**Genetics Exercises**
**M1 Genotype-Phenotype**
**September 2024**

1. The term « gene » can have several meanings (Table 1).

Table 1. Definitions of the Term "Gene"

| |
|---|
| **A) Genes IX (Lewin, 2006, p. 845 and 852, Glossary)**<br>A gene is the segment of DNA specifying a polypeptide chain; it includes regions preceding and following the coding region (leader and trailer), as well as intervening sequences (introns) between individual coding segments (exons). |
| **B) Quantitative Genetics (Falconer & Mackay, 1996, pp. 1–2)**<br>A gene is a unit of inheritance that is transmitted from parents to offspring. Suppose for simplicity that we were concerned with a certain autosomal locus, A, and that two different alleles at this locus, A1 and A2. [...] Each A1A1 individual contains two A1 genes. |

Choose which definition(s) have been implicitly used in the following sentences:
a. Many of the **genes** not targeted by our library encode olfactory receptors that are unlikely to be cell-essential. (Blomen et al., Science 2015)
b. These Polycomb-repressed domains harbour **genes** encoding key developmental transcription factors, whose misexpression can have detrimental consequences in differentiated cells. (Boettiger et al., Nature 2016)
c. There has not yet been sufficient time for the corresponding resistance **genes** to spread into environmental reservoirs. (Versluis et al., Scientific Reports 2015)
d. Parkinson Disease is generally considered a multifactorial disorder that arises owing to a combination of **genes** and environmental factors.(Hou et al., Nature Reviews Neurology 2015)
e. ARID1B and ARID2 participate in widespread cooperation to repress hundreds of **genes**. (Raab et al., PLoS Genetics 2015)
f. Simulations reveal that hybrid populations rapidly and frequently become isolated from parental species by fixing combinations of **genes** that hinder successful reproduction with parental species. (Schumer et al., PLoS Genetics 2015)
g. Higher **gene** flow in sex-related chromosomes than in autosomes during fungal divergence. (Hartmann et al., Mol Biol Evol. 2019)

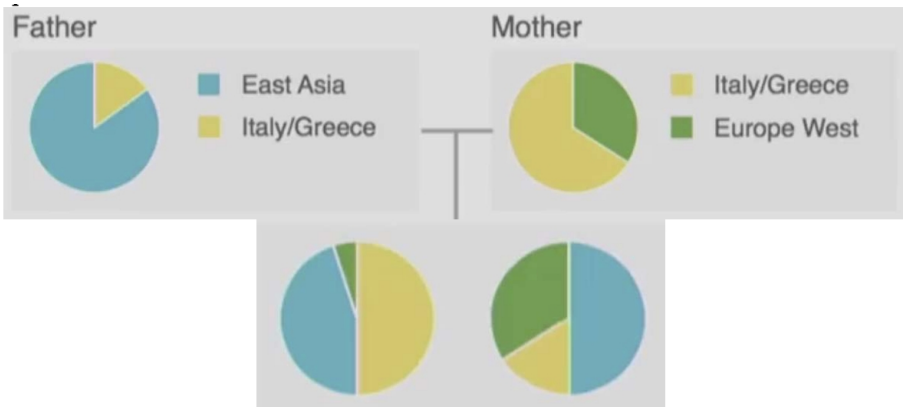
2. What are the following numbers?
a. Number of telomeres in a cell in G1 phase if its karyotype is 2n=16
b. Number of telomeres in a cell in G2 phase if its karyotype is 2n=16
c. Size of the human genome in base pairs
d. Number of recombination event per chromosome
e. % identity between human and chimpanzee DNA
f. Number of genes in the human mitochondrial genome
g. Number of different amino acids in the genetic code table
h. Total number of possible codons
i. Average number of de novo mutations in a person (germline-mutations) compared to his parents

3. How many alleles of a given gene can be found in a haploid individual? in a diploid individual? in a population of diploid organisms after a chemical mutagenesis? in a natural population of diploid organisms?

4. Two snapdragons, one red and one white, are crossed. Their progeny is pink. What do you conclude? How many genes are involved in the color difference between the two parents?

5. One albino pigeon is caught in the Luxembourg garden and another in Central Park. The albino phenotype is caused by a recessive allele. What can you do to determine whether the same gene is responsible for the albino phenotype of both pigeons?
Unfortunately both are males. What can you propose instead?

6. A father, mother and their two children sent their DNA to ancetry.com. Here are the results they obtained:




Why are the two children's results different even though they have the same parents?

7. A woman recently learnt that her aunt got tested because she had breast cancer and that unfortunately her aunts has a *BRCA1* allele which increases susceptibility to breast cancer. What is the probability that this woman also received this *BRCA1* allele? Supposing this woman were your friend, what would you advise her to do?

8. A butterfly species exists in two forms, "normal" (N) and crenelated (C). Five butterfly pairs are mated:

| | Parent phenotypes | | F1 | |
|---|---|---|---|---|
| cross | Males | Females | Males | Females |
| #1 | N | N | 100% N | 100% N |
| #2 | C | C | 100% C | 100% C |
| #3 | C | N | 50% N, 50% C | 50% N, 50% C |
| #4 | C | N | 100% C | 100% C |
| #5 | N | C | 100% C | 100% N |

Write the genotypes of the parents of each cross and the mode of inheritance and of phenotypic expression of the alleles. (NB: The chromosomal basis for sex determination is not the same in all organisms.)

9. Glass Gem corn is a stunning variety selected by Carl Barnes, a part-Cherokee farmer and breeder, from several traditional corn varieties. Explain how a multicolor corn cob can be produced, containing more than 10 different colors in a cob, given that kernel colors are genetically determined.
Note: each kernel is the result of a double fertilization. The albumen of the corn kernel, which gives the color, is triploid: it results from the fusion of a male gamete with two female gametes.

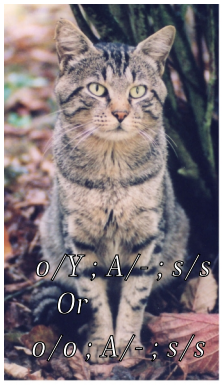
10. Genetic lottery. What are the random phenomena between parents and child that make the transmission of characters a “genetic lottery”?

11. In a black, diploid, beetle species, loss-of-function mutant lines in four genes, *A*, *B*, *C*, *D*, as well as double and triple mutant combinations are available. They show the following phenotypes:

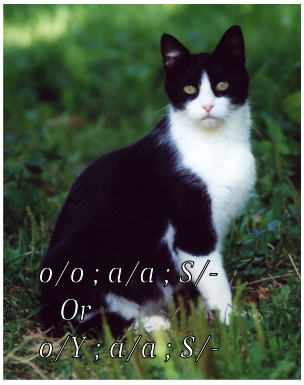
| | | |
|---|---|---|
| *A*: black | *A; D*: albino | *A; B; C*: yellow |
| *B*: brown | *C; D*: yellow | *A; B; D*: albino |
| *C*: yellow | *A; C*: yellow | *A; C; D*: albino |
| *D*: black | *B; C*: yellow | *B; C; D:* yellow |
| | *A; B*: brown | |

Draw the genetic and biochemical pathways for pigment synthesis.
Which pigment accumulates in:
- animals of genotype *B; D?*
- in the F1 progeny of A and D animals?

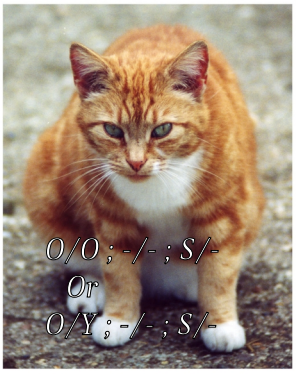
12. The main coat color phenotypes in cats are due to three genes: *Orange* (*O* and *o* alleles) on the X chromosome, *Agouti* (*A* and *a*) and *white spotting* (*S* and *s*) on two autosomes. Here are 10 different phenotypes and their associated genotypes. "-" means that it can be either allele.












What is the relationship between *white spotting* alleles and the white color?
Explain the genotype-phenotype relationship for each locus and the interactions between loci.
The last cat is a tortoiseshell cat, with orange and black spots. This coat color is only found in females. Explain how the tortoiseshell coat is produced.

Here is a mother and its two kitten. Infer the color of the father (assuming there is only one father).

13. A mutant *Drosophila* strain has no eyes. An eyeless female is crossed with a male of a wild-type line and F1 flies all have eyes. The F1 males are then backcrossed to the eyeless mother. The F2 generation displays a total of 87 flies with no eyes and 92 flies with normal eyes. What can you conclude about the genetic basis for the loss of eye? What can you conclude about the number of genes necessary for eye formation?

14. A line of *Drosophila* flies without eyes obtained after mutagenesis is crossed to a wild-type line showing a mean of 108 (+/- 5) ommatidia per eye. The F1 generation displays a mean of 35 (+/-18) ommatidia per eye. What can you conclude?
What can you expect in the F2 generation if a single locus is involved?

15. A strain of flies with no hairs on part of the anterior legs is isolated from the Orsay orchard. It is crossed to a wild strain that was isolated on the Place Monge market, which shows a stable mean of 10.8 (+/- 0.5) hairs. The F1 generation displays a mean of 3.5 (+/-1.8) hairs. What can you conclude?
What can you expect in the F2 generation?

16. Draw a cross between two parents, each homozygote for different alleles (a1,a2 and b1,b2) at two loci, *a* and *b*. Which generation may present the first recombined alleles between the two loci?
What will be the possible genotypes of the second generation (F2) after a cross among F1s?
Calculate the frequency of the different genotypes of F2 individuals:
4.1 if *a* and *b* are not linked, and
4.2 if they are located 1 cM apart on the same linkage group.

## Problem – Achondroplasia

Achondroplasia is the most common form of dwarfism in humans. In Texas, out of 2,042,554 births reported between 1996 and 2002, 79 babies were diagnosed with achondroplasia.

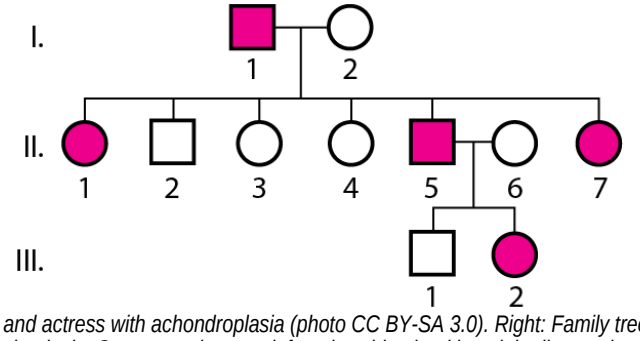



*Figure 1. Left: Mimie Mathy, French comedian and actress with achondroplasia (photo CC BY-SA 3.0). Right: Family tree of a family with members affected by achondroplasia. Square: male, round: female, white: healthy, pink: diseased.*

Figure 1 shows a typical genealogy of a family affected by achondroplasia.

**Question 1.** Assuming that a single gene with two alleles (healthy allele S and affected allele A) is involved, what type of dominance/recessivity can be invoked? Is it possible that the gene is carried by the Y chromosome? And on the X chromosome? Justify your answers.

Achondroplasia is caused by a defective allele of the *FGFR3* gene, which is carried on chromosome 4. Let *A* be the allele associated with achondroplasia and *S* the wild-type allele. The *AA* genotype is lethal: fetuses carrying this genotype do not survive to birth. Individuals are therefore *SS* or *AS* genotypes. Achondroplasia can therefore be considered a disease.

To better identify the genetic causes of this disease, researchers looked at children with achondroplasia whose parents were healthy. A parental genetic test using whole-genome sequencing was first carried out to confirm the biological link between parents and children.

**Question 2.** Explain the principle of genetic parental testing, as carried out by the researchers for a child suffering from achondroplasia.

The *FGFR3* gene was sequenced in 113 achondroplastic individuals with healthy parents and in 147 unaffected individuals from the same families.

| Mutations found in *FGFR3* | Number of cases in achondroplastic patients | Number of cases in healthy individuals |
|---|---|---|
| c1138G>A | 110/113 | 0/147 |
| c1138G>C | 3/113 | 0/147 |

*Table 1. Mutations observed in tested individuals.*

**Question 3.** What information can you deduce from Table 1? Based on these results, how can you rule out the hypothesis that achondroplasia is linked to a mutation that suppresses the function of the *FGFR3* gene?

A peculiarity of this condition is that the older the father, the greater the probability that he will have a child with achondroplasia.

**Question 4.** Propose a hypothesis explaining why the risk of achondroplastic dwarfism increases with father age.