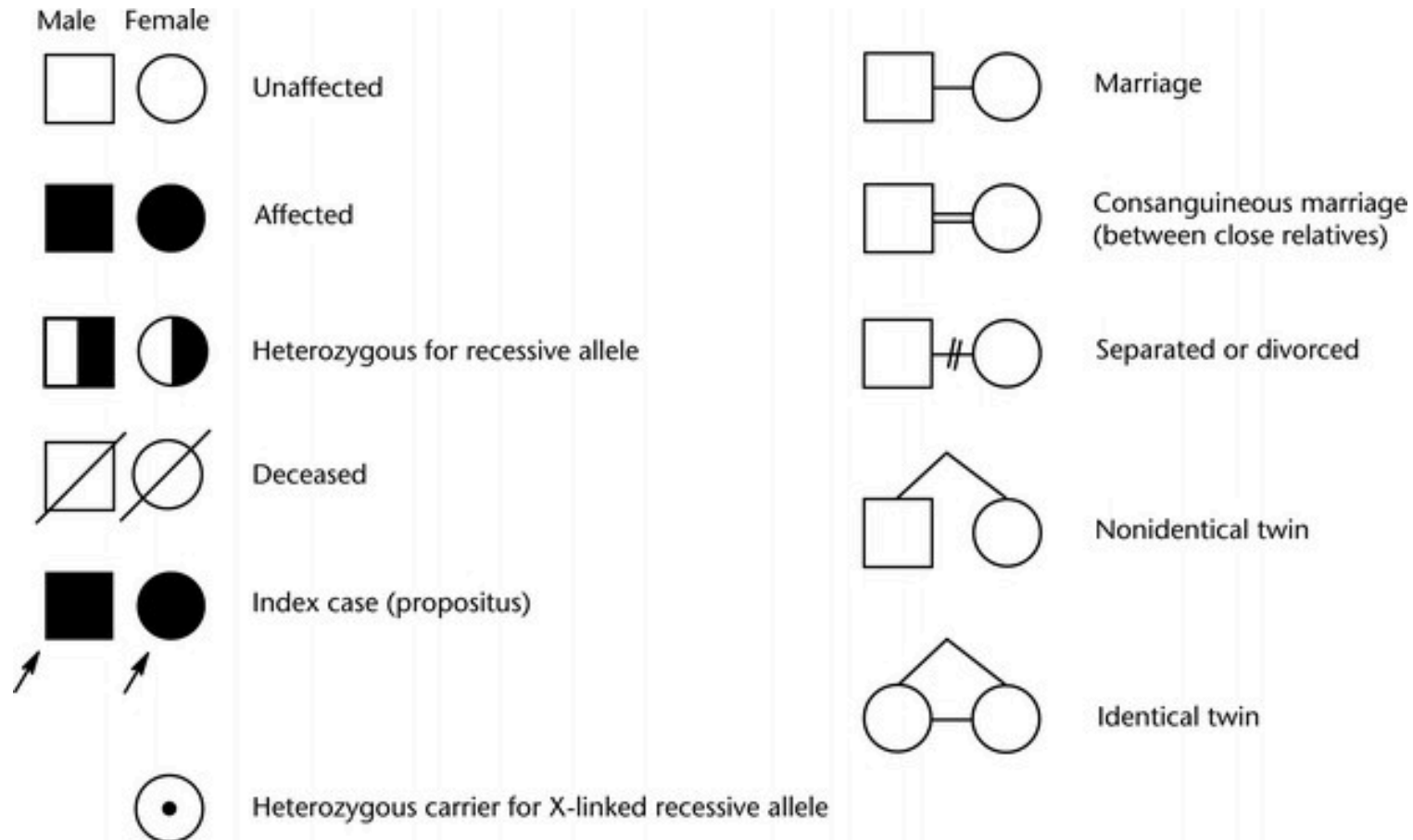


GENETICS - PROBLEMS

GENEALOGICAL TREES (PEDIGREE)

Systematic presentation of family history using standardized symbols

PROBAND: the first individual studied in which there is a certain character and from which we start to build a family tree that will help determine whether the character is hereditary and how it is transmitted



Problem 1

A female proband who suffers from an unidentified disease addresses a genetic Counsellor before starting a family.

Based on the following data, build her family pedigree:

1. The proband's maternal grandfather is affected by the disease in question
2. Proband's mother is not affected and is the youngest of 5 children, of which the first three males
3. The proband has an older sister who suffers from the disease, but the two younger brothers, twins, a boy and a girl, are not affected.

PEDIGREE

Once the pedigree is defined, Mendel's hereditary transmission principles are used to determine how is the character in question transmitted

AUTOSOMAL RECESSIVE

AUTOSOMAL DOMINANT

X LINKED DOMINANT

X LINKED RECESSIVE

Y LINKED

MITOCHONDRIAL INHERITANCE

Why is it important to establish how a character is transmitted?

Can be used to predict the risk of contracting a genetic disorder in general situations (during a pregnancy, in adulthood, for future offsprings...)

DOMINANT OR RECESSIVE?

DOMINANT: each trait or character that is expressed in the heterozygous, that is, in case of illness, where only one copy of the defective gene is sufficient to express the affected phenotype

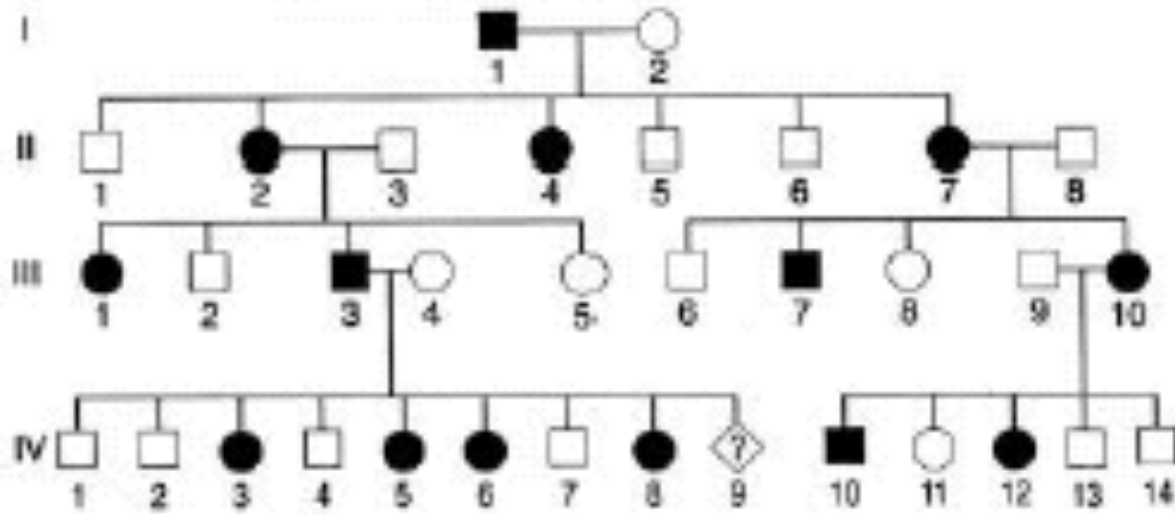
RECESSIVE: each trait or character that is expressed only in the homozygous, i.e., in case of illness, in which both copies of the defective gene must be present to express the affected phenotype

PEDIGREE ANALYSIS

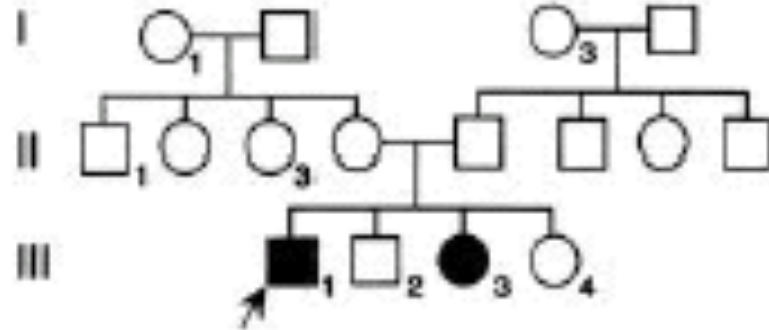
Vertical and horizontal transmission: indicative criterion, not absolute rule

1. **Vertical transmission**, i.e., successive generations of affected individuals, hereditary transmission potentially **DOMINANT**

2. **Horizontal transmission**, i.e., presence of many affected individuals within one generation, but only a few in previous or successive generations (generational jump), hereditary transmission potentially **RECESSIVE**



VERTICAL TRANSMISSION



HORIZONTAL TRANSMISSION

Problem 2

In an **autosomal dominant disease**, what is the probability of an affected individual in case of:

- a. One affected and one healthy parents?
- b. Both affected parents?

NOTE In the case of dominant autosomal diseases, **upper case letters** indicate alleles that cause the disease in a heterozygous state

Pedigree analysis: autosomal dominant inheritance (AD)

- if a parent is affected, on average 50% of the offsprings will be affected
- if the penetrance of a character is complete (100%), the children of healthy parents are not at risk of being affected
- the autosomal character expresses itself both in males and females, who are affected more or less in the same proportion
- If an affected individual has healthy parents and the penetrance of the character is complete, the individual has a new mutation; his/her children have a risk of 50% to be affected if the mutation is in the germline, but his/her siblings will have a low risk of recurrence
- individuals affected are generally heterozygous, because the affected homozygotes are much rarer

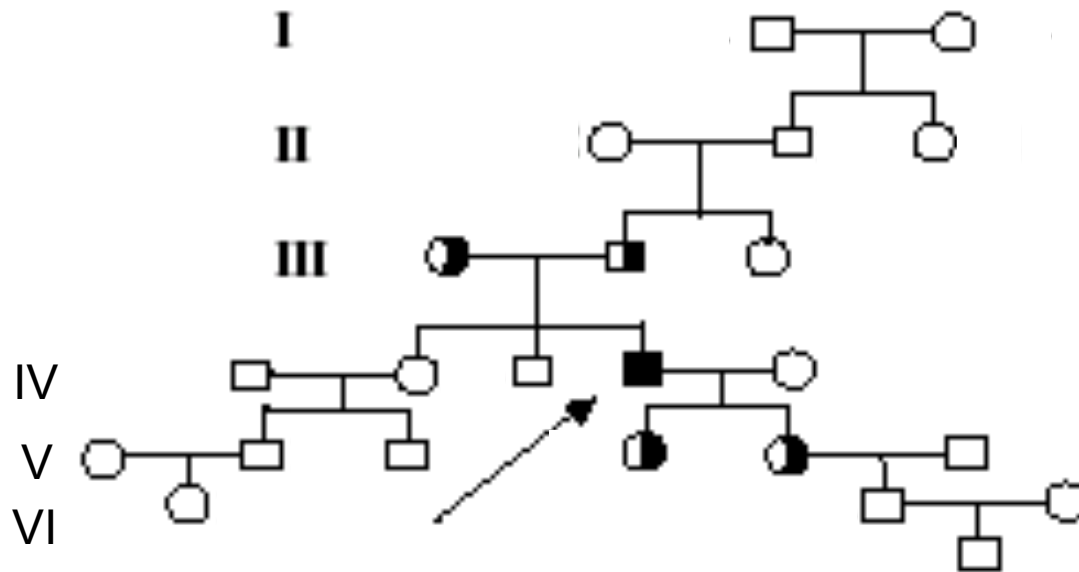
Problem 3

In a condition of **autosomal recessive disease**, what is the probability to be affected in case of:

- a. One healthy and one carrier parents
- b. Both carrier parents
- c. One affected and one carrier parents

NOTE In the case of recessive autosomal diseases, **lower case letters** indicate alleles that cause the disease in a homozygous state: both alleles have to be mutated in order to produce a pathological phenotype

Problema 4



Calculate the probability to be a heterozygous carrier for as many as possible individuals in this family affected by an autosomal recessive syndrome.

Pedigree analysis: autosomal recessive (AR)

The autosomal character is expressed in both males and females, who are affected in more or less the same proportion. Both parents can transmit the character

- parents and children of affected individuals are OBLIGED carriers
- The risk of being a carrier is divided by 2 in every generation (following and prior to that of the carrier established)
- Two carriers (heterozygous) generate children: 1/4 affected, 2/4 carriers, 1/4 homozygous normal
- the unaffected brothers have a probability of 2/3 to be carriers (1 normal homozygous+2 carriers =3 not affected)
- if the disease is rare, you can assume that people outside of the family are homozygous normal, or you can use the frequency of the carriers in the general population

Problem 5

A couple presents to the genetic counsellor: they are planning to have children, but the man's sister is affected by galactosemia, a rare autosomal recessive disease caused by an inability to degrade galactose. This disease causes the malfunction of the musculature, the nervous system and the kidneys.

What is the probability for the couple to have an affected child, knowing that the frequency of the healthy carriers for galactosemia is 2% in the general population?

Problem 6

Data:

- 1) The female proband shows the character.
- 2) Neither her husband, nor her only and older male sibling show the character.
- 3) The female proband has had 5 children from her current husband. The oldest is a male, followed by a female, then by another male and finally by two female monozygotic twins. Only the second born (a female) does not show the character.
- 4) Both proband's parents show the character.

- A. Construct the pedigree of this character in the family.
- B. Determine how it is inherited.
- C. Can you deduce the genotype of the proband's husband for this character?

Problem 7

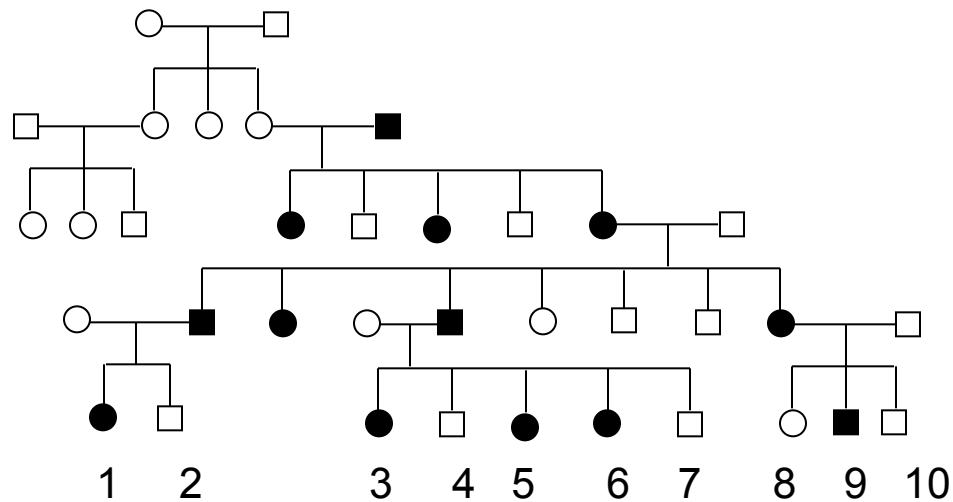
Phenylketonuria (PKU) is a human hereditary disease resulting from the inability of the body to degrade the phenylalanine, which is contained in the proteins ingested with food. The PKU manifests itself in early childhood and, if not treated, leads to mental retardation. The disease is caused by a recessive allele transmitted with simple Mendelian inheritance.

A couple wants to have children and decides to consult a genetic counselling center because the man has a sister affected by PKU and the woman has a brother with the same disease. In addition to these, in the two families there are no other cases of PKU. The two spouses ask the geneticist to determine the probability that their first child is suffering from PKU. How do you calculate this probability?

You can call p the allele that causes PKU and P the normal allele.

Problem 8

A rare human disease recurs in a family following the below presented pedigree:



- Hypothesize the most probable type of transmission for the disease.
- What will be the resultant offsprings for marriages between cousins, in particular 1x9, 1x4, 2x3 e 2x8?

Pedigree analysis (X- or Y-linked)

- From affected individual you examine the tree to previous and next generations
 - unaffected females who transmit the disease to 50% of males, are likely carriers: **X-linked recessive** inheritance is likely
 - affected males who transmit the disease to all their daughters: **X-linked dominant** inheritance is likely
 - males who transmit the disease to all sons and not to daughters: **Y-linked** inheritance is likely
- Ratio of affected males to affected females
 - more affected males in **X-linked recessive** diseases
 - Only affected males in **Y-linked** diseases

Pedigree analysis: X-linked dominant

- Affected males generate only affected daughters and no affected sons
- A heterozygous female suffering from the diseases will transmit the character to half of her children and both males and females are equally affected
- On average, females are twice as affected by these diseases

Pedigree analysis: X-linked recessive

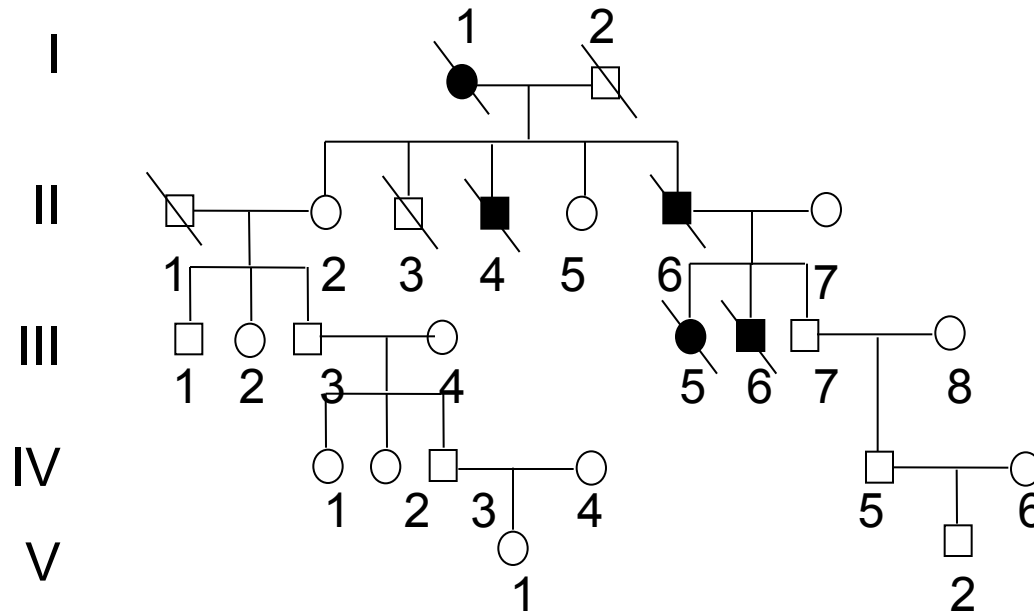
- Are affected the hemizygous males and homozygous females
- Phenotypic expression is much more common in males than females and, in the case of rare alleles, virtually only males are affected
- Affected males inherit the mutated allele from their mothers and transmit it to their daughters, but not to their sons
- Daughters of affected males are usually heterozygotes and so they are not affected; sons of heterozygous females have a 50% probability to receive the recessive mutated allele

Pedigree analysis: Y-linked inheritance

- These characters are present only in males
- Characters are transmitted directly from fathers to sons
- All Y-linked characters are expressed, as males are hemizygotes for all genes mapping on Y chromosome

Problem 9

Huntington disease (HD) is a nervous system disease with a late onset. The below pedigree regards the presence of the disease in a family.



a) What type of transmission is compatible with this pedigree?

Problem 10

The grandfather of a man is affected by galactosemia. The man has married a woman whose sister is also affected. The woman is now pregnant, expecting her first child.

- a) Draw the family pedigree
- b) What is the probability that this child develops galactosemia?
- c) If the first child is affected, what is the probability that a second child has the disease?

Problem 11

We describe a couple formed by a man and a woman, who has 2 children, a phenotypically normal daughter and a son suffering from a certain disease.

The phenotypic ratio is 1:1.

This makes it difficult to determine whether a character is autosomal or sex related.

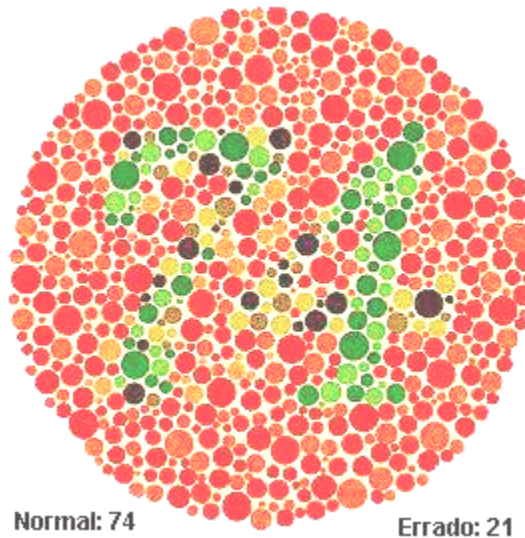
a) based on your knowledge of genetics, can you determine what are the genotypes of parents and children in the case it's autosomal?

b) and in case of transmission related to sex?

Problem 12

Daltonism in man is often caused by a recessive allele, X-linked.

Betty sees normally, but her mother is color blind. Bill is daltonic. If Bill and Betty had a child, what is the probability that this child is affected by daltonism?



Problem 13

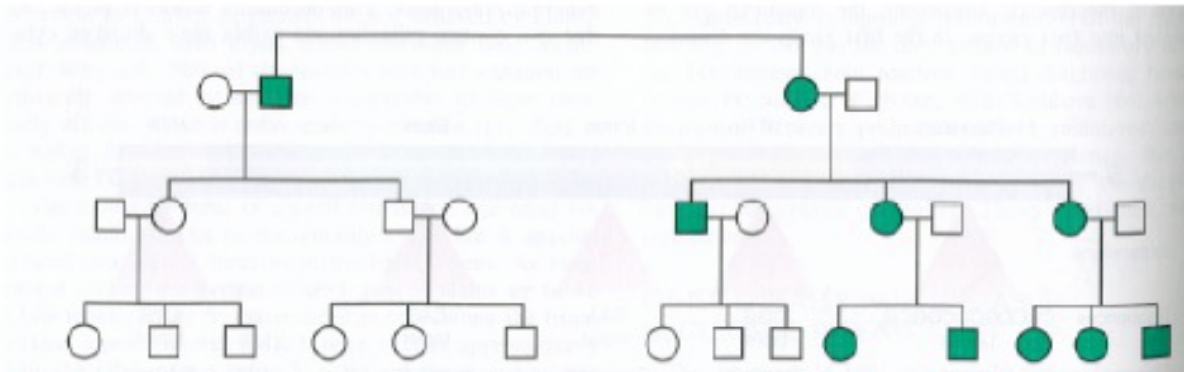
In humans, the most common form of hemophilia is controlled by a recessive gene associated with sex.

- a) An affected daughter is born from a normal couple. The husband asks for a divorce by accusing his wife of infidelity. Is he right?
- b) A healthy son is born from a couple where the husband is hemophilic. Spouses are worried that the baby had been switched at the hospital. Is it a well-founded fear?

Problem 14

Pedigree della Malattia di Leber

Leber's hereditary optic neuropathy (LHON)



What type of inheritance is compatible with this pedigree?

Problem 15

LHON is caused by a mutation in a mitochondrial gene.

- a. Assuming that the man in a couple suffers from the disease, while the woman does not, how could their first child be?
- b. What would be the result if the man was healthy and the woman was suffering from the disease?

Pedigree analysis: mitochondrial inheritance

- The mitochondria, and therefore the mtDNA, are transmitted from mothers to their children through the cytoplasm of the egg.
- **Maternal Inheritance:** mtDNA mutations are only transmitted from mother
- inheritance of the mitochondrial genome has another feature in addition to maternal transmission, a phenomenon known as **heteroplasmy**, i.e. the coexistence, in the same cell, of normal mtDNA copies and copies of mutated mtDNA, which determine characteristic familiar pathological processes

