Exercise (2021-2nd session) **Huntington Disease**

Huntington disease is a rare neurodegenerative disease of the central nervous system. It is characterized by uncoordinated and involuntary movements of great amplitude and by psychological problems. It is due to a mutation at the level of the gene coding for a protein called huntingtin which is essential for the survival of the neurons.

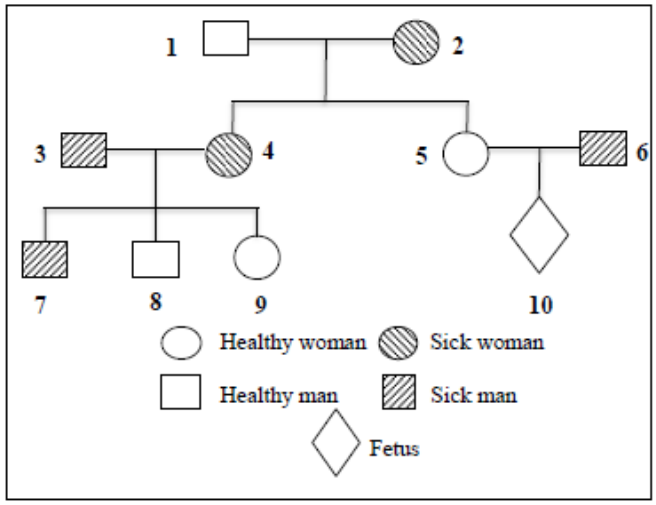
Document 1

1- Pick out from the text (doc.1):
1.1- the origin of Huntington disease.
1.2- the symptoms of this disease.

Age (years)	10	30	40	60	70
Percentage of individuals showing the symptoms of the disease (%)	0	30	60	90	100

Document 2

A study is performed on individuals carrying the mutated allele responsible for this disease. Document 2 represents the variation of the percentage of individuals showing the symptoms of the disease as a function of their age.
2- Interpret the obtained results.
Document 3 shows the genealogical tree of a family which certain members are affected by the disease.
3- Indicate whether the allele of this disease is recessive or dominant. Justify the answer.
4- Determine the localization of the gene responsible for this disease.



Document 3

DNA analysis is performed on certain individuals of this family using the Southern blot method. The used probe permits to distinguish the mutated allele from the normal one of the studied gene. The obtained results are shown in document 4.
5- Specify the band which corresponds to the mutated allele.
6- Determine the genotype and the phenotype of the fetus.

	Individuals		
Bands	5	6	Fetus
A	▬▬▬	———	———
B		———	———

Document 4

Solution

1.1- The origin of Huntington's disease is a mutation in the gene encoding a protein called huntingtin. **(0.5)**

1.2- Symptoms of this disease are disordered and involuntary movements of great amplitude and psychiatric disorders. (**0.5)**

2- The percentage of individuals showing the symptoms of this disease increases from 0 to 100%. When the age of these individuals increases from 10 to 70 years, this indicates that expression of Huntington's disease symptoms is stimulated by age. **(0.5)**

3- The allele of the disease is dominant with respect to the normal allele because affected parents (3 and 4) have healthy children (8 and 9). Then the normal allele is present in the parents and masked by the allele of the disease, thus the allele of the disease is dominant and the normal allele is recessive (D = allele responsible for the disease; n = normal allele); D> n. **(0.5)**

4- If the allele responsible for the disease is carried by the non-homologous segment of Y chromosome, transmission of the allele should take place from father to son. The diseased father 3 who would have $X//Y^D$ as genotype must transmit Y^D to his sons who should be diseased, but his son 8 is normal, then the allele is not carried by the non-homologous segment of Y chromosome.

If the allele of the disease is carried by the non-homologous segment of X chromosome, diseased father 3 who would have $X^D//Y$ as genotype should transmit this dominant allele X^D to all his daughters who should be affected, but his daughter 9 is healthy; then the allele is not carried by the proper part of the X chromosome.

If the allele is carried by the homologous part of X and Y chromosomes, normal boy 8 who should have $X^n//Y^n$ as genotype, he must thus receive an X^n from his mother (4) and Y^n from his father (3). His healthy sister (9) should have $X^n//X^n$ as genotype and receive an X^n from her father (3). This father should have $X^n//Y^n$ as genotype and be of normal phenotype, but he is affected by the disease. Therefore, this allele is not carried by the homologous segment of X and Y chromosomes.

So the allele of the disease is autosomal and not gonosomal. **(1)**

5-The B band corresponds to the mutated allele because the DNA analysis of the healthy individual 5 shows only a thick band at the A level. This indicates that the A band corresponds to the normal allele. In addition, the affected individual 6 shows a thin band at level A and another at level B. Then, the B-band corresponds to the mutated allele responsible for the disease. **(1)**

6-As the fetus has two thin bands, one at level A and the other at level B, corresponding to the normal allele and the mutated allele respectively, the genotype of the fetus is D//n. Since the mutated allele D is dominant over the normal allele n, the phenotype of the fetus is [D] and he will be diseased. **(1)**

Exercise (2021-1st session) **Fructosemia**

Congenital fructosemia is an intolerance to fructose, preventing the absorption of fructose and all sugars containing fructose**.** It is due to a deficiency in aldolase B, an enzyme located in the liver, small intestine and kidneys. Aldolase B enzyme is responsible for the cleavage of fructose -1- phosphate into two molecules: DHAP and glyceraldehyde. Children affected by this disease show a dysfunction of the liver and kidney weakness with abnormal high levels of sugar, amino acids and salts in the urine.

Document 1

1. Pick out from document 1:
1.1. the cause of fructosemia.
1.2. the consequences of this disease.

Document 2 represents the partial sequence of the nucleotide of DNA in the normal and the mutant alleles of the gene determining the synthesis of the enzyme aldolase B.

Allele	Nucleotide sequence of the **transcribed** strand of DNA
Normal	1↓ ↓24 TTA CCT GAC CAT GGA TAA CAA CTT
Mutant	1↓ ↓18 TTA CCT GGA TAA CAA CTT

Document 2

2. Compare these two sequences (document 2).
3. Indicate the type of the revealed mutation.
4. Write, referring to documents 2 and 3:
4.1. the mRNA that corresponds to each allele.
4.2. the sequence of amino acids that corresponds to each allele.
5. Explain how the modification of the nucleotide sequence of the allele leads to the appearance of fructosemia.

Solution

1.1-Deficiency of aldose B. (**1/2)**

1.2-Children affected by this disease show a dysfunction of the liver and kidney weakness with abnormal high levels of sugar, amino acids and salts in the urine. (**1/2)**

2-The number of nucleotides in the mutated allele is smaller than in the normal allele 18 <24 (**1/4)**
Nucleotides 7,8,9,10,11 and 12 (or 8, 9, 10, 11, 12 and 13) are absent in the mutated allele **(1/4).** However, the remaining nucleotides are identical **(1/4).**
Or the first six nucleotides (or the first seven nucleotides) are identical in both sequences (1/4). However, the remaining nucleotides are different **(1/4).**

3- Mutation by deletion. (**1/4)**

4.1- mRNA that corresponds to the normal allele: AAU GGA CUG GUA CCU AUU GUU GAA
mRNA that corresponds to the mutant allele: AAU GGA CCU AUU GUU GAA (**1/2)**

4.2-The amino acid sequence of the normal allele: Asp - Gly - Leu - Val- Pro - Ile- Val –Glu.
Amino acid sequences: Asp - Gly - Pro - Ile - Val – Glu (**1/2)**

5-The mutation by deletion in DNA was transcribed at the level of the mRNA by the absence of codons which results in an absence of the two amino acids Leu and VaL. This new amino acid sequence affects the three-dimensional form of the protein (Enzyme aldolase B) which becomes non-functional. As this enzyme is responsible for the cleavage of fructose 1 phosphate, the change in its function is manifested by fructose intolerance (**1)**

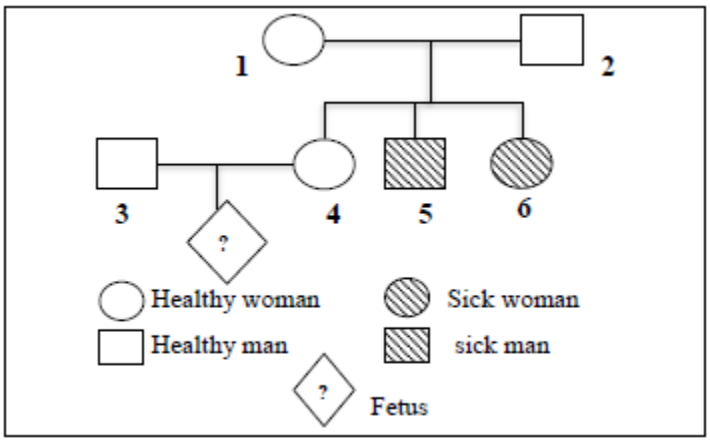
Exercise (2021-1st session) Transmission of a Hereditary Character

Fructosemia is a disease caused by deficiency of aldolase B enzyme. The following pedigree in document 1 shows the transmission of this disease in a family.

1. Indicate whether the allele responsible for the disease is dominant or recessive. Justify the answer.

2. Determine the chromosomal localization of the gene responsible for this disease.

3. Write the possible genotypes of each of the individuals 3 and 4.



Document 1

Document 2 represents the results of the electrophoresis performed on the alleles of the studied gene in individuals 3, 4 and the fetus.

4. Specify, by referring to document 2:

4.1. The real genotype of each of individuals 3 and 4.

4.2. The phenotype of the fetus.

5. What advantage does this technique provide to the determination of the genotype of an individual?

Allele \ Individual	3	4	Fetus
Normal	———	———	———
Mutant	———		

Document 2

Solution

1-The fructosemia allele is recessive (1/4). Because, parents 1 and 2 of healthy phenotype have affected children 5 and 6 (1/4). These children inherited the disease allele from at least one of the parents. This parent has the morbid allele in the masked state.
Let N be the symbol of the Normal, dominant allele. Let m be the symbol of the allele responsible for recessive fructosemia.(**1/2)**

2-If the gene is localized on the non-homologous segment of Y chromosome, then none of the female should be affected. This is not the case, since female 6 is an affected one.
Or father and son would be of the same phenotype because the boy inherits his Y from his father.
Or, sons should have the same phenotypes as their fathers (they have inherited the Y chromosome from their father). (1/4).
The affected male 5 would have as genotype $X//Y_m$, he has inherited Y_m from his father who would have as genotype $X//Y_m$. Possessing such genotype, the father should be affected, which is not. (1/4).
If the gene is localized on the non-homologous segment of X chromosome, then the affected female 6 would have as genotype $X_m//X_m$, she has inherited X_m from his father 2 who would have as genotype $X_m//Y$. Possessing such genotype, the father should be affected, which is not. (1/4).
If the gene is localized on the homologous segments of X and Y chromosomes, then the affected female 6 would have as genotype $X_m//X_m$, and similarly the affected male 5 would have as genotype $X_m//Y_m$, female 6 has inherited X_m from her father while male 5 has inherited Y_m from the same father. The father as such should have as genotype $X_m//Y_m$. Possessing such genotype, the father should be affected, which is not.
Thus the gene is not gonosomal, therefore autosomal. (1/4).

3- 3 : N//m or N//m 4 : N//m or N//m (**1/2)**

4.1-The electrophopregram of individual 3 shows a band that corresponds to the normal allele and another that corresponds to the mutant allele (1/4). Consequently, the genotype of individual 3 is N//m (1/4)..
The genotype of individual 4 is N//N (1/4) because he has one band that corresponds to the normal allele (1/4).

4.2-The fetus has only the normal allele, so he has two copies of the allele N (1/4). He has a normal phenotype (1/4).

5-The electrophoresis permits determining the real genotype of the individual.(**1/2)**

Exercise (2020 unique sessin) **Bruton Disease**

Bruton disease is a genetic disease that affects one newborn in 200,000 birth. It is manifested by recurrent bacterial infections of the respiratory tract, starting from the age of six years. The disease predisposes patients to the risk of having chronic infections with viruses that attack particularly the digestive tract and the nervous system.

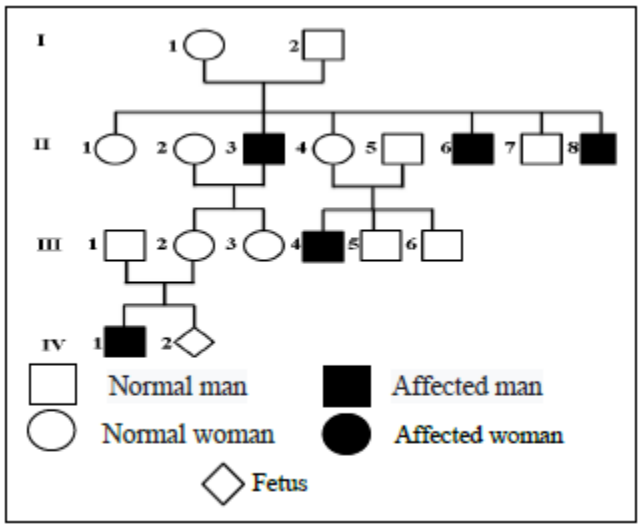
Document 1 represents the pedigree of a family, whose certain members are affected with Bruton disease.

1- Indicate whether the allele responsible for Bruton disease is dominant or recessive. Justify the answer.

2- Show that the gene responsible for the disease is localized on the non-homologous segment of chromosome X.

3- Indicate the genotypes of individuals III_1, III_2 and IV_1.

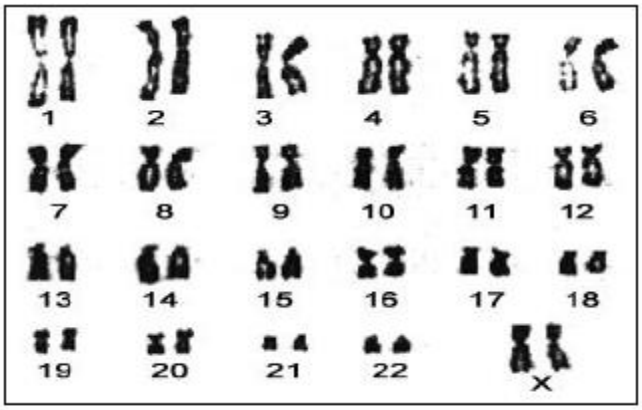
4- Determine the risk for the fetus IV_2 to be affected with this disease.



Document 1

To find out if the fetus IV_2 will be affected with Bruton disease, the doctor requests establishing the karyotype of the fetus. The obtained result is shown in document 2.

5- Determine, referring to documents 1 and 2, if the fetus IV_2 will be affected by Bruton disease.



Document 2

The doctor completes the diagnosis by performing DNA analysis using the Southern Blot technique. The used probe makes it possible to distinguish between the mutant allele and the normal allele of the gene involved in Bruton disease. The obtained results are shown in document 3.

6- Specify the band that corresponds to the mutant allele.

7- Draw out the genotype as well as the phenotype of the fetus IV_2.

	III_1	III_2	IV_1	Fetus IV_2
A	———	———		———
B		———	———	———

Document 3

Answer key **Bruton Disease**

1- The allele responsible for the disease is recessive, since individuals 3, 6 and 8 are affected from healthy parents. This means that the mutant allele is present in the parents but masked by the normal allele (N). (**0.5)**

2-There is discrimination of sex, only males are affected, so the allele of the disease is sex-linked. If the studied gene were localized on the non-homologous segment of chromosome Y, any affected boy should have an affected father, which is not the case (normal father I2 has affected boys). So the studied gene is localized on the non-homologous segment of chromosome X.(**1)**

3- N: normal allele dominant
m : affected allele recessive
III_1: X_NY
III_2: X_NX_m
IV_1 :X_mY (**0.75)**

4-The fetus IV_2 has a heterozygous mother (III2) of genotype X_NX_m. If the fetus were a boy, the risk of this fetus, in this case, to receive the chromosome Xm from his mother will be ½. He obligatory will receive chromosome Y from his father.
If the fetus were a girl, the risk will be null since she will receive obligatory X_N from her healthy father of genotype X_NY. Therefore, the fetus will be necessarily healthy regardless of the gamete received from her father, N is dominant. (**0.75)**

5-The karyotype (document 2) shows that the fetus is a girl with two chromosomes X. Referring to the pedigree (document 1), the fetus has a healthy father of genotype X_NY. Thus, he must have obligatory received X_N from his father and then the fetus will be a healthy girl since allele N is dominant, then the female is healthy.(**1)**

6-Band B corresponds to the mutated allele, because document 3 shows that male IV1 of genotype X_mY possesses a single band B. (**0.5)**

7-Fetus: genotype X_NX_m
Phenotype : Healthy [N] (**0.5)**

Exercise (5 points) **Pulmonary Emphysema (2019-2nd)**

Pulmonary emphysema is a fatal disease characterized by an increasingly severe respiratory failure. This disease is due to a progressive destruction of the lung tissue by the proteases of the white blood cells. In fact, in the normal case, there are substances in the blood plasma called alpha antitrypsin (aT) which protect the pulmonary cells from being destroyed by inhibiting the action of proteases.

Allele	Nucleotide sequence of the fragment of the non-transcribed strand
M_1	181 184 .... ATC AAC GAT TAC ...
M_2	181 184 .... ATC AAC GAT TAG ...

Document 1

1- Pick out from the text the cause of pulmonary emphysema.

Alpha antitrypsin (aT) is a protein composed of 418 amino acids produced by liver cells. Document 1 shows the nucleotide sequence of a fragment of the non-transcribed strand of the normal allele (M1) and that of the allele of the disease (M2) of the gene responsible for the synthesis of "aT".

2- Determine, using the genetic code table (document 2), the amino acid sequence of the portion of the alpha antitrypsin coded by the fragment of the allele M1 and that coded by the fragment of the allele M2.

3- Explain how the modifications in the nucleotide sequence of the allele (document 1) lead to the appearance of pulmonary emphysema.

First letter	Second letter: U	Second letter: C	Second letter: A	Second letter: G	Third letter
U	UUU Phe UUC Phe UUA Leu UUG Leu	UCU Ser UCC Ser UCA Ser UCG Ser	UAU Tyr UAC Tyr UAA stop UAG stop	UGU Cys UGC Cys UGA stop UGG Trp	U C A G
C	CUU Leu CUC Leu CUA Leu CUG Leu	CCU Pro CCC Pro CCA Pro CCG Pro	CAU His CAC His CAA Gln CAG Gln	CGU Arg CGC Arg CGA Arg CGG Arg	U C A G
A	AUU Ile AUC Ile AUA Ile AUG Met	ACU Thr ACC Thr ACA Thr ACG Thr	AAU Asn AAC Asn AAA Lys AAG Lys	AGU Ser AGC Ser AGA Arg AGG Arg	U C A G
G	GUU Val GUC Val GUA Val GUG Val	GCU Ala GCC Ala GCA Ala GCG Ala	GAU Asp GAC Asp GAA Glu GAG Glu	GGU Gly GGC Gly GGA Gly GGG Gly	U C A G

Document 2

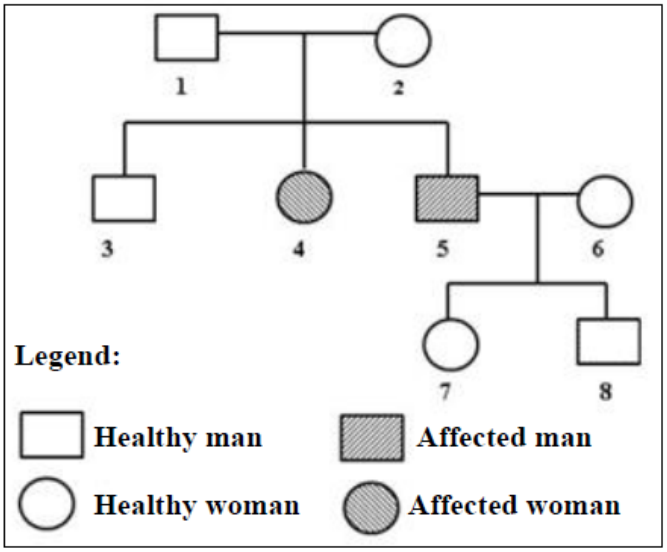
Document 3 represents the pedigree of a family of which some members are affected by pulmonary emphysema.

4- Specify whether the allele M2 which is responsible for this disease is dominant or recessive.

5- Determine the chromosomal localization of the gene responsible for pulmonary emphysema.

6- Write the genotype of individual 8. Justify the answer.
Individual 8 is a heavy smoker and has manifested the same symptoms of pulmonary emphysema.

7- Show that there is a factor other than the genetic factor that could provoke this disease



Document 3

Answer key

1- A progressive destruction of the lung tissue by the proteases of the white blood cells. (**0.5)**

2- mRNA resulting from the transcription of the allele M1: … AUC AAC GAU UAC …
Sequence of the amino acids of the polypeptide coded by the allele M1: … -Ile - Asn - Asp - Tyr - …
mRNA resulting from the transcription of the allele M2: … AUC AAC GAU UAG…
Sequence of the amino acids of the polypeptide coded by the allele M2: … -Ile - Asn – Asp **(1)**

3- The mutation by substitution at the level of the 3rd nucleotide of triplet number 184 (C is replaced by G) is transcribed at the level of mRNA gives a truncated polypeptide having 183 amino acids instead of 418, leading to an non-functional protein alpha-antitrypsin (aT). This explains why alpha-antitrypsin is not found in the blood of an individual affected by pulmonary emphysema and consequently the pulmonary tissue is not protected against protease degradation and the patient shows manifestation of pulmonary emphysema. (**1)**

4- The allele of the disease is recessive. The parents 1 and 2 are normal but gave two affected children 4 and 5. These children have taken the mutant allele from at least one of the parents. This parent does not phenotypically express the disease, so the mutant allele is being masked by the normal one. N: normal dominant allele. m: mutant recessive allele. **(0.5)**

5- If the studied gene is carried on the non-homologous part of Y, in this case, any affected boy would necessarily have a sick father. For example, the affected boy 5 must have taken Y_m from his father who would have as genotype XY_m. Possessing such genotype, father 1 should be affected, which is not the case.
If the studied gene is carried on the non-homologous part of chromosome X: in this case, the affected daughter 4 would have X_m // X_m as genotype (purity is the criterion of recessivity). She should have taken one of her mutant alleles Xm from her father 1 who would have as genotype Xm // Y who phenotypically should be affected, which is not the case.
If the studied gene is carried on the homologous parts of X and Y: in this case, the affected boy 5 would have as genotype X_m // Y_m, and his sister 4 would have as genotype X_m // X_m They have taken respectively Y_m and X_m from their father 1. This latter should have as genotype X_m // Y_m and would be phenotypically affected. It's not the case.
Therefore, the studied gene is not gonosomal but it is autosomal. **(1)**

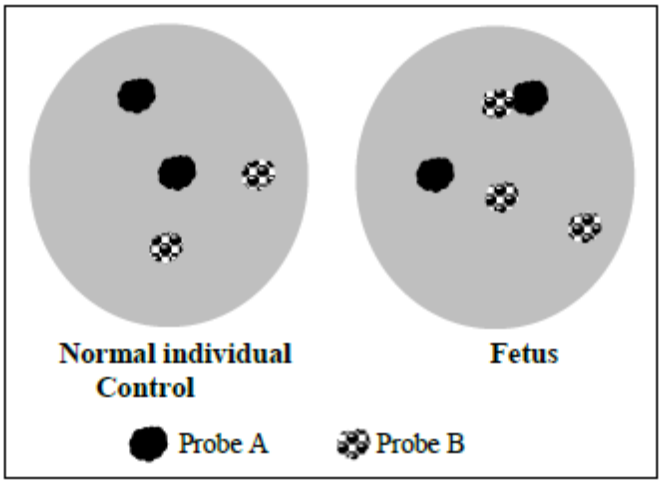
6- The genotype of individual 8 is N//m. He is phenotypically normal, possessing the normal dominant allele and the affected allele m is obligatory inherited from the homozygous diseased father 5. (**0.5)**

7- Despite the presence of a normal allele in his genotype (heterozygous), individual 8 develops the same symptoms of pulmonary emphysema. Being a heavy smoker promotes the development of the disease. This shows that smoking is an environmental factor other than the genetic factor that could provoke this disease**.(0.5)**

Exercise 1 (4.5 points) **Patau Syndrome (2018-2nd)**

Patau syndrome is caused by an excess of genetic material of chromosome 13 in the cells of the body. It affects one newborn in 10000 births. The affected children show certain abnormalities: small head, malformation of the hands and eyes, as well as various perturbations in the functioning of the organs.

1. Formulate a hypothesis explaining the presence of the excess genetic material in individuals affected by Patau syndrome.



Document 1

Mr. and Mrs. H, a healthy couple who already have a child affected by Patau syndrome, are expecting another child. They are worried that the fetus might be affected by this syndrome.

The doctor requests certain tests to be performed.

Test 1: The fluorescent in situ hybridization technique (FISH) is applied on fetal cells.

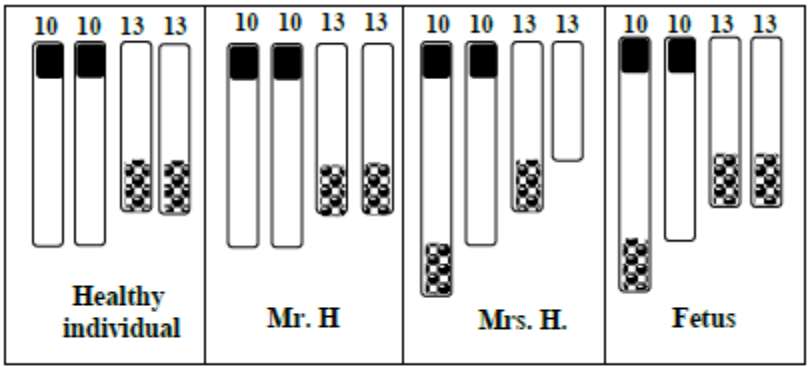
In this prenatal diagnosis technique, two fluorescent single-stranded molecular probes are used:

- Probe A complementary to a specific DNA sequence of chromosome 10.
- Probe B complementary to a specific DNA sequence of chromosome 13 that is involved in Patau syndrome.

The obtained results are shown in document 1.

Based on the analysis of the results, the doctor assures for the parents that their expected child is affected by Patau syndrome.

2. Justify, by referring to document 1, the doctor's diagnosis.



Document 2

Test 2: The doctor orders additional tests for each of the two parents and their fetus. Document 2 shows only the pairs of chromosomes 10 and 13 of the mother, the father, the fetus and those of a healthy individual. The other pairs are all normal.

3. Justify why the mother presents no phenotypic abnormalities.

4. Show that the chromosomal abnormality of the fetus is an abnormality in structure and not in number.

5.1. Schematize chromosomes 10 and 13 in the gametes produced by each of the two parents.

5.2. Indicate the two parental gametes that are at the origin of the karyotype of the fetus**.**

Answer key

1-Hypothesis:

- The excess of genetic material might be due to trisomy 13 (linked or free).
- The excess of genetic material might be due to a translocation of part of chromosome 13.
- The excess of genetic material might be due to a certain mutation at the level of chromosome 13 (duplication of a fragment of a chromosome). (**0.5)**

2- Justify: Document 1 shows that each of the healthy individual and the fetus possesses two fluorescent probes A which correspond to the two chromosomes 10.

However, the fetus presents three fluorescent probes B corresponding to three chromosomes 13 , unlike the healthy individual who presents two fluorescent probes B (two chromosomes 13). Moreover, one of the three probes B is attached to probe A.

The fetus thus has an excess of genetic material of chromosome 13. Since this excess of genetic material of chromosome 13 in the cells causes Patau syndrome, then the doctor's affirmation that the fetus will be affected by Patau syndrome is justified.(**0.75)**

3- Justify: Since one of the pair of chromosomes 13 of the mother shows a missing part , and one of chromosomes 10 has an excess of the same part, and since all the other chromosome pairs are normal; then the mother presents neither gain nor loss in the genetic material and her DNA mass is conserved. As a result, the mother has a normal phenotype. (**0.75)**

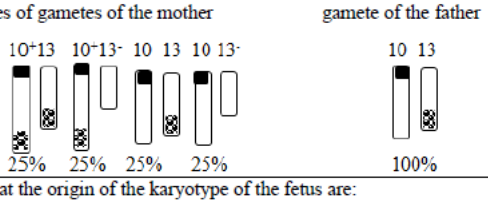
4- Show that: The fetus only presents abnormalities in chromosomes 10 and 13. Document 2 shows that the fetus possesses a pair of chromosomes 10 and a pair of chromosomes 13; so the exact total number of chromosomes is normal. Therefore, the fetus' abnormality in not in number.

However, one of the chromosomes 10 of the fetus is longer than the pair of chromosomes 10 of the healthy individual, but the other copy of chromosome 10 and both copies of chromosome 13 of the fetus have equal lengths as those of the healthy individual. It is therefore the structure of the chromosomes that is abnormal.(**1)**

5- Schematize , Indicate

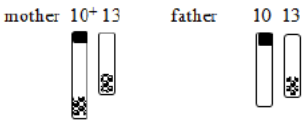
5.1

Scheme showing the types of the parental gametes



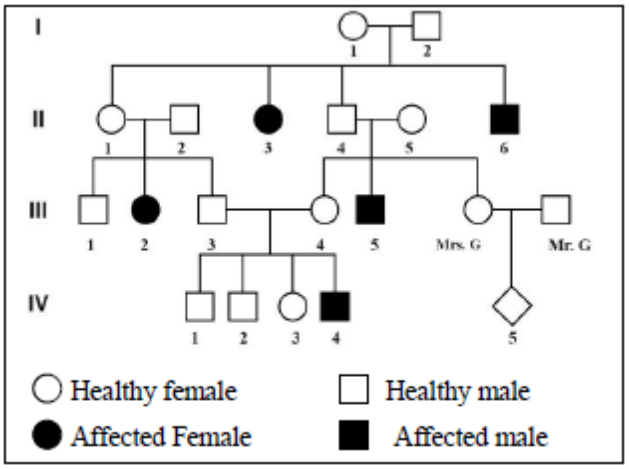
5.2

The gametes at the origin of the karyotype of the fetus are:



Exercise 1 (5.5 points) **Diagnosis of Galactosemia (2018-1st)**

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.



Document 1

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.

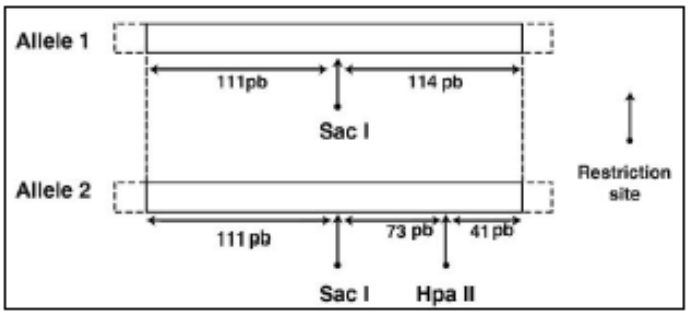
1. Indicate if the allele responsible for the disease is dominant or recessive. Justify the answer.

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.

4. Determine the risk for the expected child, IV5, to be diseased.



Document 2

The GALT gene is responsible for galactosemia.

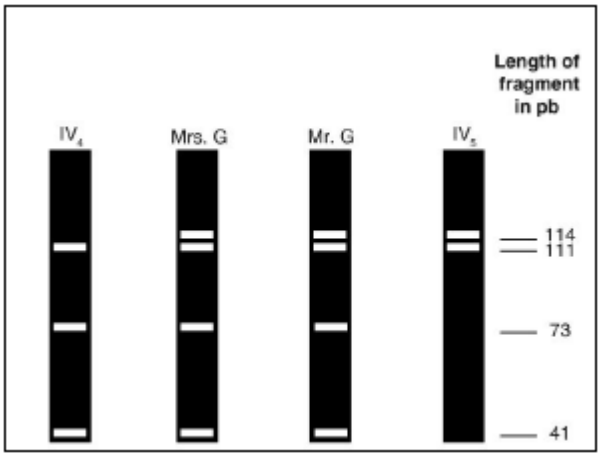
Document 2 shows the cleavage sites of two restriction enzymes, Sac 1 and Hpa II, at the level of a part **(**from nucleotide 1367 to nucleotide 1605) of two alleles of this gene: Allele 1 and allele 2.

Document 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

Solution

1- Indicate and justify: 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: normal allele dominant and m: mutated allele recessive. **(0.5 pt)**

2- Determine: 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 by should be necessarily affected since the boy inherit gonosome Y from his father. This is not the case since the affected boy II6 who must have XYm as genotype should inherit Ym from his father who must be in this case affected but the father I2 is not affected.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 XmXm should inherit Xm from her father whose genotype should be XmY and he should be diseased. This is not the case.

If the gene of the disease is carried on **the homologous part of X and Y**, the boy II6 will have the genotype XmYm and his diseased sister II3 will have the genotype XmXm. The boy will inherit Ym from his father and the girl will inherit Xm from her father. So the genotype of the father I2 should be XmYm and he will be phenotypically affected which is not the case. The gene is not localized on a gonosome .

Thus, the gene responsible for galactosemia is autosomal. (1 pt)

3- Specify: The genotype of Mrs.G is NN or Nm since the dominant allele is expressed in both homozygous and heterozygous states.

The genotype of IV4 is gg because the recessive allele is only expressed in the homozygous state. **(1 pt)**

4- Determine: The risk for the child IV5 to be diseases is:

The risk of his mother Mrs.G to be heterozygous for the gene is 2/3 since her two parents are heterozygous and have an affected child II5 of genotype mm

The risk of the father Mr.G to be heterozygous for the gene is 1/100 since the father doesn't belong to this family, he doesn't have any history of the disease, so his risk to be heterozygous is the same as that of the worldwide population (1/100)

The risk of the child to have both recessive alleles of the disease is ¼ since 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 IV5 to be diseased (having genotype mm) = 2/3 X 1/100 X ¼ = 1/600 **(1 pt)**

5- Indicate: The fragments of allele 1: 2 fragments of sizes 111 bp and 114 bp

The fragments of allele 2: 3 fragments of sizes 111 bp, 73 bp and 41 bp. **(0.5 pt)**

6- Determine: Document 3 shows that infant IV4 is diseased and have an obligatory genotype mm, and has in his electrophoregram 3 DNA fragments (111 bp, 73 bp and 41 bp), corresponding to the same fragments of allele 2. So the allele 2 is the mutated allele. **(0.75 pt)**

7- Verify: 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 NN and will be galactosemic. **(0.75 pt)**

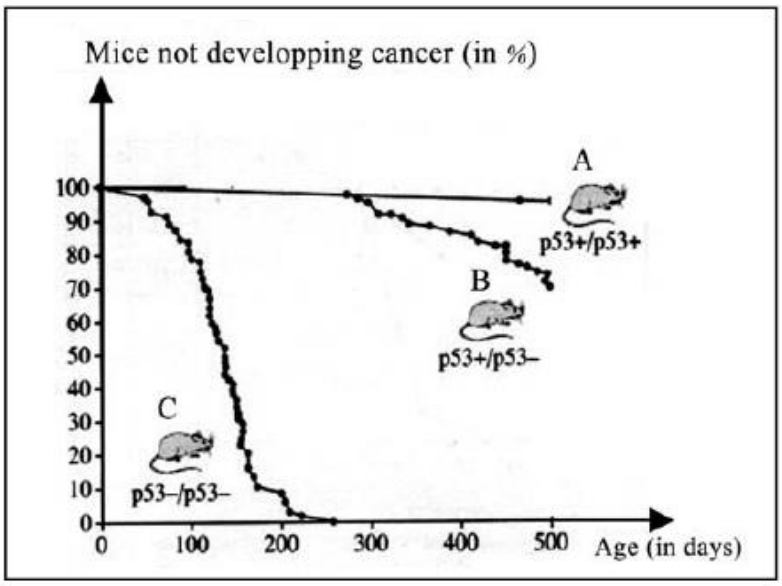
Exercise (5 points) **Genetics and Cancer (2017-2nd)**

Billions of cells of the organism, having a limited lifespan, are continuously renewed due to cellular divisions controlled by a system of regulation. The dysfunction of this system of regulation can produce a clone of cells,
thus forming a tumor. This latter, is benign as long as it is controlled but it can evolve into malignant tumor: cancer. The cancerous cells lose their contact with their neighboring cells; they tend to migrate and colonize in other tissues: this is metastasis.

1- Pick out from the text :

1-1- The cause of the appearance of tumor.

1-2- The definition of metastasis.



Document 1

In order to better understand the origin of this type of cancer, several studies have been carried out on the gene
p53 coding for the protein p53. This protein intervenes in the regulation of the cell divisions.

Study 1:

The development of this type of cancer is studied in three lots of mice as a function of their genotypes concerning the gene p53. Two alleles of this gene, p53+ (normal) and p53- (mutated) are only considered. The
results of this study are shown in document 1.

2- Interpret the obtained results shown in document 1.

Gene p53	Sequence of the nucleotides of the non-transcribed DNA strand
N° of codon	↓244 ↓250
Allele p53+	GGC GGC ATG AAC CGG AGG CCC
Allele p53-	GGC GGC ATG AAC CGG AGT CCC

Document 2

		Group 1	Group 2	Group 3
Mutations detected at the level of gene p53	Number	3	5	7
	Type	Substitution	Substitution	Substitution, deletion and insertion
Result : Number of individuals affected by cancer		Low	Moderate	High

Document 3

Document 2 shows the nucleotides sequence of the non-transcribed strand of each of the two alleles involved in this study.

3- Specify the type of mutation at the origin of this cancer.

4- Explain how the modification in the nucleotide sequence leads to the appearance of this type of cancer.

Study 2:

Researchers have studied the mutations detected in three groups of individuals: individuals of group 1 are nonsmokers and non-alcohol consumers, those of group 2 are smokers but non-alcohol consumers and those in group 3 are smokers and alcohol consumers. The results are shown in document 3.

5- Show that the consumption of tobacco is a risk factor for cancer.

6- Justify the high number of individuals affected by cancer in the case of the simultaneous consumption of alcohol and tobacco

Answer keys

1- 1-1 The dysfunction of this system of regulation can produce a clone of cells, thus forming a tumor**. (1/4 pt)**

1-2 The cancerous cells lose their contact with their neighboring cells; they tend to migrate and colonize in other tissues: this is metastasis. **(1/4 pt)**

2- In lot A of genotype p53+//p53+, the percentage of mice that don't develop cancer stays constant at 100% during 500 days. However, the percentage decreases from 100% to 70% in mice of lot B of genotype p53+//p53- between day 280 and day 500. This shows that the allele p53- favors the development of cancer when it's present in one copy.

However, in lot C having the genotype p53-//p53-,the percentage of mice not developing cancer begins to diminish from 100% on day 50 to null on day 250 days which is less that day 280 corresponding to the appearance of cancer in lot B. Therefore, the allele p53- accelerates the appearance of cancer and its action is amplified when it exists in 2 copies. **(1 pt)**

3- The origin of cancer is a mutation by substitution of gene p53. Since the nucleotides of alleles are identical except at the level of the 3rd nucleotide of codon 249 where the G nucleotide in the allele p53+ is substituted by the nucleotide T in the allele p53**-. (1 pt)**

4- The mutation by substitution at the level of codon 249 leads to an amino acid different than that translated by the normal allele. This modification of amino acid has as a consequence the synthesis of an abnormal and non-functional protein.

As a consequence, the regulatory system of cellular divisions becomes nonfunctional and the cells divide in an uncontrollable manner, producing thus a clone of cells forming tumors. **(1 pt)**

5- Document 3 shows that in the smokers, the number of mutation by substitution is 5 and the number of individuals affected by cancer is moderate; whereas, the non-smokers present 3 (3<5) mutations by substitution that limits the development of cancer in them. This shows that tobacco is a risk factor for cancer. **(3/4 pt)**

6- In the smokers and consumers of alcohol, the number of mutation is 7, a value greater than 5, which is the number of mutation in the smokers (and also greater than 3, in nonsmokers and non-alcohol consumers).

In addition to the increase in number, the mutations exit in different types: deletions and insertions in addition to substitutions, the only type mutations revealed in the two groups 1 and 2.

Since the mutations at the level of gene p53 is at the origin of tumors, the increase in the number of mutations as well as the occurrence of new types of mutations, favor the appearance of cancer and therefore justifies the high number in individuals affected by cancer which are smokers and alcohol consumers**. (3/4 pt)**

Exercise (5 points) **Cystic Fibrosis (2017-1st)**

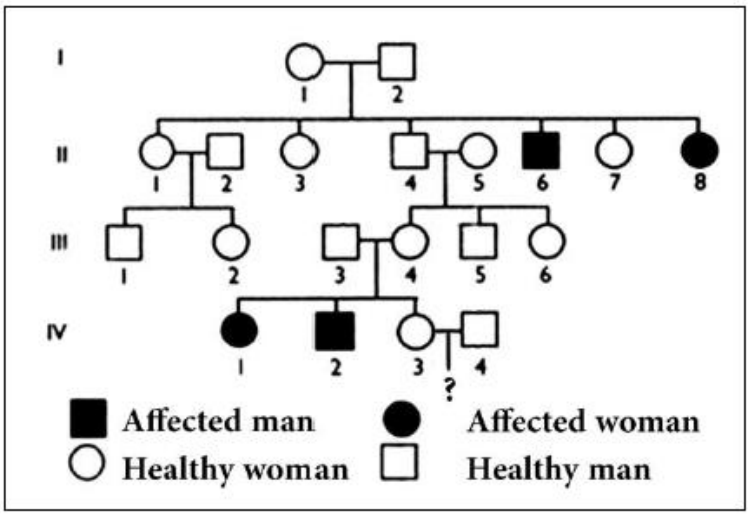
Certain mutations which are at the origin of genetic diseases may protect against other diseases. In order to clarify this observation, the following studies are performed.

Study 1:

Cystic fibrosis is a severe disease manifested by respiratory and digestive troubles.

The origin of the disease is a mutation of the gene coding for the protein CFTR leading to the modification of amino acid 508.

The protein CFTR is present in the plasma membrane of the cells. It allows the exchange of Cl^- ions and therefore, the exchange of water. The alteration of this protein blocks the passage of the Cl^- ions and water leading to an increase in the viscosity of the mucus, particularly at the level of the lungs and the digestive tract. In a well-defined population, 1 out of 20 persons are heterozygous.



Document 1

Document 1 shows the pedigree of a family whose some members are affected by cystic fibrosis.

1- Pick out:

1-1 The origin of cystic fibrosis.

1-2 The consequences of the mutation at the cellular level.

2- Indicate if the allele responsible for the disease is dominant or recessive. Justify the answer.

3- Determine the chromosomal localization of the gene responsible for cystic fibrosis.

4- Specify the genotype of each of the individuals II8, III3, IV2 and IV3.

5- Determine the risk for couple IV3 and IV4 to have a child affected by cystic fibrosis.

Study 2:

Three lots of mice are genetically modified by integrating the human gene coding for CFTR protein in their genome. The mice of lot 1 are homozygous for the normal allele, the mice of lot 2 are homozygous for the mutated allele, and the mice of lot 3 are heterozygous.

Salmonella typhi bacteria have been ingested by the mice of the three lots. The number of intestinal cells infected by *Salmonella typhi* is estimated. The results are shown in document 2.

	Lot 1	Lot 2	Lot 3
Mice	Homozygous for the normal allele	Homozygous for the mutated allele	Heterozygous for this gene
Results	Numerous infected intestinal cells	No infected intestinal cells	Few infected intestinal cells

Document 2

The infection by this bacterium leads to Typhoid fever which is manifested by a very serious inflammation of the digestive tract leading to death in the absence of any antibiotic treatment.

6- Justify, referring to what precedes, that some mutations which are at the origin of genetic diseases may protect against other diseases

Answer key

1- **1.1-** The origin of the disease is a mutation of the gene coding for the protein CFTR leading to the modification of amino acid 508**. (0.25 pt)**

1.2- the alteration of this protein blocks the exchanges of the Cl- ions and water leading to an increase in the viscosity of the mucus, particularly at the level of the lungs and the digestive tract. **(0.25 pt)**

2- The allele responsible for the disease is recessive with respect to the normal allele, since individuals II-6 and II-8 who are affected, have healthy parents I-1 and I-2. Thus,, at least one of the parents carries this mutated allele that is masked. Let N be the symbol of the normal allele and m the symbol of the allele responsible for cystic fibrosis. **(0.75 pt)**

3- If the gene was located on the non-homologous segment of chromosome Y, the transmission of the disease would be done from father to son (any affected boy should have an affected father) but this is not the case since the son II-6 who is affected by cystic fibrosis has a healthy father. Then the gene is not locted on the non-homologous segment of chromosome Y**. (0.25 pt)**

If the gene was located on the non-homologous segment of chromosome X, the affected daughter II-8, having the recessive phenotype, should have XmXm as genotype and should have inherited an Xm chromosome from her father I-2 whose genotype should be XmY and thus affected by cystic fibrosis, but this is not the case because he is healthy. Then the gene is not located on the non-homologous segment segment of chromosome X. **(0.25 pt)**

If the gene was located on the homologous segment of X and Y, the affected son II-6 would be of genotype XmYm, Ym is inherited from his father I-2, and his affected sister II-8 would be of genotype XmXm, one of these two chromosomes is inherited from the father I-2. Then the father would be of genotype XmYm and thus suffering from cystic fibrosis but this is not the case. **(0.25 pt)**

Thus, the gene is question is not carried by the sex-chromosomes, it can only be autosomal**.(0.25 pt)**

4- The genotype of II-8 is mm, because she has the recessive affected phenotype and the recessive allele is only expressed in homozygous state; thus she is homozygous **(0.25 pt)**

The genotype of III-3 is Nm, because he is a man of normal dominant phenotype, he possesses the allele N and since he gave birth to diseased children IV-1 and IV-2 of genotype mm, thus, these children must have inherited an m allele from their father III-3. Therefore the father is heterozygous. **(0.25 pt)**

The genotype of IV-2 is mm since he is affected by a recessive disease and recessivity is a criterion of purity. He is homozygous recessive.(0.25 pt)

The genotype of IV-3 may be heterozygous Nm or homozygous NN. Since she has the normal dominant phenotype and the dominant allele manifests when it is present in a single copy or two copies.(0.25 pt)

5- The risk for the child to be affected by an autosomal recessive disease: 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 copies of the mutant allele.

The normal mother IV-3 has heterozygous parent Nm that have sick children of genotype mm. her risk to carry the mutated allele is 2/3.

Father IV-4 of normal phenotype has no family history. His risk to carry the mutated allele in the studied population is 1/20.

In the case of heterozygous parents, the risk of the child to inherit the allele m from both parents is ¼.

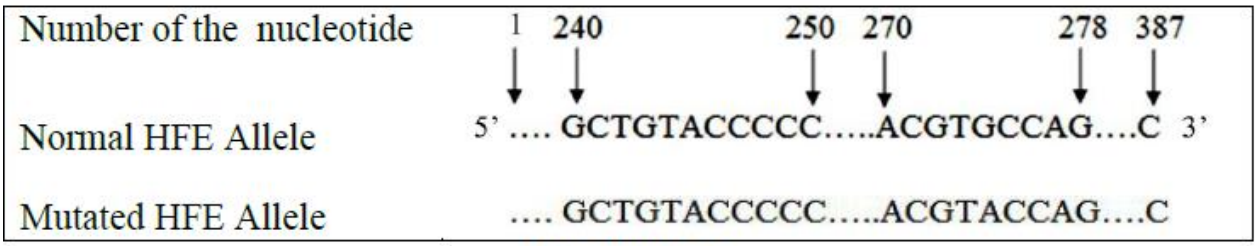
Therefore, the risk is 2/3 X 1/20 X ¼ = 1/ 120. **(0.75 pt)**

6- Document 2 shows that numerous intestinal cells are infected in the homozygous normal mice (lot 1) while no infection is detected in homozygous mice (lot 2) and only few intestinal cells are infected in the heterozygous mice (lot 3). This indicates that the presence of at least one allele of cystic fibrosis ensures a certain protection against the bacterium ***S.typhi*** in the intestinal cells.

Therefore, the presence of a mutated allele may cause the onset of a genetic disease, cystic fibrosis, but it may protect against other diseases such as typhoid fever**. (1 pt)**

Exercise (5 points) **Hemochromatosis (2016-2nd)**

Hemochromatosis appears after the age of 40 years and is characterized by the accumulation of iron in the body. It is a recessive disease linked to the HFE gene which is located on chromosome 6. This gene has two alleles: the normal allele which codes for a membrane protein that regulates the entry of iron into the cells, and the mutated allele which codes for an abnormal protein that favors the accumulation of iron inside the cells.
Document 1 presents the partial sequence of nucleotides of the two alleles, the normal and the mutated ones.

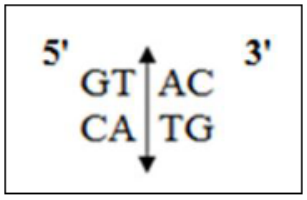


Document 1

Document 2 presents the restriction site of a restriction enzyme Rsa1.

1- Specify, by referring to document 1, the origin of hemochromatosis.

2- Determine for each of the two alleles, the number and the length of the restriction fragments obtained after cutting by Rsa1 enzyme.

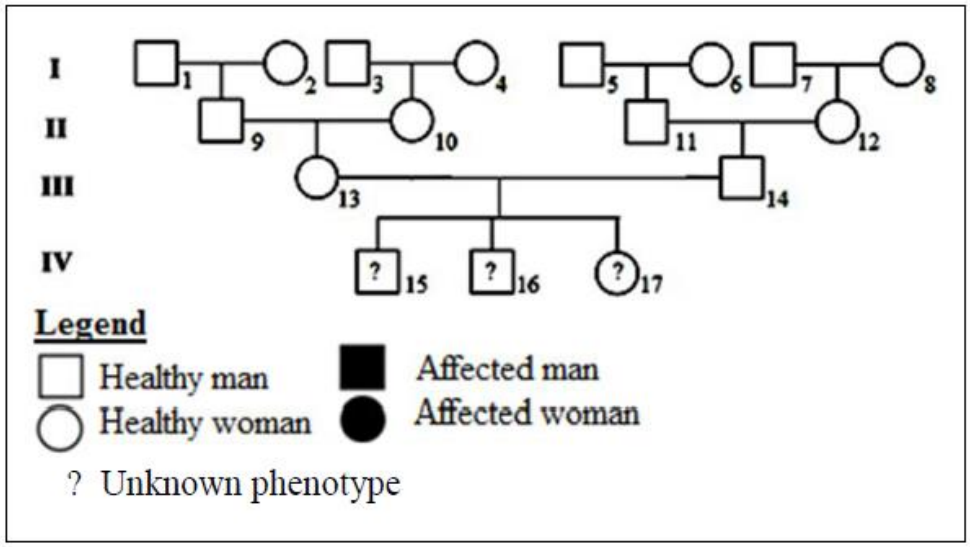


Document 2

The frequency of heterozygotes in a certain population is 1/10.

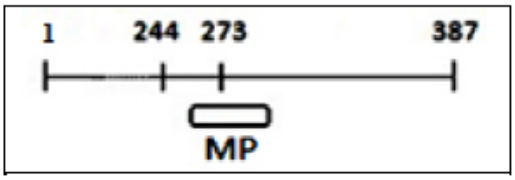
A healthy couple, older than 40 years, belongs to this population. This couple would like to know if their three children, who appear healthy, have a risk to develop the disease. That's why they consult a doctor who, as a first step, establishes for this family a pedigree which is shown in document 3.

3- Calculate the risk for this couple, III13 and III14, to have an affected child.



Document 3

As a second step, the doctor performs DNA analysis by applying the southern blot technique using the restriction enzyme Rsa1 and a radioactive molecular probe (MP) which is complementary to a specific sequence of HFE gene. This probe can fix to the whole or to a part of the recognized sequence as shown in document 4.
Document 5 shows the results obtained by this technique for certain members of this family.



Document 4

4- Explain the absence of the 244 bp fragment in the electrophoregram presented in document 5.

5- Establish the diagnosis for each of the children in document 5.

Size of DNA fragments (bp)	III13	III14	IV15	IV16	IV17
29					
114					
143					

Document 5

Answer key

1- The origin of hemochromatosis is a mutation by substitution at the level of the HFE gene, Since the nucleotides of the normal allele HFE, presented in document 1, are identical to those of the mutated allele except for the nucleotide 274 where G in the normal allele is replaced by A in the mutated one. This mutation leads to the synthesis of an abnormal protein**. (0.75 pt)**

2- When treated by the restriction enzyme Rsa1, the normal allele which presents only one recognirtion site GTAC at the level of nucleotides 243 – 246 is cut once between T in position 244 and A in position 245, thus we obtain 2 fragments the first is of 244 bp length and the second of 387-244= 143pb length **(0.75 pt)**

When treated by the restriction enzyme Rsa1, the normal allele which presents 2 recognition sites GTAC at the level of nucleotides 243-246 and at the level of nucleotides 272-275 is cut twice:
- between T in position 244 and A in position 245, giving the first fragment of 244 pb length,
- between T in position 273 and A in position 274 which gives the second fragment 273 – 244 = 29 bp length and the third fragment of 387 – 273= 114 bp length. Therefore three fragments are obtained **(0.75 pt)**

3-Since each of the two parents has no family history for hemochromatosis, the frequency for each of them to be heterozygous is 1/10 (frequency in the considered population).
Thus the risk for both of them to be heterozygotes is 1/10 x 1/10 = 1/100
Since the allele responsible for the disease is recessive, the risk for a heterozygous couple to have an affected child is 1/4.
Hence the risk for this couple to have an affected child is 1/100 x 1/4=1/400 **(0.75 pt)**

4-The electrophoregram shows only the fragments to which the radioactive molecular probe is hybridized. Since the recognized sequence to which the MP gets fixed is localized only at the level of nucleotide 273, thus the 244 bp fragment is not hybridized and doesn't appear in the electrophoregram. **(0.5 pt)**

5- The electrophoregram shows 3 bands: band 143 bp characterizing the normal allele and bands 29bp and 114 bp characterizing the mutated one.
The electrophoregram of child IV15 shows one thick band at the level of 143 bp corresponding to the normal allele. Hence he is healthy homozygote. **(1/2 pt)**
The electrophoregram of child IV16 shows the 3 bands. Thus he is heterozygote and since the allele of the disease is recessive, he is healthy. **(1/2pt)**
The electrophoregram of child IV17 shows two thick bands, 29 bp and 114 bp corresponding to the mutated allele. Thus she is recessive homozygote. She will be sick after the age of 40 years. Hence, among the three children, only the girl 17 will be sick after the age of 40 years. **(1/2pt)**

Exercise (5 points) **Dysuria (2016-1st)**

Dysuria is a disease that consists of a difficulty in urinating. It's related to excessive formation of urinary calculi ("stones" in urinary tracts). A family, which has twins suffering from dysuria, consults a doctor. He prescribed many tests whose results are represented in document 1.

Document 2 shows the reactions of metabolism of adenine related to the formation of calculi.

1- Justify, by referring to documents 1 and 2, the dysuria detected in the twins.

Measurements	Control	Twins
Quantity of adenine in urine excreted within 24h	1.5 mg	40 mg
Dihydroxyadenine (constituent of calculi)	Not detected	High quantity
Amount of active enzyme APRT	100 %	0 %

Document 1

In order to clarify the problem observed in the twins, a more detailed analysis concerning members of their family was performed. The pedigree of their family is shown in document 3.

2- Formulate, by referring to document 3, two hypotheses explaining the appearance of the disease in the twins.

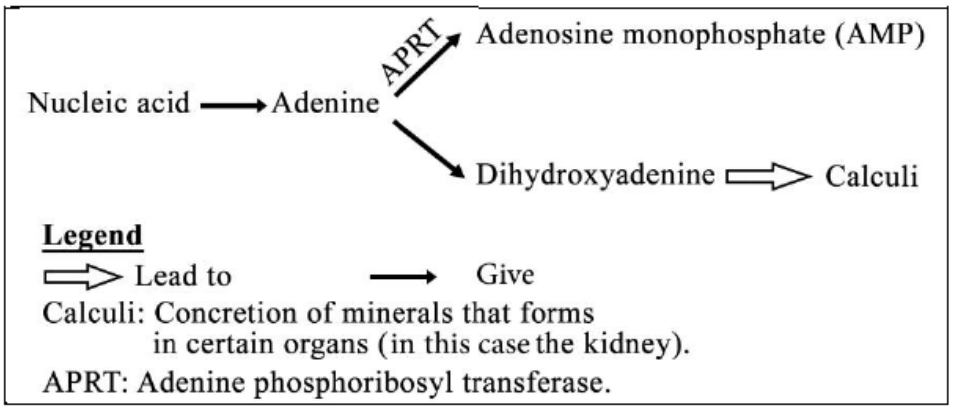
3- Knowing that the gene exists only in two allelic versions, specify if the allele responsible for the disease is dominant or recessive.

4- Show that this gene is not carried by a sex chromosome.

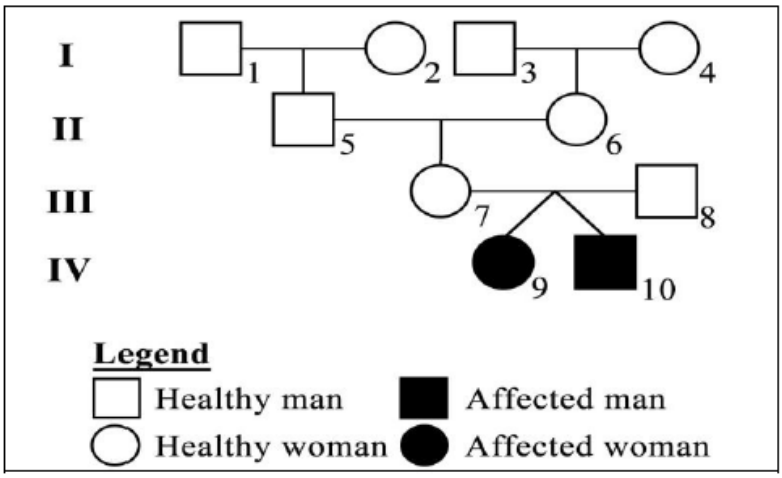
5- Indicate the possible genotype(s) of each of the individuals I1and III8. Justify the answer.

Blood tests concerning the amount of active enzyme APRT were performed in members of this family. The results are represented in document 4.

6- Show, by referring to document 4, that at the molecular level, the two alleles are codominant.



Document 2



Document 3

Member of the family	Amount of active APRT
III7	50 %
III8	50 %
II5	50 %
II6	100 %
IV9	0 %
IV10	0 %

Document 4

Answer key

1- The difficulty of urinating in the twins is due to the presence of urinary calculi. The result shows that the amount of active APRT enzyme necessary for the transformation of adenine into adenosinemonophosphate is null (document 1). This blocks the transformation and leads to the accumulation of adenine and its elimination in high amounts in the urine, 40 mg> 1.5 mg (in control).

The absence of APRT provokes the formation of dihydroxyadenine in high amounts (not detected) forming calculi leading to urinary difficulties in the twins**. (1 pt)**

2- Hypothesis :

The disease is due to a recessive allele carried by the parents.
The disease is due to congenital malformation.
The disease is related to the mutation of the gene coding for APRT in the twins.
The disease is due to a chromosomic aberration **(1 pt)**

3- Individuals IV9 and IV10 suffer from dysuria and descend from normal parents III7 and III8. So, the allele responsible for the disease is carried by the parents but it is masked. Therefore, the allele responsible for the disease is recessive, whose symbol is d, with respect to the normal allele whose symbol is N. **(0.75 pt)**

4-If the gene is located on the non-homologous part of Y, then the disease is transmitted from the father to son, but the male IV10 is diseased while his father is normal. Therefore, the gene is not located on the non-homologous part of Y.
If the gene is located on the non-homologous part of X, then the diseased female IV9 having 2X chromosomes should carry 2 alleles for the disease. She should inherit one allele from each parent. So, her father III8 should be carrying the allele responsible for the disease and would be sick but this is not the case. Therefore, the gene is not located on the non-homologous part of X.
If the gene is located on the homologous part of X and Y, then parent III8 must be sick and his genotype must be XdYd in order to give his daughter IV9 Xd and his son IV10 Yd. But he is not sick .Therefore, the gene is not located on the homologous part of X and Y.
Therefore, this gene is not carried by a sex chromosomes. **(0.75 pt)**

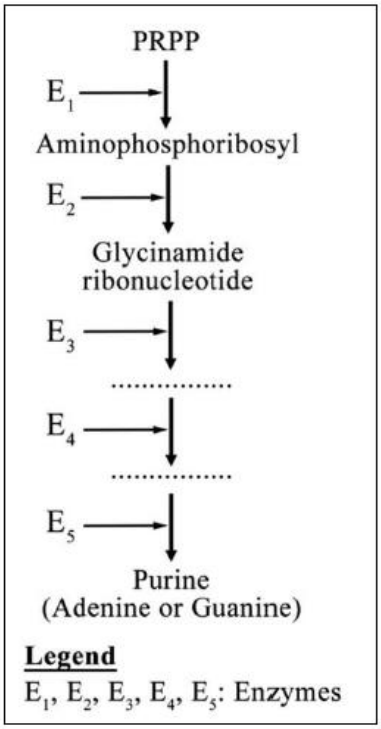
5-The possible genotypes of I1 is N//N or N//d since the normal allele is dominant and can be expressed in the homozygous or heterozygous state.
The genotypes of III8 is N//d since the diseased twins IV9 and IV10 who exhibit the recessive phenotype have genotype dd. The recessive allele is only expressed in the homozygous state. They have surely inherited one allele for the disease d from their father III8 and since he is normal he has the allele N. **(1 pt)**

6-Since the gene is carried by an autosome and it has only two allelic versions then the presence of three different amounts of APRT, 100%, 50% and 0% shows the presence of three molecular phenotypes indicating codominance. **(1 pt)**

Exercise **Origin of Mental Retardation (2015-2nd)**

Alain, son of Riad and Samar, is affected by a mental retardation. This couple who has no family history concerning mental retardation is expecting a second child and wishes to know whether he will be affected like his brother.

1- Formulate a hypothesis explaining the appearance of this retardation in Alain.



Document 1

In order to understand the possible origin of this mental retardation, the following studies are performed.

Blood analysis of Alain concerning substances involved in mental retardation shows a high amount of purines of 118 mmol/L with respect to the normal level of 79 mmol/L.

The synthesis of purines is controlled by 5 enzymes. The pathway of this biosynthesis in the body is presented in document 1.

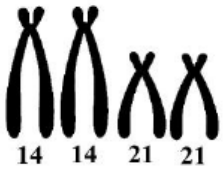
Three cell cultures are performed.

- **Culture 1:** nerve cells are cultured in a medium rich in purines. These cells degenerate.
- **Culture 2:** cells of CHO mice are cultured in a medium without purines. In these mice, the gene coding for enzyme E2 which is homologous to that of humans, is inactive. These cells degenerate.
- **Culture 3:** human cells are fused with cells of CHO mice and Hybridoma are obtained. These hybridoma are cultured in a medium without purines. Spontaneously, some hybridoma lose with time their human chromosomes. Those that lose their chromosome n° 21 degenerate and those that conserve the chromosome n° 21 remain in the medium.

2- Interpret the results obtained in cultures 1 and 2.

3- Determine the location of the gene studied in this mental retardation.

The karyotype of Alain consists of 46 chromosomes. Document 2 shows the blood level of purines as well as the karyotype of Alain, those of his parents, and that of the fetus. In these karyotypes only the pairs of chromosomes 14 and 21 are schematized; the other pairs of chromosomes are normal.

Alain's Family	Mother : Samar	Father : Riad	Alain	Fetus
Karyotype				
Blood level of purines (in mmol/L)	79	79	118.5	?

Document 2

4- Determine, from all what precedes, the origin of the mental retardation revealed in Alain.

5- Specify the diagnosis for the fetus.

6- Make the factorial analysis to determine the phenotypic proportion of this couple's children who will suffer from a mental retardation identical to that of Alain.

Answer key

1- Hypothesis: The mental retardation of Alain is due to a recessive allele masked in parents.

Or The mental retardation of Alain is due to the mutation of a gene implicated in the mental development and that occurred during his conception.

Or The mental retardation of Alain is due to a chromosomal aberration (that occurred during meiosis in one or in both parents). (**3/4 pt)**

2- Nervous cells degenerate in the culture medium rich in purines (culture 1). Similarly cells which are unable to synthesize purines degenerate in the medium lacking purines (culture 2). This shows that the synthesis of purines in amounts far from its normal range is responsible for the degeneration of cells. **(½ pt)**

3- Culture 2 shows that the cells of CHO mice having inactive E2 are unable to synthesize purines and degenerate. Culture 3 shows that the hybridoma having lost their chromosome 21 degenerate. And since the degeneration of nervous cells may lead to a mental retardation, this allows us to say that the gene coding for E2 is localized on the chromosome 21 and that its inactivation is responsible for the mental retardation**.(1/2 pt)**

4- Culture 1 shows that cells degenerate in a medium rich in purines, and Alain possesses a high purines level of 118mmol/L. This excessive synthesis is due to an additional allele. However the karyotype of Alain shows two free chromosomes for each of the pairs 14 and 21 with one chromosome 14 that is longer than its homologous. And since the allele coding for E2 is carried by the chromosome 21. This can be explained by the presence of an additional chromosome 21 linked to the chromosome 14. Thus the origin of the mental retardation of Alain is a linked trisomy 21 leading to a high enzymatic activity of E2**. (1 pt)**

5- The fetus is normal, since as his normal father he possesses a free chromosome 21 and another chromosome 21 linked on the chromosome 14. He has conserved his genetic material, he has two alleles coding for the enzyme E2 and consequently will have a normal amount of purines of 79 mmol/l indicating a normal mental activity. **(0.75 pt)**

Factorial analysis

Phenotype : normal mother X normal father

Genotype : 14//14 21//21 14//14^{21} 21//

Gametes and proportions : 14 21 (1) 14 21 (¼) , 14 (¼) , 14^{21} (¼) , 14^{21} 21 (¼)

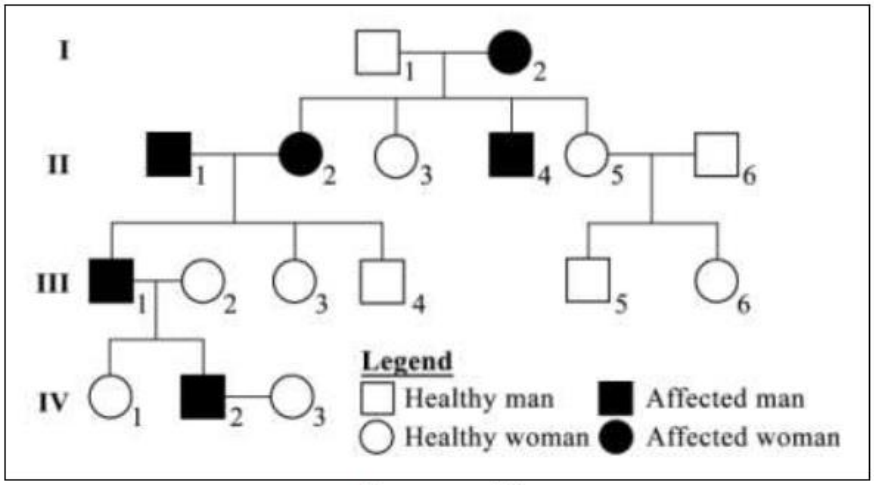
Table of cross :

	14 21 ¼	14 ¼	14^{21} ¼	14^{21} 21 ¼
1421 1	14//14 21//21 ¼	14//14 21//- ¼	14//14^{21} 21// - ¼	14//14^{21} 21// 21 ¼
				Mental retardation like that of Alain

The Phenotypic proportion of children suffering from mental retardation like that of Alain is 1/4

Exercise **Huntington Chorea (2015-1st)**

Huntington Chorea is a serious neurodegenerative hereditary disease . Its first symptoms appear in adults



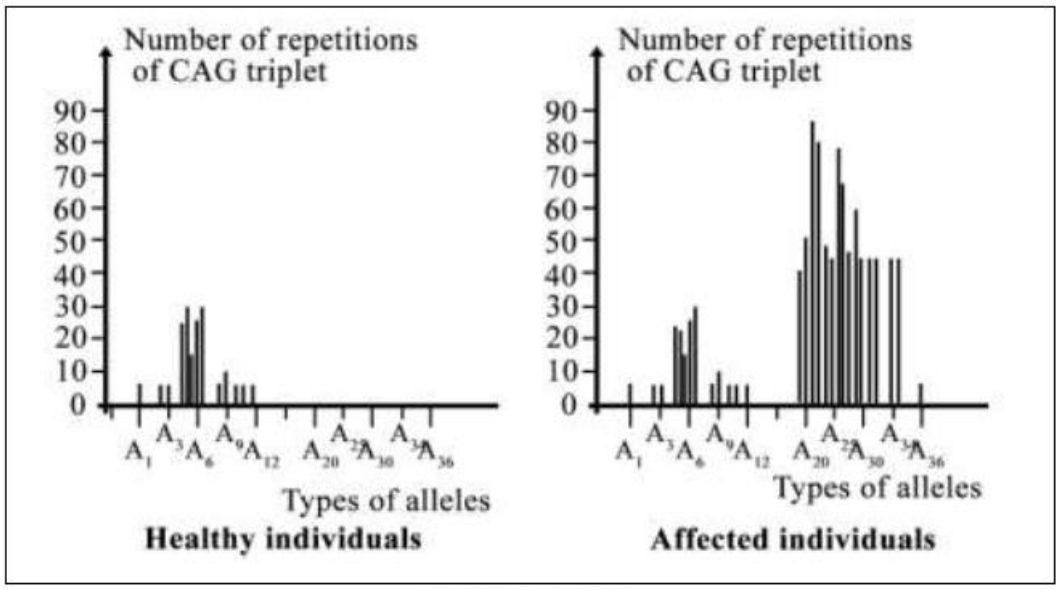
Document 1

starting from the 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 localization of the gene responsible for this disease.

All the 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.



Document 2

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

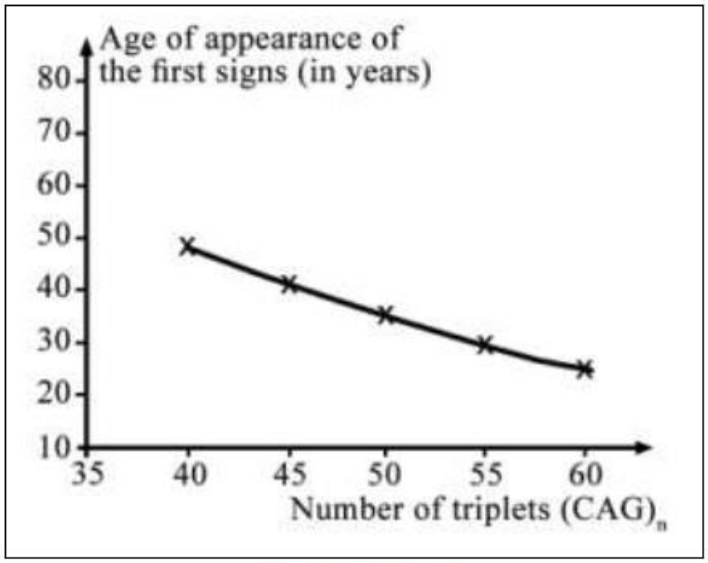
Studies have shown that the gene coding for the functional protein, huntingtin, exists in many allelic forms that differ by the number of CAG triplets. The number of repetitions of CAG triplet in each allele is studied in healthy individuals as well as in affected ones. The obtained results are presented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

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

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

5- Specify the real genotype of this woman.

A statistical study has been performed concerning the age of appearance of this disease in function of the number of CA triplets. The obtained results are shown in document 3.



Document 3

6- 6-1-Analyze the obtained results.

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

Answer key

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 pt)**

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**. (1/4 pt)**

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 the normal 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**. (1/4 pt)**

If the gene is carried by the homologous segments of X and Y, healthy girl III3should have inherited Xn 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**.(1/4 pt)**

Therefore, the gene is carried by an autosome. **(1/4 pt)**

3-The mother II-2 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 II-1is 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**. (1/2 pt)**

Since the affected allele of the disease is dominant; it is sufficient for III-3 to have at least one allele of the disease in order to be affected. The genotype of II-I3 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 II-5 and II-6 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**. (1/2 pt)**

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 pt)**

5- The real genotype of III3 is n//n or A6//A9. 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**. (0.75 pt)**

6- 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. **(1/2 pt)**

6-2 The factor determining the age of appearance of the disease is the high number of repetitions per allele (>40)**.(1 pt)**

Exercise (5 pts) **Origins of Phenylketonuria (2013-2nd)**

In hepatic cells, the enzyme phenylalanine hydroxylase, PAH, is responsible for the transformation of phenylalanine into tyrosine. Its absence or its inactivity results in the accumulation (increase in the amount) of phenylalanine in the blood which becomes toxic at a dose exceeding 20mg/dL which leads to the destruction of the nerve cells in individuals affected with phenylketonuria. This disease has different origins and is manifested by irreversible mental retardation.

1- Pick out the consequence of the high amount of phenylalanine in the blood.

Document 2 represents a part of the gene coding for the enzyme PAH of a healthy individual and that of the equivalent fragment of an individual suffering from phenylketonuria.

2- Determine, using the genetic code table (document 1), the sequence of amino acids of the part of the enzyme PAH coded by each of these two alleles.

3- Explain how the modification in the nucleotide sequence of the allele leads to the appearance of phenylketonuria.

Nucleotides position 1	Nucleotides position 2: U	Nucleotides position 2: C	Nucleotides position 2: A	Nucleotides position 2: G	Nucleotides position 3
U	UUU, UUC: phenylalanine; UUA, UUG: leucine	UCU, UCC, UCA, UCG: serine	UAU, UAC: tyrosine; UAA, UAG: non-sens	UGU, UGC: cysteine; UGA: non-sens; UGG: tryptophane	U C A G
C	CUU, CUC, CUA, CUG: leucine	CCU, CCC, CCA, CCG: proline	CAU, CAC: histidine; CAA, CAG: glutamine	CGU, CGC, CGA, CGG: arginine	U C A G
A	AUU, AUC, AUA: isoleucine; AUG: methionine	ACU, ACC, ACA, ACG: threonine	AAU, AAC: asparagine; AAA, AAG: lysine	AGU, AGC: serine; AGA, AGG: arginine	U C A G
G	GUU, GUC, GUA, GUG: valine	GCU, GCC, GCA, GCG: alanine	GAU, GAC: aspartic acid; GAA, GAG: glutamic acid	GGU, GGC, GGA, GGG: glycine	U C A G

A : Adenine U : Uracil G : Guanine C : Cytosine.

Document 1

Alleles	Nucleotide sequence of the non-transcribed strand of DNA from codon 277 to codon 283
Normal	TAT ACC CCC GAA CCT GAC ATC
Diseased	TAT ACC CCC AAA CCT GAC ATC

Document 2

Alleles	F_1	M_1	N_1		F_2	M_2	N_2
Normal	—	—			—	—	▬
Diseased	—	—	▬		—	—	

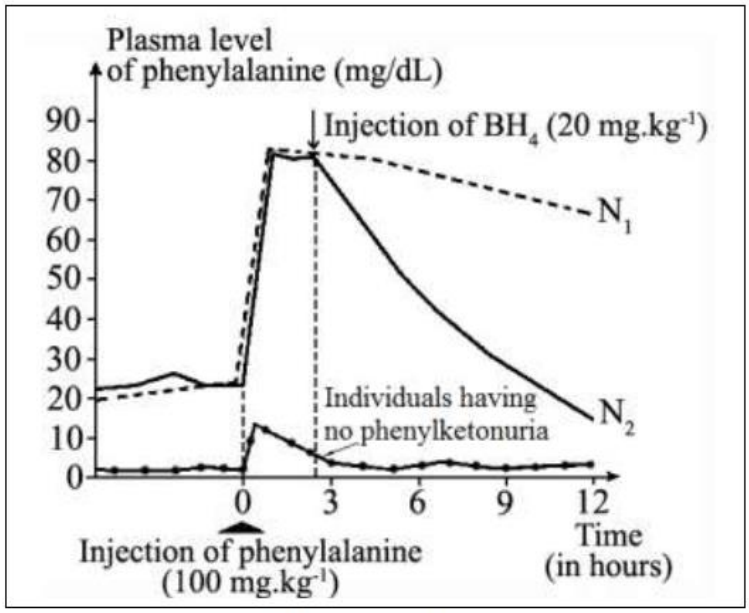
F: Father M: Mother N: Newborn

Document 3

Two normal couples had two newborns with high plasma concentration of phenylalanine that exceeds 20mg/dL.

4- Indicate if the allele of the disease is dominant or recessive. Justify the answer.

In order to determine the origin of the disease in these two newborns, N1 and N2, these couples consulted a doctor who recommended DNA analysis for all the family members. The obtained results are presented in document 3. Moreover, the doctor proposed another test, where he injected the newborns with phenylalanine followed by injection of BH4, an organic substance normally present in the organism and that is indispensable for the normal activity of PAH. The obtained results are presented in document 4.



Document 4

5- Indicate the possible origin of the disease in the case of the newborn (N1). Justify the answer by referring to documents 3 and 4.

6- Determine, by referring to documents 3 and 4, the possible origin of the disease in the case of the newborn (N2).

Answer key

1- It is toxic, leads to the destruction of the nerve cells and is manifested by irreversible mental retardation. (**0,5 pt)**

2- Portion of the amino acids sequence of the enzyme:
We establish the mRNA sequence by replacing T by U
Normal mRNA: UAU ACC CCC GAA CCU GAC AUC
Amino acids sequence : Tyr-Thr-Pro-Glu-Pro-Asp-Ile
Diseased m RNA: UAU ACC CCC AAA CCU GAC AUC
Amino acids sequence : Tyr-Thr-Pro-Lys-Pro-Asp-Ile **(1 pt)**

3-The mutation by substitution at the level of the first nucleotide of the 280th codon of the DNA where G is replaced by A is transcribed at the level of mRNA by a new codon which is translated into a new amino acid, lysine instead of the glutamic acid. This new amino acid sequence affects the tridimensional structure of the enzyme PAH which becomes inactive (nonfunctional). Since this enzyme is responsible for the transformation of phenylalanine into tyrosine. This transformation doesn't occur any more leading thus to the accumulation of phenylalanine which in high amount becomes toxic and causes phenylketonuria.(**1 pt)**

4- The allele of the disease is recessive with respect to the normal allele. Since normal parents gave birth to an affected child, thus they carry the allele of the disease that is masked in the parents.
Let N be the symbol of the normal allele.

Let m be the symbol of the allele coding for the disease. (**0,5 pt)**

5- The origin of the disease in the case of N1 is a mutation that leads to the synthesis of an inactive PAH (non-functional).Document 3 shows that affected N1 is homozygous of genotype m//m. And document 4 shows that a slight decrease in the plasma level of phenylalanine in N1 from 80 to 70 mg/dL after the injection of 20 mg/Kg of BH4. This implies that even in the presence of functional BH4, the PAH remains nonfunctional. **(1 pt)**

1- Document 3 shows that the affected newborn N2 is homozygous of genotype N//N. His allele codes for a normal PAH. Document 4 shows that in N2, the constant plasma level of phenylalanine of 80 mg/dL decreases after the injection of 20 mg/Kg of BH4to 15 mg/dL value that is inferior to the reference level of 20 mg/dL. Thus BH4 acts in N2 by decreasing the plasma level of phenylalanine toward its normal value. The PAH in the newborn N2 is functional but needs the presence of BH4 to be activated. Hence, his disease in N2 can be due to the absence of BH4 or to the presence of non-functional BH4. **(1 pt)**

Exercise (5 points)

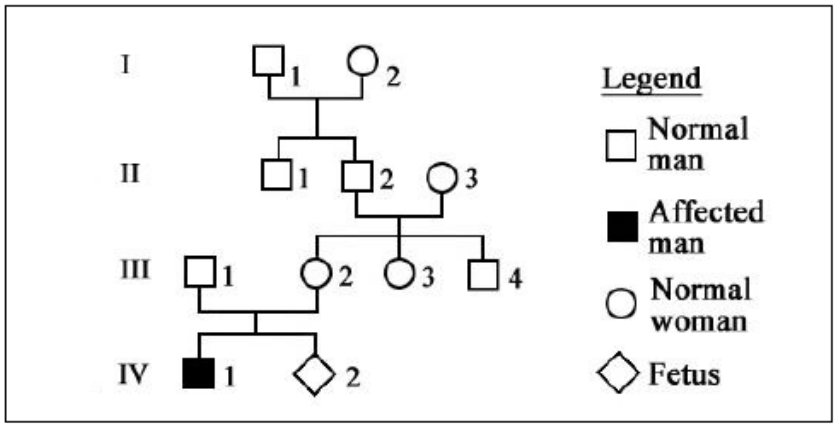
Fragile X Syndrome (2013-1st)

Fragile X syndrome is the most common cause of hereditary mental retardation. The gene FMR1 which is responsible for this disease is located on the non-homologous segment of the X sex chromosome. The alleles at the origin of the abnormal phenotype are characterized by the repetition of CGG triplets for more than 200 times.

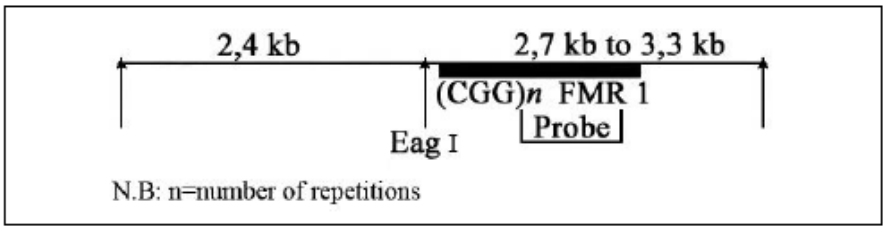
Couple III1- III2 (document 1), who already had an affected child, expects another one and would like to know if it will be affected or not.

1. Justify that the gene is localized on X chromosome.

2. Propose an explanation for the appearance of the disease in individual IV1 (document 1).



Document 1



Document 2

The fragment of DNA which carries the FMR1 gene is isolated. A very close site to this gene is recognized by the restriction enzyme EagI. For a complicated reason, this site is no more recognized by the enzyme when the number of repetitions of CGG triplets exceeds 200. Document 2 shows the position of this cleavage site in normal alleles.

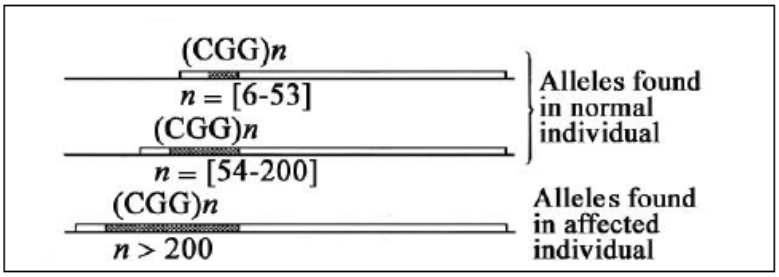
The DNA of certain individuals of this family is cut and a specific radioactive probe of the FMR1 gene is used. The obtained bands are presented in document 3.

3. Identify the band(s) corresponding to the alleles of the disease and those corresponding to the normal alleles.

4. Determine whether the fetus IV2 will be affected or not by the fragile X syndrome.

5. Pose the problem that arises from the study of document 3 concerning the origin of the disease in IV1.

Individuals	II3	III1	III2	IV1	IV2
5,8 kb				▬	
3,2 kb			▬		



Document 4

Document 4 shows the position and the number of repetitions of CGG triplet for the allele of FMRI gene. The alleles having a number of repetitions between 54 and 200 are expressed normally but might be subjected to instability during gametogenesis. This instability can be manifested by an increase in the number of triplets.

6. Explain, based on what precedes, the real origin of the disease in IV1.

Answer key (5 pts)

1-If the allele is located on the non-homologous segment of Y, then every affected boy should have an affected father. However, child IV1 is affected but his father III1 is not. So, the gene is not located on the non-homologous segment of Y but on the non-homologous segment of X. (**0.5 pt)**

2-Given that the gene is carried by the non-homologous segment of chromosome X, the sick IV1 inherits obligatory the chromosome Y from his father and a chromosome X from his mother. Thus the mother with normal phenotype should carry an allele of the disease on one of its X gonosomes without expressing it. Therefore the possible origin of the disease of IV1 is a recessive allele masked form by the normal allele in the mother**. (0.75 pt)**

3-Document two shows that the normal allele is cut by the restriction enzyme Eag1 into two fragments, and the probe fixes only on the fragment giving 2.7 to 3.3 kb. This means that the bands 2.8kb or 3.2kb correspond to a normal allele **(0.75 pt).**

The allele for the disease which has a number of repetitions of triplets that exceeds 200 can no more be cut by the restriction enzyme Eag1 and therefore, one fragment which length is more than 5.7kb is obtained. This mean the band of 5.8kb corresponds to the allele of the disease**. (0.75 pt)**

Or

The affected child IV1 possess only one allele of the gene since the gene is carried on non-homologous segment of X and the male has one X chromosome. Document 3 presents only one band of length 5.8kb. Therefore, the latter band corresponds to the allele of the disease.

The same reasoning for the normal male III1 indicating that the band which length is 2.8kb corresponds to the normal allele.

Woman III2 who is normal possesses 2 alleles for the gene since she has two X chromosomes. Document 3 shows 2 bands of lengths 2,8 and 3,2 kb respectively that correspond according to document 2 to the normal alleles. Thus, the band 3,2kb corresponds to the normal allele.

4- Doc 3 shows that the fetus has only one band of 2,8kb length same as his normal father III1 thus he is normal. Or

The fetus has only one band of 2,8kb length that corresponds to one of the fragment produced by the action of Eag1 on a normal allele thus he will be normal**. (0.75 pt)**

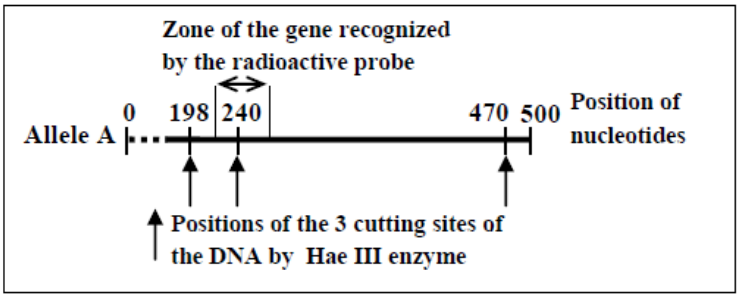
5- How come that the disease appeared in child IV1 although both of his parents carry only normal alleles?

Or Both parents of IV1 have only the normal alleles, so where does the allele of the disease of child IV1 come from? **(0.75 pt)**

6- The origin of the disease in child IV1 is due to an abnormality that occured during meiosis in the mother. Actually the mother has two normal alleles, one of them has a large number of repetition that is subjected to an expansion of triplet CGG to more than 200 during oogenesis. This gamete carries the allele of the disease which upon fertilization has given birth to the affected child IV-1. **(0.75 pt)**

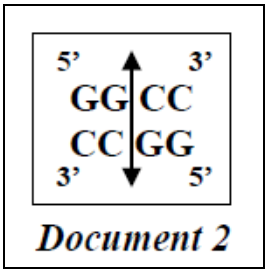
Exercise (5 points) **Transmission of Albinism (2012-2nd)**

Albinism is a hereditary deficiency characterized by the absence of skin, eyes and hair pigmentation due to the absence of a black pigment: melanin. Tyrosinase is an enzyme involved in the biosynthesis of this pigment. The gene coding for tyrosinase exists in many forms of alleles and is carried by an autosome. Only two alleles are taken into consideration: allele A which codes for an active tyrosinase that is responsible for the synthesis of melanin and allele B that codes for an inactive tyrosinase that does not permit the synthesis of melanin.



Document 1

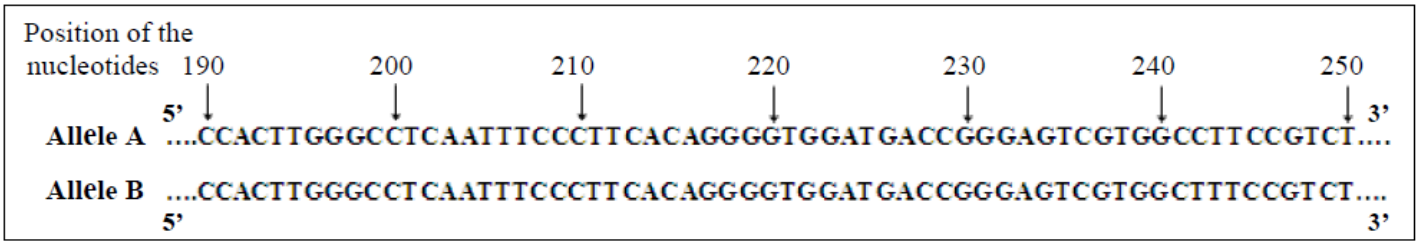
Document 1 represents the map of the restriction sites recognized by Hae III enzyme in a portion of 500 base pairs (bp) of the allele A of tyrosinase gene.



Document 2

1- Determine the number and the length of the restriction fragments obtained as a result of cutting allele A by Hae III enzyme.

Document 2 shows the restriction site of Hae III enzyme. Document 3 reveals a partial single-stranded sequence of the two alleles A and B of tyrosinase gene.



Document 3

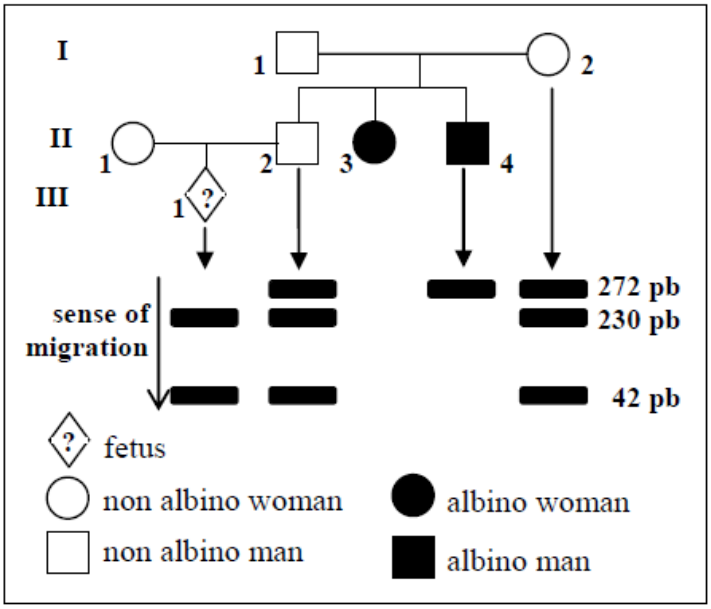
2- Compare these two sequences.

3- Draw out the position and the type of mutation that took place.

4- Determine the consequence of this mutation on the produced restriction fragments upon using Hae III enzyme on allele B.

Document 4 represents the pedigree of a family whose some members show albinism. It also shows the results of the electrophoresis of the restriction fragments obtained following the action of Hae III enzyme on a portion of the tyrosinase gene. These fragments are obtained by the Southern blot technique for four members of the family.

5- Specify by referring to the results of electrophoresis the respective alleles of individuals I2 and II4.



Document 4

6- Indicate, referring to document 4, whether the allele of albinism is dominant or recessive. Justify the answer.

7-Establish a prenatal diagnosis of albinism for the fetus III_1.

Answer key (5 points)

1- Allele A has 3 restriction sites of enzyme Hae III at the level of the nucleotide numbers 198, 240 and 470. Therefore, the enzyme cuts the allele into 4 fragments (**1/4 pt)**. The lenghth of each fragment is:

a fragment of 198 base pairs (bp) (before the site 198),
a fragment of 42 bp (between sites of 198 and 240),
a fragment of 230 pb (between the sites of 240 and 470)
and a fourth fragment which length is 30 bp (beyond the site 470) (**1/2 pt)**.

2- The nucleotide sequences of the portions of the two alleles are identical except at the level of the nucleotide number 242 where nucleotide C in allele A is replaced by the nucleotide T in allele B(**1/2 pt)**.

3- It is a mutation by substitution (**1/4 pt)** at the level of nucleotide 242 (**1/4 pt)**.

4- Hae III enzyme cuts the DNA when encountering the sequence GGCC. The cutting is done between GG and CC (document 2). Document 3 shows that the restriction site at the level of the nucleotide 240 does no longer exist for allele B due to the mutation by substitution. Instead of the GGCC sequence for allele A there is a GGCT sequence for allele B. As a result, the enzymatic treatment of allele B will give:

a fragment of 198 base pairs (bp) (before the site 198),
a fragment of 272 bp instead of the two fragments (42 and 230 bp)
a third fragment which length is 30 bp (beyond the site 470). (¾ **pt)**

5- Document 4 gives the disposition of the fragments revealed by autoradiography for the four family member. Individual I2 has two alleles A and B (**1/4 pt)** because the electrophoresis results show three fragments: 272 pb that corresponds to allele B and 42 and 230 pb that correspond to allele A(**1/4 pt)**. Individual II4 has two alleles B (**1/4 pt)** because the electrophoresis results show only the fragment of 272 pb that corresponds to allele B (**1/4 pt)**.

6- Albinism allele is recessive with respect to the normal allele (**1/4 pt)** because individual I2 having the two alleles A and B is of normal phenotype. Therefore allele A alone is expressed and allele B is masked (**1/2 pt)**.Or

Because II3 and II4 children with albinism arise from normal parents I1 and I2, then the allele of albinism is masked in the parents. Therefore allele B determining albinism is recessive with respect to the dominant allele A. (**3/4 pt)**

7- The fetus III1 possesses only the fragments of 230 and 42 pb that correspond to the allele A. So, the fetus III1 does not have except the allele A and he will not be albino but of normal phenotype. **(3/4 pt)**

Exercise (5 points) **Analysis of partial karyotypes (2012- 1st)**

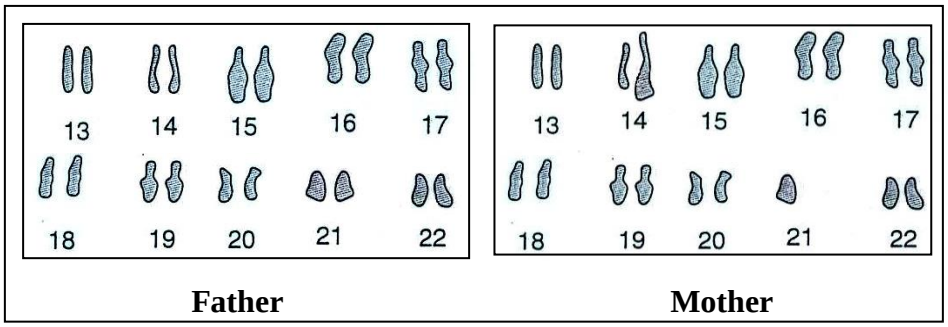
In the framework of studying human chromosomal abnormalities, we prepare the karyotypes of parents of normal phenotype (document 1) and those of their children (document 2); one of these children has trisomy 21. Only certain pairs of chromosomes, from number 13 to 22, are represented.

1- Compare the partial karyotypes of the father and the mother. What can you draw out?

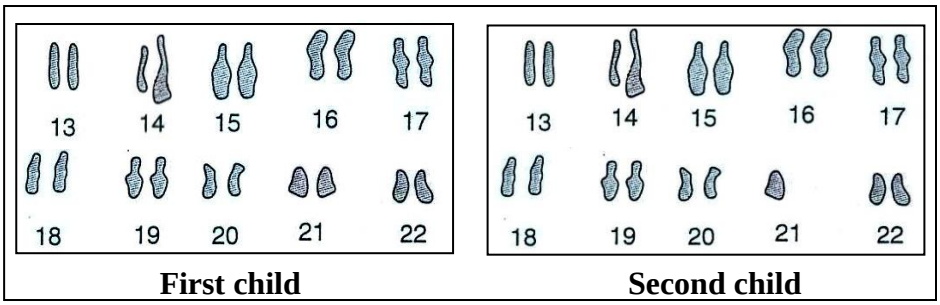
2- Explain why the first child is affected with trisomy 21 and the second presents normal phenotype.

3- Schematize, for the mother, the phase of meiosis that is at the origin of trisomy 21 in the first child. (Limit your answer to chromosomes 14 and 21)

4- Make a chromosomal analysis considering only chromosomes 14 and 21in order to determine the proportions of normal and abnormal children of this couple.



Document 1



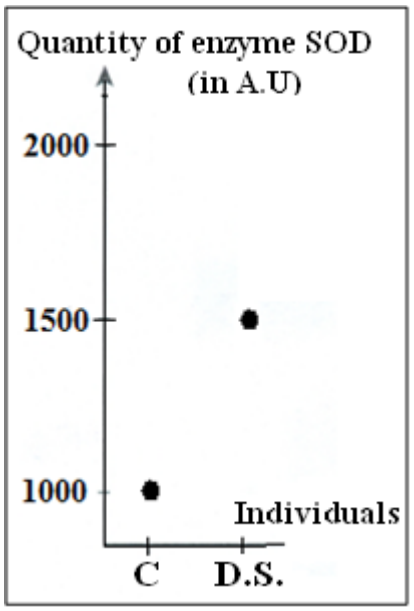
Document 2

One of the manifestations of Down syndrome (trisomy 21) is mental retardation. Biochemical analyses relate this manifestation to an abnormally high level of a protein "P" in the brain of individuals with this syndrome. This protein is coded by a gene located on chromosome 21.

5- Propose an explanation concerning the presence of protein "P" in quantities greater than normal in the brain of individuals with Down syndrome.

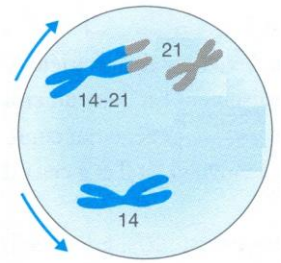
On the other hand, we measured the level of an enzyme, superoxide dismutase (SOD), in the red blood cells of unaffected control individuals(C) and in those of others with Down syndrome (D.S). This enzyme is coded by a single gene and is involved in the synthesis of protein "P". Document 3 shows the results of SOD measurement.

6- Determine, with reference to document 3, the probable chromosomal location of the gene coding for the enzyme SOD.



Document 3

Answer key

<table>
<tr><td>1</td><td>All chromosome pairs are similar in the father and the mother with the exception of pairs 14 and 21 (1/4pt)
Concerning the pair14: the two chromosomes of this pair are of the same size in the father while in the mother, one of them has the same size as those of the father while the second is longer than the others. (1/4pt)
Concerning the pair21: there are two chromosomes of the same size in the father while in the mother a single chromosome 21 is found and has same size as those of the father. (1/4pt)
The number of chromosomes in the given partial karyotype of the father is 20, higher than that of the mother, 19 chromosomes.
Thus, the karyotype of the father is normal while that of the mother of normal phenotype shows a chromosomal abnormality for pairs 21 and 14 where there is translocation of a complete chromosome 21 on chromosome 14. (1/2pt)</td><td>1 1/4</td></tr>
<tr><td>2</td><td>The first child has trisomy 21 because he has three chromosomes 21, two free chromosomes 21 (pair 21) and one chromosome 21 translocated on a chromosome 14 (14^{21}) (1/2pt)
The second child has normal phenotype because he has 2 chromosomes 14 and two chromosomes 21, one is free and the other is translocated on chromosome 14, so the genetic material is conserved. (1/2pt)</td><td>1</td></tr>
<tr><td>3</td><td>Scheme of chromosomal behavior
 

Anaphase I</td><td>1/2</td></tr>
<tr><td>4</td><td>Chromosomic analysis
Phenotypes normal mother x normal father
Chromosomes 14^{21} //14 21/ x 14//14 21//21
Gametes and their proportions 14 21 : ¼ 14^{21} : ¼ 14^{21} 21 : ¼ 14 : ¼ 14. 21 : 1
Table of cross
<table>
<tr><td>Gametes ♀
♂</td><td>14 21
¼</td><td>14^{21}
¼</td><td>14^{21} 21
¼</td><td>14
¼</td></tr>
<tr><td>14 21
1</td><td>14//14
21//21
¼</td><td>14^{21} //14 21/
¼</td><td>14^{21} //14
21//21 ¼</td><td>14//14 21/
¼</td></tr>
</table>
Phenotypes and proportions :
Children with trisomy 21 : ¼
Children with monosomy 21: ¼
Children with normal phenotype: ½
The proportion of getting normal children is ½ and that of abnormal children is ½.</td><td>1</td></tr>
<tr><td>5</td><td>The individual with Down syndrome has three copies of chromosome 21 instead of 2. Since the gene coding for protein P is located on chromosome 21, the affected individuals have three alleles of this gene that will code for this protein and this explains the high level of protein P.</td><td>1/2</td></tr>
</table>

6	In the RBCs of control individuals the amount of enzyme SOD is equal to 1000 au, while it is higher (1500a.u.) in the RBCs of the individuals with Down syndrome. Then individuals with Down syndrome synthesize 1500/1000 or 1.5 times more enzyme SOD than healthy individuals. Since 1000 corresponds to the presence of 2 chromosomes 21 in a normal individual and 1500 corresponds to the presence of 3 chromosomes 21 in the case of trisomy 21, then one can say that the gene coding for the enzyme SOD is located on chromosome 21.	**3/4**

Exercise (5 points) **DNA alteration (2011-2nd)**

The Xeroderma pigmentosum is a disease that results in skin lesions which can develop into cancerous tumors and eye lesions. We are interested in the causes of this disease and the relative influence of genes and environment on its appearance.

The body cells have, in their nucleus, enzymes that can repair DNA whenever this latter shows alterations. One of these enzymes is the ERCC3 which is coded by the gene G-ERCC3.

We present in document 2 the nucleotides sequence of a fragment of the non-transcribed strand of the gene G-ERCC3 of a healthy individual(allele G1) and the sequence of the equivalent fragment of an individual affected by xeroderma pigmentosum (allele G2).

1- Determine using the genetic code table (doc.1) the amino acid sequence of the portion of each of the enzymes ERCC3 coded by the allele G1 and by the allele G2.

NUCLEOTIDE POSITION 1	NUCLEOTIDE POSITION 2: U	C	A	G	NUCLEOTIDE POSITION 3
U	UUU, UUC: phenyl-alanine; UUA, UUG: leucine	UCU, UCC, UCA, UCG: serine	UAU, UAC: tyrosine; UAA, UAG: stop	UGU, UGC: cysteine; UGA: stop; UGG: tryptophane	U C A G
C	CUU, CUC, CUA, CUG: leucine	CCU, CCC, CCA, CCG: proline	CAU, CAC: histidine; CAA, CAG: glutamine	CGU, CGC, CGA, CGG: arginine	U C A G
A	AUU, AUC, AUA: isoleucine; AUG: methionine	ACU, ACC, ACA, ACG: threonine	AAU, AAC: asparagine; AAA, AAG: lysine	AGU, AGC: serine; AGA, AGG: arginine	U C A G
G	GUU, GUC, GUA, GUG: valine	GCU, GCC, GCA, GCG: alanine	GAU, GAC: asparatic acid; GAA, GAG: glutamic acid	GGU, GGC, GGA, GGG: glycine	U C A G

A: Adenine U: Uracile G: Guanine C: Cytosine

Document 1

Allele	nucleotides sequence of the fragment
G1	1 12 …AAG AAG AGC AAC…
G2	1 12 …AAG AAG AGA AAC…

Document 2

	Reference electrophoresis	Individual A	Individual B	Individual C
ERCC3 (coded by allele G1)				
ERCC3 (coded by allele G2)				

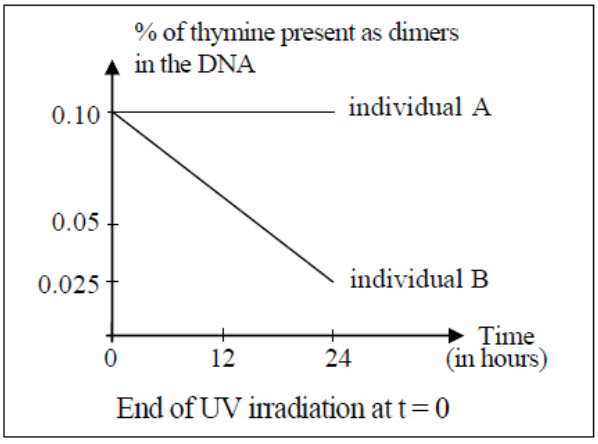
Document 3

We can separate, by electrophoresis, the enzyme ERCC3 coded by the allele G1 and enzyme ERCC3 coded by allele G2. Electrophoresis is performed for three different individuals: A, B and C. Individual A is affected with Xeroderma pigmentosum, and individuals B and C are not. The results are presented in document 3.

2- Write the genotypes of individuals A, B and C. Justify the answer.

3- Specify the dominant allele and the recessive one.

Upon exposure to ultra violet sunlight rays, the DNA of skin cells undergo alterations, particularly the formation of dimers between two successive thymines T-T. We measure the evolution of the percentage of dimers in the two individuals A and B after being subjected to irradiation with ultraviolet rays. The measured results are presented in document 4.



Document 4

4- Analyze the obtained results in document 4.

5- Based only on the previous given:

5-1- Explain the results of document 4.

5-2- Specify the factors that determine the development of the studied disease.

Answer key

1- mRNA resulting from the transcription of the allele G1: AAG AAG AGC AAC

Amino acid sequence of the polypeptide coded by the allele G1: Lysine – Lysine – Serine – Asparagine
mRNA resulting from the transcription of the allele G2: AAG AAG AGA AAC
Amino acid sequence of the polypeptide coded by the allele G2: Lysine – Lysine – Arginine – Asparagine
Or
We can obtain it directly from the non-transcribed strand of DNA by replacing T by U. Thus; we obtain the same sequence for both the mRNA and the DNA non-transcribed strand.
Amino acid sequence of the polypeptide coded by the allele G1: Lysine – Lysine – Serine – Asparagine
Amino acid sequence of the polypeptide coded by the allele G2: Lysine – Lysine – Arginine – Asparagine **(0.75 pt)**

2- The genotype of individual A G2//G2 **(0.25 pt)** because the result of his electrophoresis shows one type of enzyme ERCC3 that is coded by allele G2. **(0.25 pt)** The genotype of individual B is G1//G1 **(0.25 pt)** because the result of his electrophoresis shows one type of enzyme ERCC3 that is coded by allele G1. (**0.25 pt)** The genotype of individual C is G1//G2 **(0.25 pt)** because the result of his electrophoresis shows the two types of enzymes. **(0.25 pt**)

3- The allele G1 is dominant **(0.25 pt)** and the allele G2 is recessive **(0.25 pt)** because individual C who is heterozygous of genotype G1//G2 is not affected by Xeroderma Pigmentosum, Allele G2 is masked and not expressed phenotypically in the presence of allele G1 which dominates allele G2 **(0.25 pt)**.

4- The percentage of thymine dimers in the DNA remains constant (0.10%) through the 24 hours in individual A affected by xeroderma, while it decreases from 0.10% to 0.025% through the 24 hours in the healthy individual B after their exposition to ultraviolet irradiation**.(0.5 pt)**

5- **5.1-** Individual A (doc. 3) affected with xeroderma has no functional enzyme ERCC3 which is responsible of repairing the DNA alterations . The thymine dimers formed due to the exposition to ultra violet radiation cannot be repaired in this individual and thus the percentage of dimers T-T remains stable **(0.25 pt).** In the healthy individual B, which possesses functional ERCC3 enzyme, the altered DNA formed by ultraviolet irradiation is gradually repaired by this enzyme thus the percentage of thymine dimers decreases **(0.25pt)**

5.2- Two factors determine the development of Xeroderma pigmentosum:

- The genetic factor(**0.25pt**): the disease develops only in homozygous individuals with two mutant alleles of a gene coding for the enzyme ERCC3 involved in the repair of DNA damage**(0.25pt);**
- The environmental factor**(0.25 pt)**: exposure to sun ultraviolet rays provokes the alteration of DNA

(0.25 pt).

Exercise (5 points) **Retinitis pigmentosa (2011-1st)**

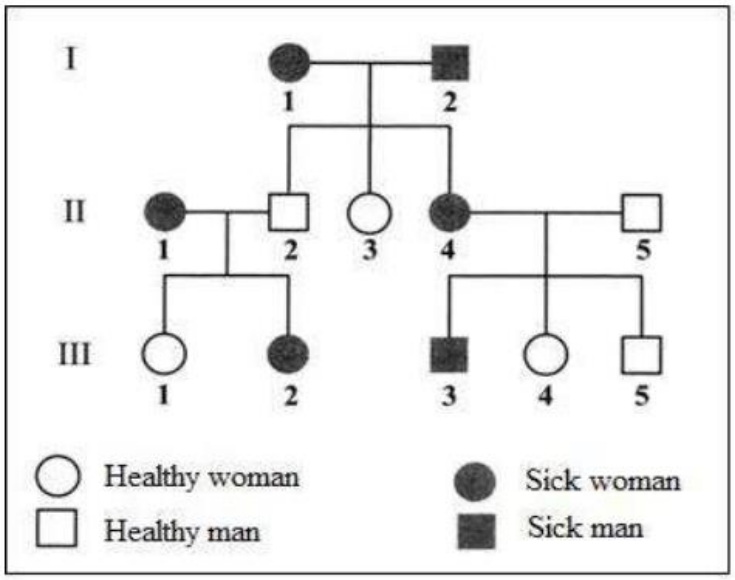
Retinitis pigmentosa, a hereditary disease, is the main cause of visual impairment (30% of visual deficiencies). The disease starts by affecting night vision and reducing the visual field. It is caused by progressive degeneration of rod cells, which are photoreceptor cells of the retina containing the protein rhodopsin.
To understand the origin of this disease, we study the structure of proteins encoded by different alleles of the rhodopsin gene.
The rhodopsin gene consisting of 1044 pairs of nucleotides encodes a protein of 348 amino acids. Document 1 represents a portion of the nucleotide sequences of the alleles of the rhodopsin gene and that of the amino acids sequences of the corresponding proteins in individuals with normal phenotype and individuals with retinitis pigmentosa.

Individual's phenotype	Portion of the nucleotides sequence of the allele	portion of the amino acids sequence of the protein
normal	391 ↓ 408 ↓ …CTG GCC ATC GAG CGG TAC…	131 ↓ 136 ↓ …Leu-Ala-Ile-Glu-Arg-Tyr…
Affected with retinitis pigmentosa	391 ↓ 408 ↓ …CTG GCC ATC GAG CTT TAC…	131 ↓ 136 ↓ …Leu-Ala-Ile-Glu-Leu-Tyr…
Leu = leucine, Ala = alanine, Ile = isoleucine, Glu = glutamic acid, Arg = arginine, Tyr = tyrosine.		

Document 1

1- Pick out from the text the cause of retinitis pigmentosa.
2- Compare the two nucleotides sequences and the two amino acids sequences presented in document 1. Draw out the origin of this disease.
3- Explain how the modifications in the nucleotides sequence of the allele (doc.1) lead to the appearance of the previously mentioned symptoms of retinitis pigmentosa.

Document 2 presents the pedigree of a family having some of its members affected with retinitis pigmentosa.
4- Indicate if the allele responsible for the disease is dominant or recessive and indicate its chromosomal location. Justify both answers.
5- Determine the genotypes of individuals II3 and II4.
6- Woman III2 married her cousin III3; determine the risk for this couple to have children with retinitis pigmentosa.



Document 2

Answer keys

1- It is caused by progressive degeneration of rod cells which are photoreceptor cells of the retina containing the protein rhodopsin. (**0.25 pt)**

2- The allele of the individual with normal phenotype and that of the affected individual are identical except at their nucleotides 404 and 405: the normal allele has two GG nucleotides, while the allele responsible for retinitis has two nucleotides TT. The two amino acids sequences are identical except at their 135th amino acid: arginine (Arg) in the sequence of the normal individual and leucine (Leu) in the sequence of the affected individual.

Thus the modification of the nucleotides sequence of the rhodopsin gene is translated in a modification of the protein which is at the origin of the disease. **(1 pt)**

3- The mutation by substitution of nucleotides 404 and 405 of the DNA was transcribed at the mRNA level by a new codon that results in a new amino acid leucine instead of arginine. This new amino acid sequence affects the three-dimensional structure of the protein rhodopsin, which becomes non-functional. Since this protein exists in the rod cells (photo receptor cells), the change in its function is manifested by impaired night vision in a person with retinitis pigmentosa. **(0.75 pt)**

4- The allele of the disease is dominant with respect to the normal allele since the healthy man II2 has both his parents I1 and I2 affected by retinitis pigmentosa, thus, the parents carry the normal allele which is masked by the allele of the disease.(D = allele of the disease, n = normal allele)

The allele of the disease is localized on an autosome. Since:

If the allele of the disease is carried by the non –homologous segment of chromosome Y then, it should be transmitted from father to son, however sick father I2 has a healthy son II2. Therefore, the allele is not carried by the non homologous segment of chromosome Y.

If the allele of the disease is carried by the non homologous segment of chromosome X, then the sick father I2 should transmit this dominant allele to all his daughters who will be all sick, however daughter II3 is healthy ,thus the allele is not carried by the non homologous segment of X chromosome.

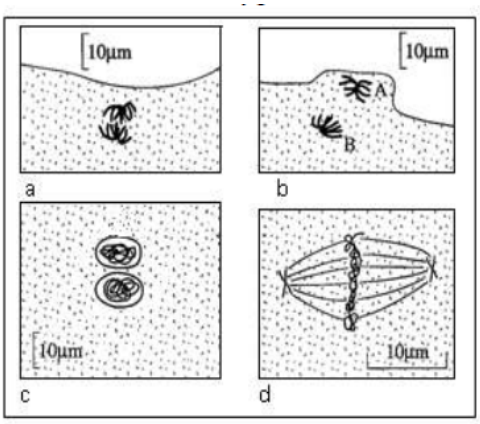
If the allele is carried by the homologous segment of chromosome X and Y, then boy II2 who is normal (recessive) should have received Y chromosome carrying the normal allele from his father . Similarly, girl II3 who is normal should have inherited X chromosome carrying the normal allele from her father . Therefore, their father should have the genotype XnYn and would be normal which is not the case. Therefore, the allele is not carried by the homologous segment of chromosomes X and Y. (**1.25 pt)**

4- II3 has a normal phenotype; since the normal recessive allele is only expressed under homozygous state then her genotype is: n//n II4 is diseased , and has a healthy child that should have inherited one normal allele from each of the two parents, thus she carries the normal allele which is masked by the allele causing the disease. Therefore she is heterozygous D//n**. (1 pt)**

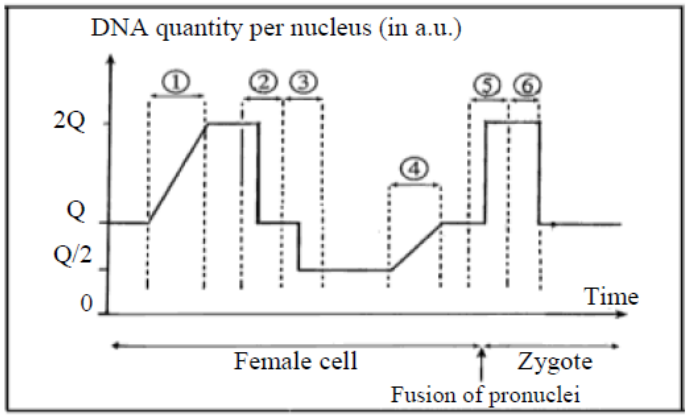
5- III2 and III3 have necessarily inherited the normal allele from their healthy father and are thus heterozygous D//n, each of them gives two types of gametes 1/2n and 1/2 D. (**0.75 pt)**

Exercise 1 **Sexual reproduction in mammals (2010-2nd)**

Document 2 reveals, in chronological order, some steps of the evolution of the fertilized oocyte II and that of the zygote. Document 3 represents the evolution of the DNA quantity per nucleus of the female cell and that of the zygote.



Document 2



Document 3

3- 3-1- Name the two principal mechanisms of the sexual reproduction in mammals.
3-2- Specify, referring to doc.2, the importance of each of these mechanisms. .
4- Match each of the schema b, c and d of document 2 with a numbered step of the curve of document 3. Justify the answer.

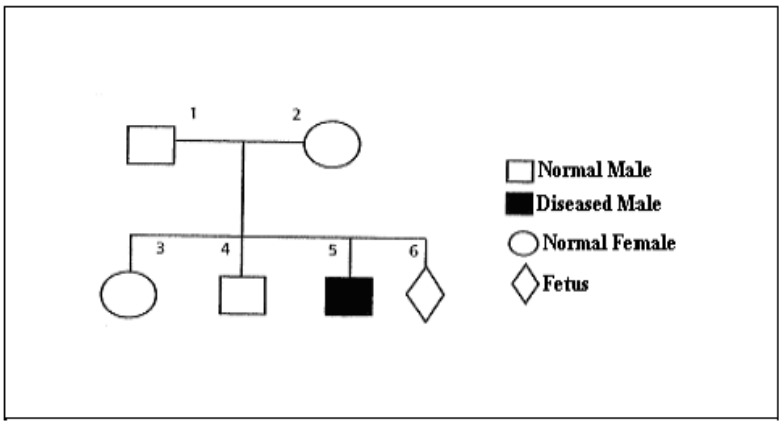
Answer keys

3- 3-1- Meiosis and fertilization .
3-2- Meiosis allows the reduction of the chromosomal number to obtain haploid cells. This is revealed in scheme a and/or b that show anaphase II and the separation of chromosomes into two haploid sets.
Fertilization restores the diploid state of the species. This is revealed in scheme c that shows the male and female pronuclei before their fusion.

4- Scheme b corresponds to step 3 since there is separation of the two haploid lots of chromosomes each with one chromatid. This corresponds to the second meiotic division where the DNA quantity is reduced from Q to Q/2.
Scheme c corresponds to step 4 since it shows the male and female pronuclei just before their fusion. The female pronucleus undergoes replication of its DNA resulting in an increase of its DNA quantity from Q/2 to Q.
Scheme d corresponds to step 6 since it shows the metaphase of the first mitotic division of the zygote having 2n chromosomes with 2 chromatids each and that corresponds to a DNA quantity of 2Q.

Exercise (5 pts) **Duchene Myopathy (2009-1st)**

Duchene Myopathy is a degenerative disease of muscle fibers which is due to a gene carried on the non- homologous segment of chromosome X. Boys affected with myopathy do not synthesize the muscle protein, dystrophin, or synthesize an inactive form of dystrophin. Document 1 represents the pedigree of a family having one member of its family affected with the disease.



Document 1

1-Specify, by referring to the pedigree, whether the allele responsible for the disease is dominant or recessive.

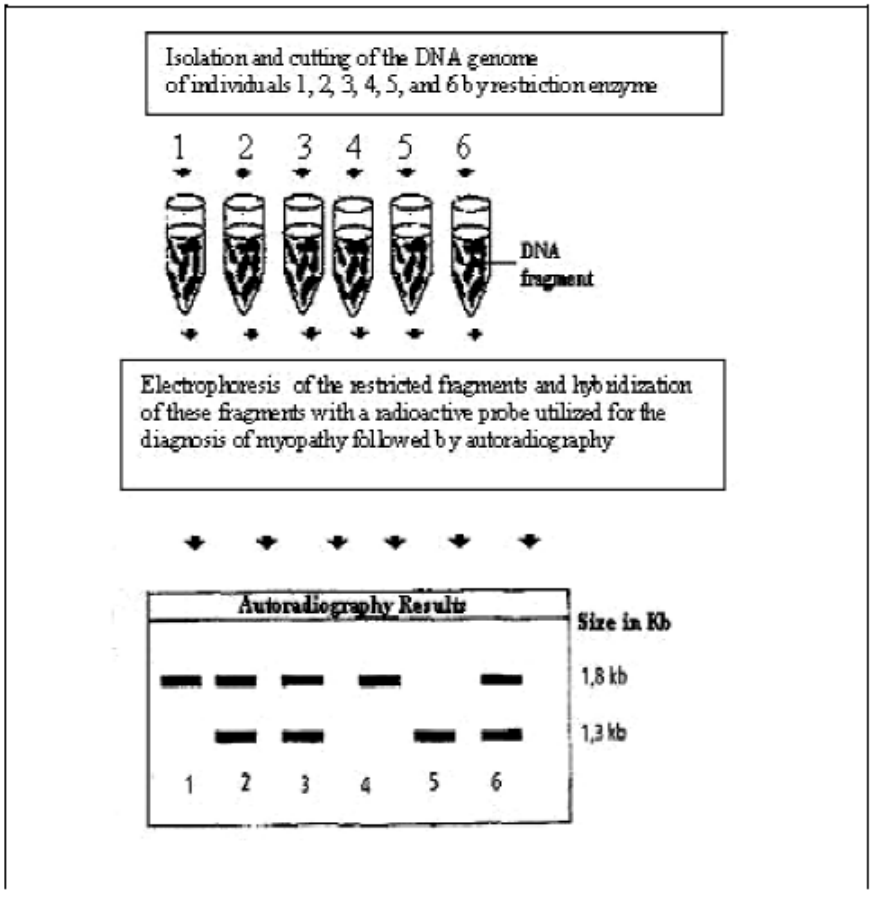
2-Indicate the genotypes of the parents. Justify the answer.

3-Determine the probability of the fetus to be affected.

Parents (1&2) who are expecting a baby want to know whether their fetus is at risk of developing the disease. They consult a doctor who proposes a prenatal diagnostic test by applying Southern Blot technique. The results are shown in document 2.

4-Identify, by referring to document 1 and the autoradiography of document 2, the allele causing the disease.

5-Specify the sex and the phenotype of the fetus.



Document 2

A gene therapy is applied for the first time on mice attaining myopathy similar to Duchene myopathy in humans. This technique consists of injecting the dystrophin gene into a diseased organism by means of a virus vector which is harmless to mice and human species. After this treatment, transversal sections are taken from the diaphragm muscle (respiratory muscle) of 3 groups of mice (A, B and C); then incubated with anti-dystrophin fluorescent antibodies and observed under a fluorescent microscope. The results obtained within 16-18 weeks are shown in document 3.

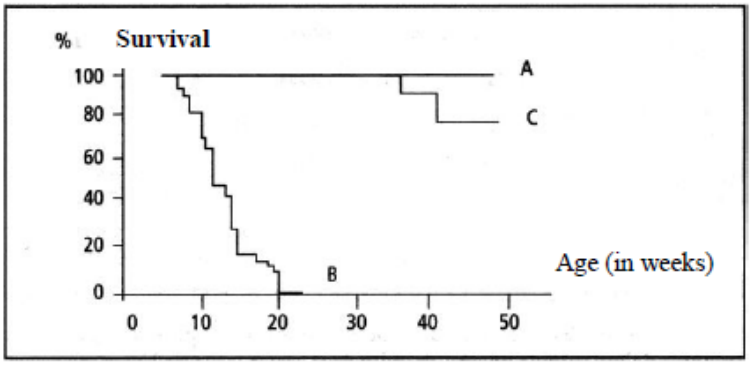
Mice	Results
A. Normal	Presence of fluorescence
B. Myopathic, non-treated	Absence of fluorescence
C. Myopathic, treated by injecting the dystrophin gene through a virus vector	Presence of fluorescence

Document 3

Document 4 reveals the percentage of survival of the three groups of mice in function of time.

1- **6.1-** Interpret the results obtained in each of documents 3 and 4.

6.2- What can be concluded about the efficiency of the used gene therapy?



Document 4

Answer key

1. Couple 1 and 2 who are normal have a child No.5 affected by the disease. This means that the allele causing the disease (m) is recessive masked by the dominant normal allele (N) found in the parents**. (0.5 pt)**

2. Father 1 is healthy and possesses the normal allele N on chromosome X. thus, his genotype is X_NY **(0.5 pt)** Mother 2 is also normal and possesses the allele m on one of her chromosome X since she had a diseased boy. Thus, she is heterozygous with genotype X_NX_m **(0.5 pt)**

3. The father produces two gametes of equal probabilities ½ X_N and ½ Y. the mother produces two gametes of equal probabilities ½ X_N and ½ X_m . All the girls would inherit an XN from their father and would be normal therefore, the probability to have affected girls is zero. **(1/4 pt)**. The boys inherit Y chromosome from their father and either an XN or Xm from their mother. This means that the probability to have affected boys is ½ or 50% from all boys or ¼ or 25% of all children**. (1/4 pt)**

4. The autoradiography of boy 5, who is affected, shows one band at the level of fragment 1.3 Kb. Thus, this fragment corresponds to allele m. **(1/2 pt)**

5. The autoradiography of fetus 6 reveals two fragments, one fragment at the level of 1.3 Kb which corresponds to the mutant allele and another fragment at the level of 1.8 Kb which corresponds to the normal allele. This means that the fetus possesses 2 X chromosomes and would be a girl with normal phenotype since XN dominates Xm**. (1 pt)**

6. Document 3 reveals the absence of fluorescence in the non-treated myopathic mice (group B) and its presence in both normal mice (group A) and diseased mice treated with dystrophin gene (group C). this means that dystrophin is absent in the affected non treated mice and present in the normal and the treated mice. **(0.5 pt)**

Document 4 shows that the % of survival in groups A and C is constant at 100% from week zero to week 37. This % of survival remains constant at 100% in group A until week 50, but decreases to about 75% in mice C. on the other hand, the % of survival in the diseased non treated mice which was 100%, similar to mice A and C at week 10, decreases sharply to reach zero at week 20. This means that the gene treatment improves the survival of the myopathic mice **(1/2 pt**). Therefore, treatment by the introduction of the dystrophin gene has allowed for the synthesis of dystrophin in the muscle cells of the diaphragm and has improved the survival of the myopathic mice and thus this treatment is efficient **(1/2 pt)**

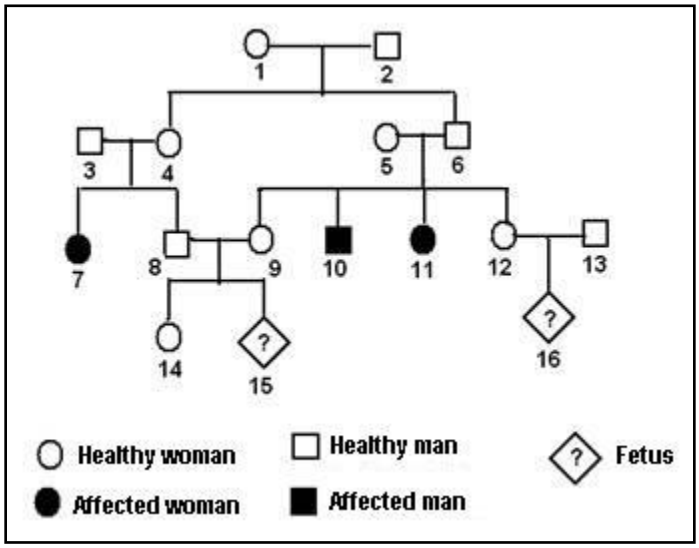
Exercise (5pts) **Phenylketonuria Transmission (2008-2nd)**

Phenylketonuria is a recessive autosomal disease that affects 1/10,000 of newborns worldwide. This disease is related to a deficiency in an enzyme called PAH. In normal conditions, this enzyme metabolizes phenylalanine into tyrosine, in the presence of a co-factor DHBP. This deficiency leads to an increase in the amount of phenylalanine in the blood accompanied with serious troubles.

A study performed on 1,200 children selected from an isolated community, showed that 30 children were heterozygous for PAH.

1. Calculate the proportion of heterozygous children in this community
2. Determine the genetic risk for a child to be affected with phenylketonuria.
3. Compare the genetic risk obtained to the world wide risk.
4. Formulate a hypothesis that explains the difference between these two risks.

In order to verify the formulated hypothesis, a study was carried out on a family of this community, which pedigree is shown in the adjacent document.



5. By referring to the pedigree, justify that the disease is recessive and autosomal.
6. Determine, for each of the fetuses 15 and 16, the risk to be affected.
7. Do the obtained results confirm the formulated hypothesis? Justify the answer.

Daughter 7 marries an affected man. Their first child was normal. All the tests performed confirm that the child is legal, and that the husband, unlike his wife, has a normal amount of PAH.

8. Determine the probable cause of the disease of the husband of daughter 7.
9. Justify, genetically, the birth of a normal child by this couple.

Answer key (5pts)

1 – The proportion of heterozygotes: 30/1200 = 1/40. **(0.25pt)**

2- It is autosomal transmission, for get a child of normal parents to be affected, parents mustbe heterozygous. The probability of each parent to be heterozygous is 1/40, the probability for heterozygous parents to have a sick child is ¼. Therefore, the risk of the birth of a child affected with phenylketonuria in this community is : 1/40 X 1/40 X ¼ = 1/6400. **(0.5 pt)**

3- The obtained risk 1/6400 is greater than the world wide risk 1/10000. **(0.25pt)**

4-Hypothesis: the consanguineous marriage in this community increases the risk of phenylketonuria**. (0.25 pt)**

5-The normal couples (3-4) and (5-6) had children (7, 10, and 11) affected by the disease. This means that each parent carries the allele of the disease in a masked state; then the disease allele is recessive. (m symbol of the sick allele). **(0.25pt)**

The disease is transmitted by autosomal mode. If the mode was gonosomal and the gene is carried by the proper part of Y chromosome, then all the affected boys must have affected fathers. child 10 is affected and his father 6 is healthy , thus, this is not the case.

- If the gene is carried by the proper part of X chromosome then girls 7 and 11 should have as genotype Xm /Xm and each parent should give them an Xm, which is not the case, because the father of each of these girls is healthy. If the gene is carried by the common part of chromosomes X and Y then the affected children 10 and 11 should have for genotype, respectively, Xm /Ym and Xm /Xm. The father should give an Xm to his daughter and Ym to his son, in this case he must have as genotype XmYm and become diseased, which is not the case**. (0.75 pts)**

6- Fetus 15: the two parents of this fetus is normal, however, the grand parents of the fetuses are heterozygous. Thus, the probability for each of the fetuses parents to be heterozygous is 2/3. The risk for both parents to be heterozygous is 2/3 X 2/3, and the risk to have an affected child is ¼. Therefore, the risk for fetus 15 to be affected is 2/3 X 2/3 X ¼ = 1/9. **(0.5 pt)**

Fetus 16: his/her mother has the same risk as his/her sister 9 to be heterozygous: 2/3. The father is a member of the community and the risk to be heterozygous is 1/40. If the parents of this fetus are heterozygous, then the probability to have an affected child is ¼. Therefore, the risk of fetus 16 to be affected is 2/3 X 1/40 X ¼ = 1/240 **(0.5 pt)**

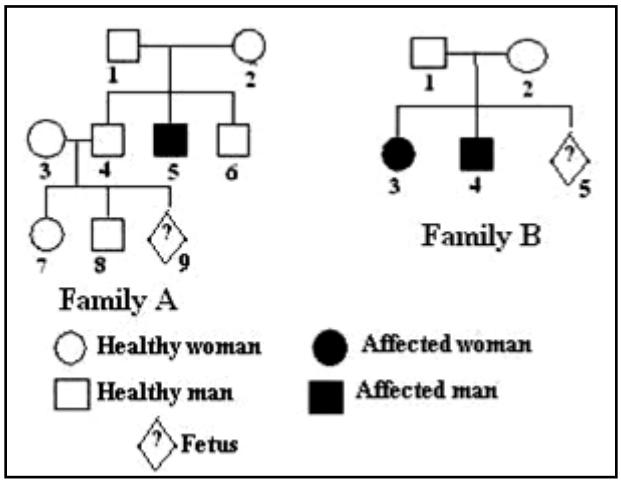
7- Yes, fetus 15 has a risk of 1/9 to be affected, this is greater than the risk in the case of fetus 16 (1/240). The parents of fetus 15 are cousins of the same family, which presents the disease. On the contrary, only the parents of fetus 16 do not belong to the same family. Therefore, the hypothesis is valid and the intermarriage favors the appearance of the disease**. (1 pt)**

8- The husband of daughter 7 is affected and yet with a normal PAH amount. Therefore, it can be said that the disease must have an origin other than PAH. Based on the data, PAH converts phenylalanine into tyrosine in the presence of a co-factor DHBP. This makes us say that the probable cause of the disease in the husband of daughter 7 is due to an absence or a deficiency in DHBP. **(0.75 pt)**

9- A normal child inherits the normal allele of the PAH gene from the father and the normal allele of the DHBP gene from his mother. This is why he has a normal phenotype. **(0.5 pt)**

Exercise (5pts) **Phenylketonuria cause (2008-1st)**

Phenylketonuria is a disease caused by a deficit in a hepatic enzyme – PAH – responsible for the transformation of an amino acid, phenylalanine, into another one called tyrosine. In Europe the risk of being heterozygous is 1/50.
Document 1 shows the pedigrees of two families A and B which some members are affected with this disease. Couples (3, 4) of family A and (1, 2) of family B ask for a prenatal diagnosis.



Document 1

1- Through a rigorous analysis of the pedigree of family B, determine:
- whether the allele responsible for the disease is dominant or recessive.
- The location of the gene responsible for the disease.

2- Determine the genetic risk for each fetus to be affected with this disease.

Three mutations were determined to be at the origin of phenylketonuria. Document 2 shows a part of the codon sequences that correspond to three regions X, Y, and Z of the normal allele, and of the three mutant alleles that are responsible for this disease.

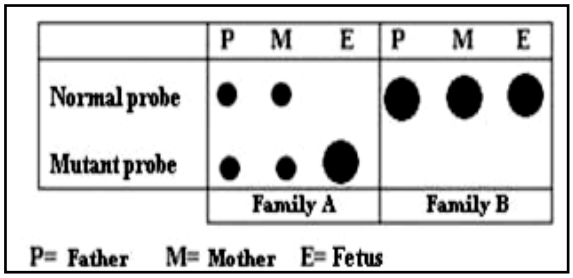
Codon / RNA	278……...282…. (Region X)	310……..…….314…. (Region Y)	406…….……410 (Region Z)
Normal allele	**ACC CCC GAA CCU GAC...**	**UCU CUG GGU GCA CCU …**	**AUA CCU CGG CCC UUC**
Mutant 1	**ACC CCC AAA CCU GAC…**	**UCU CUG GGU GCA CCU…**	**AUA CCU CGG CCC UUC**
Mutant 2	**ACC CCC GAA CCU GAC...**	**UCU CCG GGU GCA CCU…**	**AUA CCU CGG CCC UUC**
Mutant 3	**ACC CCC GAA CCU GAC...**	**UCU CUG GGU GCA CCU …**	**AUA CCU UGG CCC UUC**

Document 2

3- For each allele responsible for the disease, locate the mutation and indicate its type.

In order to diagnose the fetuses, the following DNA tests were carried out in both families.

1st test: DNA is extracted from parental and fetal cells and is subjected to restriction enzymes. Hybridization technique is then carried out using two radioactive DNA probes that are complementary to a specific "region X". One of the probes is specific for the normal allele; the other is specific for a mutant allele. The results are shown in document 3.

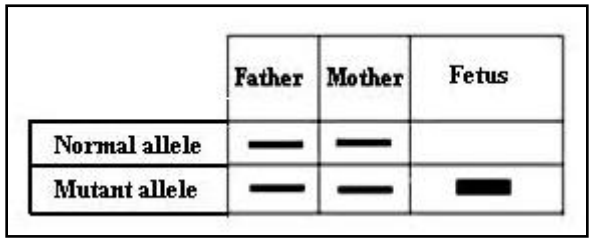


Document 3

4- Draw out the genotypes of the individuals of family A in document 3.

5- Justify that the test performed is not sufficient to establish the diagnosis of family B.

2nd test: Family B is subjected to a second DNA test yet using other restriction enzymes. This method reveals a restriction site (cleavage site) at the level of region Z, while regions X and Y remain intact. The results of this test are shown in document 4.



Document 4

6- Show the importance of the second test in order to obtain an exact diagnosis concerning the fetus of family B.

Answer key (5 pts)

1- The pedigree of family B reveals that normal parents have a daughter and a boy both affected. This means that the allele responsible for the disease is recessive **(0.25pt)**.
The allele is not transmitted by sex chromosomes because if it was Y-linked on the non-homologous segment of Y the daughters could not be affected, while the father would be; this is not the case **(0.25pt)**..
If the allele was X-linked on the non-homologous segment of X, the daughter would have inherited from the father the X chromosome carrying the allele responsible for the disease; this is not the case. **(0.25pt)**.
If it was linked on the homologous segment of X and Y, then the father should have been affected in order to give an X and a Y, both carrying the affected allele, to his daughter and son respectively; this is not the case. **(0.25pt)**.
Therefore, the allele responsible for this disease is autosomal. **(0.25pt)**

2- The risk for family A: Mother 3 is healthy with no family history of phenylketonuria, then the probability to be heterozygous is 1/50 and in this case, half of the gametes carry the mutant allele. Father 4 is healthy but has an affected brother, then the probability to be healthy and heterozygous is 2/3 and to be healthy homozygous is1/3. If the father is healthy homozygous, the risk is nil since he can only transmit the normal allele to his descendance. However, if he is healthy and heterozygous, half of his gametes carry the mutant allele. Then the risk will be:
2/3 x1/2x1/2 x1/50= 1/300. **(0.5pt)**
The risk of family B: Parents are necessarily heterozygous, then the half of the gametes carry the allele of the disease and the probability of having an affected child is ¼. Then the risk is ¼.

3- Mutant allele 1: Mutation at the level of region X of the gene; 1st nucleotide of codon 280 where G is replaced by A. The nature of this mutation is substitution.
Mutant allele 2: Region Y of the gene; 2nd nucleotide of codon 311 where T is replaced by C. Mutation by substitution.
Mutant allele 3: Region Z of the gene; 1st nucleotide of codon 408 where C is replaced by T. Mutation by substitution. **(1pt)**

4- In family A, the parents carry a normal allele and an allele that has a mutation at the level of region X; they are heterozygous. The fetus has a mutation at the level of region X on both alleles. Therefore, the fetus will be homozygous and affected. **0. 5pt)**

5- Test 1 shows that the individuals of family B are all normal and homozygous. However, the pedigree shows that the parents are normal and heterozygous. Moreover, this test was performed only at the level of region X, while the mutation can affect regions Y or Z. **(0.5pt)**

6- The 2nd test allows detecting the presence of a morbid allele in family B at the level of region Z. If it was only referred to the 1st test, the diagnosis of the fetus would have been "healthy" which is not the case. **(0.5pt)**

Exercise (5pts) **Hemophilia B (2007-2nd)**

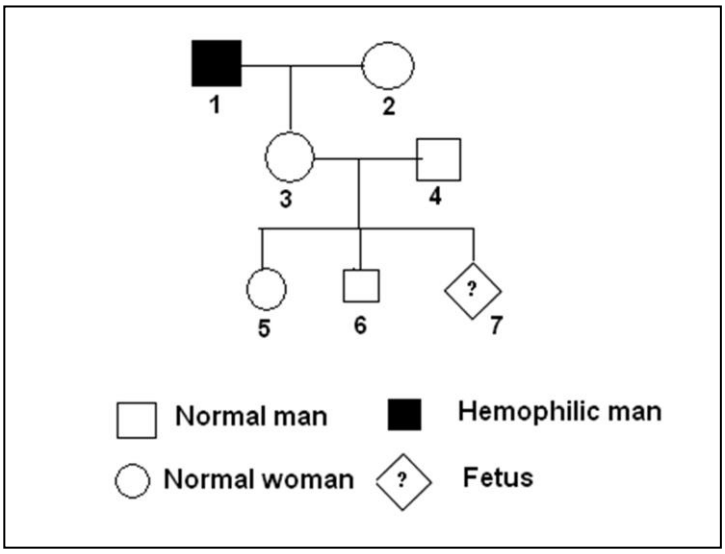
Hemophilia B is characterized by the absence of blood clotting, which may lead to significant hemorrhage. It is linked to the absence of a clotting factor, factor IX, whose synthesis is controlled by a gene located on the non-homologous segment of the X chromosome. This abnormality affects boys and not girls.

1- Explain the absence of this abnormality in girls?

Document 1 shows the pedigree of a family, one member of whom has the abnormality.

2- Show that this disease is recessive.

3- Determine the genetic risk that the fetus will be hemophilic.

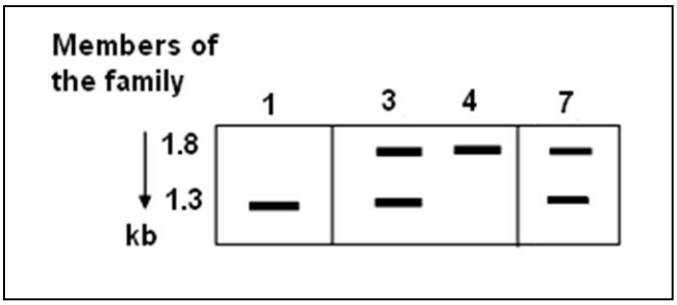


Document 1

Ultrasound scan was done to determine the sex of the fetus. It revealed that it is a boy. The doctor then prescribed analysis of DNA by the method of Southern blotting. The used probe permits to distinguish the mutated and normal forms of the implicated gene. The obtained results appear in document 2.

4- Specify the band that corresponds to the defective allele.

5- Identify, from the DNA analysis, the problem of the child that will be born.



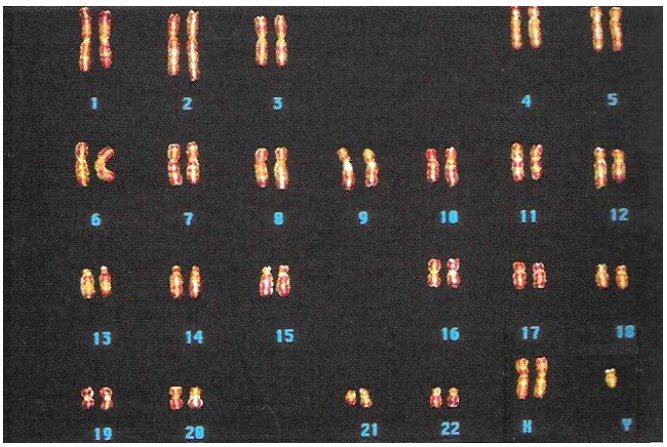
Document 2

The doctor completed the diagnosis by establishing the karyotype of the fetus, document 3.

6- Establish, based on documents 2 and 3, the diagnosis of the fetus.

7- Indicate the stage of meiosis at which the abnormality took place. Justify the answer.

8- Schematize the behavior of chromosomes at the origin of this abnormality.



Document 3

Answer Key (5pts)

1- The allele of hemophilia is lethal in the homozygous state. The girl has two X chromosomes. If she is X^hX^h, she dies before birth. **(0.5pt)**

2- The disease is carried by the X chromosome. The sick individual 1 has only one X, which carries the allele responsible for hemophilia, which he will certainly transmit it to his daughter 3. Girl 3 is normal. She carries an X chromosome having the allele without expressing it. Hence the disease is recessive. **(0.5pts)**

3- Fetus 7 has a heterozygous mother. If it is a boy, there is a risk of ½ to have the X chromosome carrying the allele of hemophilia. If it is a girl, the risk is null because her healthy non-hemophilic father cannot give her except one normal X. **(0.5pt)**

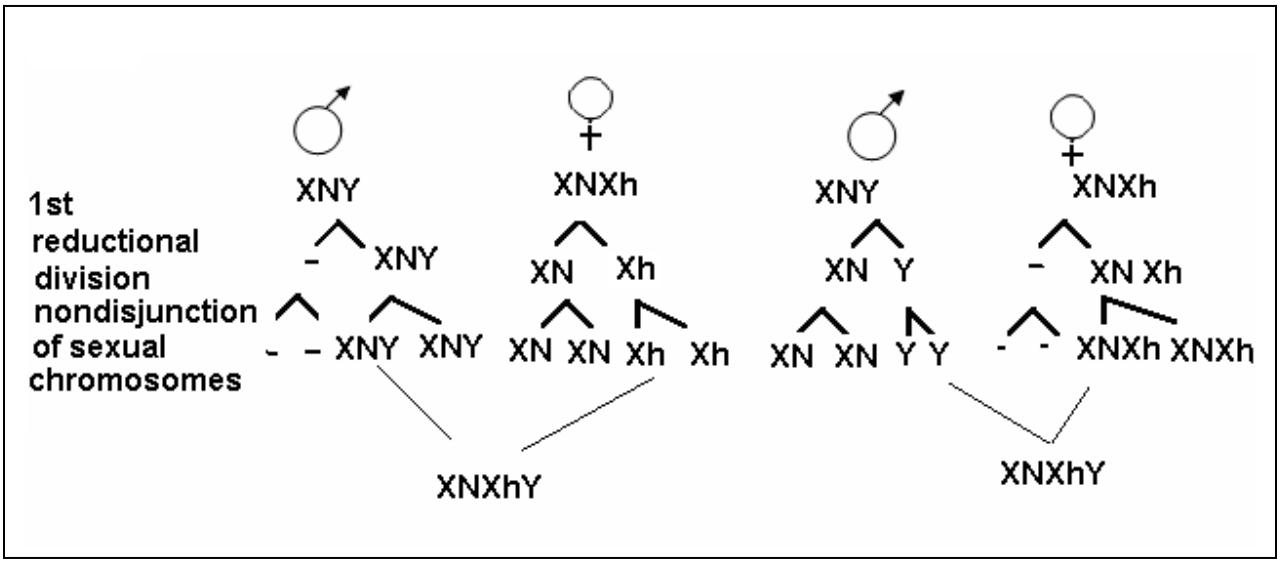
4- The 1.3 kb-band, because document 2 reveals that individual 1, who is a sick man and has only one X, has only one band of 1.3 kb. **(0.5pt)**

5- The fetus is a boy, hence he has only one X chromosome, then he must have only one band of DNA, but according to document 2 he presents two bands. Therefore, it is a boy with 2 X. **(0.5pt)**

6- Fetus 7 is a nonhemophilic boy (doc 2), but he has XXY (doc 3). Thus he will have Kleinfelter syndrome. **(0.5pt**

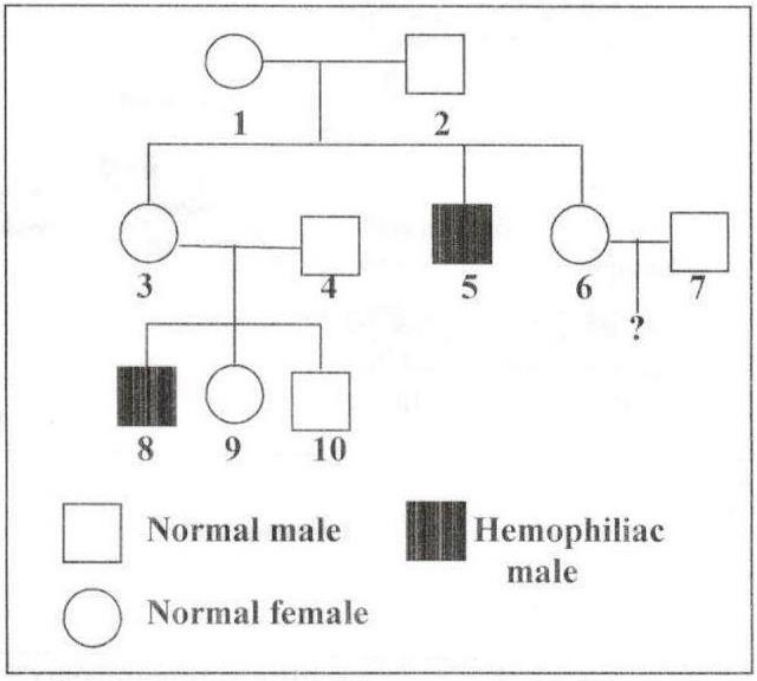
7- The abnormality of meiosis had taken place during the anaphase of the reductional division by nondisjunction of chromosomes XX or XY, because upon the analysis of DNA there are two different bands that correspond to two X and not to two chromatids of the same X chromosome. In this case the father or the mother could be at the origin of this abnormality. **(1pt)**

8- (1pt)



Exercise (5 pts) **Hemophilia A (2007-1st)**

Hemophilia A, is a genetic recessive disease due to an abnormality of a blood coagulation factor: factor VIII. This factor is the expression of a gene located on the non-homologous segment of chromosome X. We designate, by h, the allele responsible for the disease and by N the normal allele.
Document 1 reveals the pedigree of a family that expresses this disease. Woman 6 is pregnant and asks for prenatal diagnosis for her fetus.

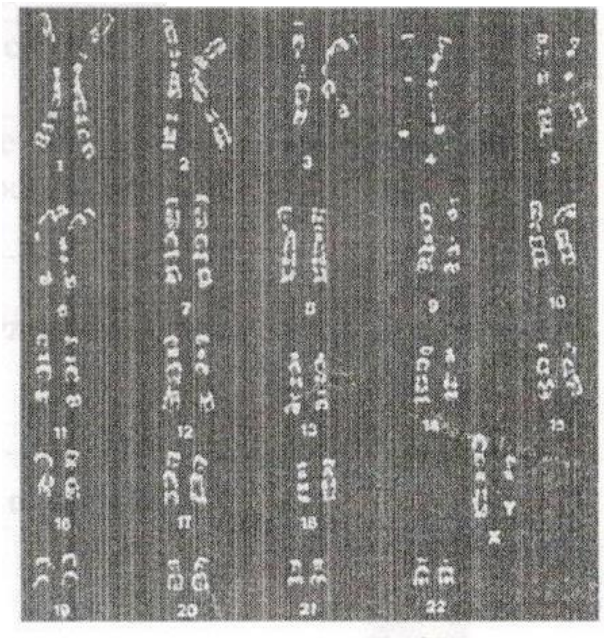


Document 1

1- Indicate the genotypes of persons 6 and 7. Justify the answer.
2- Show by logical reasoning, that this pedigree does not permit a sure diagnosis concerning the fetus.
3- Determine the genetic risk of this child to be hemophiliac.

To clarify the diagnostic problem of hemophilia in the fetus, two tests were done. The first test is a karyotype of the fetus (document 2) .

4- Does this karyotype solve this problem? Justify the answer.



Document 2

The second test is the analysis of the DNA of chromosome X. The DNA of the mother, the fetus, and the sick person 8, are subjected to restriction enzymes. The obtained DNA fragments are separated by gel electrophoresis, then hybridized by a probe. Because we cannot use an intragenic probe to distinguish the hemophilia allele from the normal allele that codes for factor VIII, we use probe ST14 that can mark a polymorphic zone, very close to this gene. This zone has 10 alleles, but only alleles 3 and 5 are present in this family. An autoradiography is done and the results are shown in document 3.

5- Specify, starting from the analysis of the obtained autoradiogram, the real genotype of the mother and the fetus.

6- We estimate a 4% recombination between the polymorphic zone and the gene coding for factor VIII. In this case, is the second test reliable for diagnosing hemophilia in the fetus? Justify the answer.

	Mother	Fetus	Person 8
Allele 3	[redacted]	[redacted]	
Allele 5	[redacted]		[redacted]

Document 3

Answer keys

1- Woman 6 : Normal woman but having a hemophiliac brother, she can be either homozygous $X^N X^N$ or heterozygous $X^N X^h$. **(¾ pt)**

Man 7: X^NY; normal man and having only one X, thus he carries the normal allele. **(½ pt)**

2- The child to be born can be either a girl or a boy. If it was a girl, this pedigree permits a sure diagnosis; she will be normal because her father can give her only X^N. But if he was a boy, the diagnosis is sure if the mother was homozygous and he will be normal, but if the mother is heterozygous we cannot determine whether the boy is normal or hemophiliac because his mother can give him either X^N or X^h. **(1pt)**

3- If this child was a girl, the risk is null.
If this child was a boy, its phenotype depends on the allele provided by his mother. The possibility of the mother of being heterozygote is ½. If she was heterozygous there is a possibility of ½ for giving him X^h and since we do not know the sex of the fetus there is a chance of ½ to be a boy. Hence the genetic risk becomes ½ x ½ x ½ = 1/8 . **(1pt)**
Or
The probability of the mother to be heterozygous is ½ , in this case ¼ of her children will be hemophiliac. Hence, the genetic risk = ½ x ¼ = 1/8

4- - No, because the karyotype reveals that it is a boy. If it was a girl the problem would have been solved.

(½ pt)

5- - Person 8, has only allele 5. Being hemophiliac, we can say that allele 5 is linked with allele h that

codes for hemophilia.
Mother 6, who is normal, has the two alleles 3 and 5 each one is on an X chromosome. Since allele 5 is linked with allele h, then allele 3 must be linked with the normal allele N. She is thus, healthy but has the allele h, her genotype is X^NX^h. **(¾ pt)**

The fetus has only allele 3, thus he received X^N from his mother and Y from his father, thus, he will be normal of genotype X^NY. **(½ pt)**

6- No, because there is a possibility of crossing over between the polymorphic zone and the gene.

Non-sister chromatids of the two homologous X chromosomes will exchange segments leading to the formation of a chromosome X on which allele 5 is linked with the normal allele N and another

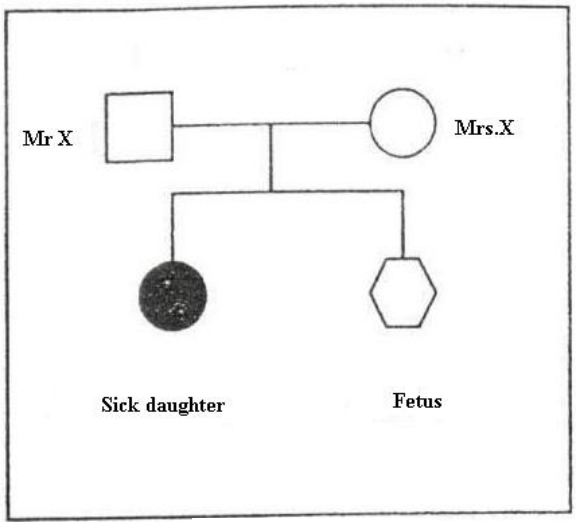
chromosome X on which allele 3 is linked with the hemophiliac allele h. Thus, the fetus will be hemophiliac even if his autoradiogram shows the presence of allele 3. **(½ pt)**

Exercise (5 pts) **Sickle cell anemia (2006-2nd)**

Mr. and Mrs. X have a daughter suffering from sickle cell anemia, document 1. This hereditary sickness, whose mode of transmission is autosomal recessive, is characterized by an abnormality in the β-globin molecule which leads to the deformation of the red blood cells. Mrs. X is pregnant and the couple demand prenatal diagnosis to know if their second child will be affected by sickle cell anemia.

1- Indicate the genotype of Mr. and Mrs. X and that of their daughter. Justify the answer.

2- Based on logical reasoning, find the probability for this couple to have an affected child.



Document 1

Document 2 reveals the sequences of parts of the non-transcribed strands of the β-globin alleles: HbA is the normal allele while HbS is the mutant allele of the β-globin gene responsible for sickle cell anemia.

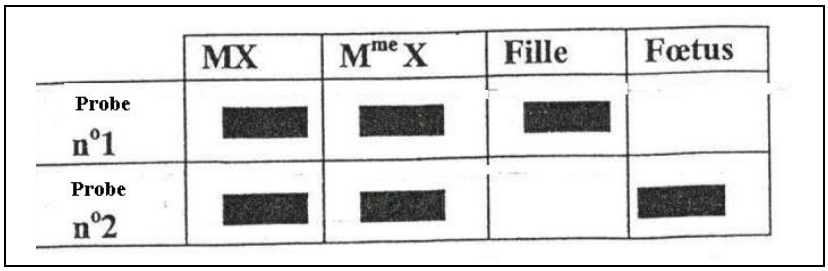
A direct diagnostic method by radioactive probe is done for this family. Many copies of the parts of the β-globin gene can be obtained from the DNA of each person by this technique. These copies are separated in two lots, and each lot is placed in the presence of a different radioactive probe, document 3; each probe is capable to bind with either allele HbA or HbS. The results of autoradiography are shown in document 4.

Nucleotides position	1 10 20
HbA	CTCCTGAGGAGAAGTCTGCC
HbS	CTCCTGTGGAGAAGTCTGCC

Document 2

Probe n°1	**GAGGACACCTCTTCAGACGG**
Probe n°2	**GAGGACTCCTCTTCAGACGG**

***Document* 3**



Document 4

3- Specify, based on document 2, the location of the mutation and its type. Justify the answer.

4- Determine, in reference to documents 2 and 3, which allele corresponds to each probe used.

5- Do the results of document 4 confirm the genotypes you have indicated in question a? Justify the answer.

6- Draw out the genotype and the phenotype of the fetus.

7- Justify why prenatal diagnosis is more accurate than a pedigree in detecting a genetic disease.

Answer keys (5 pts)

1- **N** is the symbol of Normal and **s** is the symbol of the sickled.

Mr, and Mrs. X: N//s **(¼ pt).** They have normal phenotype but have a sick child, the parents carry the allele of the sickness which is masked.**(¼ pt)**
The daughter: ss **(¼ pt)** having sickle cell anemia, a recessive sickness cannot appear unless when it is pure. **(¼ pt)**

2- Both parents are heterozygotes, since half of their gametes have the sick allele s

The probability for this couple to have sick children is 1/2 x 1/2 = 1/4 **(½ pt)**

3- The mutation is located on position 7. It is a mutation by substitution because the two alleles of the β-globin gene have the same sequence of nucleotides but differ at position 7 where adenine is replaced by thymine. **(1 pt)**

4- The radioactive probe binds to the part of the alleles by complementing with the nitrogenous bases.

Probe n°1: **GAGGACACCTCTTCAGACGG**
Complementary DNA : **CTCCTGTGGAGAAGTCTGCC**

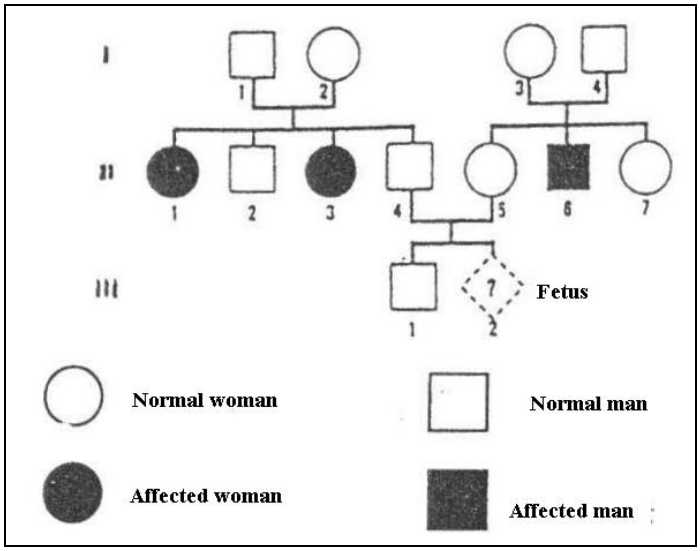
This DNA is that of HbS, thus, probe 1 permits visualizing the mutant allele while probe 2 permits visualizing the normal allele **(1 pt)**

5- Yes, in the two parents the two probes are visualized, which confirms that the parents are heterozygotes of a genotype Ns **(¼ pt).** With respect to the daughter we visualize only probe 1 that corresponds to the mutant allele, which confirms that she has the genotype ss
(¼ pt). The DNA of the fetus does not permit to visualize except probe 2, which corresponds to the allele N, thus, the fetus has the genotype NN and he has a normal phenotype **(½ pt)**.

6- Prenatal diagnosis is more accurate because it depends on the gene itself and gives the real genotype of the concerned person. On the other hand, the pedigree permits to detect the phenotype and the possible genotype **(½ pt)**

Exercise (5 pts) Cystic fibrosis origin (2006-1st)

Document 1 represents the pedigree of a family of whom some members, figured in black, are affected by a disease called cystic fibrosis, a hereditary disease manifested by respiratory and digestive troubles. This disease is determined by a mutant allele of a gene called CF. this gene is located on chromosome 7, and very close to a non-coding region that has restriction sites recognized by the restriction enzyme Taq 1.



Document 1

1- Indicate the possible genotypes of individuals II-4 and II-5. Justify the answer.

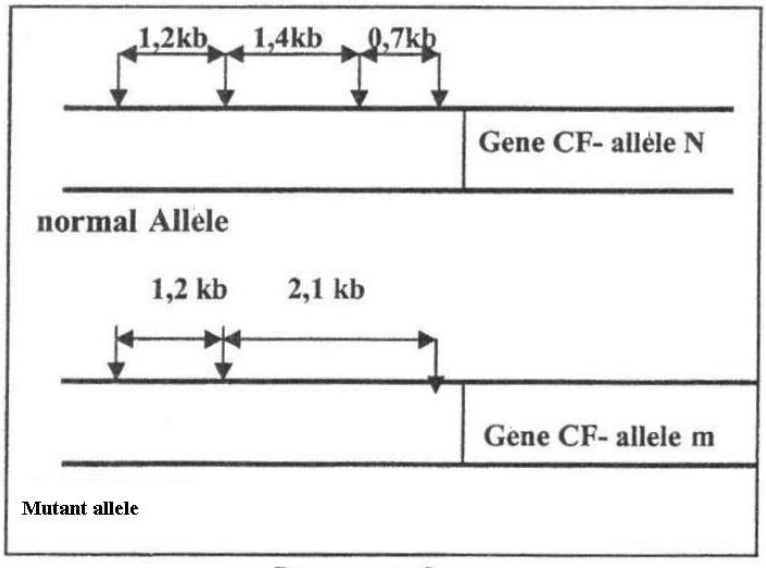
2- Determine the genetic risk of couple II-4 and II-5 to have a sick child.

3- Specify the site at which mutation took place, document 2. Justify the answer.

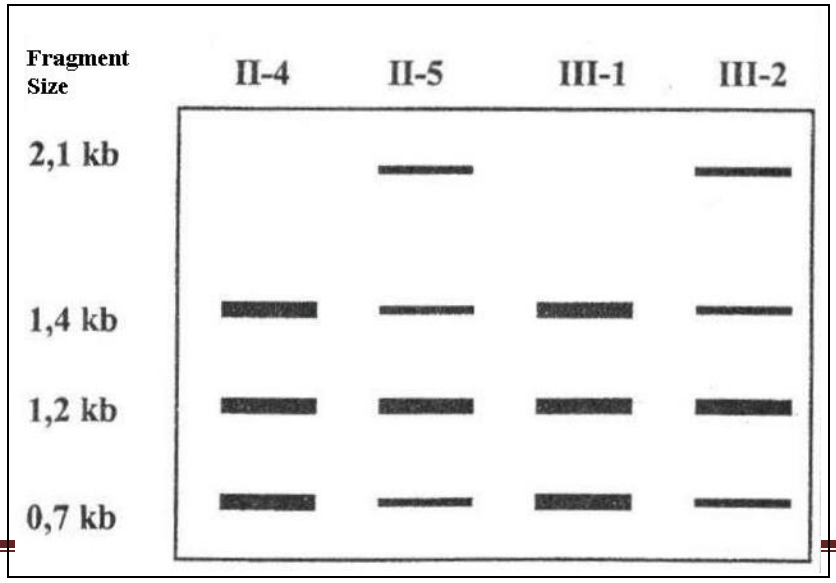
4- Document 3 shows the results of electrophoresis of the restriction fragments obtained by Southern blot technique for individuals II-4, II-5 and their children.

5- After analyzing the obtained results, indicate the real genotype of each of individuals II-4, II-5 and the fetus.

6- Based on the above analysis, is this couple in risk of having affected children? Justify the answer.



Document 2



Document 3

Answer keys

1- II4 and II5: NN or Nd. Since they are phenotypically normal, each should have a dominant allele N and another allele that can be either N or d. **(1 pt)**

2- II-4 and II-5 present the normal phenotypes. The risk for each of the two parents to be heterozygous is 2/3 and the risk for two heterozygous couple to have an affected child is ¼, therefore, the risk of having a sick child is 2/3 X 2/3 X ¼ = 1/9 **(1 pt)**

3- Mutation has occurred at the site between 1.4 Kb and 0.7 Kb, because the mutant allele shows one fragment of 2.1 Kb instead of two fragments 1.4 Kb and 0.7 Kb. **(1 pt)**

4- II-4 has two of each fragment 1.4 Kb and 1.2 Kb, and 0.7 Kb. These fragments correspond to the normal allele. Thus he is homozygous normal of genotype NN. **(1/2 pt)**
II-5 has one fragment 2.1 Kb and 1.2 Kb , which corresponds to the mutant allele, and fragments 1.4 Kb, 1.2 Kb and 0.7 Kb, which correspond to the normal allele. Thus, he is heterozygous normal of genotype Nd **(1/2 pt)**
Fetus III-2 has a fragment 2.1 Kb, which implies that he has received the mutant gene from his mother. He also has fragments 1.4 Kb, 1.2 Kb and 0.7 Kb, which correspond to the normal allele that he received from his father. Thus, he will be normal heterozygous of genotype Nd. **(1/2 pt)**

5- No, because the two parents are not heterozygous and the father II-4 who is homozygous gives only one type of gamete N**. (1/2 pt)**