## Examen

# Classe:12-SV **Matière : Biologie**

#### **Exercice I (5pts)** Etude d'une maladie génétique : la phénylcétonurie

### Le

La phénylcétonurie est une maladie génétique grave en relation avec un trouble du métabolisme de la phénylalanine .Elle est responsable d'une arriération mentale progressive en l'absence de traitement approprié .

Dans les cellules du foie, une enzyme la PAH permet de transformer la phénylalanine en excés en tyrosine.

Chez les phénylcétonuriques, la transformation de la phénylalanine ne peut se produire et cette molécule s'accumule dans le sang ,alors que le taux de tyrosine diminue.Cetexcés de phénylalanine est toxique pour le système nerveux et perturbe le développement du cerveau de l'enfant entrainant un

retard mental.L'abaissement du taux de tyrosine entraine un abaissement de production de la mélanine ce qui fait que les enfants atteints ont des cheveux, blancs ,un teint et des yeux pâles(albinos).Le gène codant la fabrication de la PAH existe sous deux formes alléliques .(PAH+) codant à un phénotype normal et l'autre (PAH - ) codant à un phénotype malade.

pédigrée ci-contre (doc 1) présente le mode de la transmission de cette maladie dans une famille.

1-Déduire si l'allèle de la maladie est dominant ou récessif.

2-Déterminer la localisation du gène étudié.

**3-Préciser** le génotype des individus : II (4) et III(4). 4-Calculer les risques pour que les fœtus IV(3) et IV(4) soient atteints ,sachant que le père III(6) est hétérozygote .

Le pédigrée ci-contre (doc 2) représente une autre famille dont certains membres sont atteints par cette maladie.

5-Formuler une hypothèse expliquant l'apparition de l'enfant de phénotype normale

Les chercheurs ont montré la présence d'une deuxième forme de la maladie dans laquelle la PHA est normale mais où son cofacteur (le BH4) n'est pas synthétisé par le patient (le cofacteur est indispensable à l'activité de l'enzyme ). Il existe un gène le DHPR sur le chromosome 4 ,son allèle normal N code à la synthèse d'une enzyme qui intervient dans la synthèse du BH4.

Un allèle muté de ce gène (m) entraine l'absence de ce cofacteur.

Le document 3 présente l'empreinte génétique de cette famille

6-En se référant à l'ensemble de l'exercice préciser les génotypes possibles de chacun des parents 1 et 2 (en prenant en considération les deux gènes étudiés qui sont non liés )









### Exercise 1: (5 pts) Achondroplasia, a form of hereditary Dwarfism

**Achondroplasia** is a hereditary constitutional bone disorder. It is the most common type of dwarfism, in which the child's arms and legs are short in proportion to the body length. This disease is caused by a mutation of the fibroblast growth factor receptor-3 (FGFR3) gene on human chromosome 4. Document 1 represents the pedigree of a family where some of its members are affected with Achondroplasia



- 1- Precise the mode of transmission of this anomaly.
- 2- Determine the chromosomal location of the gene for Achondroplasia.
- 3- Identify the genotypes of individuals (I,1), (III,9), (IV,4).

Homozygous fetuses that possess two copies of the mutant gene are not viable, and pregnancy is naturally interrupted

4- Determine the risk for the couple III (9,10) to give birth to a third child having this anomaly.

Nucleotide sequences, located close to the locus of the gene responsible for this anomaly and corresponding to the normal allele and to the mutant one, are presented in the table of document 2.

Sequence corresponding to normal allele	ATC TGC AGA TTT CGA TAG ACG TCT AAA GCT
Sequence corresponding to mutant allele	ATC TCC AGA TTT CGA TAG AGG TCT AAA GCT
DOCUMENT 2	

These sequences present 5 restrition sites for the enzyme Pstl.\*4 sites are common for the two sequences

\*A polymorphic site ,corresponding only and uniquely to the normal allele Document 3.

### The recognition site of this enzyme is : CTGCA/G



5- Explain the absence of the polymorphic site at the level of the mutant allele.

The couple III (13,14) is expecting a child, worried that this child might be affected by this anomaly, their doctor recommended a prenatal diagnosis whose results are shown in document 4.

6- Interpret the results of document 4. What do you conclude about the diagnosis of the fetus?

### Exercise 2 ( 5 pts).

The testicles has two functions: it produces testosterone (male hormone) and also produces spermatozoa. Sertoli cells,located in the seminiferous tubules, are involved in some of them. We deposit adjudine, a molecule that acts on these cells and modifies their activities. To understand the effect and the mode of action of adjudine, we carry out the experiments and the observation which are listed below.

### Experiment 1

Fertility in male rats was tested before and after treatment with adjudine. The rats were mated with virgin and fertile females; the fertility rate is measured From the pregnancy rate in females.

Document 1 shows the results.

- 1. Interpret the results of document 1
- 2. The adjudine is considered as a "male contraceptive" pill. Justify this naming.

**Experiment 2**:Testosterone level is measured with respect to time in two lots of rats. One receiving an injection of adjudine and another receiving injection of placebo (medical preparation which does not contain any active

Substance. Document 2 shows the production of testosterone.

3. Verify ,after the analysis of document 2,that adjudine has an effect on the production of testosterone.

**Observation** During spermatogenesis, cell junctions are formed between germinal cells and Sertoli cells.

Document 3 shows these junctions with or without adjudine.



Document 1



Document 2



- 4. Deduce the consequence of the addition of adjudine on the fertilizing capacity of the spermatozoa.
- Explain, based on what precedes, the mode of action of adjudine and its efficiency as a male contraceptive pill. 5.

### Exrecise 3 (5 pts)

There are drosophilae with wild type phenotype having red brick eyes and others with mutant phenotype having lemon yellow eyes (Zest phenotype). We try to localize the allele "Zest" involved in the character eye color. For this reason, we cross drosophilae that differ in the "eye color" phenotype, a character determined by a pair of alleles of a gene, red and zest. The results appear in document 1.

	Crossed individuals	Results of the cross   50% males with red eyes and   50% females with red eyes   50% males with zest phenotype   50% females with red eyes	
Cross 1	Female with red eyes x male with zest phenotype homozygous		
Cross 2	Female with zest phenotype x male with red eyes homozygous		
Cross 3	Male with red eyes x female with zest phenotype Irradiated homozygous by X rays non irradiated	50% males with zest phenotypes 50% - Females with red eyes Rare Females with zest phenotype	

### Document 1

- 1. Specify whether the allele responsible for zest phenotype is dominant or recessive.
- 2. Discuss by referring to crosses 1 and 2 of document 1, the chromosomal localization of the zest allele responsible for the "lemon yellow" eye phenotype.

The irradiation by X rays can, in some cases, provoke a loss of chromosome fragments in drosophila. In case of a loss of a fragment of one of the two chromosomes, the chromosome which does not present any loss forms a loop in the region where the other chromosome has a loss.

Document 2 shows a diagram of an observation of the two X chromosomes of one of the rare "zest" females obtained in the 3<sup>rd</sup> cross (document 1).

3. Justify , using the information provided by document 2, the appearance of the females with phenotype zest in the 3<sup>rd</sup> cross.

4. Make a chromosomal analysis verifying the results of the 3<sup>rd</sup> cross in document 1.



**Document** 2

### EXERCISE 4. ( 5 pts).

We aim to study the ovarian and uterine cycles by performing experiments on adult mammals.Document 1 illustrates the hypothalamo-pituitary complex implicated in the regulation of these cycles.

**Experiment 1**: The ablation of the anterior pituitary is followed by the atrophy of both the ovaries and the uterus along with the disappearance of the cycles.

**Experiment 2:** In animals submitted to the ablation of the pituitary gland and receiving regular injections of anterior pituitary extracts, we can observe a redevelopment of the ovaries and sometimes a reestablishment of the ovarian and uterine cycles. However in an ovariectomized animal, injected by anterior pituitary extracts, we never observe a reestablishment of the uterine cycle.

**Experiment 3:** Lesions of the posterior hypothalamus have the same effect as the ablation of the anterior pituitary





1. Interpret the results of each of the three experiments

**Experiment 4:** Bilateral ovariectomy provokes a hypertrophy of the pituitary gland followed by an abnormal high production of gonadotropic hormones. This experiment allows us to admit the existence of a feedback mechanism exerted by the overies on the production of FSH and LH. In order to determine the types of this feedback, an ovarieectomized female monkey receives ,for four periods of 15 days each, injections of ovarian hormones with different doses and compositions. For each period the average level of FSH and LH production is measured (document 2)

Pariods of Characteristics of		e injections	Plasmatic levels	
15 days	Composition	Plasmatic levels	of FSH in ng/ml	of LH in ng/ml
1	Estrogen	0	> 15	> 50
~ .*	Progesterone 0	0		
2	Estrogen	70 pg/ml	Around 6	Around 4
2 Progesterone	Progesterone	0		
3	Estrogen	300 pg/ml	1	1 1 10
Progesterone	0	Around 12	Around 40	
4	Estrogen	300 pg/ml	~ 1	
Progesterone	4 pg/ml	~4	< 3	

- 2. State the types of the feedback revealed in document 2. Justify the answer
- 3. Establish, by referring to the four experiments, a functional diagram showing the relations between the different organs involved in the regulation of the sexual cycles.

#### ANSWER KEY

#### Exercise 1 (5 pts.)

- 1. The allele responsible for disease is coded by dominant allele since affected individuals are present in all generation and since for each affected enfant one of the parents is also affected. (0.5 pts).
- 2. If the gene responsible for the disease is located on non homologous fraction of y", all males should be affected and no girls should be affected which is not the case. If the gene responsible for the disease is located on the non homologous fraction of X, the girl II-4 should take the XM from her father who is affected and she should be affected ,which is not the case. If the gene responsible for the disease is located on the homologous part of X and Y, the boy IV (16) and his sister IV (17) should take the Xn and Yn from their father to be normal, and it is not the case. Therefore studied the gene is autosomal. (1.0 pts.)
- I (1) is affected and gave birth to a normal child, so he is heterozygous and carries the normal allele masked by the allele of the anomaly: M/n. III (9) is affected and give two affected children and can give normal children so it may be :M/M or M/n. IV (4) is normal, and the allele recessive is expressed only in homozygous case recessivity is a citeria of purity, so it will be :n/n. (1.5 pts.)
- 4. Female III (9) is thus heterozygous, as the allele M is lethal, therefore it provides two types of alleles (M and n) in the proportions 1 to 2. For each Male III (10) is normal, so it is n/n and does not give gametes(M), so the female determines the proportion of affected children which becomes half.(0.5 pts)
- 5. The sequence of the normal allele presents the recognition site of the enzyme Pst1 which is CTGGCA/G, or a substitution mutation at the level of the polymorphic site, the fifth nucleotide is replaced by C. While this is no longer recognized by the enzyme Pst I, resulting in lack of the polymorphic site in the mutated sequence. (0.5 pts)
- 6. The fetus has in its electropherogram 3 bands as the bands of length 3 and 1 Kb corresponding to the normal allele presenting the polymorphic site, and the band length 4 Kb corresponding to the mutant allele, so the fetus is a heterozygous patient. (M/n). (1.0 pts)

### Exercise 2 ( 5 pts.)

- Before treatment with adjudine, the fertility rate in male rats is 100%. On the other hand, the rats treated rates drops to 50% at 42<sup>nd</sup> day, and becomes nul at 56 days after treatment. This indicates that adjudine lowers male fertility and even made him sterile. (1 pts.)
- 2. The pill is considered as a contraceptive pill if it reduces or blocks fertilization. Since adjudine decreases the fertility and even blocks it in males, thus it is qualified as a male contraceptive pill. (0.5 pts.)
- 3. Both lots of rats which are treated with placebo or adjudine show similar variation of the level of testosterone. With placebo, the level of testosterone decreases from 4 ng/ml to 2.5ng/ml between zero and twenty days. Also this level decreases from 3 ng/ml to 2ng/ml from day 28 till day 35 with adjudine. Testosterone level increases from 2.5 till 5 ng/ml from day 20 to day 80. Also this level increases from 2 ng/ml to 4 ng/ml from day 35 to day 70. This shows that adjudine has no effect on the production of testosterone. (1.5 pts.)
- 4. Document 3 shows that without adjudine, the junction between germinal cells and fertoli cells are only broken when the spermatozone is mature. On the other hand, this junctions are broken before the maturation of spermatozone in the presence of adjudine. Since an immature spermatozone is a non fertilizing spermatozone, thus adjudine reduces the fertilizing capacity of the sperm cell. (1.0 pts).
- 5. Adjudine rupture the junctions between germinal cells and fertoli cells early (document 3). This rupture blocks the function of the certoli cell and leads to the production of immature and infertile sperms, therefore adjudine can be used as a contraceptive pill. On the other hand, document 2 shows that adjudine does not affect the

secretion of testosterone so man can use it without affecting his sexual activity. But since spermatogenesis lasts for 74 days and document 1 shows that at 42 days, 50% of the spermatozoa are mature and the efficiency of adjudine reaches 100% at 56 days of ist administration, hence adjudine is a contraceptive pill that blocks the maturation of the spermatozoa and its efficiency is not completed until after 56 days of its administration. (1 pt).

### Exercise 3. ( 5 pts)

- The first cross between true breeding line parents gives 100% individuals with red eyes, where 50% are males and 50% are females. Only the allele "red" is expressed in the phenotype of hybrids then this allele is dominant over the recessive allele "zest", the allele "red" is symbolized by R and the allele "zest" is symbolized by z. (1.0 pts).
- 2. Document 1 shows that a cross and its inverse (crosses 1 and 2) give different results: 50% males with red eyes and 50% females with red eyes and 50% are males with "zest" eyes. These results indicate that the transmission of alleles responsible for these phenotypes is sex linked. In addition, document 1 shows that the phenotype of the male descendents obtained from different crosses has always the same phenotype as their mother. This indicates that the spermatozoa produced by the father carrying chromosomes Y have no effect on the phenotype of the male off springs. Only X chromosomes present in the ova seem to determine the phenotype of male off springs. The allele "zest" involved in the eye color is therefore located on the non homologous segment of X chromosome. **OR**

Document 1 shows that cross 1 and the inverse (cross 2) give different results: 50% males with red eyes and 50% females with red eyes in the first cross which is different than the results obtained in cross 2 where 50% are females with red eyes and 50% are males with zest phenotype. These results indicate that the transmission of alleles responsible for these phenotypes is sex linked. If the allele is carried by the non homologous segment of Y chromosome, the transmission occurs from father to son; in the second cross the obtained male descendents have the zest phenotype which is unlike their father's phenotype who has red eyes. Then the allele "zest" is not located on non-homologous segment of Y chromosome but rather on the non-homologous segment of X chromosome. (1.5 pts.)

3. The third cross shows that when males (R) are irradiated by X rays, female off springs are the only ones who are affected by the irradiation: the proportion of males ( 50%(Z) ) is identical to that obtained in the previous cross, while the proportion of females varies, where few females of zest phenotype (Z) appear. These results confirm that the allele zest (z) is located on non-homologous segment of chromosome X. In this cross, the irradiated males have produced some spermatozoa carrying an X chromosome with the dominant allele R; bearing in mind that the irradiation by X-ray can cause loss of chromosome fragmant. The phenotype of the individual after fertilization is directly determined by the allele carried by the maternal X-chromosome. This is because the female of phenotype zest is homozygous and not irradiated. This explains the appearance of the fema; le off springs with zest phenotype. (1.5 pts.)

Gametes:			
Table of cross			
		Non-irradiated gametes, frequent	Gametes irradiated less frequently
Gametes produced by O Gametes produced by Q	9	R	X
N N N N N N N N N N N N N N N N N N N	× Q	R CON	Z Auri X
	50 % (2)	Q [R] very frequent	<b>9</b> [Z] less frequent

### Exercise 4 ( 5 pts.)

1. Atrophy of ovaries and utiris with the disappearance of the cycles occur after ablation of the anterior pituitary. This indicates that the anterior pituitary controls the ovarian and utirine cycles.

After ablation of anterior pituitary and injection of its extracts, redevelopment of the ovarian and uterine cycles occur, however in an ovariectomized animal, these injections do not allow the reestablishment of the utirne cycle. This indicates that the utirne cycle is controlled by the ovarian cycle.

Lesions of the posterior hypothalamus will stop the ovarian and utirne cycles. This indicate that the hypothalamus controls via the anterior pituitary the ovarian and pituitary cycles. (1.5 pts).

2. In the first experiment, there is anegative feedback since estrogen and progesterone are low, while FSH and LH are high.

In experiment 2 ,a positive feed back occurs. Both estrogen ,FSH and LH are increasing.

In experiment 3 a positive feed back occurs, where estrogen is very high, and FSH and LH are high too.

In experiment 4 a negative feed back occurs, where estrogen is high, and progesterone is high, while FSH and LH are low. ( use numbers given in document 2). ( 2.0 pts.)

3. Scan from book (1.5 pts)