Chapter 5: Human Genetics

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

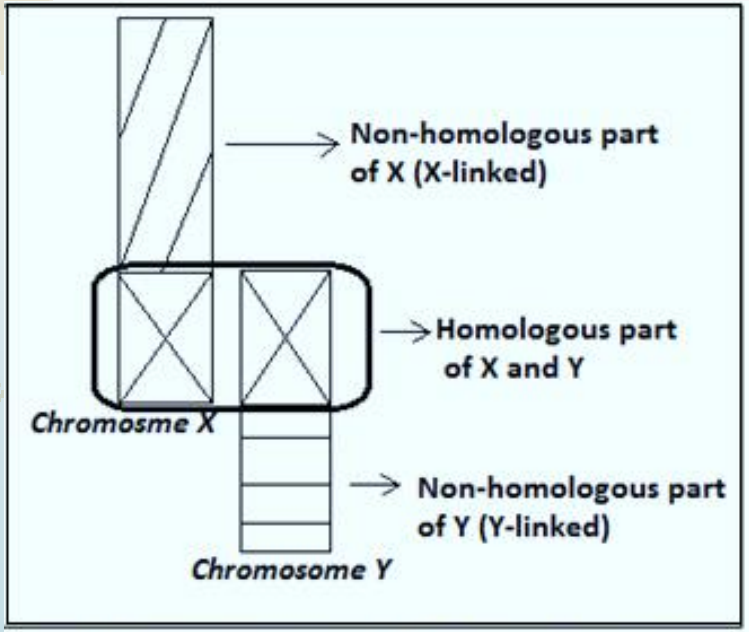
Document 3

Sex-linked Diseases

What is Sex-linked Trait?

A sex-linked trait is a trait determined by its presence on the sex chromosome.

X and Y chromosomes are not similar in size although they possess a homologous segment as well as non-homologous ones.



Doc.1 A schematic representation of X and Y gonosmes

I. Sex-linked (Gonosomal) Diseases

- Application 1:

Duchenne Muscular Dystrophy (DMD) or myopathy is caused by a defective gene for dystrophin (muscle protein). It occurs primarily in males, though in rare cases it may affect females. The symptoms of DMD include progressive weakness and loss (atrophy) of both skeletal and heart muscle. Early signs may include delayed ability to sit, stand, or walk and difficulties learning to speak.

1- Pick out from the text:

1.1- the origin of DMD

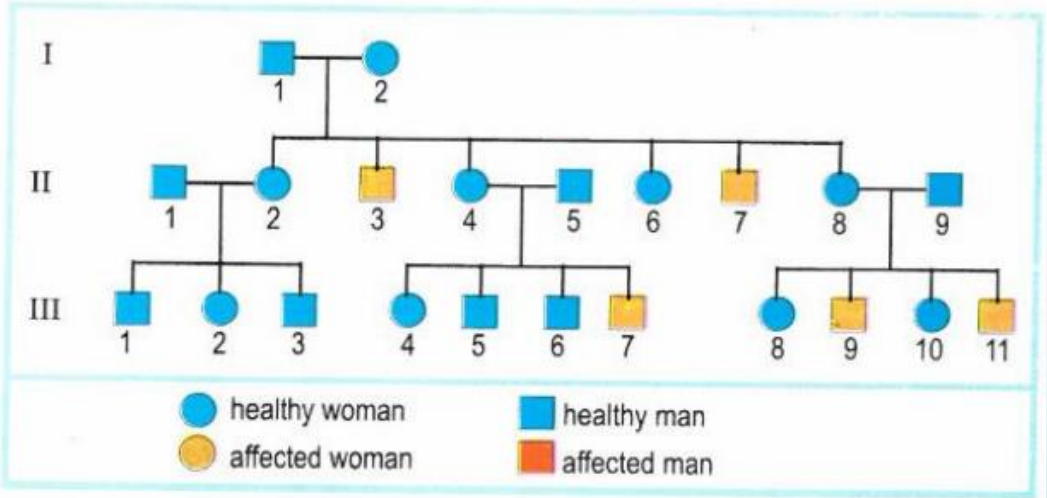
Duchenne Muscular Dystrophy (DMD) or myopathy is caused by a defective gene for dystrophin (muscle protein).

1.2- the symptoms of DMD

The symptoms of DMD include progressive weakness and loss (atrophy) of both skeletal and heart muscle.

Document b p.97 represents the pedigree of a family affected by DMD.

*** Referring to Doc.b, answer the following questions**



Doc.b *Pedigree of a family affected by Duchenne muscular dystrophy.*

2. Specify if the allele of the disease is dominant or recessive.

The allele of DMD disease is recessive with respect to the normal allele, since the affected boys II-3 and II-7 have healthy parents I-1 and I-2. Thus, at least one of the parents has the allele of the disease that is masked by the normal allele in the phenotype.

Let "N" be the symbol of the dominant normal allele.

Let "d" be the symbol of the recessive allele responsible for DMD disease.

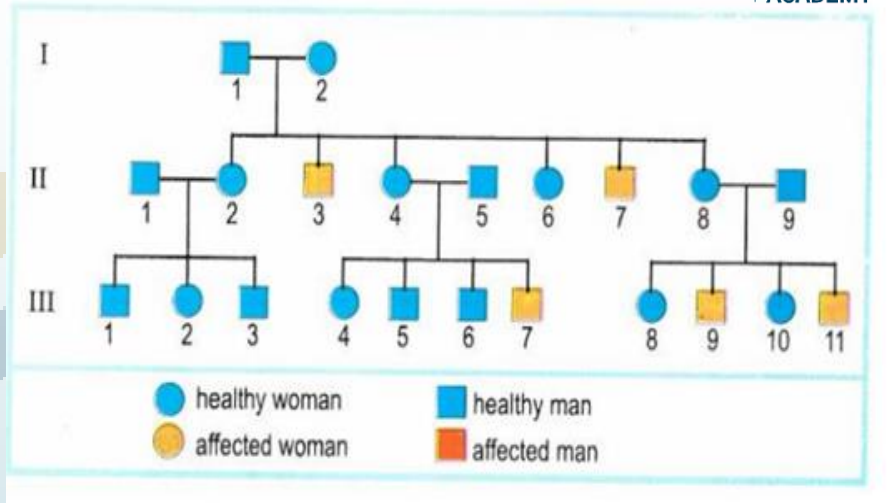
3- Determine the localization of the gene of DMD.

Document b shows that DMD disease affects only males (II-3,II-7,III-7,…); this indicates that the gene of the disease is sex-linked .

If the gene is carried by the non-homologous segment of Y chromosome, the affected males II-3 and II-7 who would have $X//Y^d$ as genotype must inherit Y^d from their father I-1 who would have $X//Y^d$ as genotype and he must be diseased, but he is normal, which is not the case.

If the gene was carried on the homologous part of X and Y, there must be affected siblings, but the pedigree doesn't show affected siblings which is no the case.

Therefore, the gene of DMD is carried by the non-homologous segment of X chromosome.



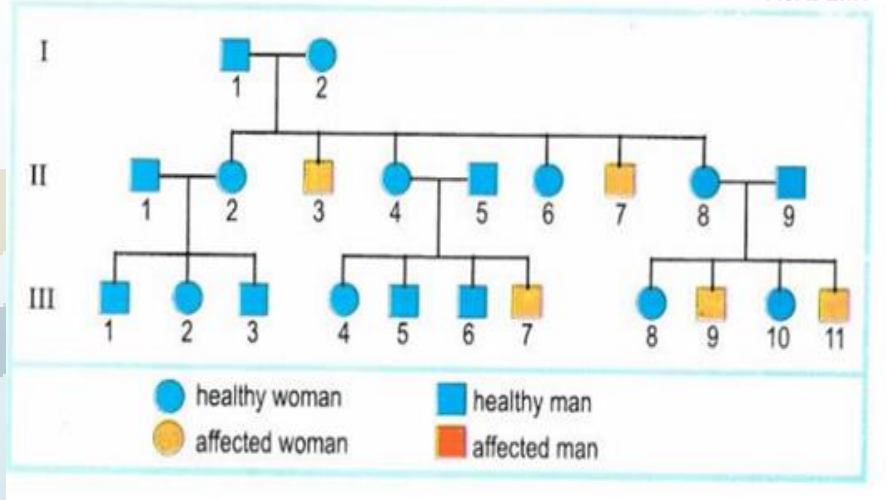
4- Write the genotype of I1,I2 II6 and III7. Justify.

I-1: X^NY since he is normal male where the normal allele is dominant, and the gene is X-linked so he must carry only 1 normal allele on X gonosome.

I-2: X^NX^d since she is normal female having an affected child II-3 of genotype X^dY and must inherit X^d from his mother , so she must be carrier heterozygote.

II-6:.X^NX^d or X^NX^N since she is normal female and the gene of the disease is X-linked and normal is dominant. She will receive the normal allele from her father and either the normal or diseased allele from her mother ,so she can be in homozygous or heterozygous state.

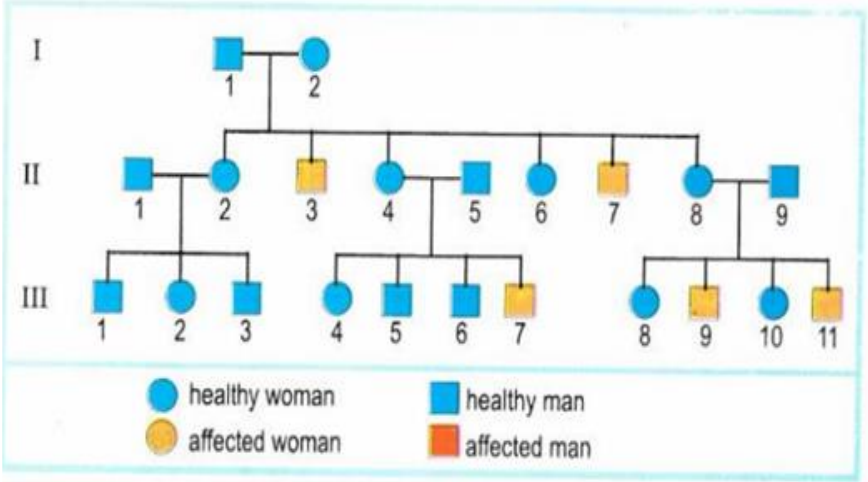
III -7: X^dY, since he is an affected male where the diseased allele is recessive and the gene is X-linked so he must carry only 1 diseased allele on X gonosome.



5-Determine the risk for couple II-4 and II-5 of having another affected child.

The mother II-4 is normal then she must carry the normal dominant allele and gave birth to an affected son III-7 having X^dY as genotype, and who must inherit the diseased allele from his normal mother which means that she is heterozygous of genotype X^NX^d .

The father II-5 is normal and since the gene of the disease is X-linked then he must carry only one normal allele and has genotype X^NY. If the fetus is a girl, all girls would inherit an X^N from their father. Since the normal allele N is dominant, it is expressed in their phenotype whatever the allele inherited from their mother. Therefore, the risk of having affected girls is zero.



If the fetus is a boy, the risk of inheriting X^d from their mother is 1/2.

The risk of having a boy who would inherit Y from his father is ½.

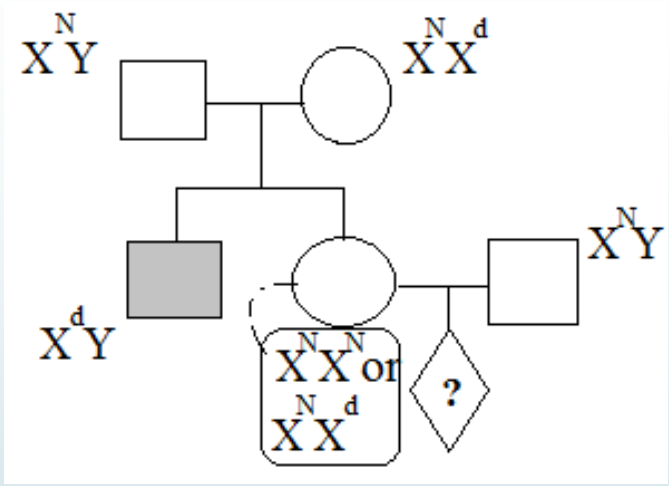
Hence, the risk of having affected boys among children is ½ X ½ = ¼.

II. Genetic Risk

How to calculate the risk to have an Affected Child in case of:

X-linked Recessive Diseases? N> d

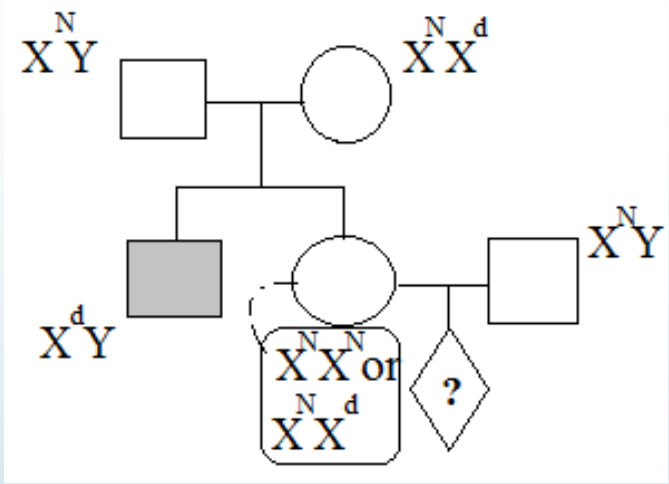
→ **Case 1:Normal parents where the mother has affected sibling and normal parents.**



The father is normal and since the gene of the disease is X-linked then he must carry only one normal allele and has genotype X^NY.

The mother is normal then she must carry the normal dominant allele and has an affected brother having X^dY as genotype, and who must inherit the diseased allele from his normal mother that must be heterozygous of genotype X^NX^d . Thus, the mother will inherit the normal allele from her father and the normal or diseased allele from her heterozygous mother, so she may be pure X^NX^N or hybrid X^NX^d. So the probability for the mother to be heterozygous is ½.

If the fetus was a girl: The risk of being affected is, since she will inherit X^N from her father which is the normal dominant allele, so she will be normal whatever the allele she will inherit from her mother.



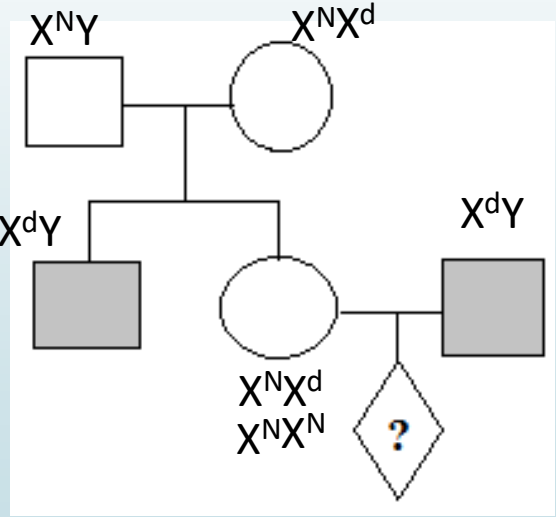
- If the fetus was a boy, then its phenotype will be provided by his mother (the boy will inherit Y from his father, but he will inherit either X^N or X^d from his mother, if X^NY (normal) if X^dY (affected). The possibility of the mother to be heterozygous is ½. If she was heterozygous there is a possibility of ½ for giving him X^d and a possibility of ½ to give Y from the father, to become an affected boy.
- G.R = $P_{HM} \times P_{AC}$ = 1/2 x (1/2 X^d ♀ x 1/2 Y ♂) = 1/8.

→ Case 2: Affected father and normal mother having affected sibling and normal mother.

1. Designate the possible genotype(s) on the given pedigree.
2. Calculate the genetic risk for the fetus to be affected.

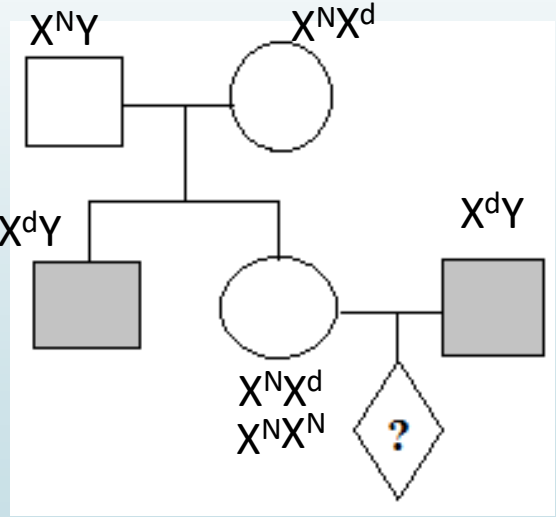
The father is affected and since the gene of the disease is X-linked then he must carry only one diseased allele and has genotype X^dY.

The mother is normal then she must carry the normal dominant allele and has an affected brother having X^dY as genotype, and who must inherit the diseased allele from his normal mother that must be heterozygous of genotype X^NX^d . Thus, the mother will inherit the normal allele from her father and the normal or diseased allele from her heterozygous mother, so she may be pure X^NX^N or hybrid X^NX^d. So the probability for the mother to be heterozygous is ½.



If the fetus was a girl: The risk of inheriting X^d from their father is 1/2. The risk of their mother to be heterozygous is ½, and the risk to inherit X^d from their mother is ½. Thus, the risk of having affected girls is ½ x ½ x ½ = 1/8 among children .

If the fetus was a boy: The risk of inheriting Y from their father is 1/2. The risk of their mother to be heterozygous is ½, and the risk to inherit X^d from their mother is ½. Thus, the risk of having affected boys is ½ x ½ x ½ = 1/8 among children .



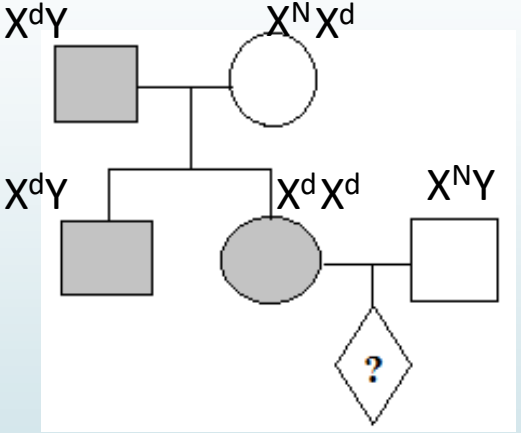
→ Case 3: Normal father and affected mother

1- Designate the possible genotype(s) on the given pedigree.

2- Calculate the genetic risk for the fetus to be affected.

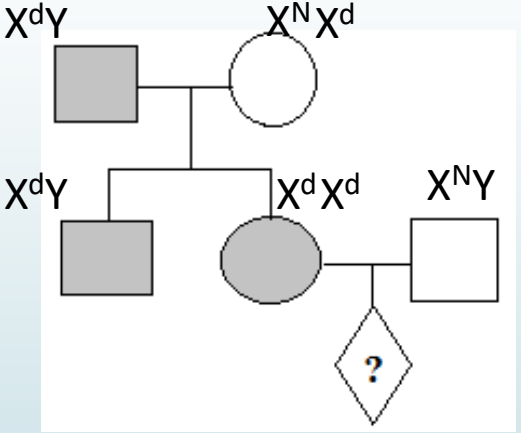
The father is normal and since the gene of the disease is X-linked then he must carry only one normal allele and has genotype X^NY.

The mother is affected then she must carry the diseased recessive allele, and since the gene responsible for the disease is X-linked then she must have 2 diseased alleles in order to be expressed on X gonosome and has genotype X^dX^d



If the fetus was a girl: Her father is normal of genotype X^NY. All girls would inherit an X^N from their father. Since the normal allele N is dominant, it is expressed in their phenotype whatever the allele inherited from their mother. Therefore, the risk of having affected girls is zero.

If the fetus was a boy: His mother is affected of genotype X^dX^d. All boys would inherit X^d from their mother and Y from their father and will be affected. Therefore the risk of having affected boys is 1.



-Application 2:

Vitamin Resistant Rickets VRR is a rare disease that affects fewer than 200,000 people. When affecting a family, Vitamin Resistant Rickets appears in every generation. Document c shows a pedigree of a family affected by this disease.

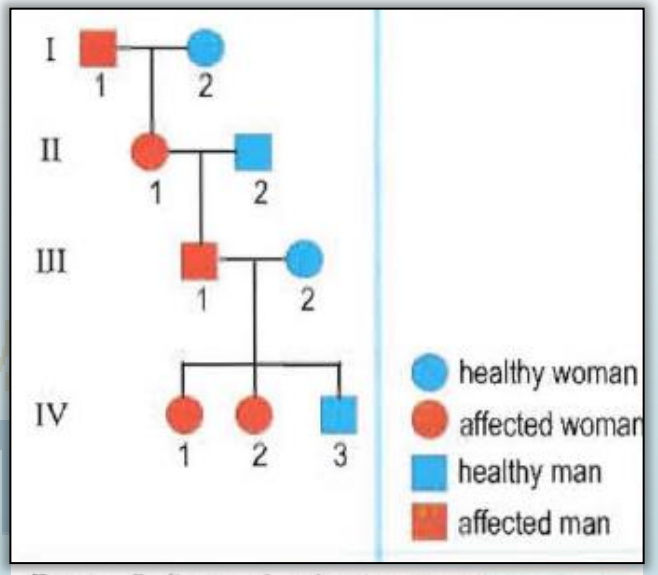
- Referring to Doc.c, answer the following questions:

1-Indicate whether the allele of VRR is dominant or recessive. Justify your answer.

The allele of the disease is dominant with respect to the normal allele since there is an affected individual in every generation; every affected individual (II-1) has at least an affected parent I-1.

Let "R" be the symbol of the dominant allele of the disease.

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

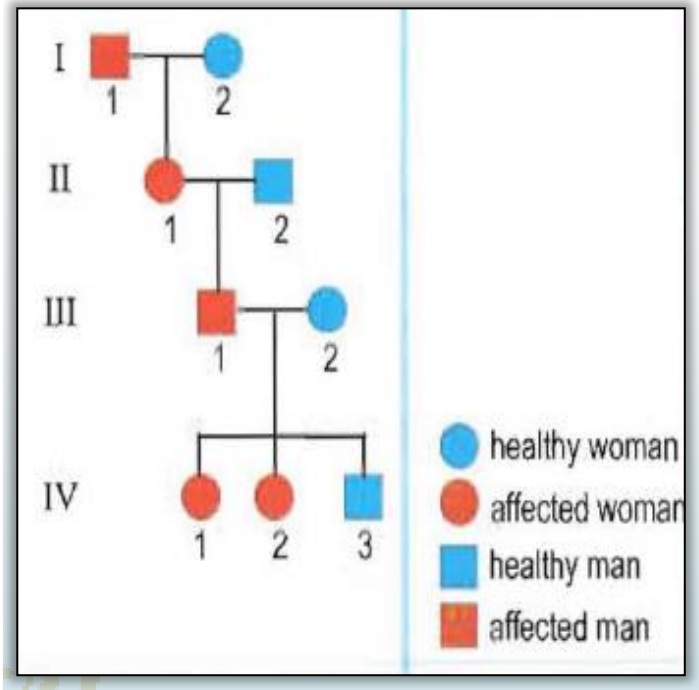


Doc.c *Pedigree of a family affected by vitamin-resistant rickets.*

2- Show that the gene of VRR disease is X-linked.

Every affected father has daughters affected by this disease. The affected father I-1 has affected daughter II-1.The affected father III-1 and the healthy mother III-2 , have all their daughters IV-1 and IV-2 affected. Moreover, their son IV-3 is normal, and he inherits Y chromosome from his father III-1. This means that the inheritance of this disease is discriminated by sex and the gene responsible for VRR is Sex-linked; it is not carried on the non-homologous segment of Y chromosome, but it is carried on the non-homologous segment of X chromosome.

Therefore, the gene of Vitamin Resistant Rickets disease is X-linked.

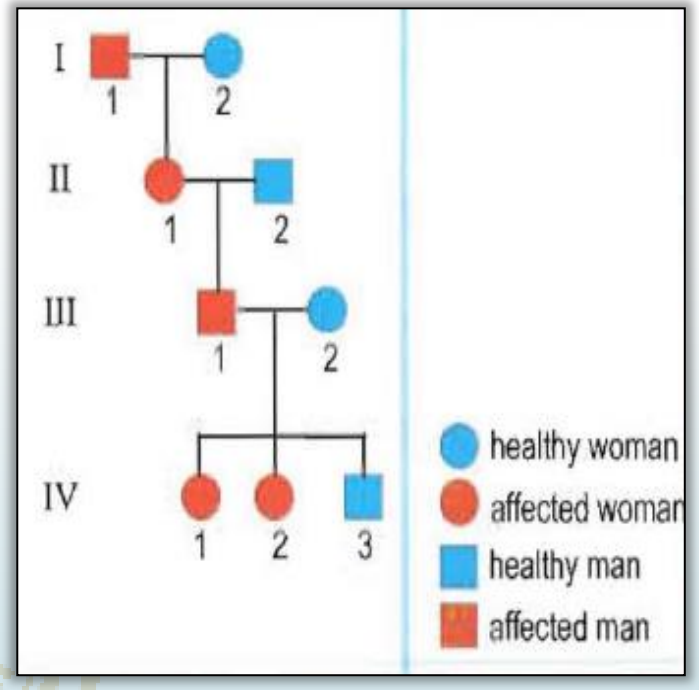


Doc.c *Pedigree of a family affected by vitamin-resistant rickets.*

3- Specify the genotypes of individuals I-1 and IV-1.

Genotype of I-1 is X^RY since he is diseased and the allele responsible for the disease X-linked. Then affected males must carry one diseased dominant allele on X chromosome.

Genotype of IV-1 is $X^R X^n$ since she is diseased and the allele responsible for the disease X-linked which means that she possesses the dominant allele responsible for the disease which is carried by X chromosome, then she possesses X^R. Furthermore, her mother III-2 is normal having X^nX^n as genotype, then woman IV-I receives X^n from her mother. Thus, IV-1 is heterozygous.



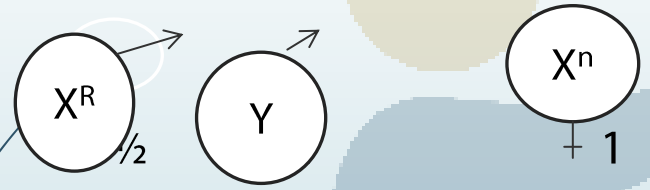
Doc.c *Pedigree of a family affected by vitamin-resistant rickets.*

4- Make a factorial analysis to find the probability for couple III-1 and III-2 of having another affected child.

Parents: affected father III-1 Healthy mother III-2

Genotypes: X^RY x X^nX^n

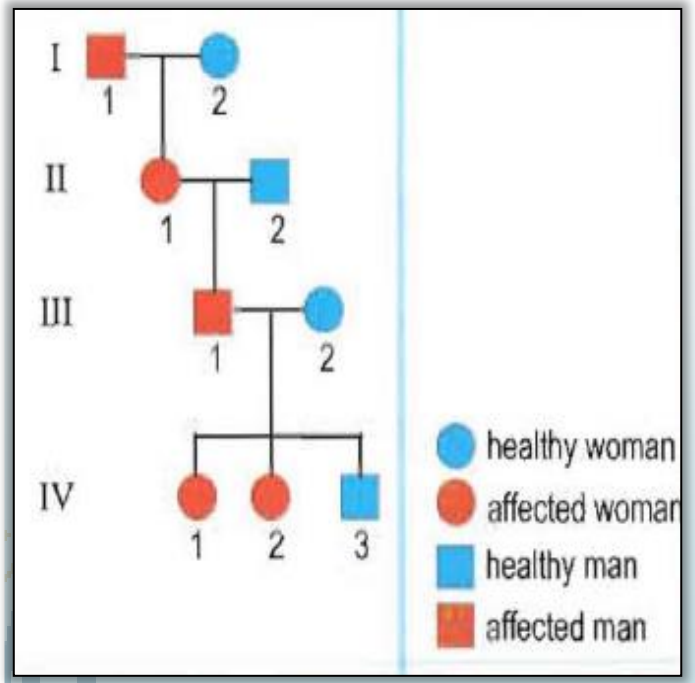
Gametes :



♀ \ ♂	X^R 1/2	Y 1/2
X^n 1	X^R //X^n 1/2	X^n//Y 1/2

Among girls, all girls will be affected; their probability is 1 (among children the probability is ½).

All boys will be normal; their probability is zero.



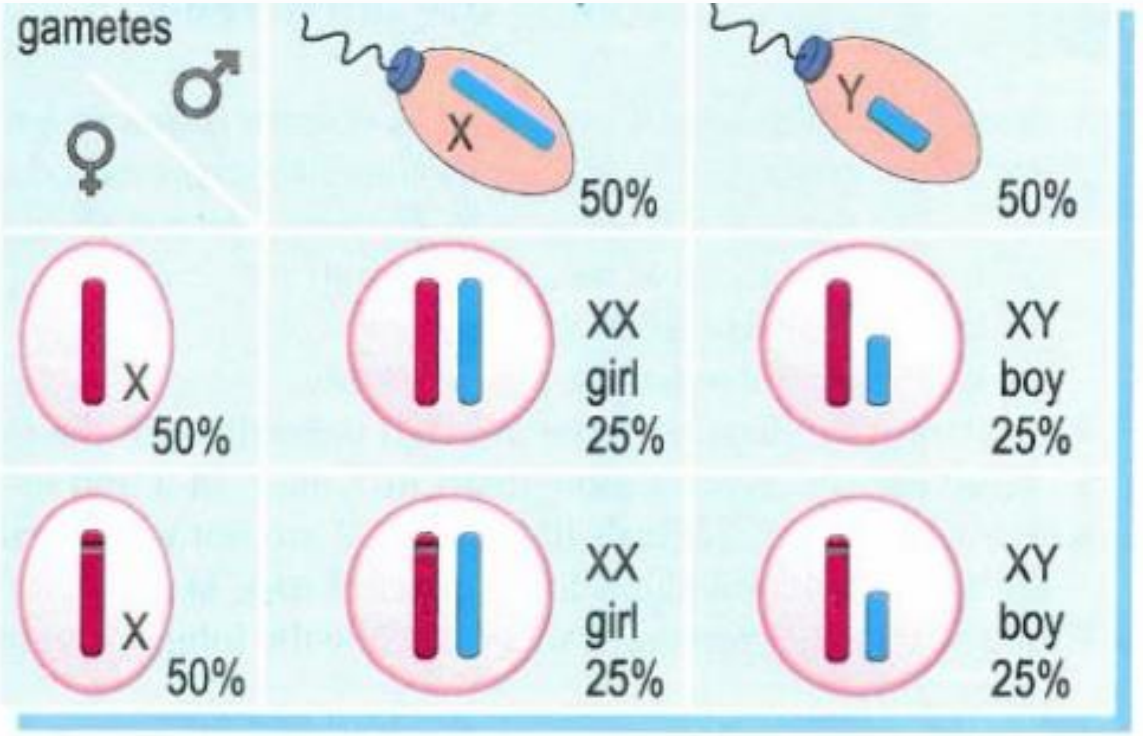
Doc.c *Pedigree of a family affected by vitamin-resistant rickets.*

III. Sex Determination

During fertilization, it is the sperm cell that determines the sex of the future child.

Since gametes meet randomly, a sperm cell carrying an X chromosome has the same probability as a sperm cell carrying a Y chromosome to fertilize an oocyte.

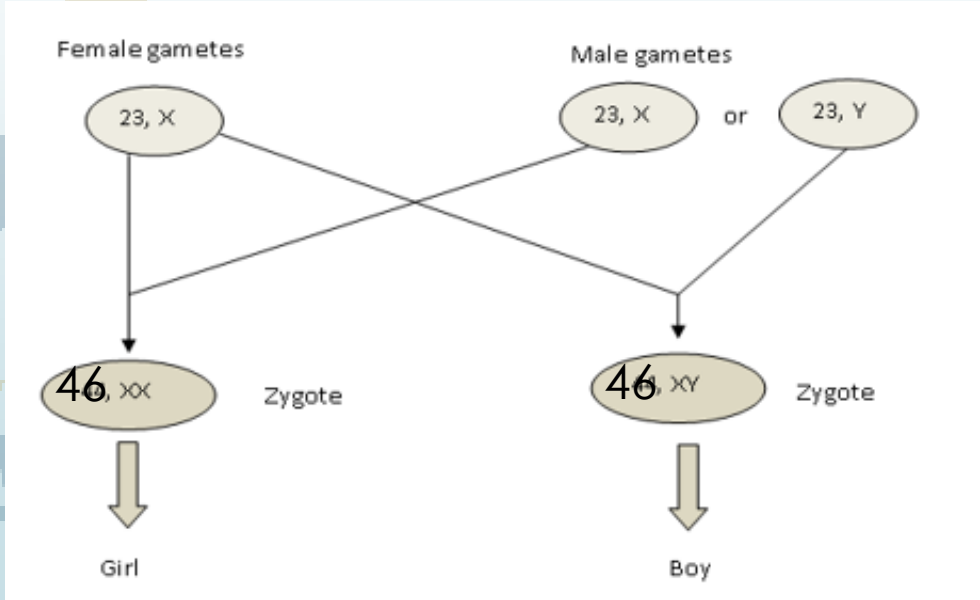
In fact, this equal (or about equal) probability of both sexes is observed in the population.

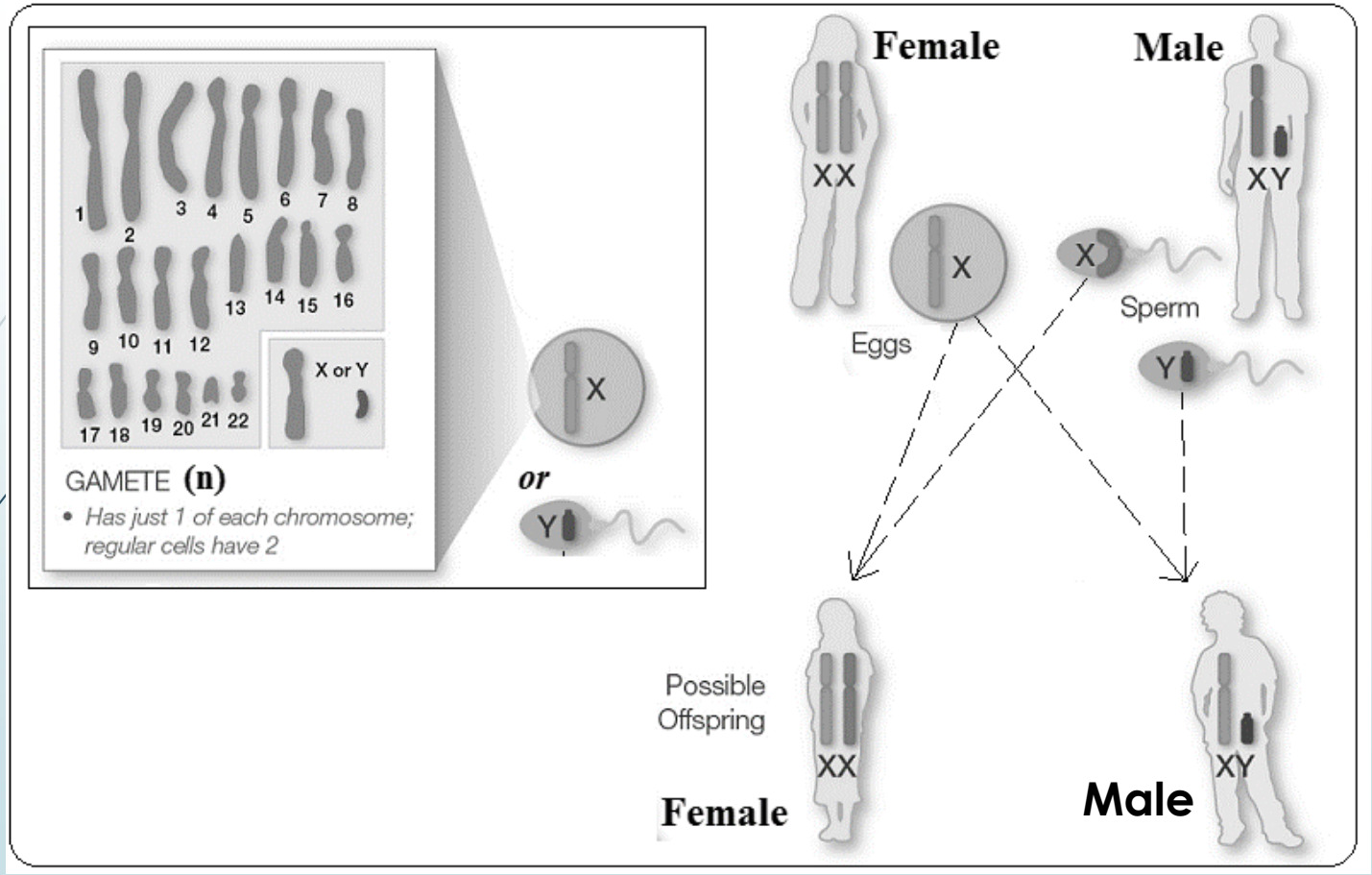


- All gametes produced by females carry X gonosome.
  → C.F of oocytes: 23,X
- Gametes produced by males may carry either X or Y gonosome at the same probability.
  → C.F of sperms: 23,X or 23,Y

⇨ Probability to have a baby boy is 50%.

⇨ The Sperm (male) determines the sex of the baby.

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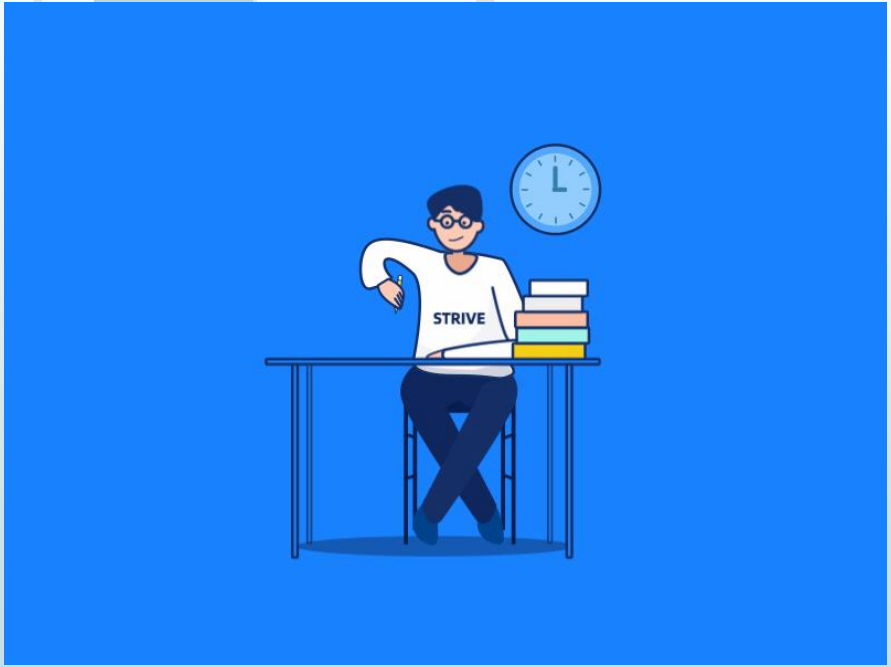
21
22
X or Y
GAMETE (n)
• Has just 1 of each chromosome; regular cells have 2
X
or
Y
Female
Male
XX
XY
X
X
Sperm
Eggs
Y
Possible Offspring
XX
XY
Female
Male

Selected Exercises of Official Exams

Official exam 2016 (2)

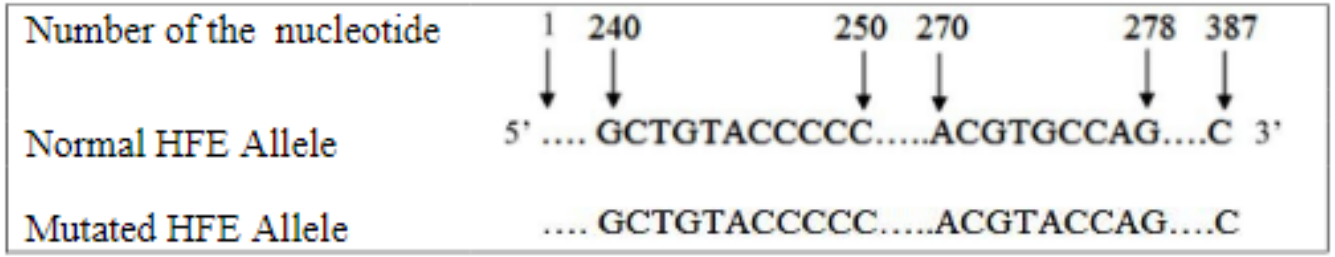


Exercise 1 (5 points)

Hemochromatosis

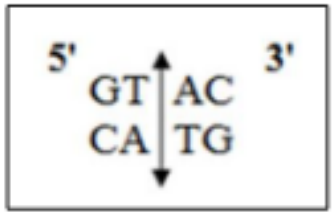
Hemochromatosis appears after the age of 40 years and is characterized by the accumulation of iron in the body. It is a recessive disease linked to the HFE gene which is located on chromosome 6. This gene has two alleles: the normal allele which codes for a membrane protein that regulates the entry of 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 2 presents the restriction site of a restriction enzyme Rsa1.



Document 1

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.



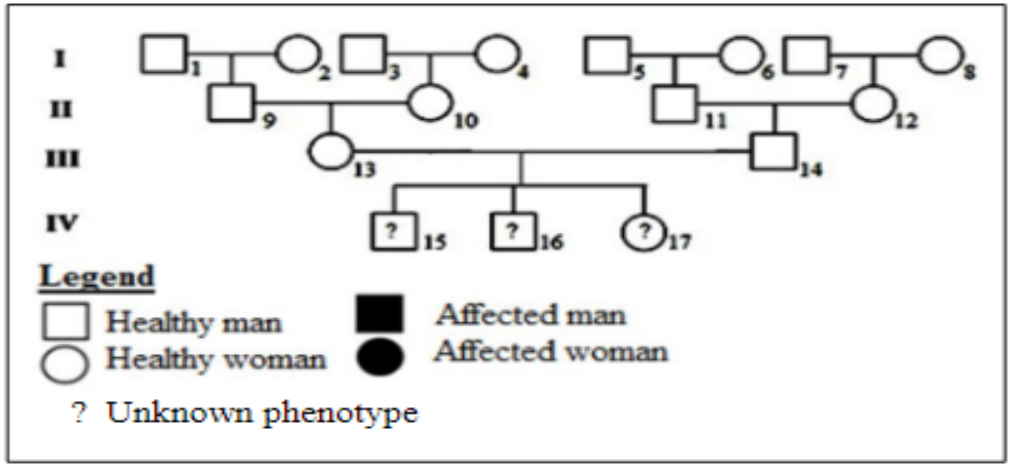
Document 2

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

Q.	Exercise 1 (5 points)	Grade
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.	3/4
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 (3/4 pt) When treated by the restriction enzyme Rsa1, the mutated 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 (3/4 pt)	11/2

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.



Document 3

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

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.

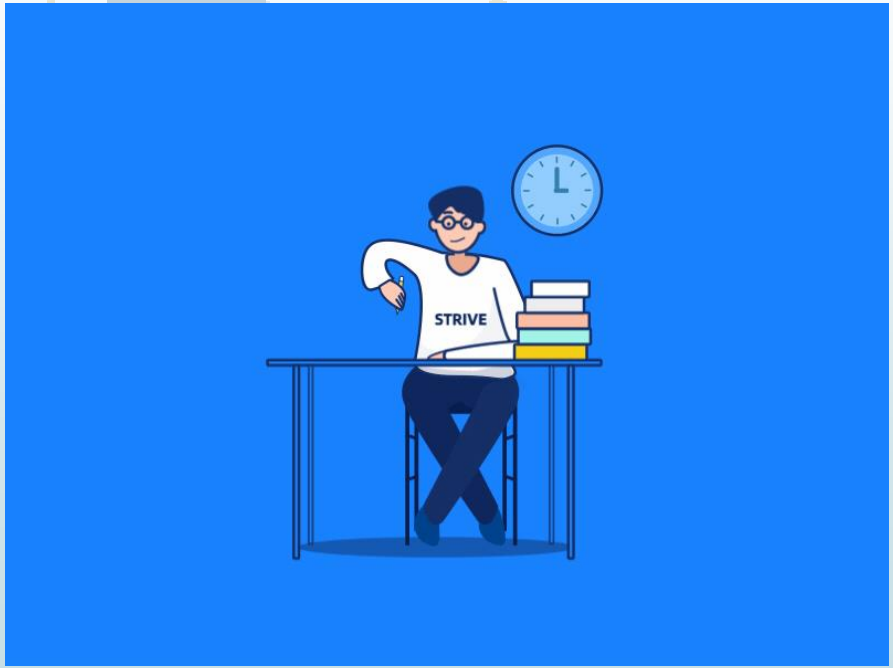
Size of DNA fragments (bp)	III13	III14	IV15	IV16	IV17
29	▬	▬		▬	▬
114	▬	▬		▬	▬
143	▬	▬	▬	▬	

Document 5

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	1/2
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.	3/4
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)	11/2

Selected Exercises of Official Exams

Official exam 2007 (1)



Answer the following questions.

Question I (5 ½ pts)

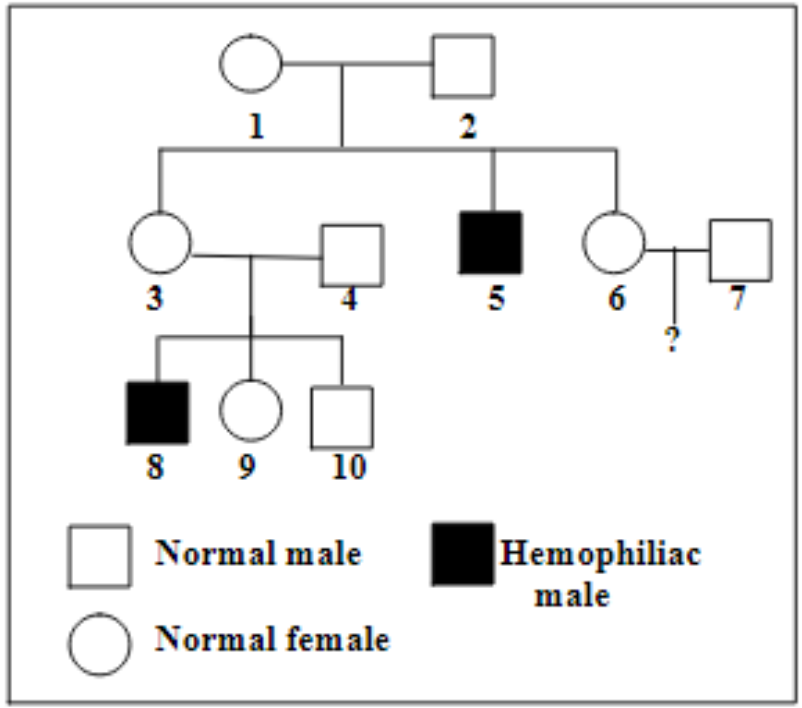
Hemophilia A, is a genetic recessive disease due to an abnormality of a blood coagulation factor: factor VIII. This factor is the expression of a gene located on the non-homologous segment of chromosome X. We designate, by h, the allele responsible for the disease and by N the normal allele.

Document 1 reveals the pedigree of a family that expresses this disease. Woman 6 is pregnant and asks for prenatal diagnosis for her fetus.

a- Indicate the genotypes of persons 6 and 7. Justify the choice.

b- Show by logical reasoning, that this pedigree does not permit a sure diagnosis concerning the fetus.

c- Determine the genetic risk of this child to be hemophiliac.



Document 1

Answer Key

Question I (5 ½ pts)

a- 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: $X^N Y$; normal man and having only one X, thus he carries the normal allele. **(½ pt)**

b- 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)**

c- 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

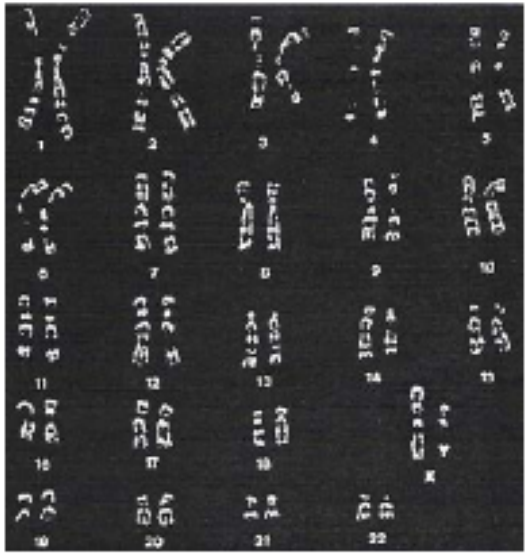
To clarify the diagnostic problem of hemophilia in the fetus, two tests were done. The first test is a karyotype of the fetus, document 2.

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

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.



Document 2

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

f- 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			
Allele 5			

Document 3

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

e- 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 $X^{N}X^{h}$. **(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 $X^{N}Y$. **(½ pt)**

f- 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)**