (Patients have short stature).

Because it's dominant, even heterozygous females will be affected, but the severity of the disorder will be less than the severity of the disorder in hemizygous mutant males.

X-linked Dominant	
VITAMIN D RESISTANT RICKETS	Rickets Short stature Low serum phosphate **Less severe in heterozygous females**

Now look at the pedigree.



There are twice as many affected females as there are for males.

That makes sense, right?

Females have 2 X chromosomes (which can carry the mutation) so the risk is doubled.

Also, there is no male-to-male transmission. On the contrary, the affected male will affect all his daughters. If one of his daughters skipped the disease, it is not X dominate, it looks like one but it is not. (**This is a TRICK in The Question**.)

So, males transmit to females, and females transmit to both; females and males.

Keep in mind when we talk about dominate, weather it is autosomal dominate or X linked dominate, we are assuming that the affected individuals are heterozygous mutant not homozygous mutant.

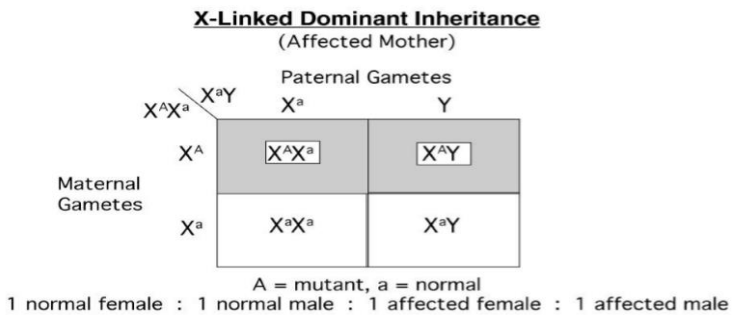
Again, let's go through these slides:

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

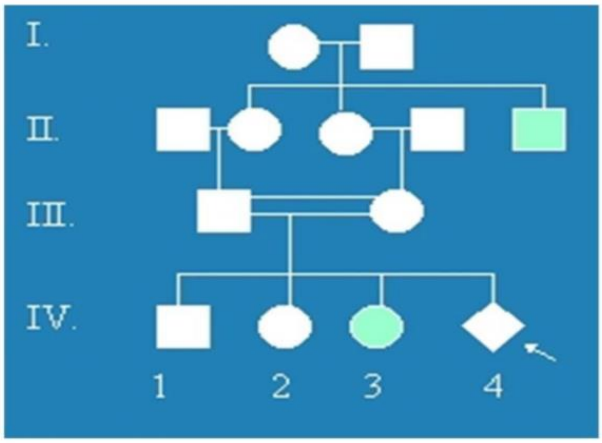
1. A son never inherits the disorder from his father
2. All daughters of male with the disorder will also have the disorder
3. Sons of affected females have a 50% chance of inheriting the disorder
4. Daughters of affected females also have a 50% chance of inheriting the disorder
5. Can distinguish between autosomal and X-linked dominant by looking at offspring of affected males



Now this is the fun part (Pedigree Practice)

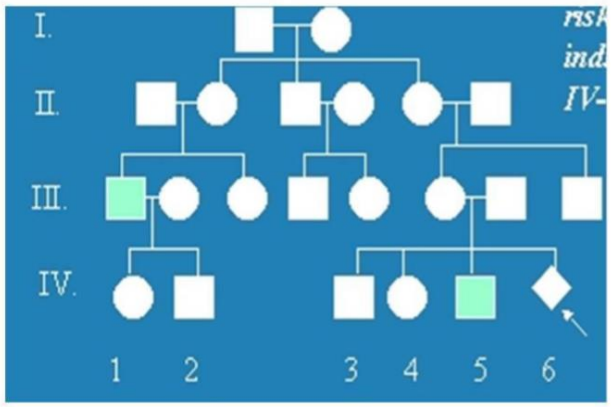
Try to answer the question by yourself first, Enjoy.

What is the mode of inheritance in the following pedigrees?

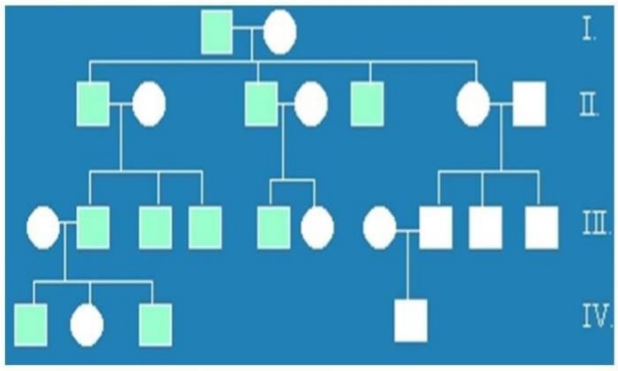


Keep in mind these questions:
Is it horizontal, vertical, …?
Male to female ratio…
Is there or is not a consanguinity?

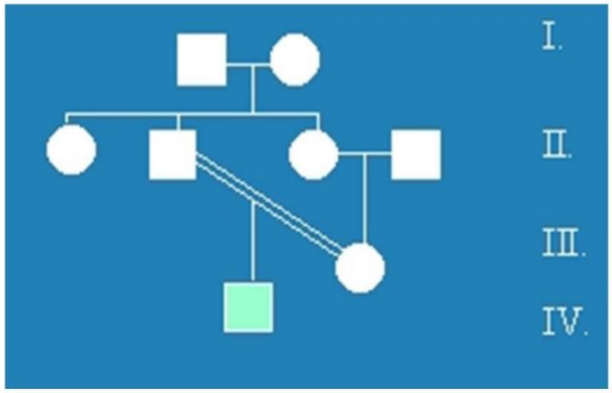
It is an autosomal recessive disorder; It is skips generations, there is a consanguinity, and the male to female ratio is (1:1)



It is X-linked recessive, Why?
Males affected rather than females
It is skipping generations (recessive)

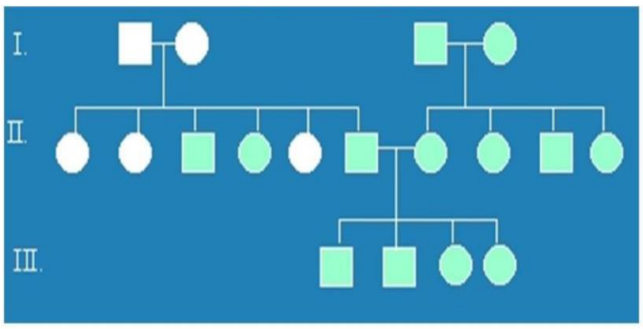


All affected males transmitted the mutation to their sons, so it is Y-linked.
Notice the daughters are not affected.



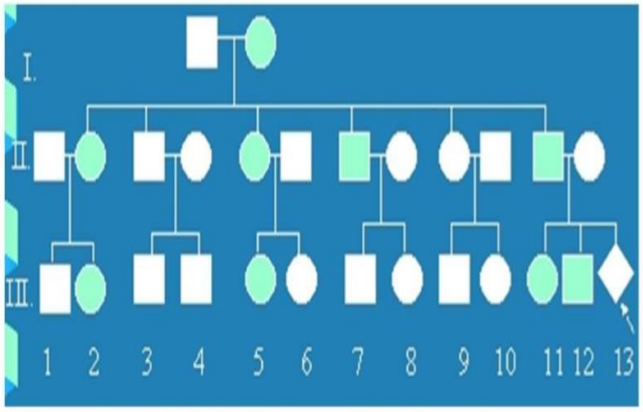
Autosomal recessive.

It is autosomal recessive.



This one is tricky.
Every generation is affected, you may say it is dominate, but if it is dominate how come the parents in the first generation (on the left) are not affected and they have affected children.

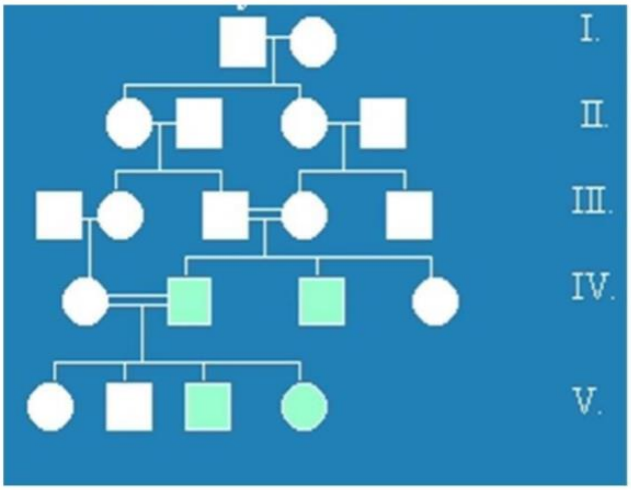
Male to female ratio is almost 1:1. So, it is autosomal.



You may think it is X-linked dominant because there are twice females as many as males, and every generation is affected.

But the male III 12 gets the disorder from his father, however, the Y chromosome doesn't carry X-linked mutations - .

There is something else, see the female III 8; If her father is affected why she is not? So, you must think in something other than X-linked recessive disorders. The right answer is that it's an autosomal dominant disorder. The mother in the first generation is heterozygous (remember we said that when someone is affected with dominant disorder, assume that her/she is heterozygous).



X-linked recessive; inbreeding (consanguinity) shows apparent male to male transmission.

"You don't have to be great to start, but you have to start to be great."
- Zig Ziglar
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