GENETICS

Sheet no. 11

Writer:

Doaa Sharawi

Corrector:

Doctor:

Mohammad al Shboul

*Don't get stunned by the number of pages of this sheet, it's a fun and easy one.

Pedigree Drawing

When we do genetic testing for any reason, we draw a family pedigree, which shows us:

• A pedigree shows generations and relationships among biological parents and offsprings.

• It also tracks which of those individuals have a specific trait or a disease.

• is aimed at determining the type of inheritance pattern that a gene will follow. (autosomal or sex linked, dominant or recessive, mitochondrial, …)

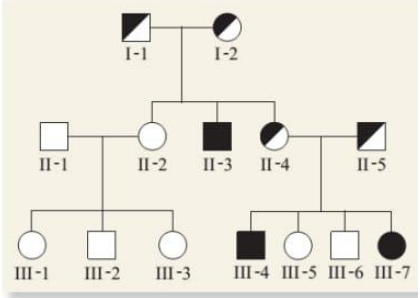
Some traits are recessive in some families and dominant in others, that's why it's crucial to make a family pedigree.

• Determine the probability of an affected offspring for a given cross, and to council the family for future pregnancies accordingly.

• In this section, we will examine a few large pedigrees that involve diseases inherited in different ways.

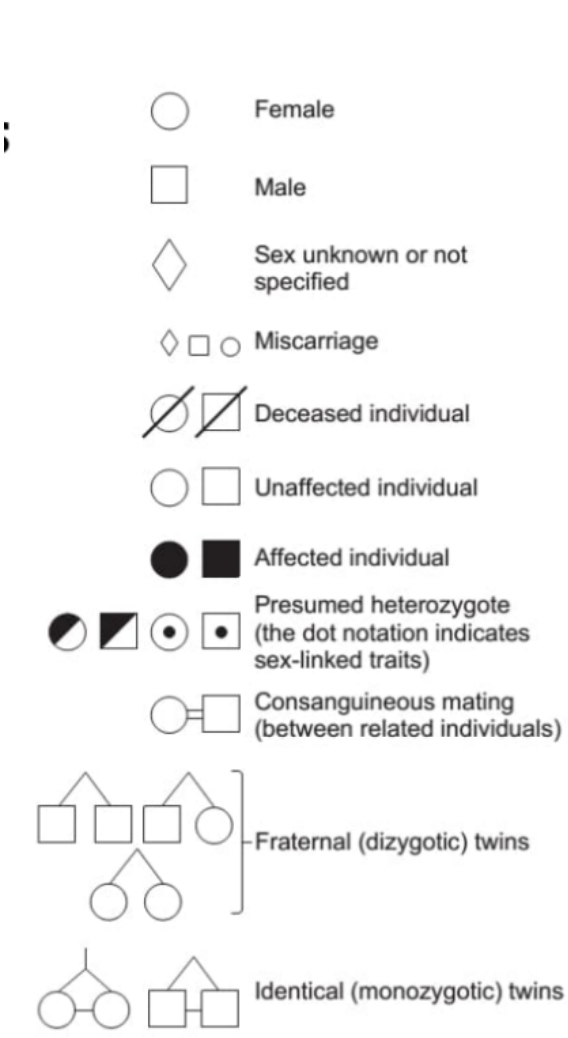
Pedigrees are useful in cases of Mendelian inheritance, but can be hard to solve in cases of multifactorial diseases such as hypertension or diabetes.

On the right is an example of a family pedigree, let's get to know what all these symbols mean to become able to interpret pedigrees well.

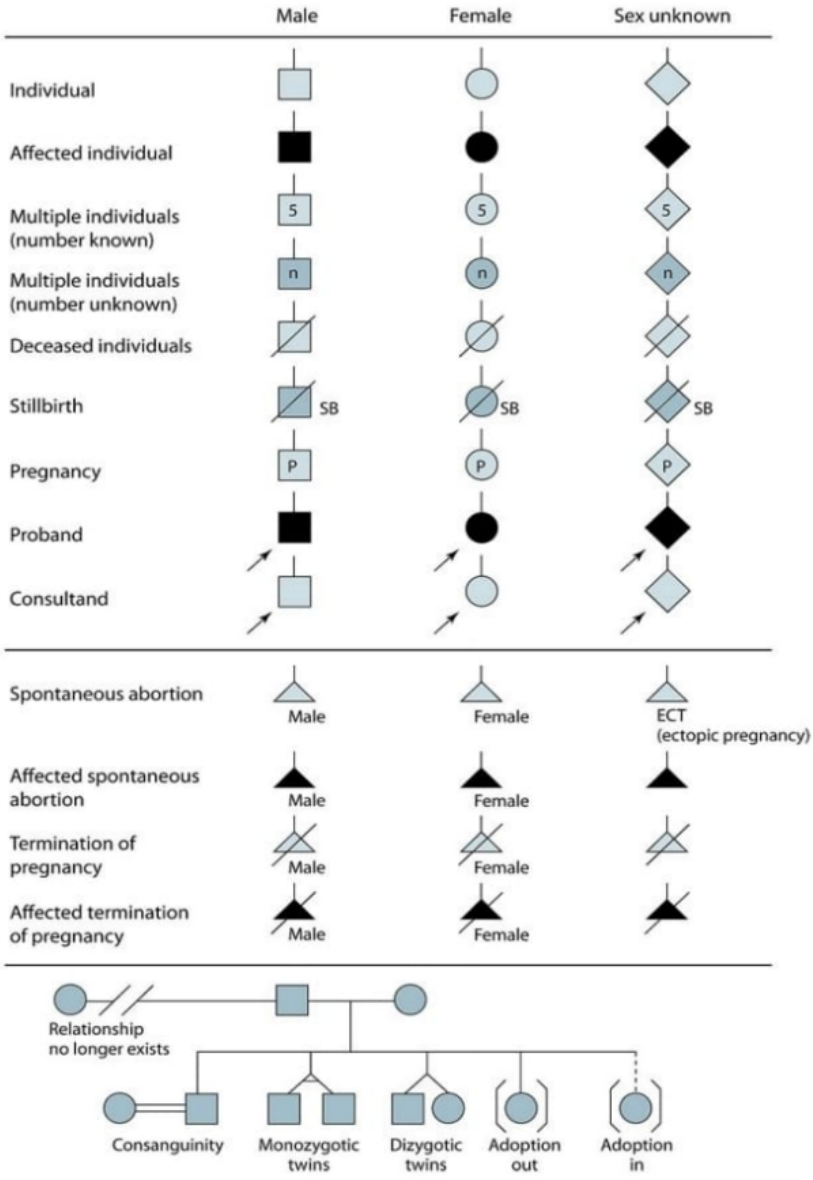


(a) Human pedigree showing cystic fibrosis

Symbols used in pedigree analysis



(b) Symbols used in a human pedigree



- An empty shape indicates the individual is not affected.
- A filled symbol (by whatever color) means the individual is affected.
- The unknown sex symbol is used in pregnancies when the gender of the fetus is unknown.

- The miscarriage is denoted by small symbols, or, more recently, a single dot (.).

- Spontaneous abortions are denoted by a triangle. Whether the fetus is affected or not is determined by its age. For example, abnormalities in the first trimester of pregnancy are hard to detect because the phenotype can't be determined. An example of this is skeletal abnormalities, which can't be detected until the 4th month of gestation.

- For carrier patients, a dot is drawn inside the symbol if it's a sex-linked disease, but in autosomal recessive ones the symbol is half full.

- If the parents are relatives (consanguineous mating), two horizontal lines are drawn between them.

*The previous two points are not necessarily present, meaning that they are used to draw attention to those features, but their absence does not necessarily mean that a person is not a carrier, or that a union is not consanguineous.

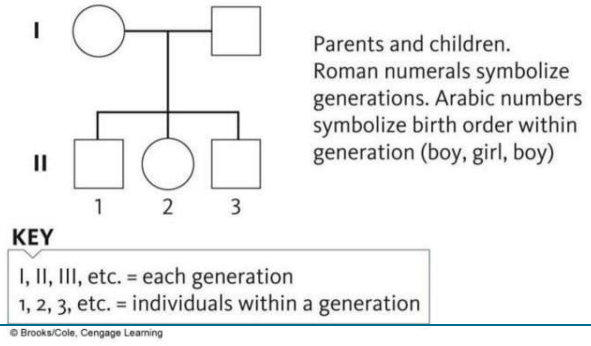
- As for twins, a line is drawn between them to indicate they're identical, and the absence of the line means they're non-identical.

- Stillbirths are represented like any deceased individual in addition to the letters SB (for **s**till**b**irth)

- In cases of pregnancies, we write the date of the start of gestation (the age of the fetus). Ex: 13 GA (Gestational Age)

Designation of generations and individuals

1. Each horizontal line is a generation.
2. Place the oldest generation at the top



Parents and children. Roman numerals symbolize generations. Arabic numbers symbolize birth order within generation (boy, girl, boy)

3. Use Roman numerals to identify generations. Usually there are 3 generations (at least) in a family pedigree, except in complicated cases where we need more insight into older generations.

4. Use Arabic numbers to identify individuals within a generation (1,2,3,…)

5. List siblings from oldest to youngest, from left to right (sibling number 1 is the eldest).

Sometimes, in case of a big number of siblings that share the same features (ex: five male siblings who are not affected), we draw a single empty square and write number 5 inside it.

6. Male partner is usually placed to the left of the female partner (not necessarily).

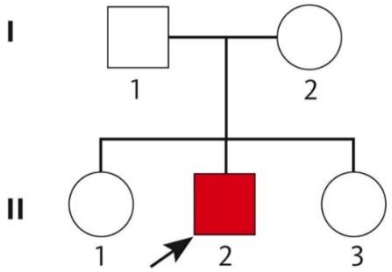
7. Record full name, current age and date of birth, or age at death for each individual.

8. Record race and ethnic origin of each individual, because there are some diseases or mutations that are common in certain ethnic groups more than others.

9. Note health problems and/or cause of death for each individual.

We have to be cautious to collect every single detail so it can lead us to the right genotype, mode of inheritance, etc.

- The proband (aka index case/ affected child) is an affected individual coming to medical attention independently of other family members. It is the person in whom the disease is diagnosed, the history is taken from and consequently the family pedigree is drawn for (The person who we start with by doing genetic testing).



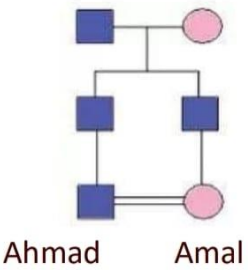
• The proband is designated with an arrow in the pedigree directed toward a filled symbol, and there may be more than one proband per family.

-Note that the consultand is denoted in the same way as the proband (refer to the symbols table above), except that the symbol is shaded (not empty nor filled). The consultand represents any individual in the family whom we don't know the diagnosis of, and genetic testing must be done to them so we can determine if they're affected or not.

Shading or fill (hatches, dots,etc.) is used to denote medical status or symptoms of individuals. A key legend is used to define meaning. Sometimes when there are more than one disease present in the same family (like autism and hypertension at the same time for example), we can divide the symbols into regions, and then fill or shade each region with a different color for each disease, providing a key for each color, for example red for autism, blue for hypertension.

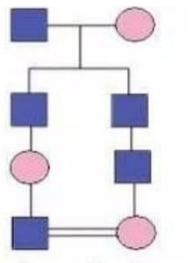
Consanguinity

It's important to understand because in our culture it's very common.



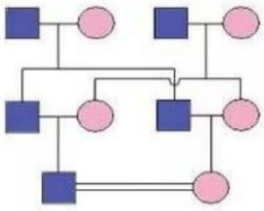
First Cousins

In this figure, Ahmad and Amal are first cousins because their parents are siblings.



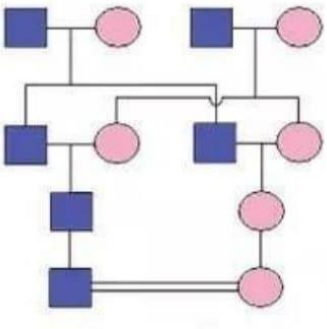
Second Cousins

Here they are second cousins because their parents are first cousins.



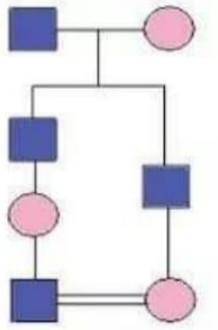
Double First Cousins

Double first cousins are first cousins from both the father's and mother's side of the family (ولاد عم وولاد خالة) at the same time.



Double Second Cousins

Here the parents are cousins from both of their parents' sides (the parents are double first cousins).



First Cousins one's removed

Here the wife's father and the husband's grandfather are siblings.

Over all, in consanguinity we don't really care about the kind of relative parents are to each other, but rather if they're relatives or not, because that increases the chance of inheriting certain mutations and autosomal recessive diseases that run in the family.

Cousins:

(fill the blanks)

• Ahmad and Amal are **first** cousins if one of Ahmad's parents is a sib of one of Amal's parents.

• If both of Ahmad's parents are sibs of both of Amal's parents, Ahmad and Amal are **double first** cousins.

• They are **second** cousins if one of Ahmad's parents is first cousin of one of Amal's parents.

Dominant and Recessive Inheritance

– Nomenclature: For dominant traits the capital letter (e.g. A) represents the mutant allele and the small letter (e.g. a) represents the normal allele.

For recessive traits, the small letter (e.g. a) represents the mutant allele and the capital letter (e.g. A) represents the normal allele.

- **Autosomal dominant traits** are those traits in which the phenotype of the heterozygote and the homozygote for the dominant allele are the same, i.e., Aa and AA have the same phenotype where A=dominant allele. These traits are expressed when only one copy of the dominant allele is present. In practice, if the heterozygote expresses the trait, then the trait is classified as dominant, even if the phenotype of the homozygote (AA) and heterozygote (Aa) are different. But keep in mind that the homozygous form is more severe in case of a disease, and it's rare to happen because usually it's lethal early in life. An exception is achondroplasia.

Also, if one of the children is affected with an AD trait, at least one of the parents must be affected.

Male to Female ratio is 1:1

Generally, affected individuals with an AD trait can be seen in every generation of the family pedigree (non-skip generations). But this rule doesn't always apply and can be misleading.

- **Autosomal recessive traits** are those traits in which the phenotype is expressed only if homozygous for the recessive allele, i.e., aa where a=recessive allele. Two copies of the recessive allele are necessary for expression.

Seen in family pedigrees with two horizontal lines between the parents (consanguinity).

Parents of an affected child are carriers of the alleles and not necessarily affected.

If both parents are affected with an AR trait, ALL of their children will be affected.

If the heterozygote (AB) has a different phenotype than either of the homozygotes (AA or BB), then the alleles are said to be codominant.

– **X-linked dominant traits** are those expressed when either males or females have one copy of the dominant allele, i.e., X^AY (the male is said to be homozygous) or X^AX^a, where A=dominant allele.

Female to male ratio is around 2:1, because females have two x's, and one of them is enough to produce the disease, so they have a higher chance to get affected.

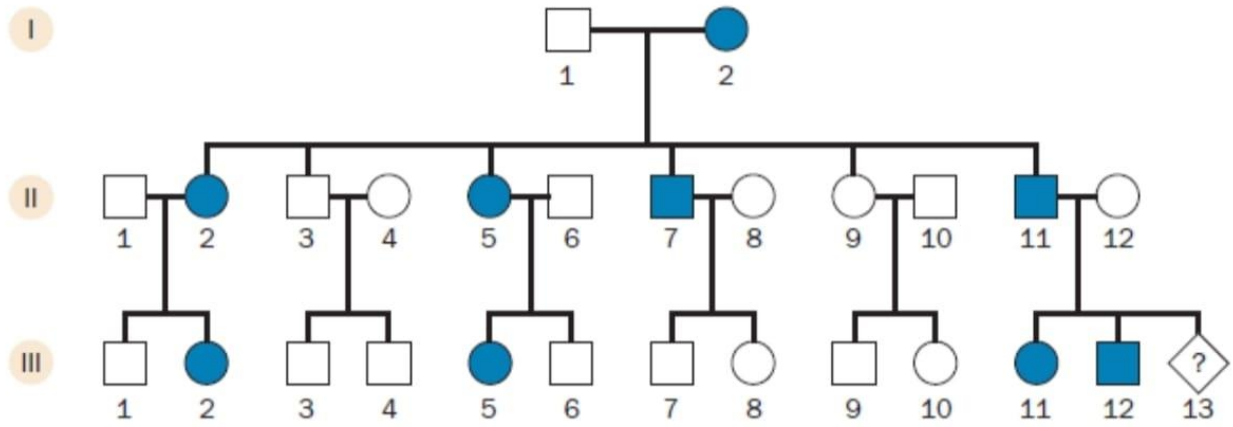
No-skip generations rule applies here, but again, not all the time.

– **X-linked recessive traits** are those expressed in males who carry one copy of the recessive allele (i.e., are hemizygous, X^aY where a=recessive allele). Two copies of the recessive allele are generally required for females to express the trait, i.e., X^aX^a.

Here males are affected more than females because it requires one allele for them to be homozygous.

We apply the previous criteria on family pedigrees to expect the mode of inheritance.

Now let's apply what we've just learnt in interpreting the following family pedigrees:



-What is the mode of inheritance of this trait?

Let's try first to determine whether it's x-linked or autosomal:

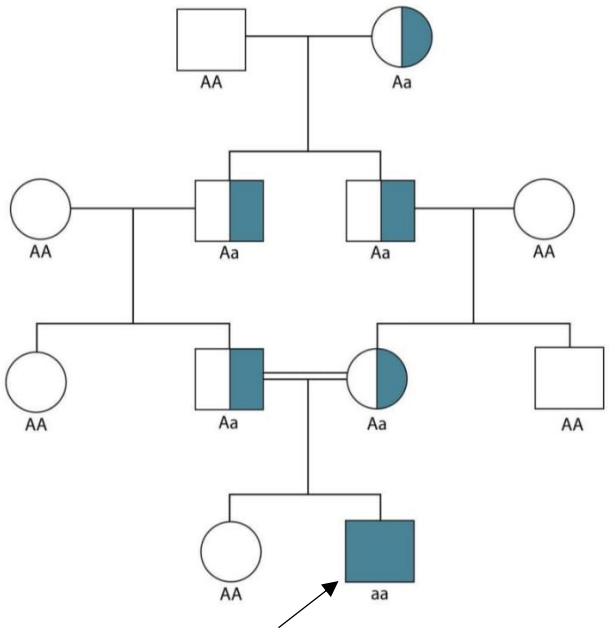
We notice that boy no.12 in the third generation is affected to an affected father, which makes it impossible to be an x-linked disease, because boys only have one x chromosome that they got from their mother, so there's no male to male transmission in x-linked traits.

Let's see if it's autosomal dominant or recessive:

- Each generation has at least one affected individual (no-skip generation)
- Female to male ratio is comparable (1:1): this applies to both autosomal dominant and recessive traits.
- No double horizontal lines to indicate consanguinity doesn't necessarily mean it's not present, because sometimes we don't know enough information about the family.

All the previous clues guide us to this conclusion: autosomal dominant.

What about the following family:



Remember what the half full symbols mean? Right, they indicate carriers of the trait.

Answer: autosomal recessive, pretty obvious.

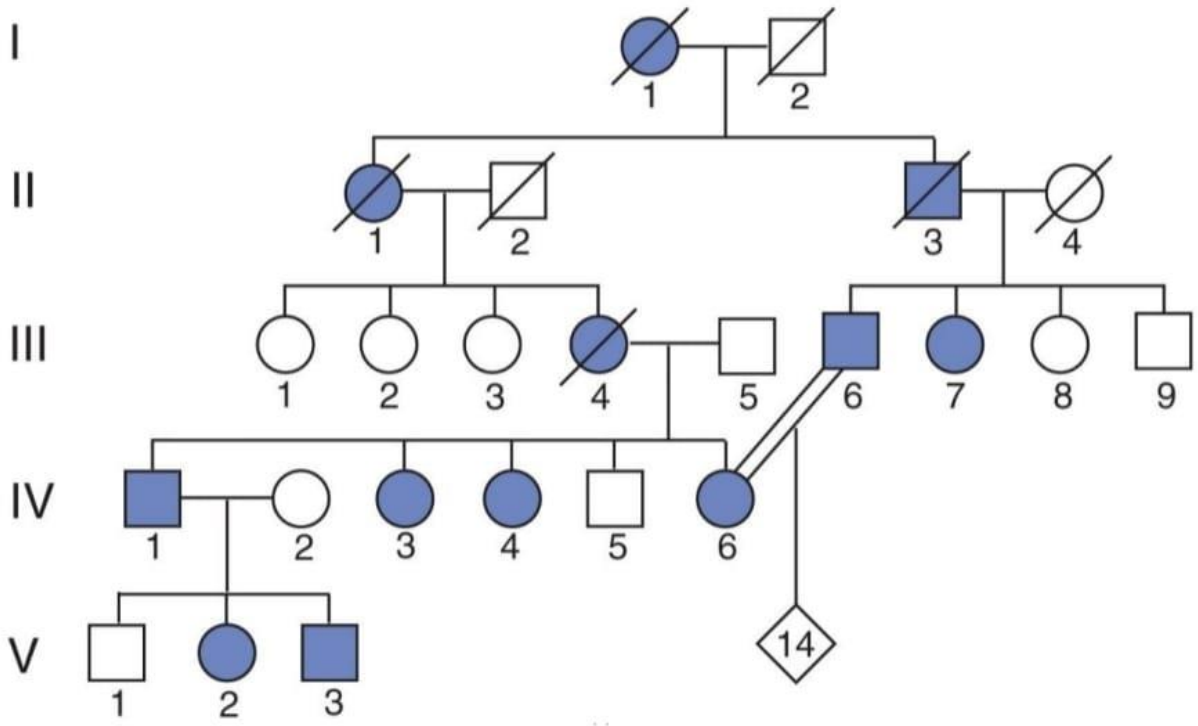
More clues: no-skip generation rule doesn't apply, the affected child doesn't have an affected parent.

*Notice the proband .

- What is the degree of relationship between the relative parents?

First cousins.

Pedigree no.3:



Remember, a slashed symbol indicates a deceased individual.

Let's gather some clues:

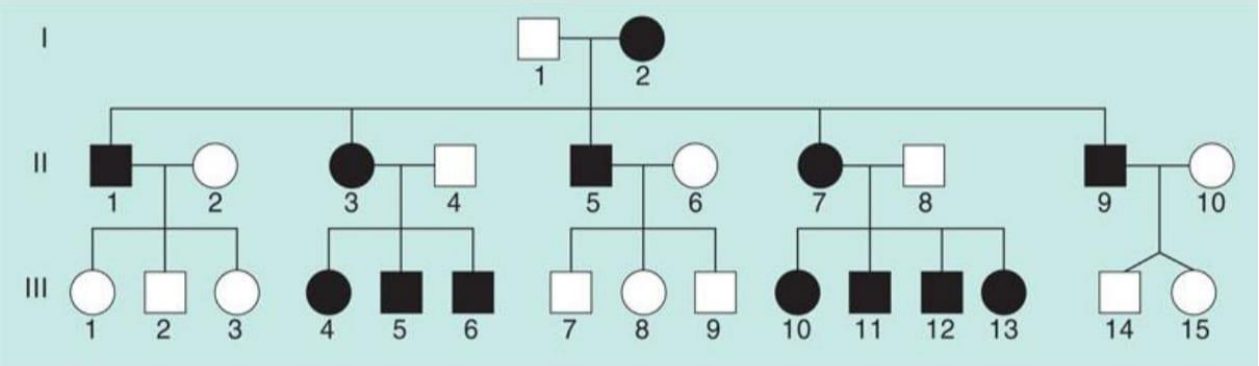
- No-skip generation.
- Every affected child has an affected parent.

- Notice boy no.3 in generation five is affected to an affected father, which excludes a sex-linked trait.

So, it's an autosomal dominant disease.

This disease is a rare disease called Huntington disease; it starts manifesting in adulthood (usually after 30). It's caused by a huge number of trinucleotide repeats.

Pedigree drawing 4:

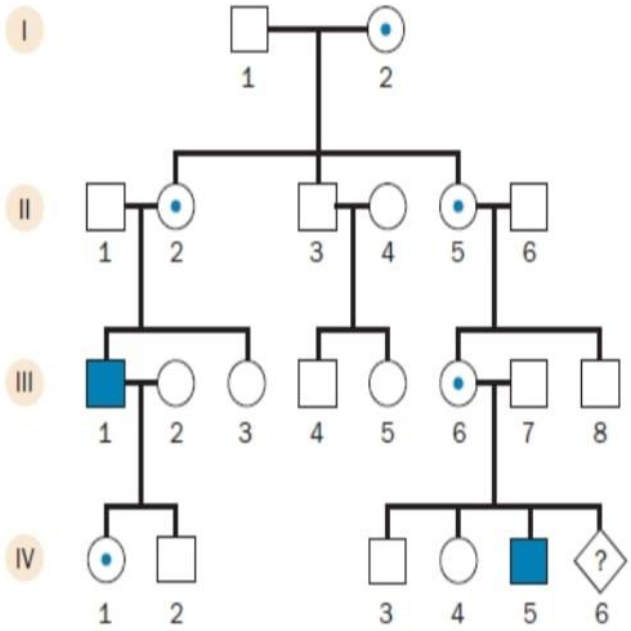


What features characterize this pattern of inheritance?

Notice every mother affected has all her children affected, which indicates it's mitochondrial inheritance. Remember, the egg is the source of mitochondria in the zygote because the sperm doesn't have any cytoplasm, which means the mother is the one responsible for providing all her children with the mitochondrial genome.

Remember what we said about individuals 14 & 15? They're non-identical twins.

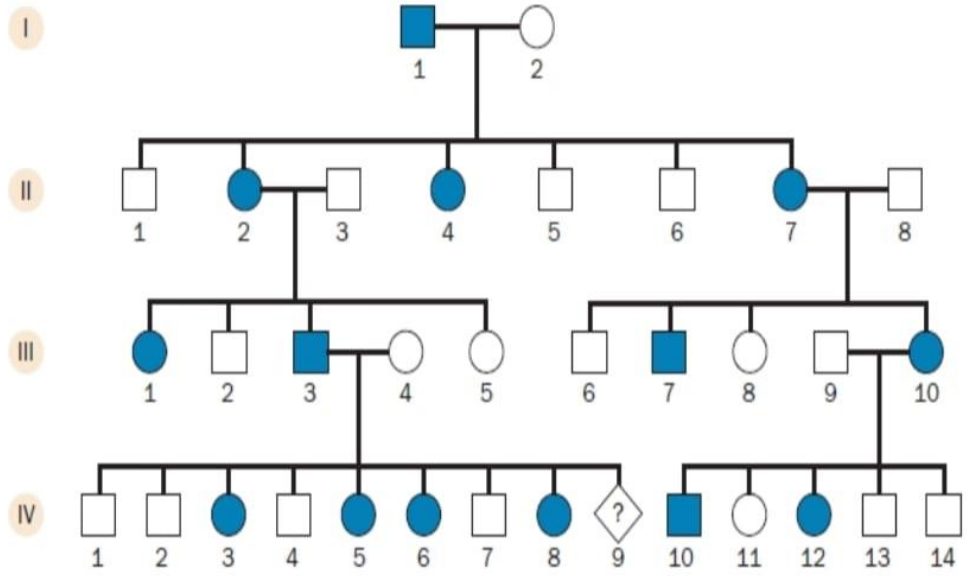
No.5:



This one is clear, since the dot symbol means a carrier for sex-linked traits, it's an x-linked recessive disease.

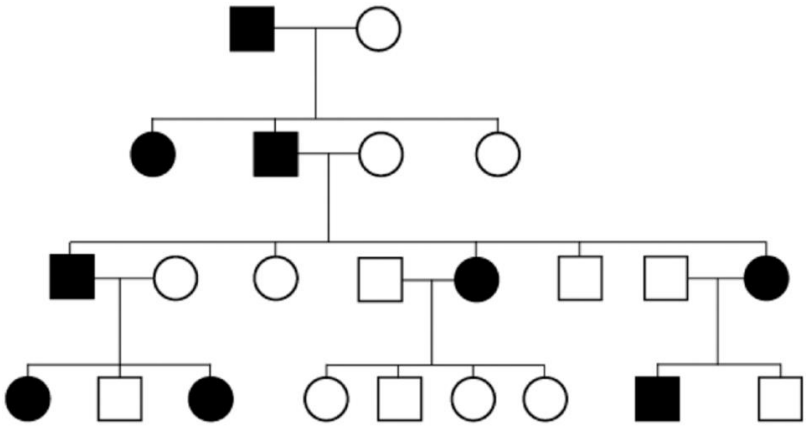
Let's assume that the dots are not present, how can we know it's an x-linked recessive trait?

- No females affected (M>F).
- Skip generation is present.



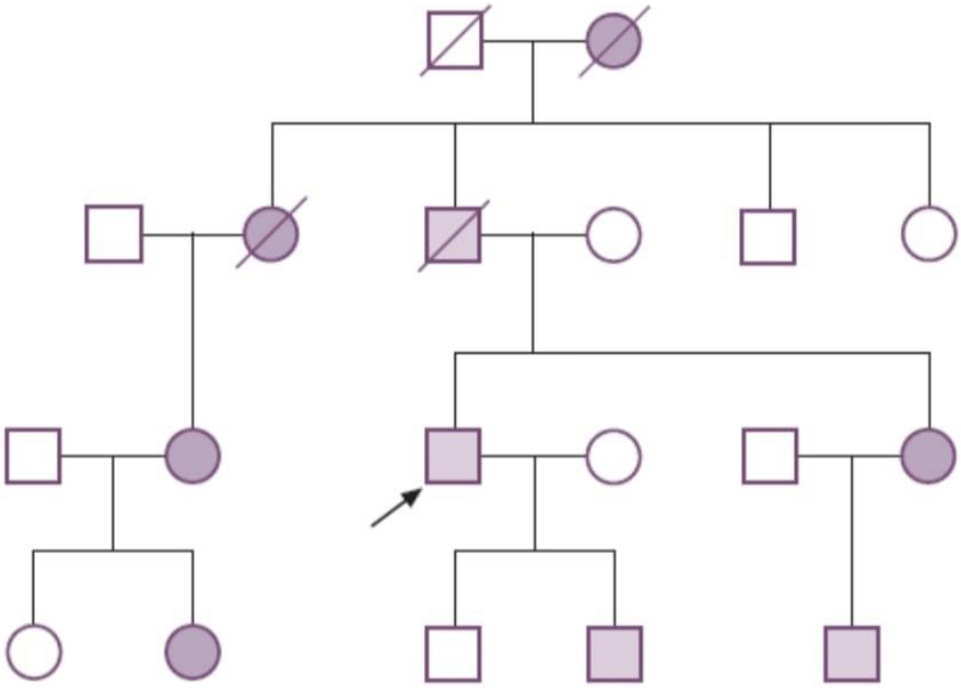
Here every affected father passed the disease to all of his daughters, which means it's x-linked dominant.

Next pedigree:



Which of the modes of inheritance is the most likely based on the pattern of people with the condition in this family?

Autosomal dominant. We can notice female to male ratio is 1:1.



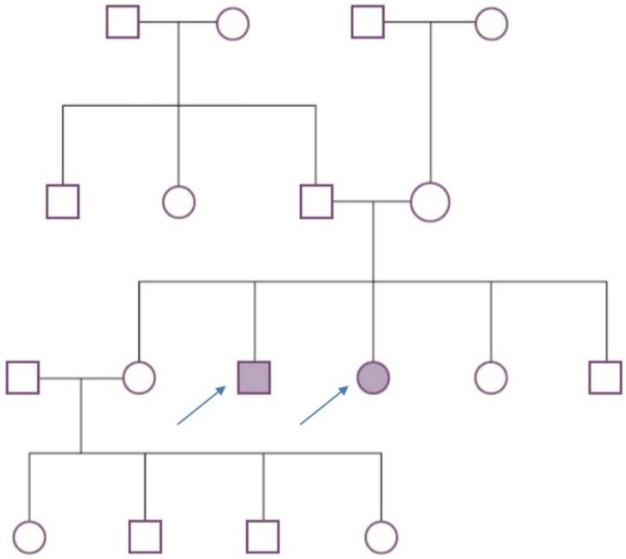
Which of the modes of inheritance is the most likely based on the pattern of people with the condition in this family?

We notice:

- No-skip generations
- Autosomal because there is male to male transmission (from the proband to his son)
- Every affected child has an affected parent

So, it's most probably autosomal dominant.

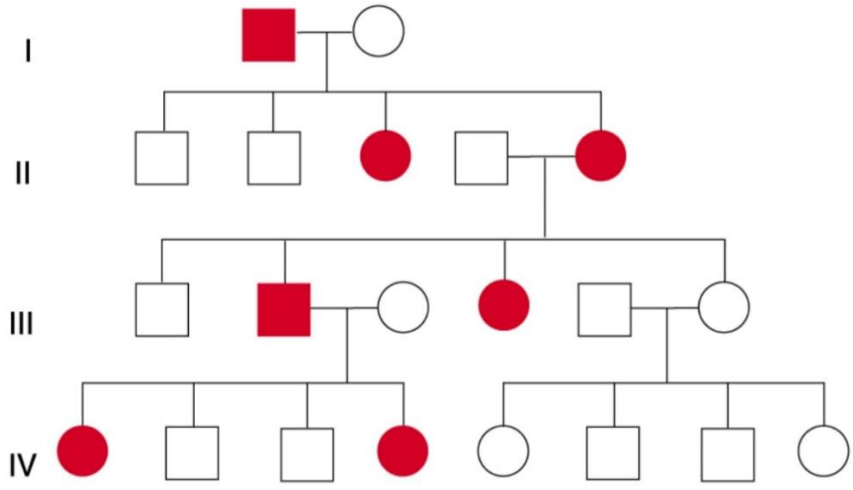
*This disease is familial hypercholesterolemia.



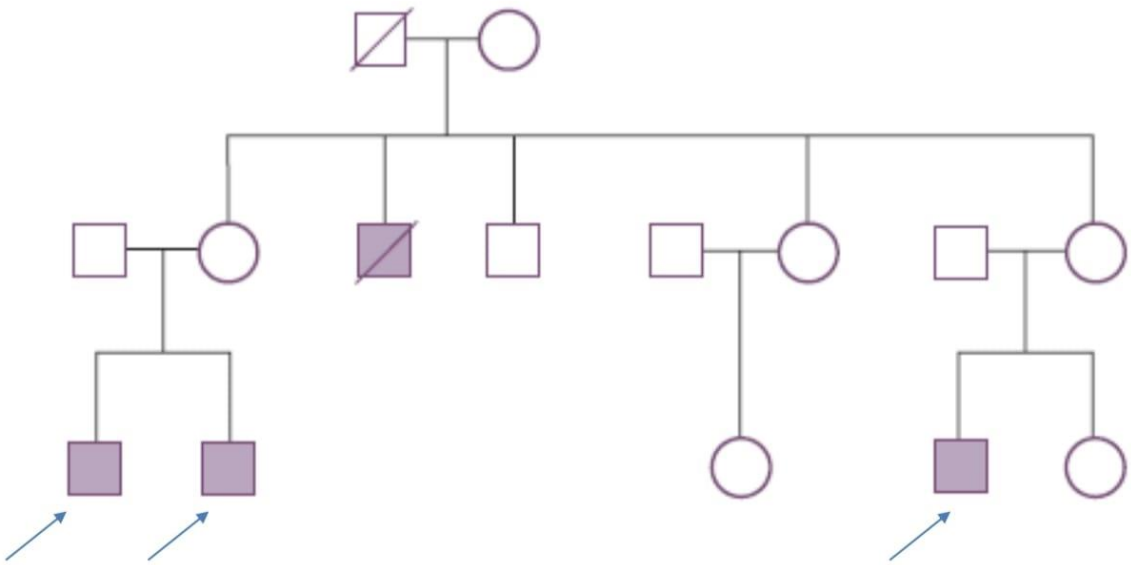
We can notice it's recessive because of the skip generation, and it's definitely not x-linked because there is an affected daughter to an unaffected father. So autosomal recessive it is.

Other clues: F:M is 1:1, affected children to unaffected parents.

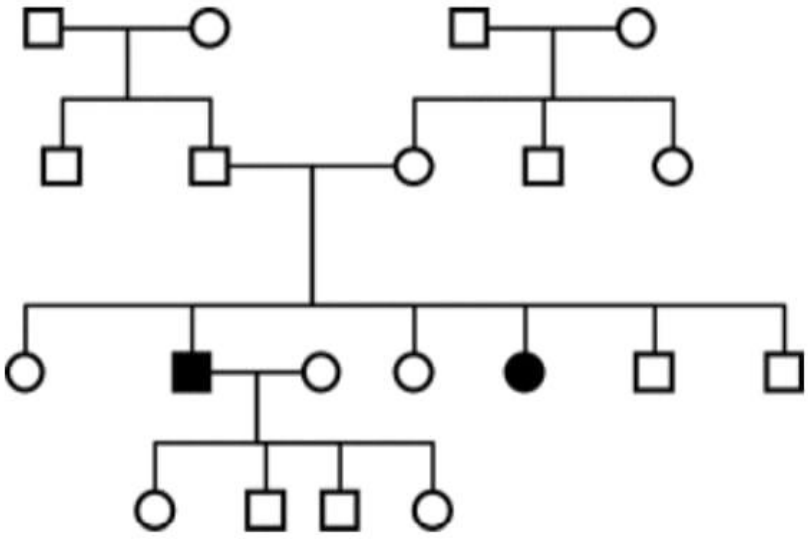
Let's move to the next one:



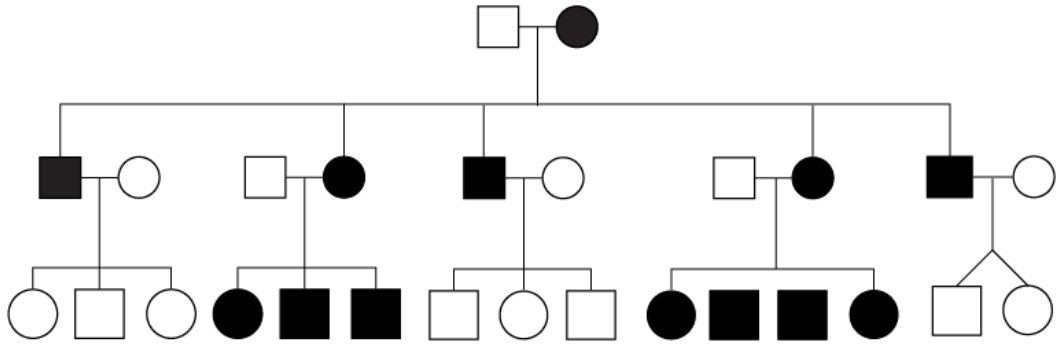
X-linked dominant, because every affected father has all of his daughters affected.



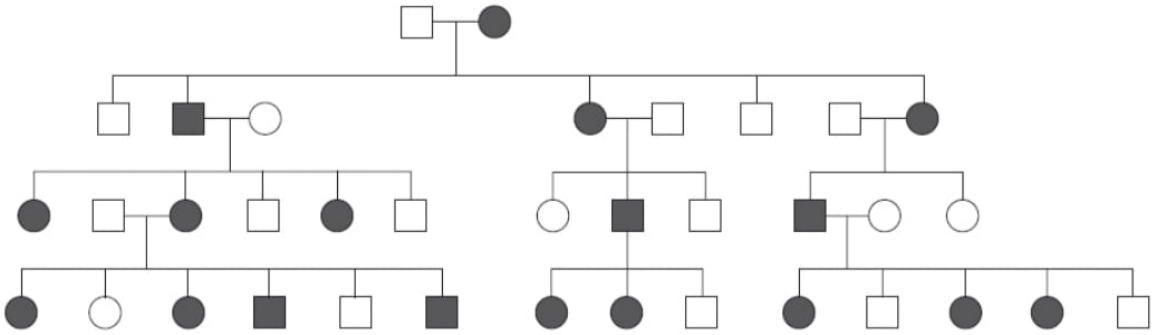
This on is X-linked recessive



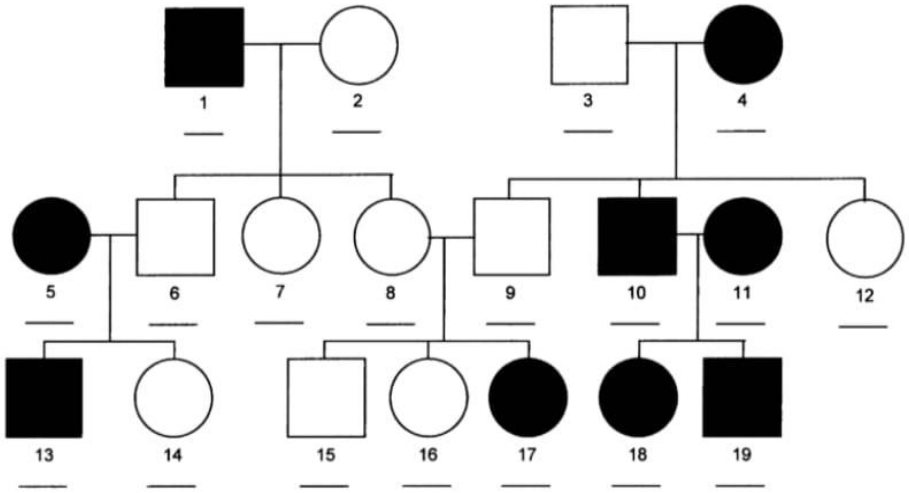
This one is also autosomal recessive.



The mode of inheritance in this one is mitochondrial.



X-linked dominant, affected fathers have all their daughters affected.



Autosomal recessive, because no.17 is affected but has no affected parents. You might think it's AD at first because of no-skip generations, but as mentioned before this rule is not always applicable.
Notice also that if both parents are affected (no. 10 & 11), all of their children are.

Assuming A: wild type, a: mutant allele, what is the genotype of the following individuals:

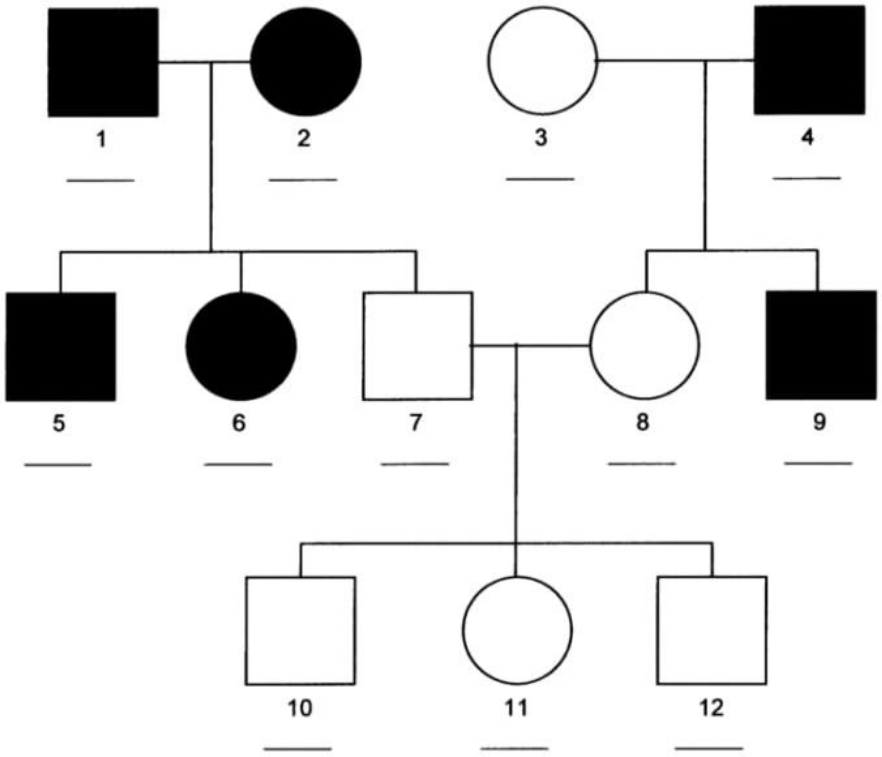
No.1: aa

No.3: Aa, why not AA although both have same phenotypes? Because he has affected children, meaning that he has passed to them a mutant allele.

No.6: Aa

No. 8&9: Aa

Last one:



Autosomal dominant. Not recessive because both parents 1&2 are both affected but they have unaffected offsprings.

Considering A: dominant allele, a: recessive allele, what is the genotype of:

No. 1&2: both are Aa, because their son no.7 is unaffected.

No.3: aa

No.4: Aa

No. 7&8: aa

The End

رَبَّنَا أَفْرِغْ عَلَيْنَا صَبْرًا وَثَبِّتْ أَقْدَامَنَا وَانصُرْنَا عَلَى الْقَوْمِ الْكَافِرِينَ

V2: highlighted