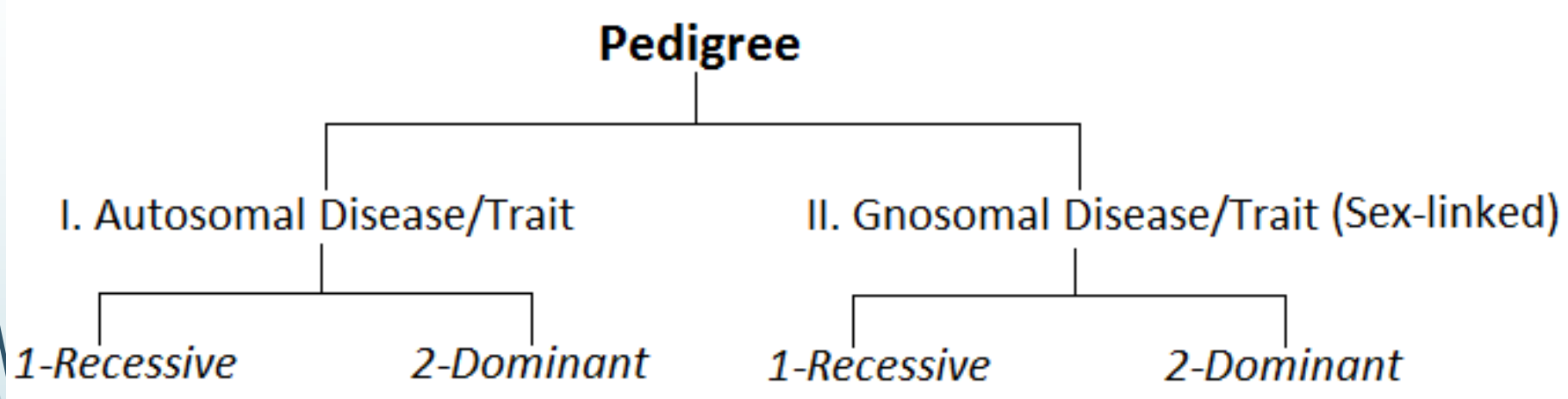
Chapter 5: Human Genetics

- Document 1: Inheritance of Genetic Traits
- Document 2: Autosomal Diseases
- Document 3: Sex-linked Diseases
- Document 4: Chromosomal Abnormalities
- Document 5: Prenatal Diagnosis

Document 2

Autosomal Diseases


Pedigree
I. Autosomal Disease/Trait
II. Gnosomal Disease/Trait (Sex-linked)
1-Recessive
2-Dominant
1-Recessive
2-Dominant

I. Autosomal Diseases:

- They are caused by genes located on autosomes.
- example:

1) Cystic fibrosis, a recessive disease; the gene for this disease is carried by autosomal **chromosome 7.**

• Cystic fibrosis is a severe disease due to the secretion of excessively viscous mucus by mucus glands, leading to respiratory and digestive problems.

- In the respiratory tract, the excessive mucus blocks the bronchi, causing difficulties in breathing and providing a permanent site for infection.

- In the pancreas, the secretory canaliculi and the excretory cells of the pancreas degenerate.

The gene for cystic fibrosis is found on the pair of autosomal chromosomes 7.

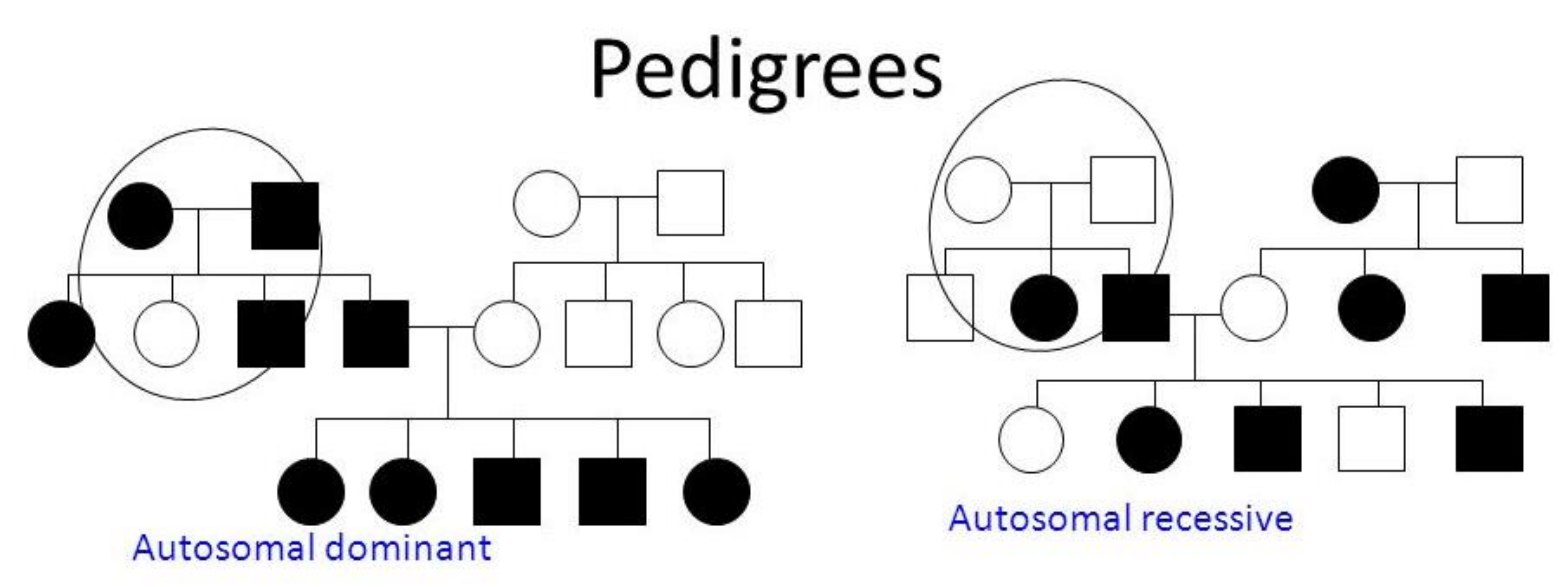
2) Huntington's Chorea, a dominant disease; the gene for this disease is carried by autosomal **chromosome 4.**

Huntington's disease, also known as Huntington's chorea, is a hereditary disease that appears only in adults between 30 and 50 years old. The symptoms are uncontrolled incoherent movements and psychological troubles. This disease is due to a lesion of certain neurons of the central nervous system. It occurs with a very low frequency: 0.4 to 0.8 in 10000 individuals.

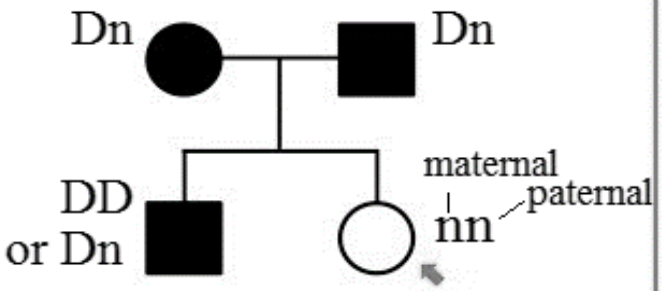
The gene for Huntington's chorea is carried by the autosomal chromosome 4.

II. Criteria for determining if a Disease or Trait is Dominant or Recessive

- ***If the disease is recessive*** ⇨ affected children have usually unaffected parents in any generation I, II…)
- ***If the disease is dominant*** ⇨Every affected child should have at least 1 affected parent in any generation.



AUTOSOMAL DOMINANT



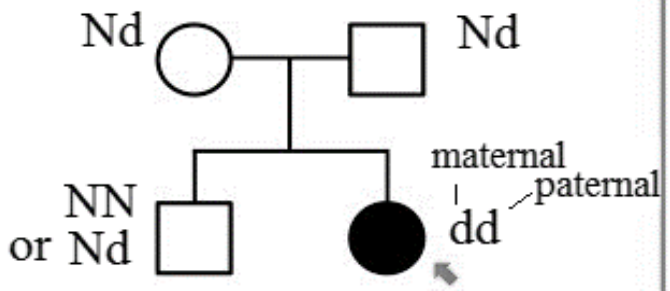
Cannot be recessive as two affected parents could **not** have an unaffected offspring

Parents MUST be heterozygous

- D : symbol of the **disease** which is **dominant**.
- n : symbol of the normal which is recessive.

♀ \ ♂	D	n
D	DD	Dn
n	Dn	nn

AUTOSOMAL RECESSIVE



Cannot be dominant as two unaffected parents could **not** have an affected offspring

Parents MUST be heterozygous

- N : symbol of the normal which is dominant.
- d : symbol of the **disease** which is **recessive**.

♀ \ ♂	N	d
N	NN	Nd
d	Nd	dd

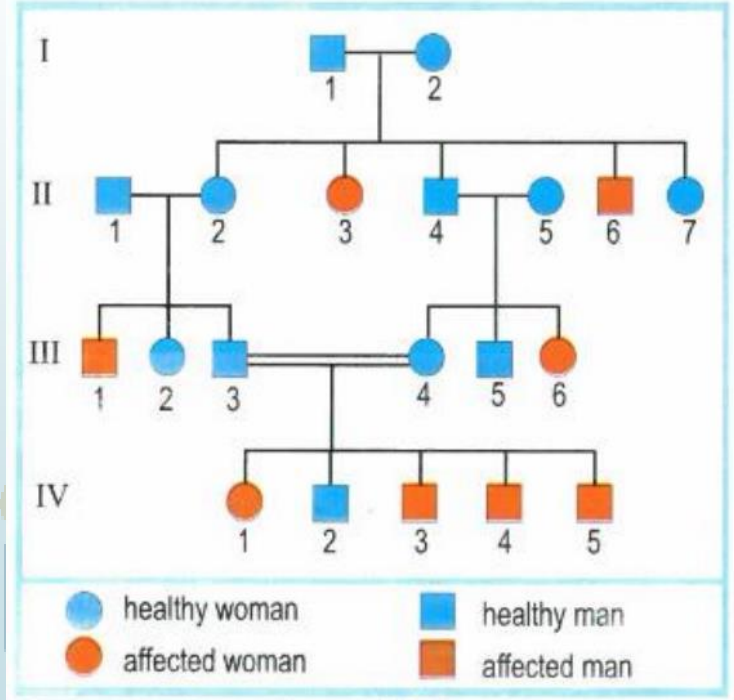
- **Application 1:**

Document a shows the inheritance of cystic fibrosis.

1- Indicate if the gene of Cystic fibrosis is dominant or recessive. Justify.

The allele responsible for Cystic Fibrosis is recessive with respect to the normal allele. Since the parents I-1 and I-2 are phenotypically normal but they gave birth to two diseased children II-3 and II-6. This proves that the parents carries this mutated allele that is masked by the normal allele in the phenotype.

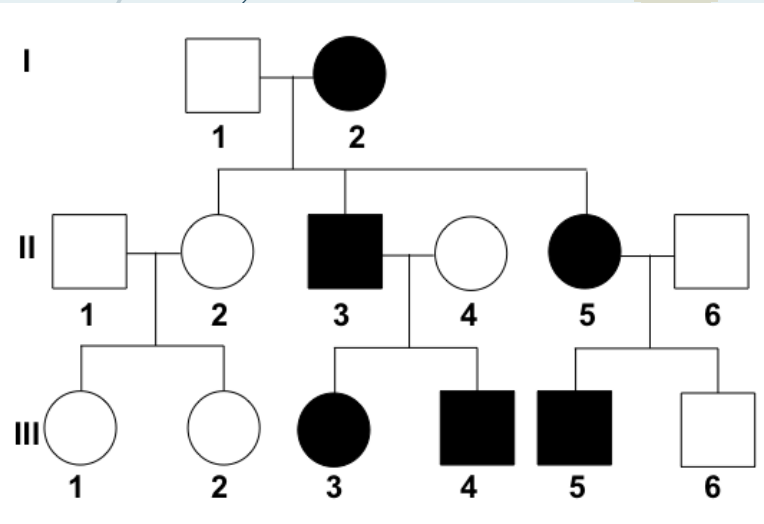
Let "N" be the symbol of the normal dominant allele and "d" the symbol of the recessive allele responsible for cystic fibrosis disease.

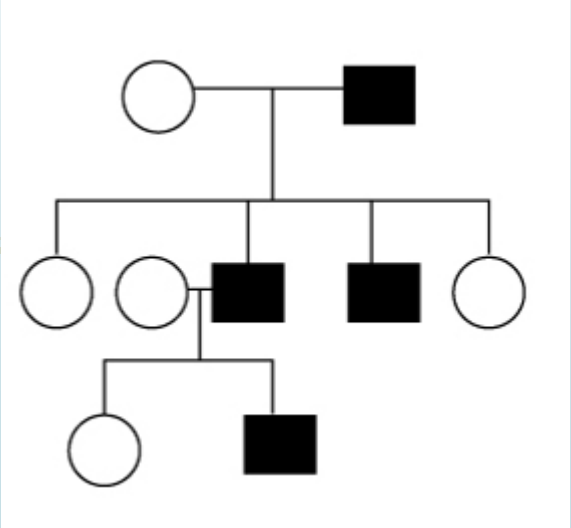


Doc.a Inheritance of cystic fibrosis.

III. Localization of the Allele or Gene (Autosomal or Gonosomal)

- If it is given that the disease is rare ⇨ most probably it would be gonosomal.
- If the disease affects only 1 gender (either males or females) ⇨it is gonosomal.
- If the disease affects both genders (males and females) ⇨ most probably it is autosomal.

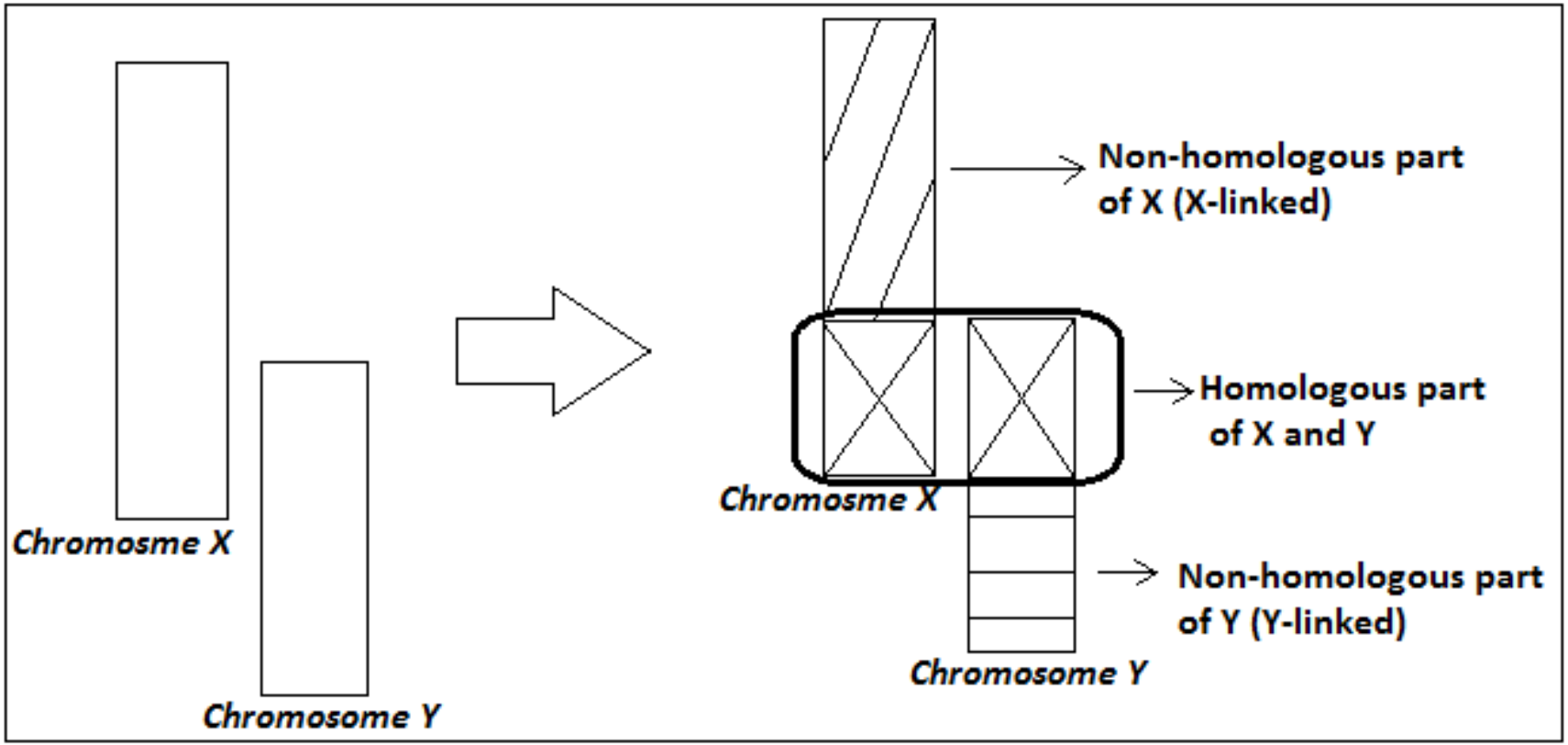




→ To determine that the disease is autosomal using a pedigree, we should prove that it's not gonosomal (by negation).

→ Not gonosomal ⇨ autosomal.

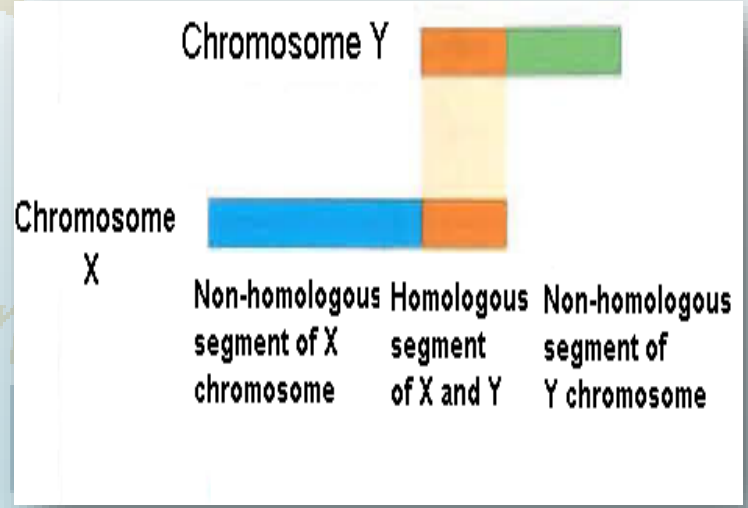
- Doc.1 shows a schematic representation of X and Y sex chromosomes.



Doc.1 A schematic representation of X and Y gonosmes

➢ In case of gonosomal diseases, the gene may be located on:

1. Non-homologous part of X (X-linked) or
2. Non-homologous part of Y (Y-linked) or
3. Homologous part of X and Y.



- Doc.2 shows the possible genotypes for males and females at different gonosomal gene localization.

Note: - Gonosomes in male are: X and Y (non-homologous).
- Gonosomes in female are: X and X (homologous).

Localization of a gene on gonosomes / Gender	***X-linked***	***Y-linked***	***Homologous part of X and Y***
Female	(females will carry 2 alleles) X^NX^N ***or*** X^NX^d ***or*** X^dX^d	(females will not carry any allele) XX	(females will carry 2 alleles) X^NX^N ***or*** X^NX^d ***or*** X^dX^d
Male	(males will carry 1 allele) X^NY ***or*** X^dY	(males will carry 1 allele) XY^N ***or*** XY^d	(males will carry 2 alleles) X^NY^N ***or*** X^dY^N X^NY^d X^dY^d

Doc.2

SEX CHROMOSOMES

Document 3 represents the sex chromosomes X and Y and their segments.

2- Indicate the true statements and correct the false ones.

2.1- The male possesses two identical sized sex chromosomes.

False, The male possesses two different sized sex chromosomes.

2.2- Genes located on the non-homologous segment of X chromosome exist in one copy in males and two copies in females.

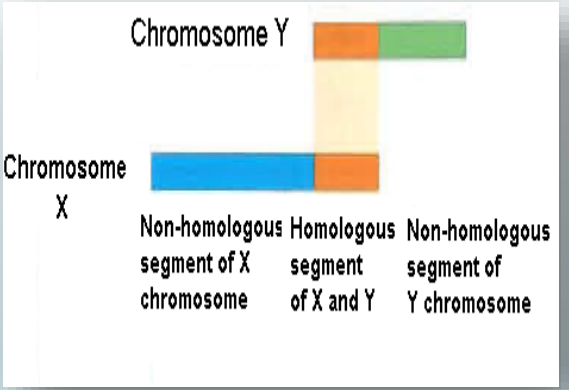
True.

2.3- A gene located on the non-homologous segment of Y chromosome is transmitted from the father to his male and female children.

False, a gene located on the non-homologous segment of Y chromosome is transmitted from the father to his male children.

2.4- Genes located on the homologous segment of X and Y chromosomes have two alleles in both males and females.

True.



Document 3: Sex chromosomes segments (CRDP)

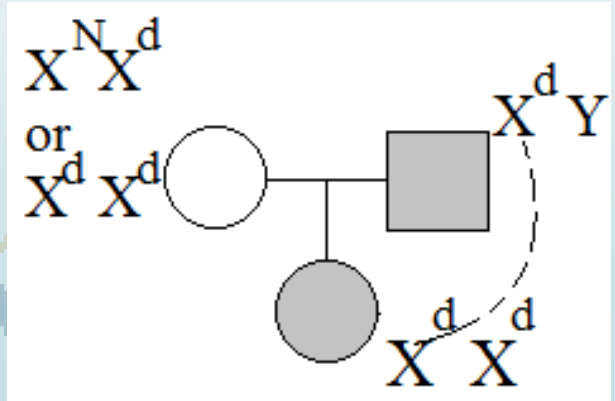
- **How to know if the gene is X-linked, Y-linked or if it is located on the homologous part of X and Y?** (For a recessive case).

→ If the gene is X-linked

⇨ all affected daughters must have affected fathers.

☞ Look for affected girl and her father.

-Any affected girl must have an affected father, or it's not the case.

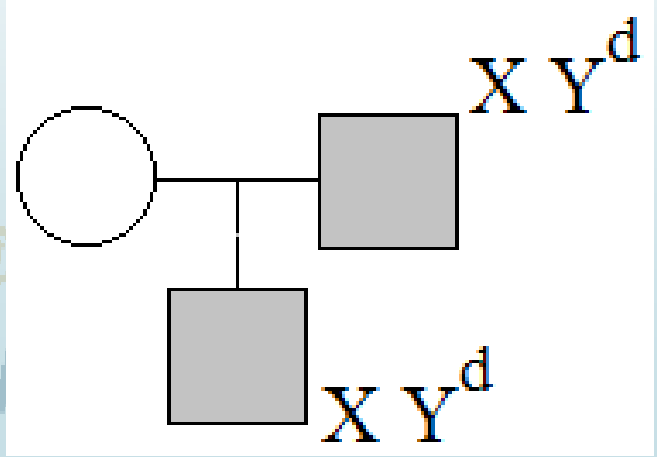


→ If the gene is Y-linked

⇨ all affected sons must have affected fathers.

☞ Look for affected son and his father.

-Any affected boy would necessarily have an affected father (or girls should not be affected), or it's not the case.

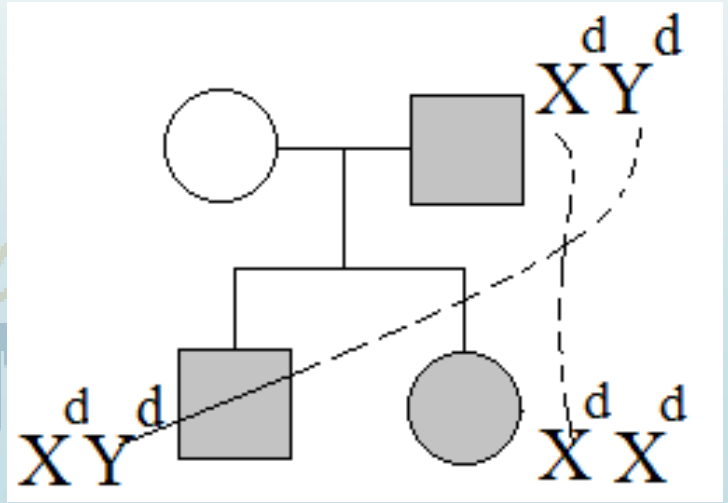


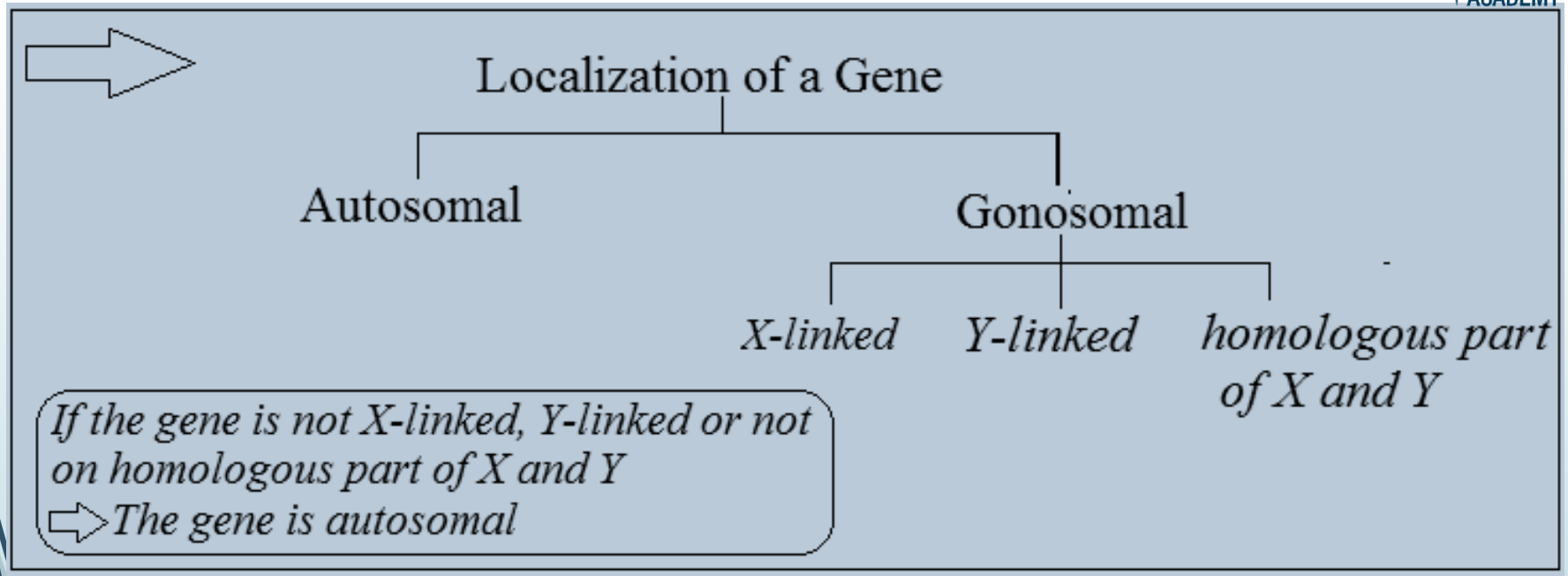
→ If the gene is located on homologous part of X and Y

⇨affected siblings (daughter and son) should have an affected father.

☞ Look for affected siblings and their father.

-Any affected siblings must have an affected father, or it's not the case.



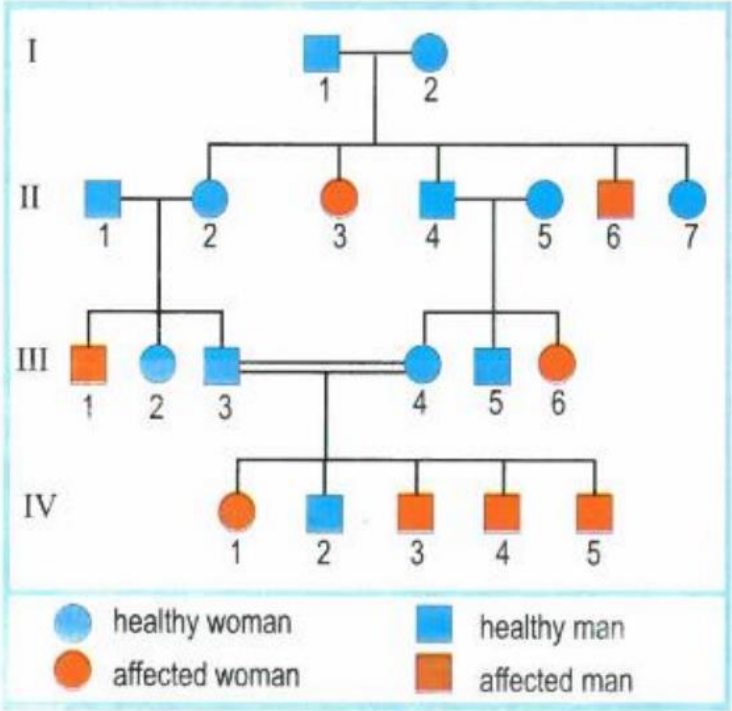

Localization of a Gene
Autosomal
Gonosomal
X-linked
Y-linked
homologous part of X and Y
If the gene is not X-linked, Y-linked or not on homologous part of X and Y
The gene is autosomal

- Application 2:

- Referring to Doc.a, p.94, answer the following questions:

1. Determine the localization of the gene of cystic fibrosis.

The pedigree shows that both genders are affected , so most probably it is autosomal.
Suppose its gonosomal:
If it is carried by the non-homologous segment of Y chromosome (Y-linked), any affected boy would necessarily have an affected father (or girls should not be affected). The affected boy II-6 who has XY^d as genotype must have taken Y^d from his father I-1 who would have as genotype $X//Y^d$ and he would be affected, but he is not, which is not the case.

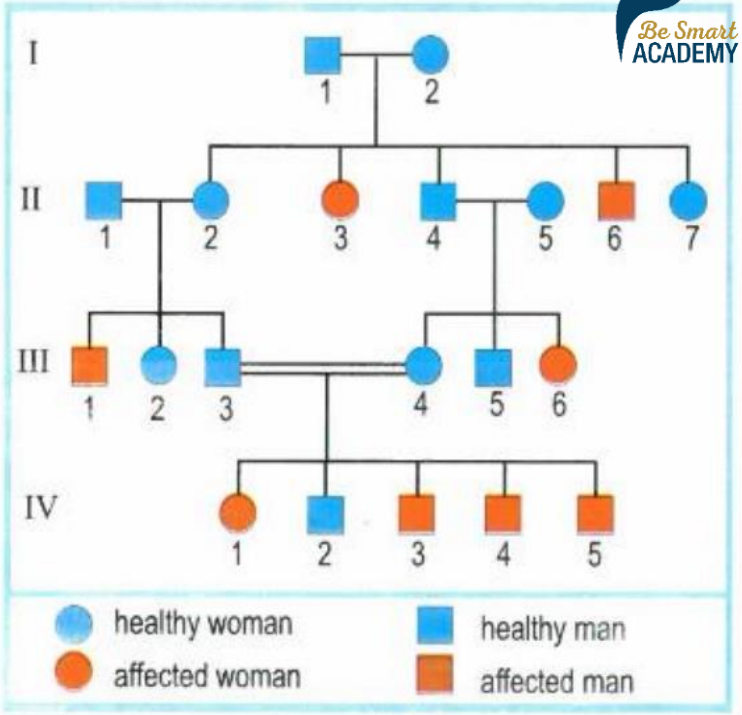


Doc.a Inheritance of cystic fibrosis.

If the CF gene is carried by the non-homologous segment of X chromosome(X-linked), the affected daughter II-3 would have $X^d//X^d$ as genotype (purity is the criterion of recessivity), she should have taken X^d from her father I-1 who would have as genotype $X^d//Y$ and who phenotypically should be affected, but her father is healthy, which is not the case.

If the CF gene is carried by the homologous segment of X and Y, the affected boy II-6 would have as genotype $X^d//Y^d$, and his sister II-3 would have as genotype $X^d//X^d$. They have taken respectively Y^d and X^d from their father I-1. This latter should have as genotype $X^d//Y^d$ and would be phenotypically affected, but he is healthy, which is not the case.

So CF gene is autosomal.



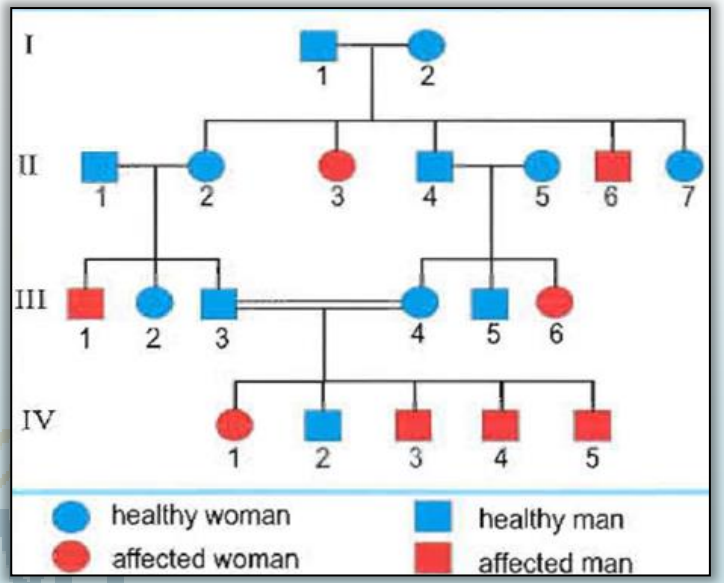
Doc.a *Inheritance of cystic fibrosis.*

GENOTYPES IN A CF PEDIGREE

In a pedigree, the real genotype of an individual can be drawn out from his phenotype and from the phenotype of his parents or his children.

2- Specify the genotype(s) of individuals I-1, III-6 and IV-2.

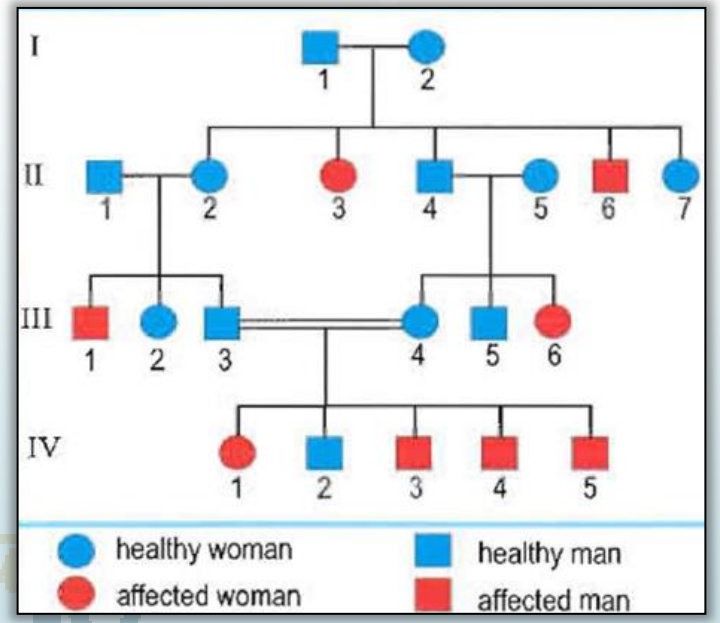
The genotype of individual I-1 is N//d, since he is normal which means that he possesses the dominant normal allele N. Furthermore, he has diseased children II-3 and II-6 of genotype d//d, where each of the two alleles is received from one parent, then the father I-1 possesses the allele d. Thus, I-1 is heterozygous of genotype N//d.



Document 5: Inheritance of cystic fibrosis (CRDP)

The genotype of individual III-6 is dd since she is diseased which means that she has the allele responsible for the disease that is recessive. This allele is expressed phenotypically only when it is present in two copies (purity is a criterion of recessivity). Thus, she is homozygous and inherited the allele d from each one of her parents.

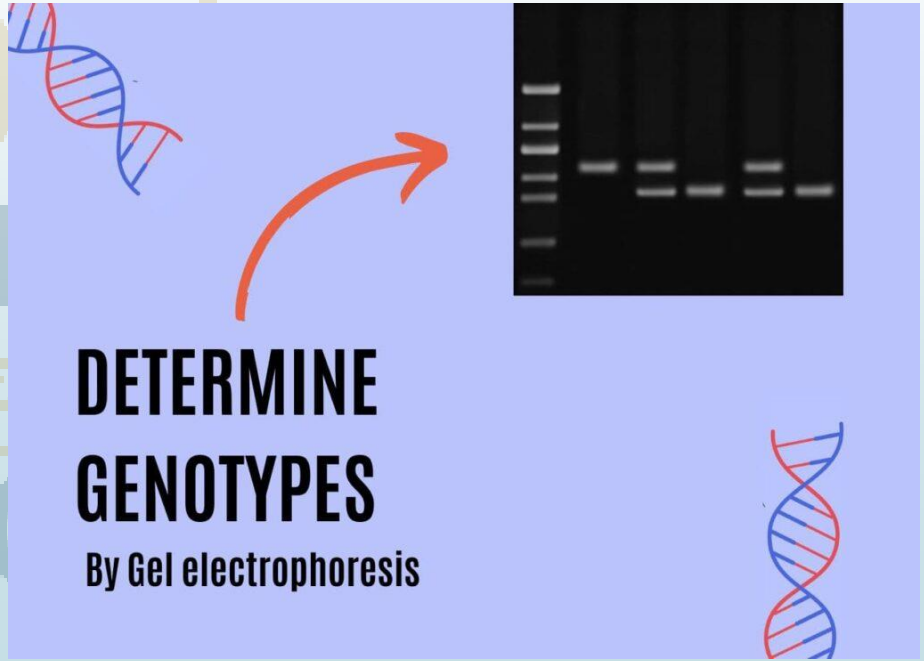
The genotype of individual IV-2 could be NN or Nd since he is normal; then he possesses the dominant normal allele N. This allele is expressed phenotypically in the case of homozygous or heterozygous genotype. He may inherit either two alleles N from each parent or allele N from one parent and allele d form the other parent.



Document 5: Inheritance of cystic fibrosis (CRDP)

3- Indicate how can we determine the real genotype of II7.

By gel electrophoresis.



4- Determine the **risk** of having an affected child:

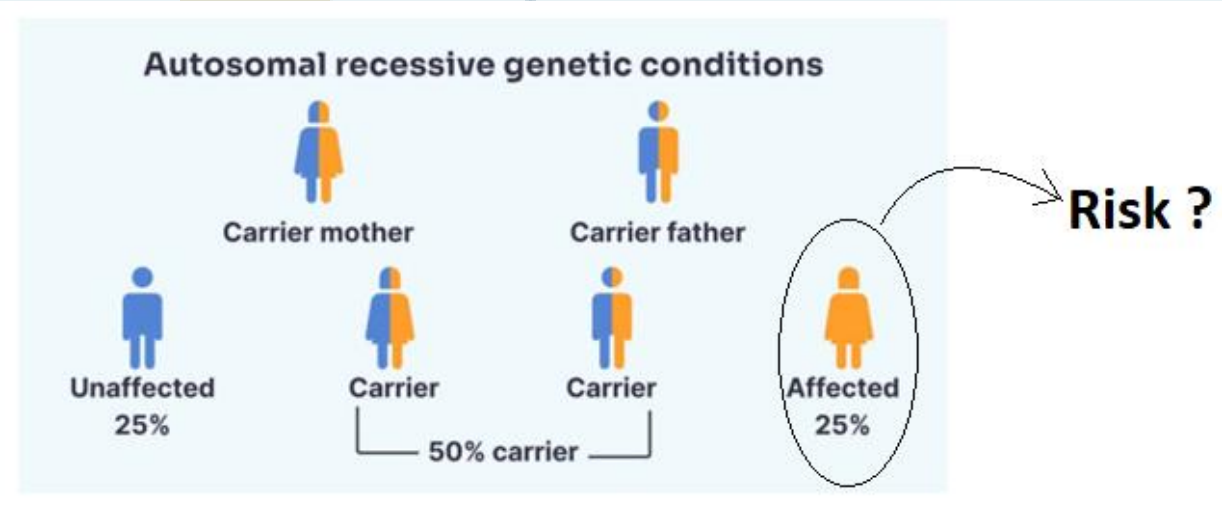
4.1- For couple III-3 and III-4 who already have affected children.

How to calculate the genetic risk?

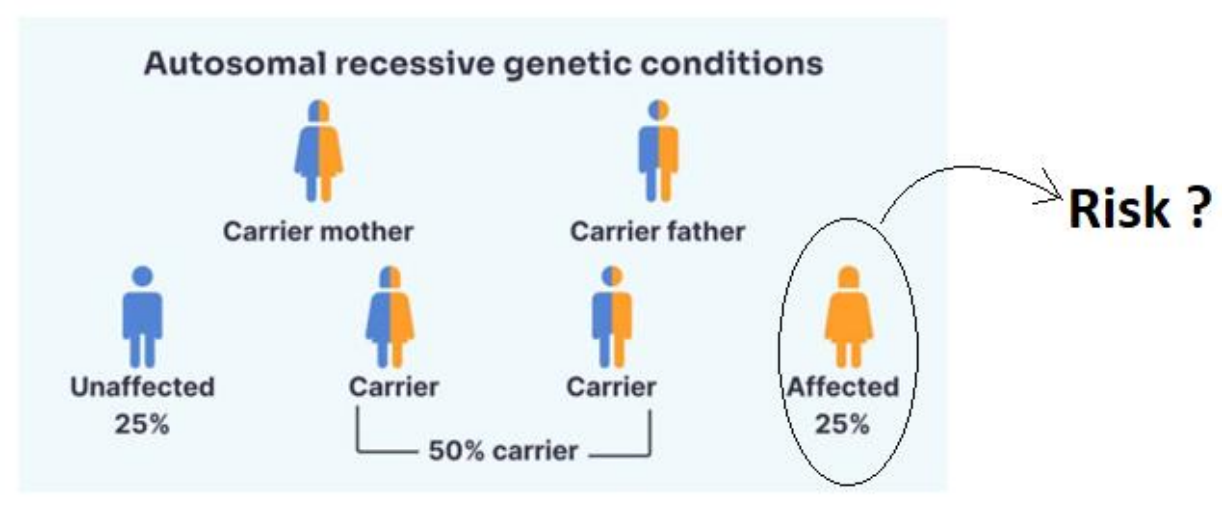
IV. Genetic Risk

Calculation of Genetic Risk for having an Affected Child in case of Autosomal Recessive Diseases . N > d

- For a child to be affected, he/she must be homozygous inheriting 1 recessive (disease) allele from each of his/her parents, who must be heterozygotes for this disease.



⇨ **Genetic risk (G.R) =** Probability of heterozygote father (PHF) x Probability of heterozygote mother PHM x Probability of affected child (PAC)



* Cases to Calculate Genetic Risk:

→Case 1: There is no family history for a couple for a certain autosomal recessive disease.

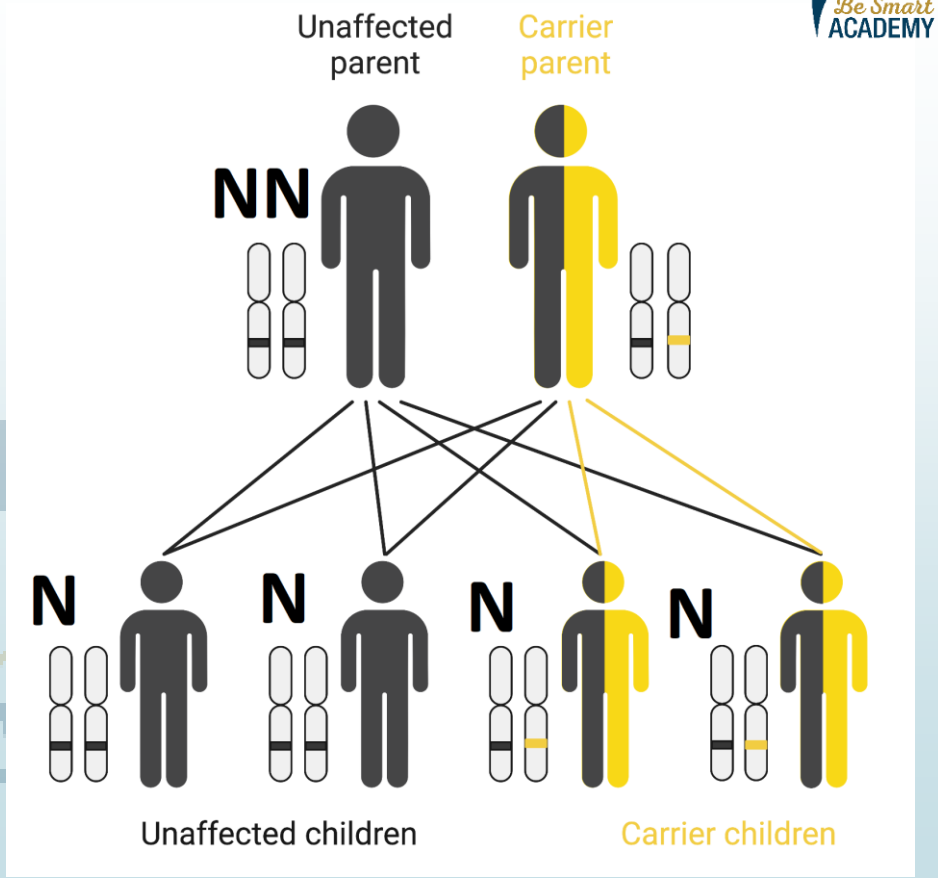
Example: Given, the frequency of the disease (=frequency of heterozygotes for the disease) is 1/20, in a randomly chosen couple without a family history for this disease. Heterozygotes produce gametes, half of which contain the recessive allele and the other half contain the dominant allele.

The probability for the offspring to be recessive homozygous is :1/2 d ♂ x 1/2 d ♀ =1/4.

The risk for the couple to be both heterozygous is: 1/20 x 1/20 = 1/400.

The risk for this couple to have an affected child is : 1/400 x 1/4 = 1/1600.

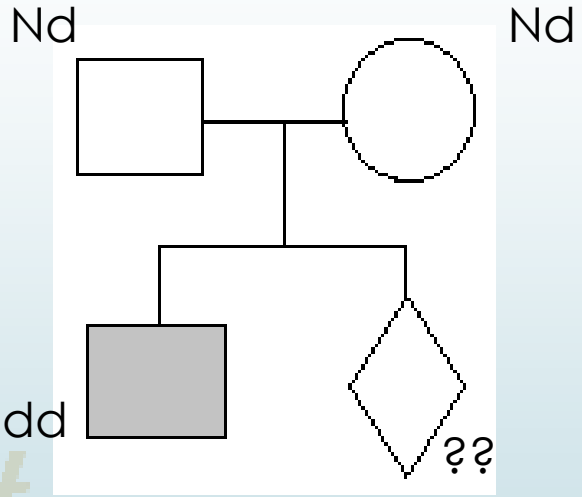
* ***Note: If one of the parents is normal and homozygous (NN), then the risk to have an affected child will be zero.***



→Case 2: Normal couple who already have an affected child.

Since this normal couple has an affected child then they must be carriers for the diseased allele and must be heterozygous. So. the risk for the couple to be both heterozygous is: 1

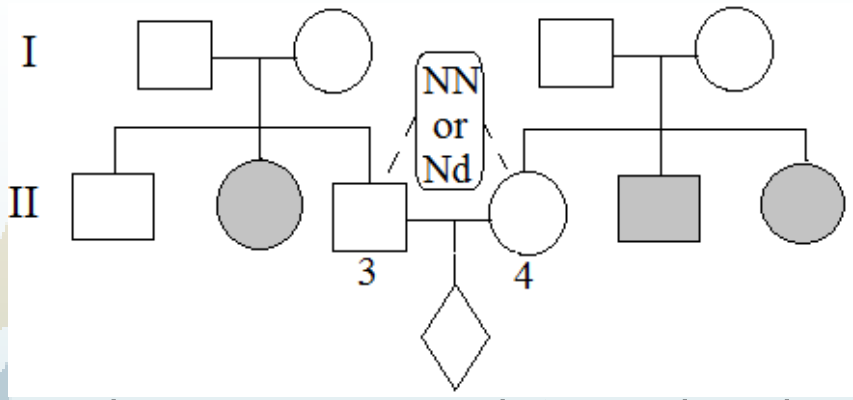
The probability for the offspring to be recessive homozygous is : 1/2 d ♂ x 1/2 d ♀ =1/4.



Genetic risk (G.R) = Probability of heterozygote father (PHF) x Probability of heterozygote mother PHM x Probability of affected child (PAC)

= 1 x 1 x (1/2 d ♂ x 1/2 d ♀) = ¼.

→Case 3: Normal couple who has affected siblings.



- To have an affected child, II 3 and II 4 must have genotype Nd (normal and heterozygous).
- This couple has affected siblings and normal parents, so their parents must be normal carriers (heterozygotes), so the probability for this couple to be Nd is 2/3.

♀ or ♂	N	D
N	NN	Nd
d	Nd	dd

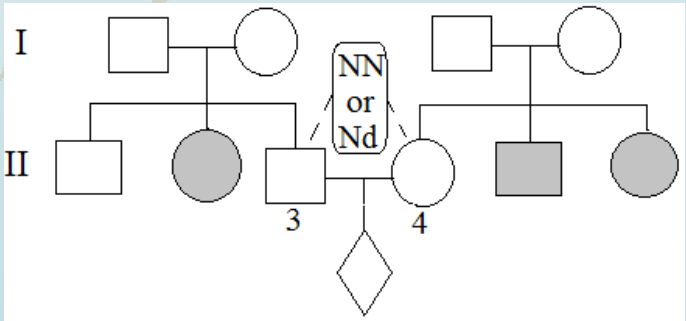
2/3 to be Nd

- To have an affected child, II 3 and II 4 must have genotype Nd (normal and heterozygous).
- The probability for each parent of this couple to be Nd is 2/3.
  - The probability for the offspring to be recessive homozygous is by inheriting the diseased recessive allele from each of his/her parent :

    1/2 d ♂ x 1/2 d ♀ =1/4.
- **Genetic risk (G.R) =** Probability of heterozygote father (PHF) x Probability of heterozygote mother PHM x Probability of affected child (PAC)

  =2/3 x 2/3 x (1/2 d ♂ x 1/2 d ♀)

  = 4/6 x 1/4 = 1/6.



→Case 4:

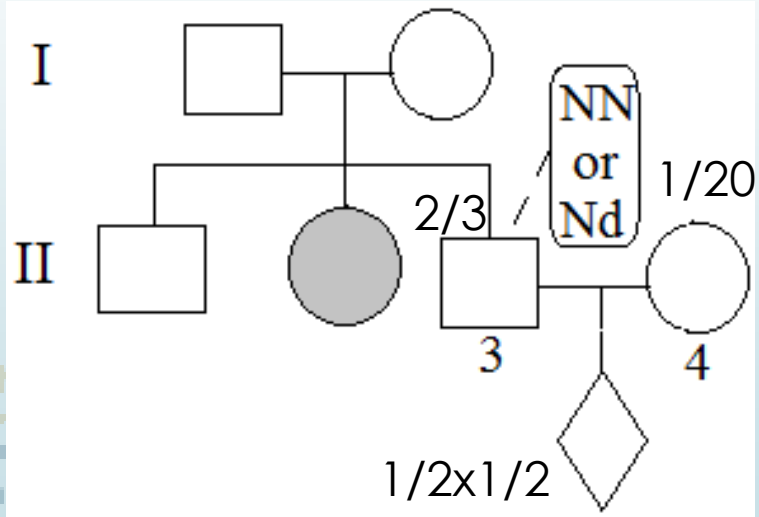
Normal couple one having an affected sibling and the other without family history.

*Given frequency of the disease is 1/20

The father has affected sister and normal parents, so his parent must be normal carriers (heterozygotes), so the probability for this father to be Nd is 2/3.

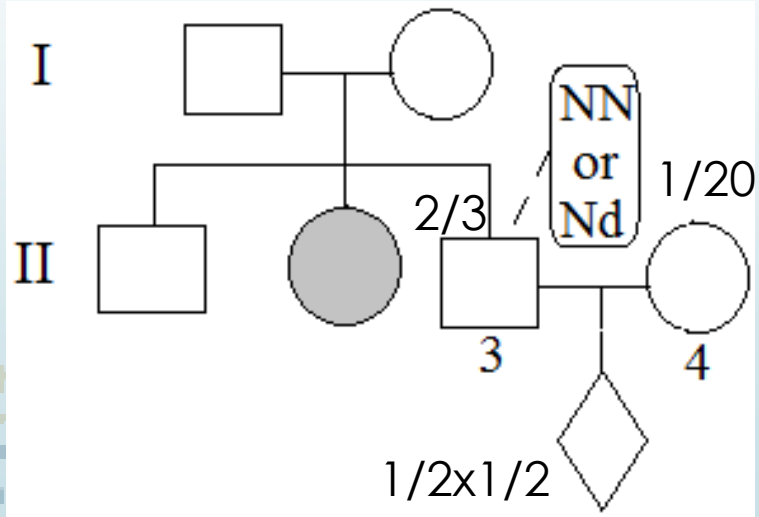
The risk for the mother to be heterozygous is: 1/20 (given)

- The probability for the offspring to be recessive homozygous is by inheriting recessive allele from each of his/her parent : 1/2 d ♂ x 1/2 d ♀ =1/4.



- **Genetic risk (G.R) =** Probability of heterozygote father (PHF) x Probability of heterozygote mother PHM x Probability of affected child (PAC)

= 2/3 x 1/20 x (1/2 d ♂ x 1/2 d ♀)= 1/120.

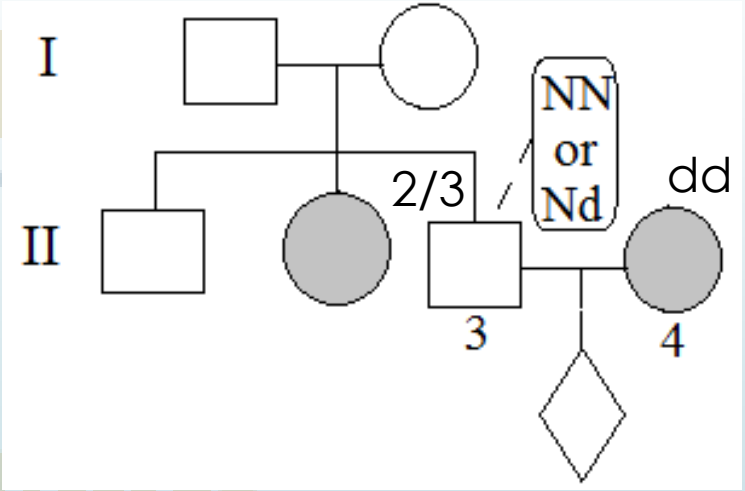


→Case 5:

One of the parents is normal having an affected sibling , and the other is affected.

The father has affected sister and normal parents, so his parents must be normal carriers (heterozygotes), so the probability for this father to be Nd is 2/3 .

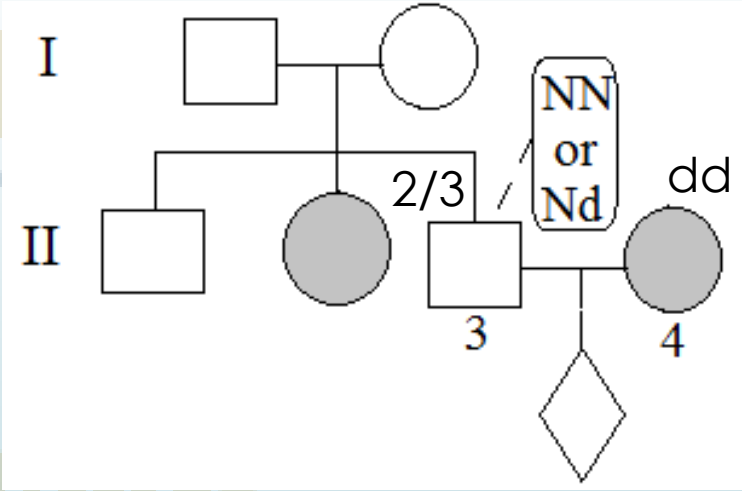
The mother is affected so her genotype is dd where diseased allele is recessive and must be present in 2 copies in order to be expressed (purity is criterion for recessivity).



- The probability for the offspring to be recessive homozygous is by inheriting recessive allele from each of his/her parent : 1/2 d ♂ x 1 d ♀ =1/2.

Genetic risk (G.R) = Probability of heterozygote father (PHF) x possible genotype of the mother x Probability of affected child (PAC) = 2/3 x 1 x (1/2 d ♂ x 1 d ♀)

= 1/3.



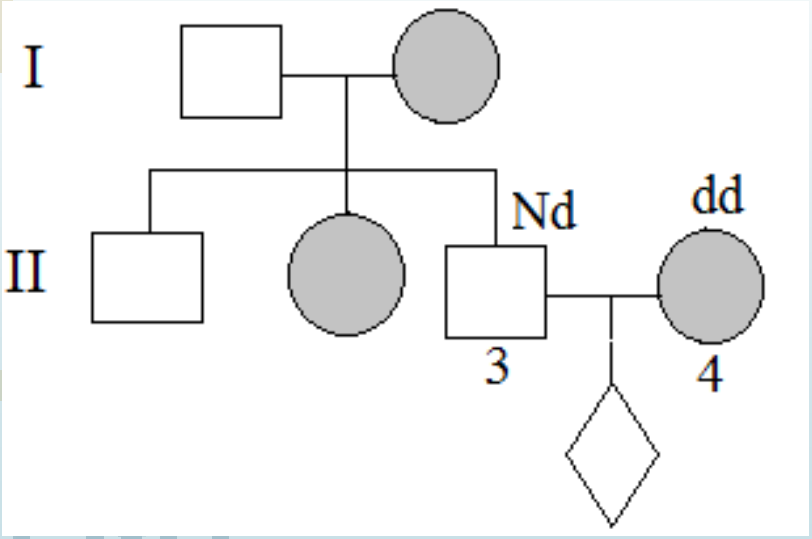
→**Case 6:**

One of the parents is normal having an affected sibling and mother, and the other is affected.

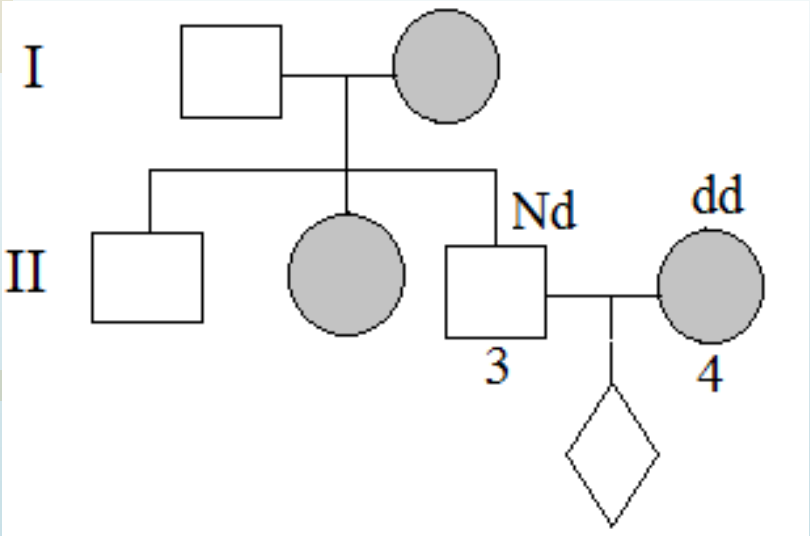
The normal father 3 must carry the normal dominant allele, but since he has affected mother having genotype dd , then hem must take the diseased allele from his mother, and must be heterozygote of genotype Nd. The probability to be heterozygote is 1.

The mother is affected so her genotype is dd where diseased allele is recessive and must be present in 2 copies in order to be expressed (purity is criterion for recessivity).

- The child to be affected he/she must be homozygous inheriting recessive allele from each of his/her parent with probabilty: 1/2 d ♂ x 1 d ♀ =1/2.



Genetic risk (G.R) = Probability of heterozygote father (PHF) x possible genotype of the mother x Probability of affected child (PAC) = = 1 x 1 x (1/2 d ♂ x 1 d ♀) = ½.



GENETIC RISK OF AN AUTOSOMAL RECESSIVE DISEASE

The risk for a normal couple of having a child affected by an autosomal recessive disease can be obtained by using the following formula:

$$\text{Risk}_{\text{affected child}} = \text{Risk}_{\text{carrier mother}} \times \text{Risk}_{\text{carrier father}} \times \text{Risk}_{\text{child receiving mutant allele from each carrier parent.}}$$

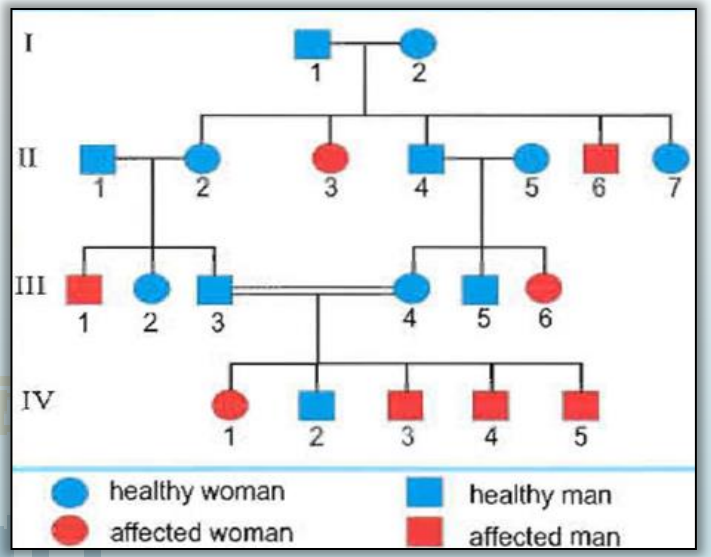
The family shown in document 5 lives in France, where heterozygotes form 5% of the population (1/20).

4- Determine the risk of having an affected child:

4.1- For couple III-3 and III-4 who already have affected children.

The risk for a couple to have a child affected by an autosomal recessive disease (G.F)=

The risk for the father to be normal heterozygous X The risk for the mother to be normal heterozygous X the risk for the child to receive mutant allele from each carrier parent.



Document 5: Inheritance of cystic fibrosis (CRDP)

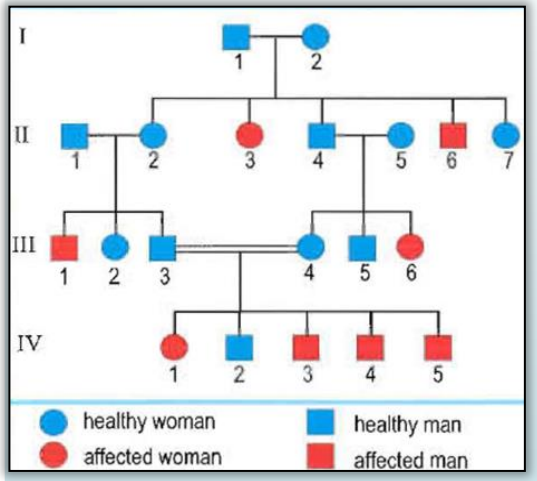
Parents III-3 and III-4 are normal and gave birth to diseased children IV-1,3,4 and 5 of genotype d//d. Thus, their risk to be normal heterozygous is 1.
The allele of the disease is recessive it is not expressed unless it is homozygous. The risk for a child to inherit the allele d from each one of the carrier parents is ½ X ½ = ¼.
Hence, the risk for parents III-3 and III-4 to have another child affected by CF: 1 x 1 x 1/4 =1/4.

4.2- For individual II-7 who wants to marry a French healthy man.

The healthy individual II-7 has affected sister and brother(II-3 and 6) which means that her parents (I-1 and I-2) are heterozygous. Thus, the risk for II-7 to be heterozygous is 2/3.

The French normal man has no family history. His risk to be heterozygous is that of the French population: 1/20.

The allele of the disease is recessive; it is not expressed unless it is homozygous. The risk to inherit the allele d from each one of the carrier parents is ½ X ½ = ¼.
Hence, the risk for individual II-7 and her future husband to have an affected child is : 2/3 x 1/20 x 1/4 = 1/120.



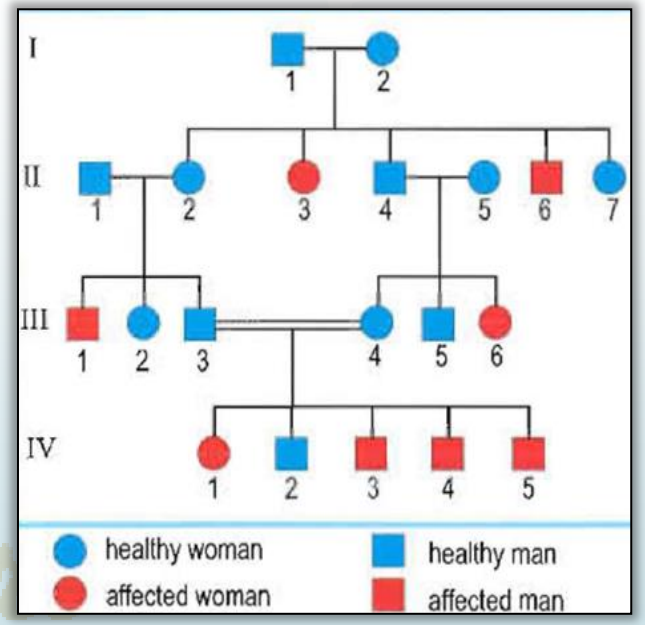
Document 5: Inheritance of cystic fibrosis (CRDP)

5.1-Compare the risk of having an affected child in both previous mating: (4.1) and (4.2).

The risk of having an affected child from mating between III-3 and III-4 (consanguineous mating) is 1/4 higher (30 times) than that in mating between II-7 and the French man which is 1/120.

5.2- What can you conclude?

We conclude that mating between cousins (consanguineous mating) favors the birth of affected children.



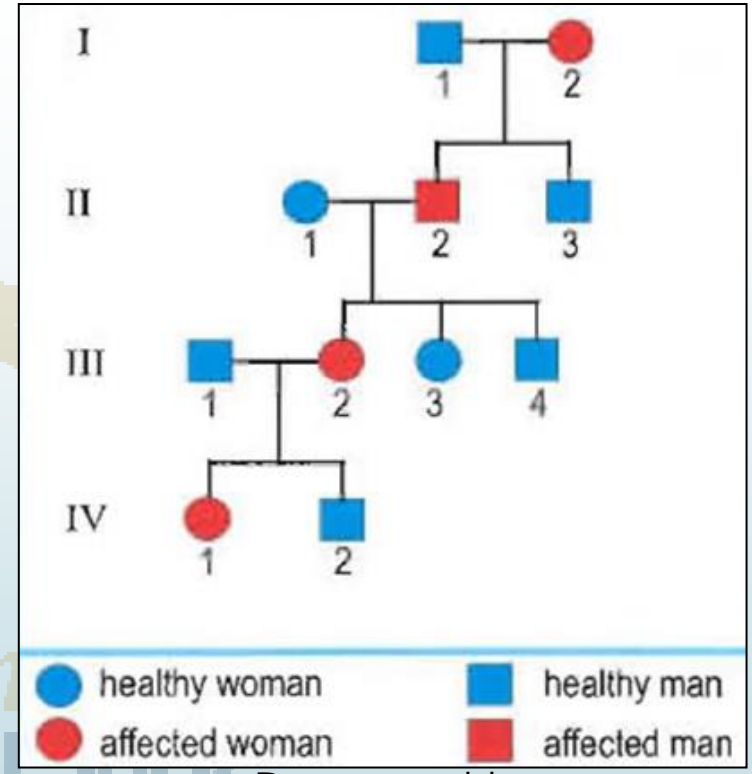
Document 5: Inheritance of cystic fibrosis (CRDP)

V. Autosomal Dominant Disease

-Application 2:

Autosomal dominant diseases are rare. The affected persons by these diseases must have an affected parent. Document b represents the pedigree of a family where some members are affected by HC disease.

- Referring to Doc.b, p95, answer the following questions:



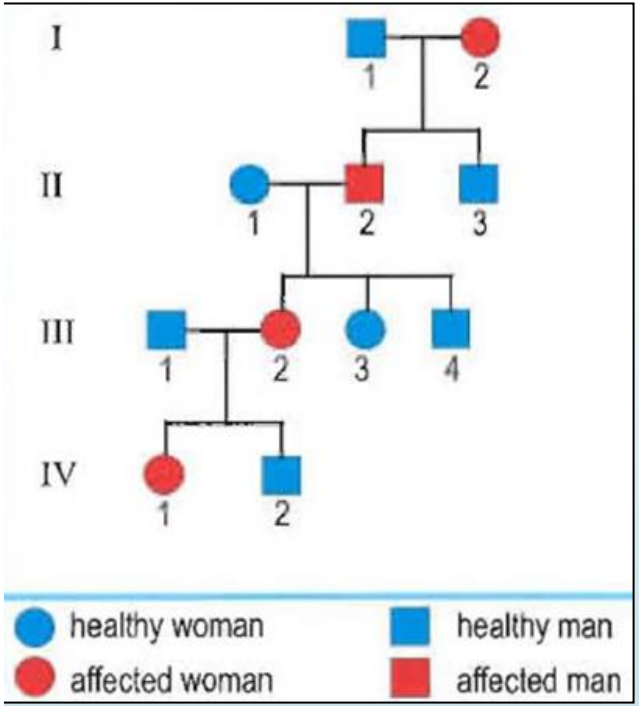
Document b

1- Show that the HC allele is dominant.

There is an affected individual in every generation of this family and every affected individual has at least one affected parent, such as the affected individual II-2 has an affected mother I-2. This shows that the allele of HC disease is dominant.

Let "H" be the symbol of the dominant mutant allele of the disease.

Let "n" be the symbol of the recessive normal allele.

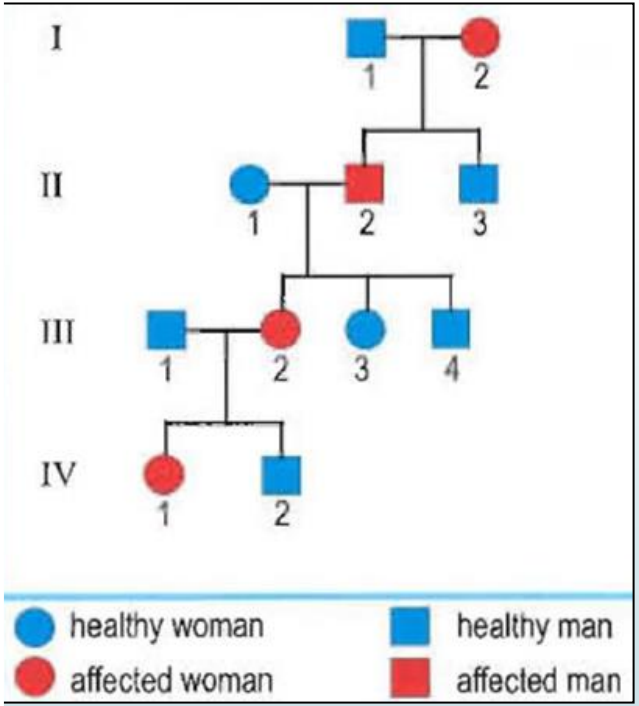


Document b

2-Determine the localization of the gene responsible for Huntington Chorea.

If the gene is carried by the non-homologous segment of Y chromosome, any affected boy would necessarily have an affected father (or girls should not be affected). The affected boy II-2 who has $X//Y^H$ as genotype, must have taken Y^H from his father I-1 who would have as genotype $X//Y^H$ and he would be affected but he is not, which is not the case. Thus, the gene is not carried by the non-homologous segment of Y chromosome.

If the gene is carried by the non-homologous segment of the chromosome X, the healthy girl III-3 must be homozygous of genotype $X^n//X^n$; she should have inherited X^n from her father II-2 who should be healthy of genotype $X^n//Y$, but her father is affected which is not the case.

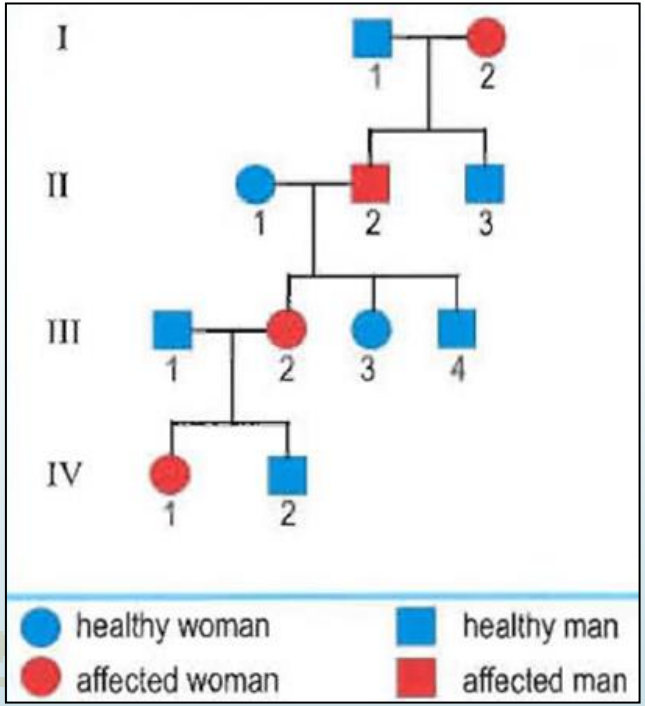


Document b

Thus, the gene is not carried by the non-homologous segment of X chromosome.

If the gene is carried by the homologous segments of X and Y, healthy girl III-3 of genotype X^nX^n should have inherited X^n from her father II-2; the healthy boy III-4 of genotype X^nY^n should have inherited Y^n from his father II-2. Father II-2 should be healthy of genotype X^nY^n which is not the case, he is affected. Thus, the gene is not carried by the homologous segments of X and Y.

Hence, the gene of HC is carried by an autosome.

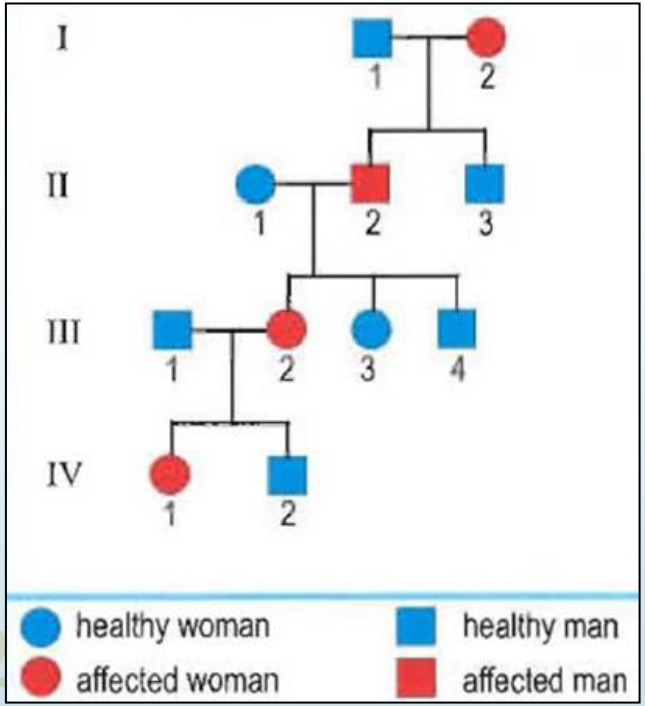


Document b

3-Indicate the genotype of each of the individuals I-1 and II-2 of document 8. Justify the answer.

The genotype of I-1 is n//n, since he is normal, then he possesses the allele n which is recessive. The recessive allele is expressed phenotypically when it is present in two copies (purity is a criterion of recessivity). Thus, he is homozygous.

The genotype of II-2 is H//n, since he is diseased, then he possesses allele H which is dominant and he had two normal children III-3 and III-4 having n//n as genotype, each one of these alleles is received from both parents. Thus, II-2 possesses the allele n, so he is heterozygous.



Document b

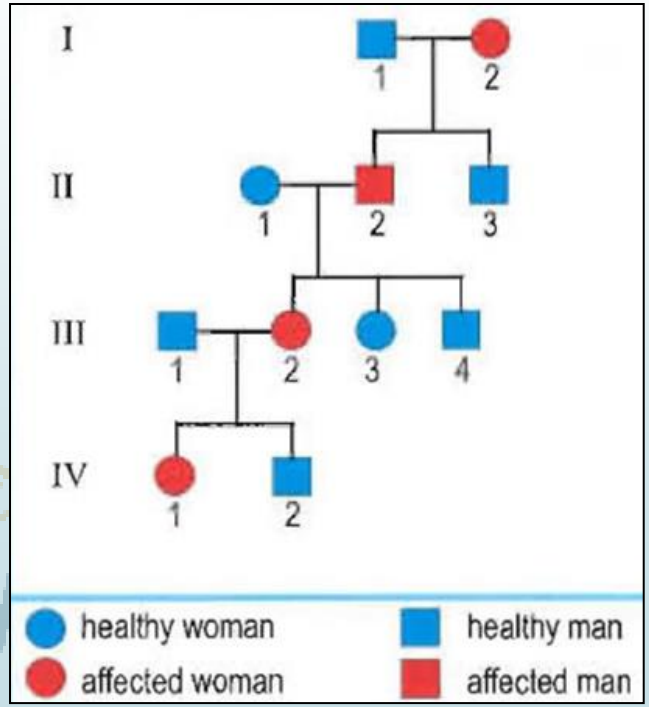
GENETIC RISK OF AN AUTOSOMAL DOMINANT DISEASE.

The gene of HC is carried by the autosomal chromosome 4. HC is characterized by a dancing like movements (chorea means dance). The symptoms of this disease appear between 30 and 50 years of age.

4-Determine the risk of the healthy individual III-3, who is under the age of 30, to be affected by HC disease.

The individual III-3 has a healthy homozygous mother II-1 of genotype n//n. Thus, the risk to inherit the allele H from her is zero.

The father II-2 is affected and has a normal father I-1. Thus, II-2 is heterozygous. The risk for III-3 to inherit the allele H from her father II-2 is ½.



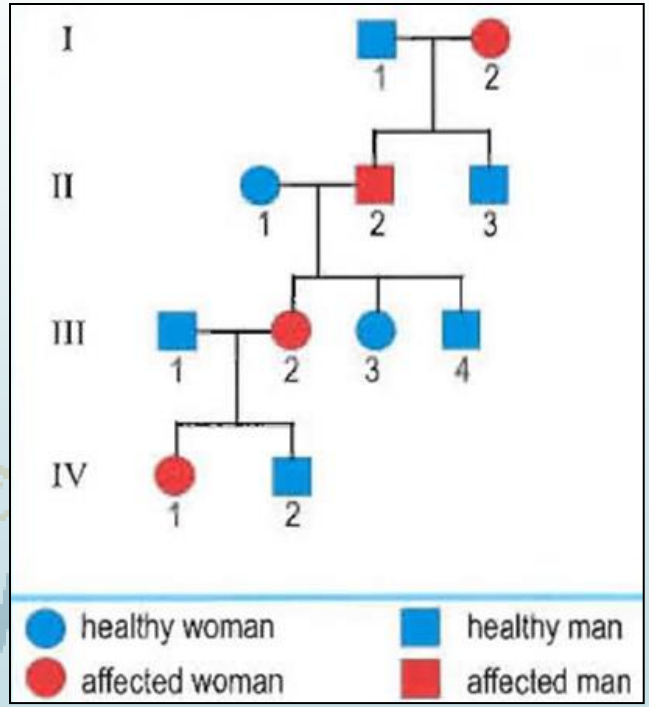
Document b

GENETIC RISK OF AN AUTOSOMAL DOMINANT DISEASE.

Title:Table of cross

	H	n
n	Hn	nn

The allele H of the disease is dominant; it is expressed in heterozygous as in homozygous. Hence, the risk for III-3 to be affected by Huntington Chorea and heterozygous is 1/2.



Document b

Selected Exercises of the National Book

- Exercise VII p.109

Exercise VII

Cystic fibrosis is a hereditary disease manifested by an abnormality in cell exchange, which leads to progressive blockage of respiratory and digestive functions.

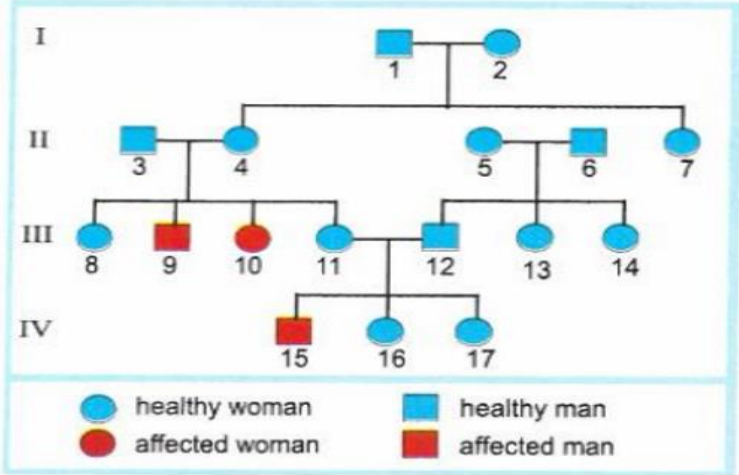
Document 1 represents the pedigree of a family suffering from this disease.

a- Is the allele responsible for the disease dominant or recessive? Justify the answer.

b- Discuss logically the chromosomal localization of the gene responsible for cystic fibrosis.

c- Write the genotypes of parents 3 and 4 and their children. Justify the answer for each genotype.

Researchers associate cystic fibrosis to a modification in the structure of a single gene located on a pair of human chromosomes.

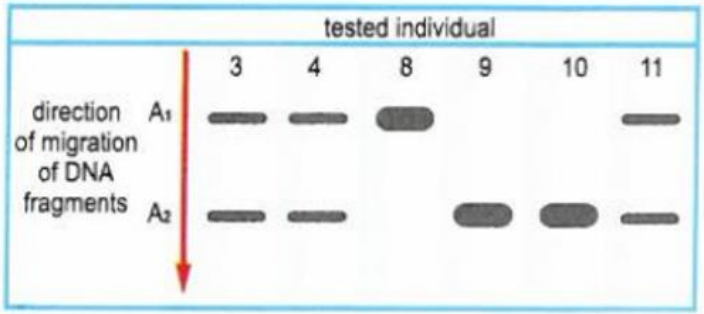


A technique of chromosome fractioning permits to obtain fragments of DNA, which can be separated by migration on a gel and identified by labelling. ***Document 2*** shows the result of the migration of DNA fragments, termed A_1 and A_2 issued from the chromosomes of different members in the family presented in ***document 1***.

d- Link each of the fragments A_1 and A_2 to its corresponding allele for each individual in ***document 2***, with reference to the phenotypes revealed in the pedigree.

e- Discuss and write the genotypes of the tested individuals, which are presented in ***document 2***. Compare these genotypes to those of individuals 3 and 4 and their children, which were obtained previously.

f- What advantage does this genetic labelling technique provide to the determination of the genotype of a certain individual?



Document 2

Document 1

N.B. All individuals have a normal karyotype.

Exercise VII solution:

a- Recessive, since individuals III-9 and III-10 are affected with cystic fibrosis, but have normal parents II-3 and II-4 . Then the parents are carriers for the alleles responsible for the disease but its masked.

- Let “N” be the symbol for normal dominants allele.

-Let “c” be the symbol of the recessive allele coding for cystic fibrosis.

b- The pedigree shows that both genders are affected ,then most probably the disease is autosomal. Suppose it's gonosomal.

If the gene was carried by non – homologous part of y, then the females can never be sick and all sick male should have a sick father, but the pedigree shows affected female III 10 and affected male IV-15 has normal father. So, its not the case.

- If the gene was carried by non – homologous part of x, then female III 10 should be homozygous $x^c\ x^c$ having received x^c y, who in this case would be sick, but the pedigree shows that he is normal. So its not the case.
- If the gene is located on the homologous part of x and y then male 9 would have a genotype $x^c\ y^c$, where y^c should have been inherited from his father 3 ; female 10 would have a genotype $x^c\ x^c$ where 1 of the x^c should have come from here normal father 3, who in this case should be affected having genotype $x^c\ y^c$. So, its not the case.
- Thus, the gene responsible for the disease is autosomal.

c- 3 and 4: Nc, since they are normal and have affected children (9 and 10), so they must be carries for the gene coding for the disease.

- 9 and 10: cc , since they are affected, and the allele coding for the disease is recessive which must be only under the homozygous state to be expressed.
- 11: Nc, since she is normal and have a sick child15, so she must be heterozygous to transmit the allele coding for the disease C to her son.
- 8: NN or Nc, since she is normal, where normal allele is dominant, may be homozygous or heterozygous.

d- Individuals 9 and 10 who are sick, are homozygous having genotype cc, Doc.2 shows only one thick bond of type A_2 corresponds to allele c and consequently, fragment A_1 corresponds to allele N_1 .

e- Individuals 3, 4 and 11 have a fragment of DNA of type A_1 , and a fragment of DNA of type A_2 . The have the alleles N and C and hence they are heterozygous.

Individuals 9 and 10 have a big band of A_2 , where they have 2 copies of allele c and d hence they are homozygous.

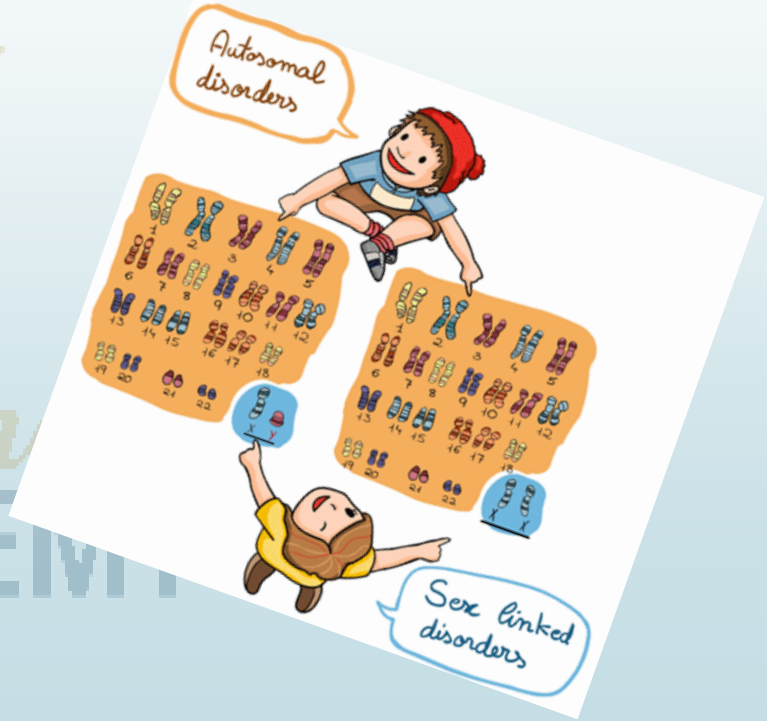
Induvial 8 has a thick band A then 2 copies of N (NN and Not Nc).

Then, the result of Doc.2 confirms the answer of part c.

f- This technique permits us to determine the real genotype of an individual.

Selected Exercises of the Official Exams

2015 (1)

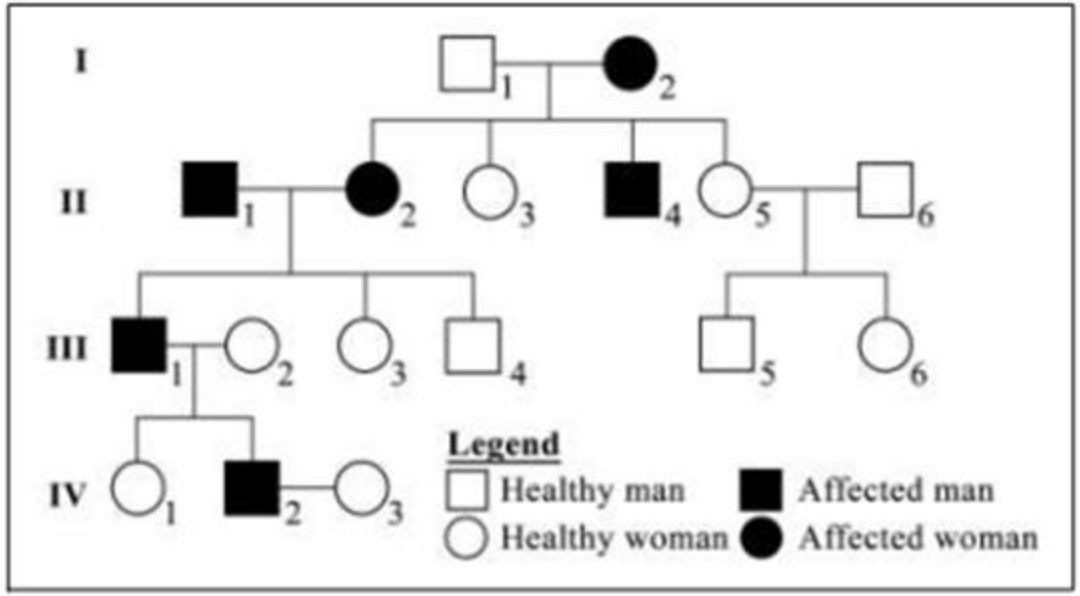


Exercise 3 (5 points) **Huntington Chorea**

Huntington Chorea is a serious neurodegenerative hereditary disease. Its first symptoms appear in adults starting fromthe age of 25 years.
We seek to determine the mode of transmission of this disease as well as its origin.

Document 1 shows the pedigree of a family whose certain members are affected by this disease.

1- Indicate whether the allele determining this disease is dominant or recessive. Justify the answer.
2- Determine the localizationof the gene responsible for this disease.



Document 1

All members of this family are over 25 years old except individuals III3 and III5. The latter are willing to get married but are afraid of being affected by this disease.

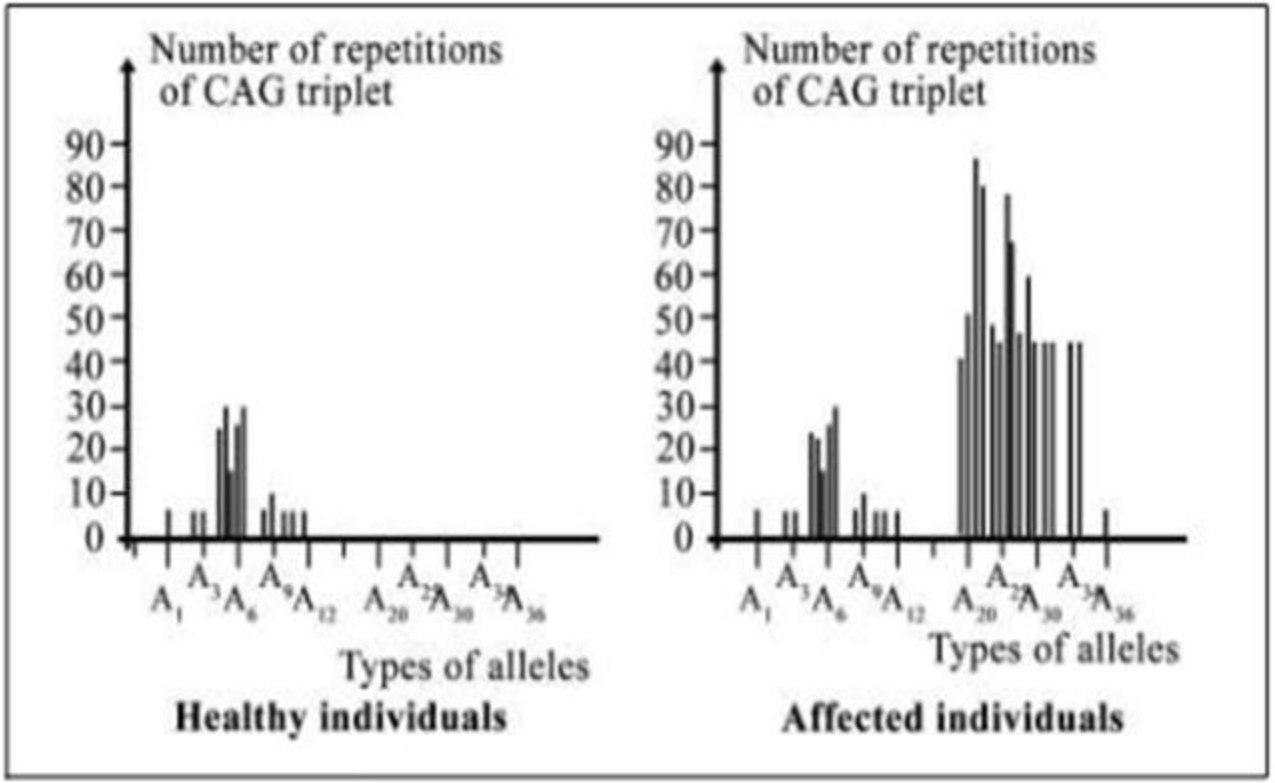
3- Determine the risk for each of individuals III3 and III5 to be affected by this disease.

Answer Key

Part of the exercise	Exercise 3 Huntington Chorea	Grade 5 pts
1	The allele of the disease is dominant with respect to the healthy allele, since normal children III3 and III4 have affected parents II1 and II2. Thus the normal allele is carried at least by one of the parents and masked by the allele of the disease. Let H be the symbol of the dominant allele of the disease and nthe symbol of the recessive normal allele.	1/2
2	If the allele is carried on the non-homologous segment of the chromosome Y, the disease would be transmitted from father to son, but the affected son II4 has a healthy father I1. Thus the gene is not carried on the non-homologous segment of the chromosome Y. If the gene is carried by the non-homologous segment of the chromosome X, the healthy girl IV1 must be homozygous of genotype Xn//Xn; she should have inherited thenormal allele from her father III1who should be healthy of genotype Xn//Y . But her father is affected. Thus the gene is not carried by non-homologous segment of X. If the gene is carried by the homologous segments of X and Y, healthy girl III3should have inheritedXn from her father II1; the healthy boy III4 should have inherited Yn from his father II1. Father II 1 should be healthy of genotype XnYn which is not the case (II1 is affected) . thus the gene is not carried by the homologous segments of X and Y.	¼ ¼ ¼ ¼

3	The mother II2 is affected by the disease and is heterozygous since she inherited the allele H from her mother and the allele n from her homozygous healthy father who produces only one type of gametes having the allele n. Thus she produces two types of gametes of equal probabilities: ½ H and ½ n. The affected father II1is heterozygous since he already has a healthy homozygous son III4 to whom he must have transmitted the recessive allele n. Thus he produces two types of gametes equal probabilities: ½ H and ½ n. Since the affected allele of the disease is dominant; it is sufficient for III3 to have at least one allele of the disease in order to be affected . The genotype of III3 can be either H//H ¼ or H//n ½ . Thus the risk for III3 to be affected is 3/4 of the children. Couple II5- II6 is healthy and recessivity is a criterion of purity. These parents produce only one type of gametes carrying the normal allele n. Thus all their children will be healthy. Therefore the risk for III5vto be affected is null.	½ ½

Studies have shown that the gene coding for the functional protein, huntingtin, exists in many allelic forms that differ by the number of CAGtriplets. The number of repetitions of CAG triplet in each allele is studied in healthy individuals as well as in affected ones. The obtained results are presented in document 2.



Document 2

4- Deduce,based on the statistical results of document 2, the origin of this disease.

4	In healthy individuals, the number of repetitions of CAG varies between 8 and 30 for the types of alleles A1 till A12. Thus these alleles are associated to the normal phenotype.However, affected individuals present two groups of alleles: the first is identical to that present in healthy individuals with a number of repetitions of CAG between 8 and 30. The second group corresponds to alleles having a number of repetitions of CAG between 39 and 70. Thus these alleles which have a number of repetitions of CAG higher than 39 are associated to the disease. The origin of the disease is the high number of repetitions of CAG greater than 39	**1**

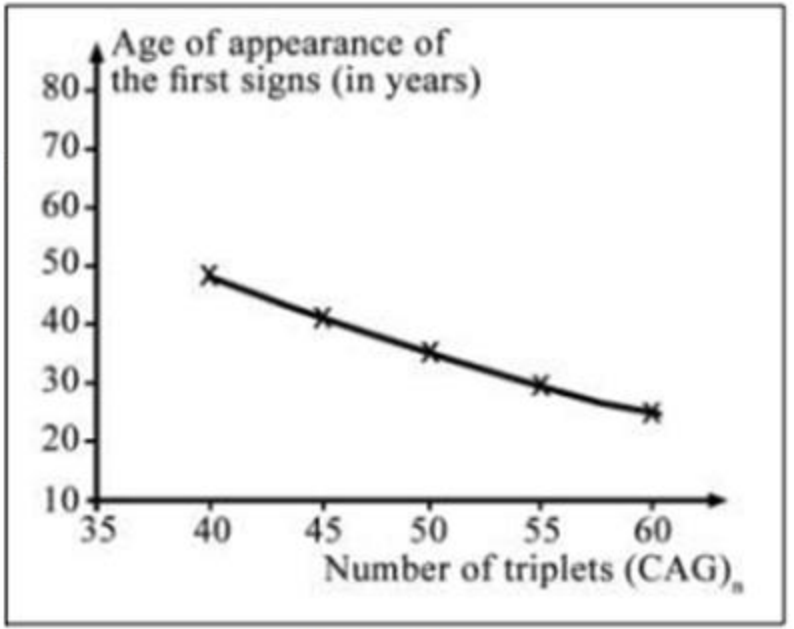
The analysis of the genein woman III3 has revealed that she possesses two alleles.The number of repetitions of CAG in one of them is 10 andin the other it is 15.

5- Specify the real genotype of this woman.

A statistical studyhas been performed concerning the age of appearance of this disease in function of the number of CAGtriplets. The obtained results are shown in document 3.

6- **6-1**-Analyze the obtained results.

6-2- Conclude the factor that determines the age of appearance of this disease.

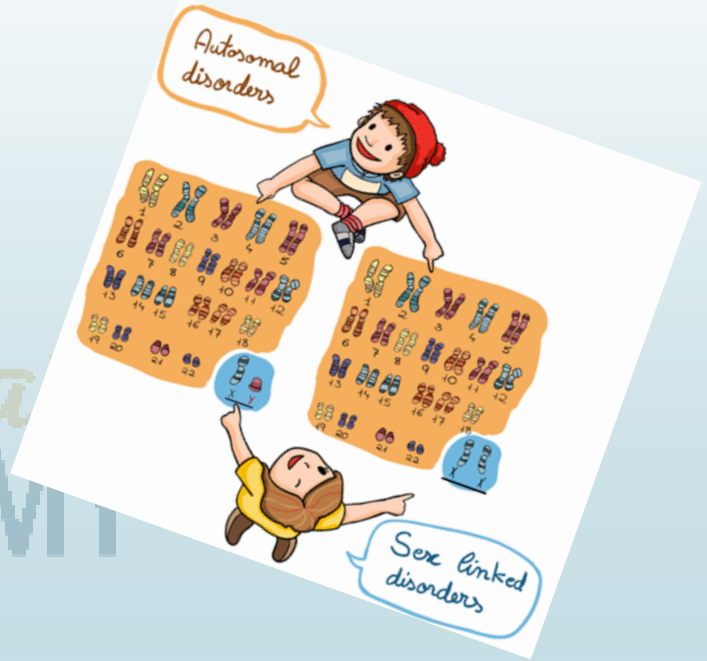


Document 3

5	The real genotype of III3 is n//n or A_6//A_9. Since she has two alleles with a number of repetitions CAG that is respectively 10 and 15 which is less than 30 repetitions and thus correspond to the group of alleles of healthy individuals. These two alleles are among the ones that determine the normal phenotype.	¾
6-1	The average age of appearance of the disease decreases from 49 years to 25 years, when the number of repetitions of CAG triplet increases from 40 to 60.	½
6-2	The factor determining the age of appearance of the disease is the high number of repetitions per allele(>40).	¼

Selected Exercises of the Official Exams

2018 (1)



Official exam 2018 (1)

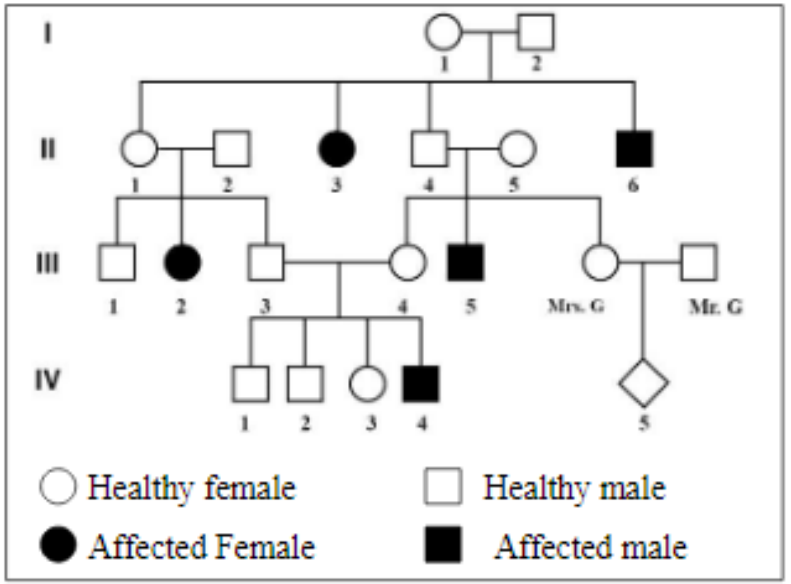
Exercise 1 (5.5 points) **Diagnosis of Galactosemia**

Galactosemia is a genetic disease which results from a deficiency in the enzyme transforming galactose to glucose. Several days following the consumption of milk or milk products, the following clinical signs appear: vomiting, diarrhea, ….. . On the long term, infants would show retarded growth and later they may have mental retardation.

Mr. and Mrs. G are expecting a child. Mrs. G is worried because several members in her family are affected by this disease as shown in the pedigree presented in document 1.

1. Indicate if the allele responsible for the disease is dominant or recessive. Justify the answer.
2. Determine the chromosomic location of the gene responsible for this disease.
3. Specify the possible genotype(s) of Mrs. G and individual IV-4.

Worldwide, the probability of individuals to be heterozygous for the gene responsible for this disease is 1/100.



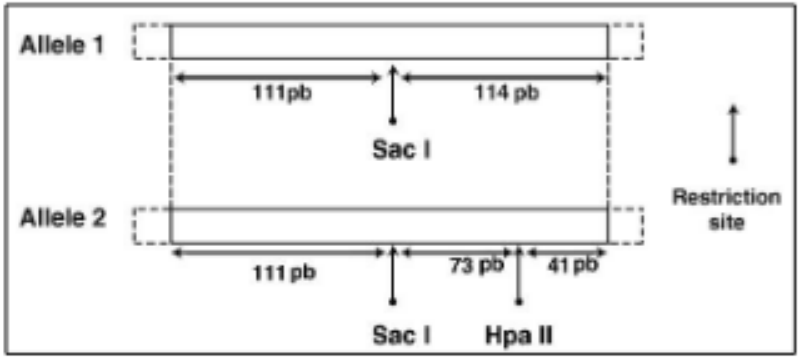
Document 1

4- Determine the risk for the expected child IV 5 to be diseased.

Q	Exercise 1 Diagnosis of Galactosemia	Mark
1	The allele of the disease is recessive. Parents I1 and I2 are normal but have two affected children II3 and II6.This shows that the allele of the disease is carried at least by one of the parents who phenotypically doesn't express the disease, so the allele is masked, thus it is recessive (g) with respect to the normal allele (N). N allele: Normal dominant m allele: mutated recessive	0.5
2	**If the gene is carried by the non-homologous part of Y ,** First argument: there shouldn't be affected girls since girls do not have the gonosome Y. This is not the case since The girl II3 is affected. Second argument: The father of each affected boy should be necessarily affected since the boy inherit gonosome Y from his father. This is not the case since the father I2 of boy II6 is healthy. Thus, The gene is not carried by chromosome Y. **If the gene is carried by the non-homologous part of X**, the diseased girl II3 of genotype $X^m//X^m$ should inherit should X^m from her father whose genotype should be $X^m//Y$ and should be diseased. This is not the case. **If the gene of the disease is localized on the homologous part of X and Y**, the boy II6 will have the genotype X^mY^m and his sister II3 will have the genotype $X^m//X^m$. The boy will inherit Y^m from his father and the girl will inherit X^m from her father. So the genotype of the father should be X^mY^m and he will be phenotypically affected. The gene is not localized on a gonosome. Thus, the gene responsible for galactosemia is autosomal.	1

3	The genotype of Mrs.G is N//N or N//m since the dominant allele is expressed in both homozygous and heterozygous states. The genotype of IV4 is g//g because the recessive allele is only expressed in the homozygous state.	1
4	The risk for the child IV5 to to be diseased is: The risk of the mother Mrs.G to be heterozygous for the gene = 2/3 x The risk of the father Mr.G to be heterozygous for the gene = 1/100 x The risk of the child to have both recessive alleles of the disease = 1/4 **Justification :** Her two parents are heterozygous and have an affected child II5 of genotype m//m. The father doesn't belong to this family, he doesn't have any history of the disease: His risk to be heterozygous is the same as that of the worldwide population : 1/100 In the case of heterozygous parents, the risk that the child inherits the mutant allele from both parents is : ½ x ½ = ¼ The risk for the child IV5to to be diseased (genotype m//m) : **2/3 x 1/100 x 1/4= 1/600**	1

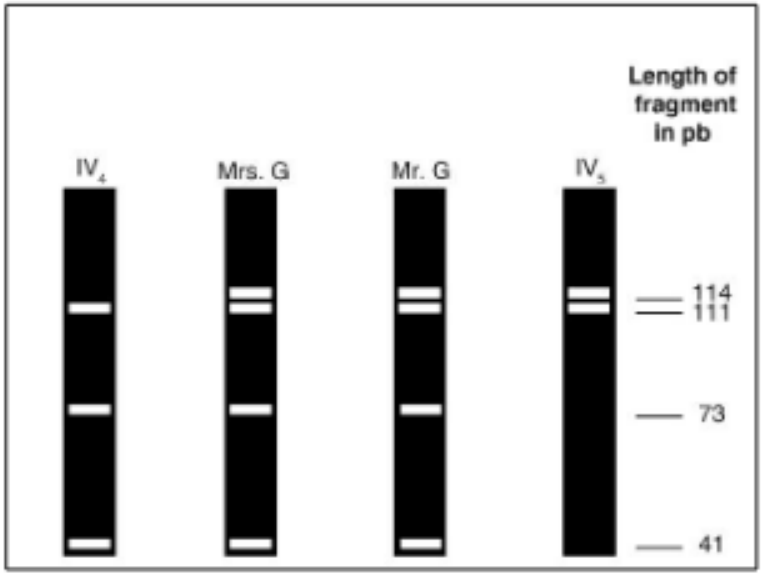
The GALT gene is responsible for galactosemia.
Document 2 shows the cleavage sites of two restriction enzymes, Sac 1 and Hpa II, at the level of a part (from nucleotide 1367 to nucleotide 1605) of two alleles of this gene: Allele 1 and allele 2.



Document 2

Document 3 represents the results of electrophoresis obtained after the combined action of enzymes, Sac 1 and Hpa II on allele 1 and allele 2 of GALT gene of certain family members.

5. Indicate, by referring to document 2, the number and size of restriction fragments obtained by the enzymatic digestion of allele 1 and allele 2.
6. Determine the allele which corresponds to the mutant one.
7. Verify if the fetus IV5 will be affected by galactosemia.



Document 3

5	The fragments of allele 1 : 2 fragments of sizes 111 and 114 bp. The fragments of allele 2 : 3 fragments of sizes 111, 73 and 41 bp.	0.5
6	Document 3 shows that infant IV4 is diseased and have an obligatory genotype m//m, and has in his electrophoregram 3 DNA fragments (111bp ; 73bp ; 41bp), corresponding to the same fragments of allele 2. So the allele 2 is the mutated allele.	0.75
7	The electrophoregram of the DNA of the fetus shows two fragments of sizes 114 bp and 111 bp, resulting in a unique action of enzyme Sac I, corresponding to the normal allele 1. So the genotype of this fetus is N//N and will not be galactosemic.	0.75