Lesson 07: Mutations

1. Definition And origins mutations

The mutations are **the changes** of sequences of genetic material (DNA).

They can be produce in any region of genome. However, we observed only phenotypic changes of the body if a mutation product in **there sequence of a gene** (coding sequence).

Fortunately, most genes are relatively stable and mutation is a rare event. Mutations result in the appearance of different versions of the same gene (alleles).

Certain families of genes control the development of organisms and their organisational plan: developmental genes. Mutations in these genes can lead to the appearance of new organisational plans and new species!

The nucleotide sequence, located at the same place on the chromosome (same locus), is modified, resulting in the synthesis of a different protein with different (or even non-existent) properties, leading to a change in the coded character.

Mutations are the source of genetic variability; they are stable hereditary changes that may or may not be passed on:

- **Organizations asexual** (with clonal reproduction): all mutation id immediately transmitted.

- **Organizations exually reproducing organisms:** there are two cases:

  - If the mutations affect germ cells, they are probably passed on to the next generation.

  - If the mutations affect somatic cells, they will never be passed on to the next generation.

- Origin of mutations (causes) There are two main origins:

1.1 Spontaneous mutation

Mutation that occurs during cellular activities such as cell division, mainly DNA replication and normal cell repair. A random phenomenon with no apparent cause, characterised by its very rare frequency of occurrence.

1.2 Induced mutation

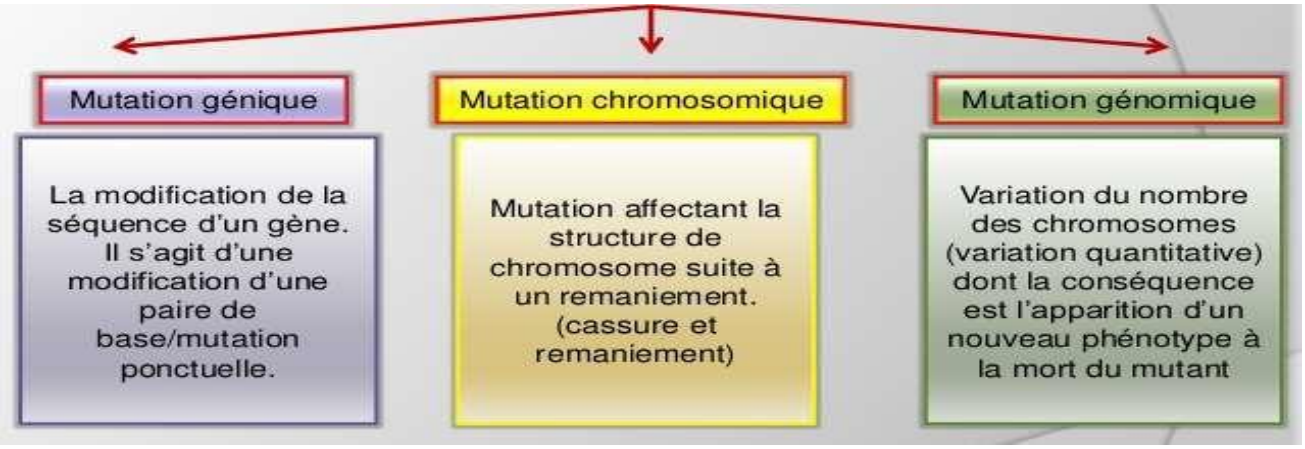
Mutation that occurs as a result of treatment with a mutagenic agent or by the environment, the mutation rate is usually higher. There are two types of mutagen:

 Physical mutagenic agent: e.g. X-rays, UV radiation.

 Chemical mutagens: chemicals that interact with DNA to create base changes. They can be base analogues, base modifiers or intercalating agents.

2. Types of the mutations

According to The level of structure reached, we distinguished three types of the mutations :



2.1. Gene mutation (point)

Kind of mutation	**Consequence**	**Consequences At level of protein (Phenotype)**
- Substitution - Inversion	Silent	No modification (same amino acid)
	Missense	A acid amine modified : mutant protein (inactive, less effective Or thermosensitive)
	Nonsense	- A acid amine replaced by A codon STOP : protein incomplete (non -functional) - Or the opposite : protein more long (non - functional)
- Addition (insertion) - Duplication - Deletion	Gap of frame reading	- Protein amended In its length And In its sequence (non -functional) - Early appearance of a STOP codon
- Addition of triplet - Deletion of triplet	Gap of frame reading	- Addition / deletion of acids amino acids : - Protein amended In its length And In its sequence (non -functional) - Appearance anticipated of a STOP codon

Gene mutations affect a single gene. There are several classes:

2-1- Base substitutions

This is a change of a single nucleotide in DNA:

- **A transition:** Replacement of one purine by another purine, or of one pyrimidine by another pyrimidine

- **A transversion :** A purine is replaced by a pyrimidine or vice versa.

2-2- Insertions and deletions

- Insertion is the addition of one or more pairs of nucleotides.

- Deletion is the loss of one or more pairs of nucleotides.

Insertions and deletions in a protein-coding sequence can cause frameshifts. These mutations typically change all of the amino acids encoded by the nucleotides downstream of the mutation in the gene, so they have very pronounced effects on the phenotype. However, an insertion or deletion of three or a multiple of three nucleotides will not change the reading frame. These mutations are called in-frame insertions or deletions.

2-3- Amplification of trinucleotide repeats

These mutations consist of an increase in the number of copies of a three-nucleotide repeat motif. Example: Fragile X syndrome is associated with mental retardation that results from an increase in the number of repeats of a trinucleotide CGG motif beyond a certain threshold. Sometimes, fragile sites are susceptible to breakage.

3- Phenotypic effects of mutations

The phenotypic effect of a mutation is defined by comparison with the wild-type phenotype:

- Direct mutation: changes a wild-type allele.

- Reverse mutation (reversion, or back mutation): restores the wild-type allele from a mutant allele.

- Missense mutation: a base substitution that results in the incorporation of a different amino acid into a protein.

- Nonsense mutation: changes a sense codon into a nonsense codon. If a nonsense mutation occurs at the beginning of a gene's coding sequence, the corresponding protein will be seriously shortened and most likely nonfunctional.

- Silent mutation: creates a different DNA sequence, but which specifies the same amino acid as the wild-type sequence, due to codon redundancy.

- Neutral mutation: a missense mutation that changes the amino acid sequence of a protein without altering its function. Neutral mutations replace one amino acid with another of similar chemical nature or they affect an amino acid that has little effect on the function of the protein.

- Loss-of-function mutation: causes the complete or partial absence of a function. These mutations can alter the structure of a protein and render it partially or completely inactive. They can also occur in regulatory regions that affect the transcription, translation, or maturation of a protein.

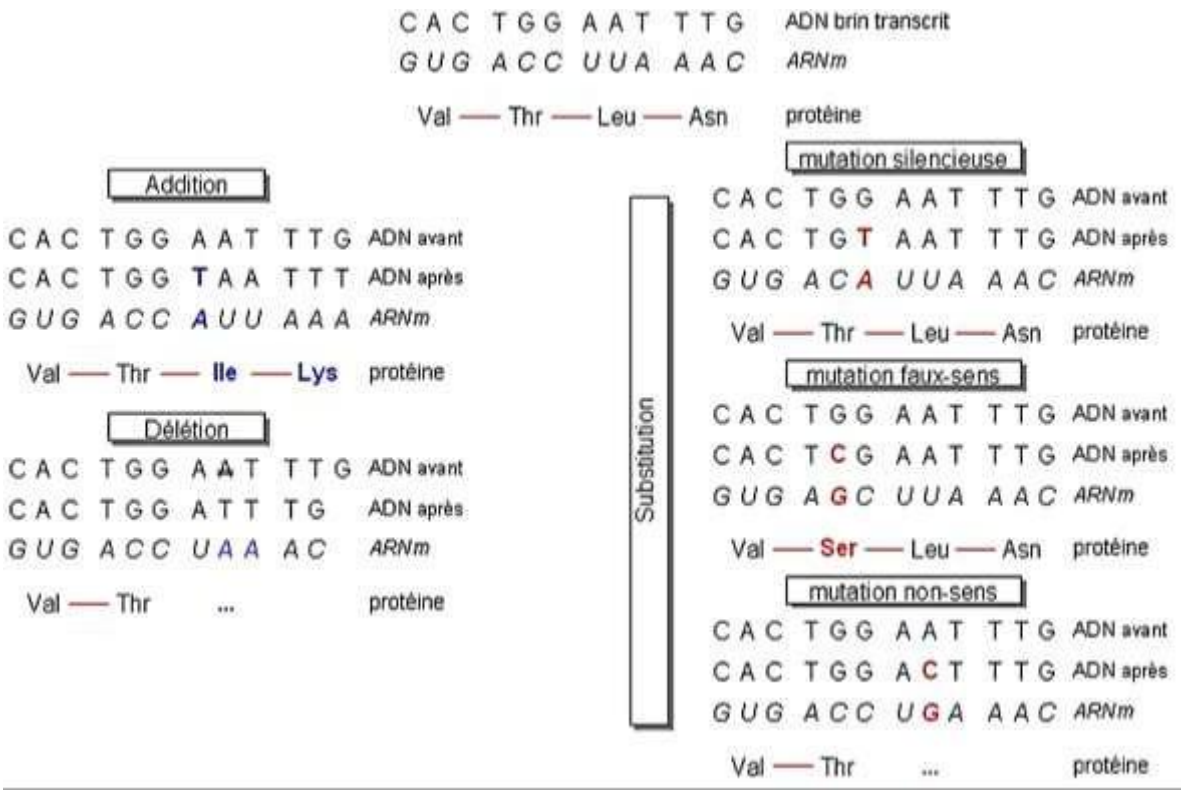
- Gain-of-function mutation: causes a new trait to appear or causes a trait to appear in an inappropriate tissue or at an inappropriate time in development. Its effect may affect the

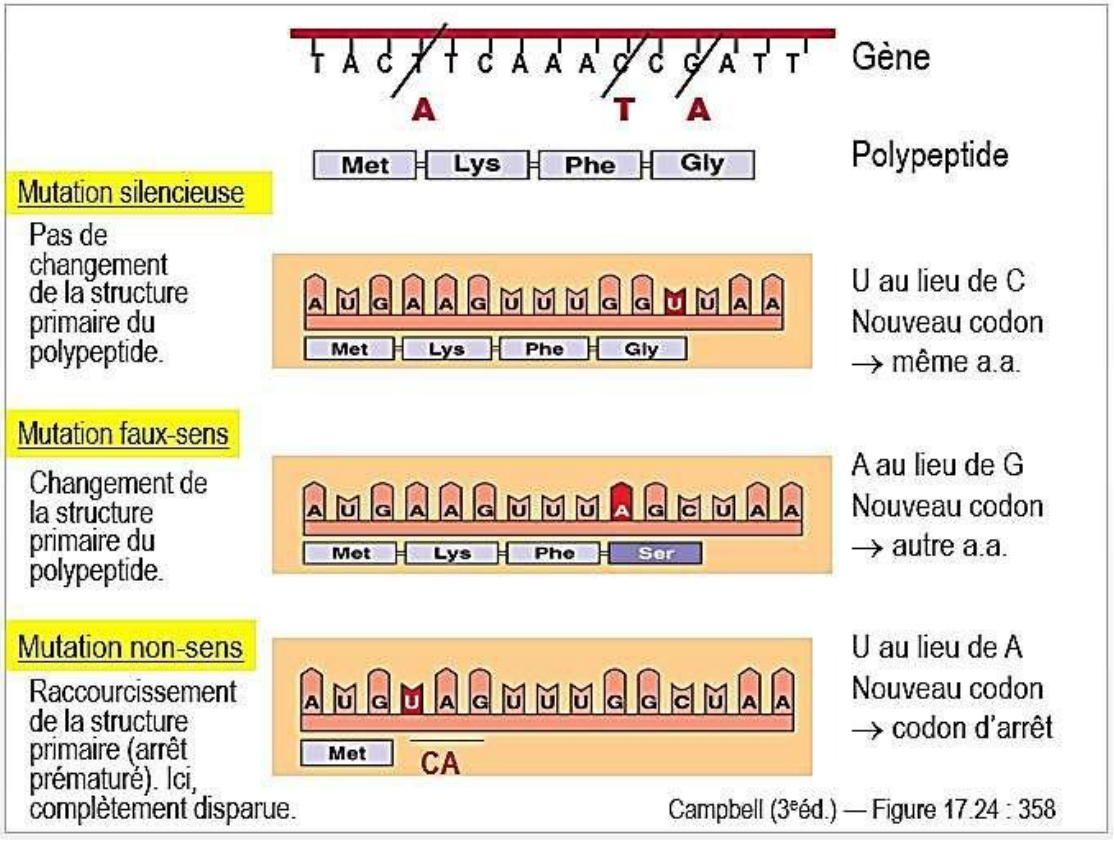
viability of the mutant organism

- Conditional mutation: is only expressed under certain conditions

- Lethal mutation: causes premature death of the affected organism

- Suppressor mutation: masks or eliminates the effect of another mutation. This type of mutation is distinct from a reversal mutation which restores the original wild-type sequence. A suppressor mutation occurs at a different site than the original mutation.




T A C T T C A A A C C G A T T
Gène
A T A
Met Lys Phe Gly
Polypeptide
Mutation silencieuse
Pas de changement de la structure primaire du polypeptide.
A U G A A G U U U G G U U A A
Met Lys Phe Gly
U au lieu de C
Nouveau codon
→ même a.a.
Mutation faux-sens
Changement de la structure primaire du polypeptide.
A U G A A G U U U A G C U A A
Met Lys Phe Ser
A au lieu de G
Nouveau codon
→ autre a.a.
Mutation non-sens
Raccourcissement de la structure primaire (arrêt prématuré). Ici, complètement disparue.
A U G U A G U U U G G C U A A
Met
CA
U au lieu de A
Nouveau codon
→ codon d'arrêt
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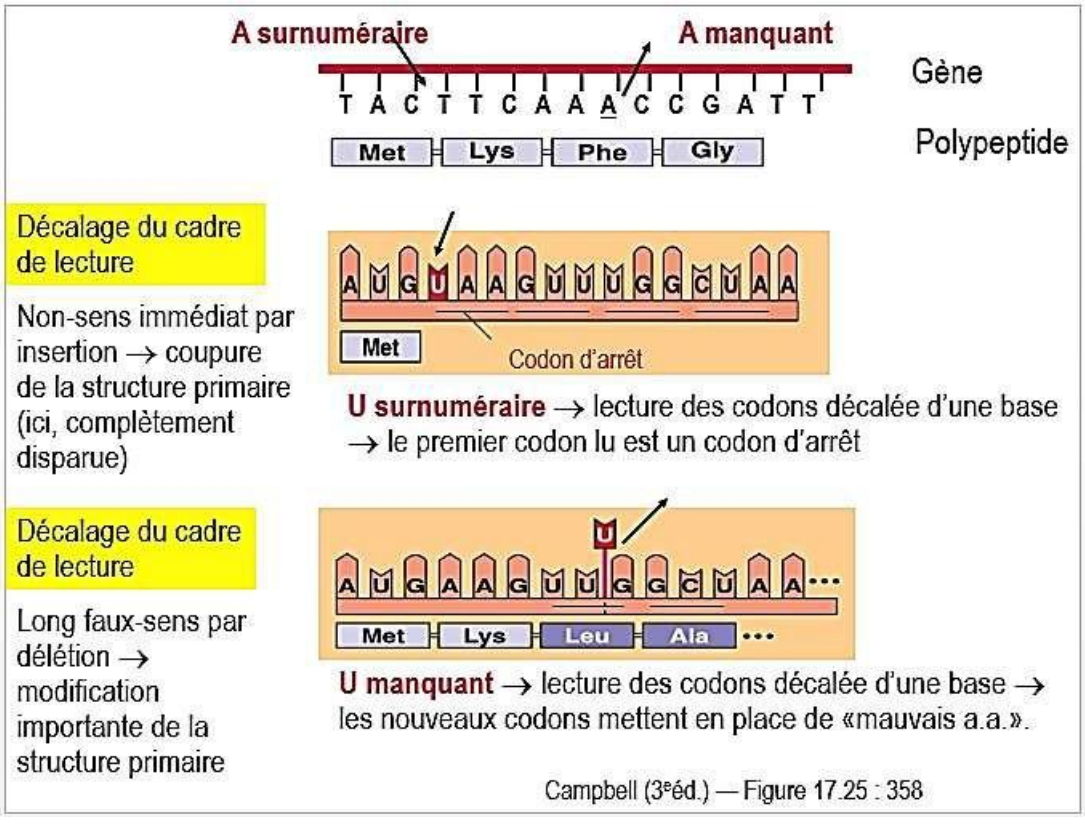
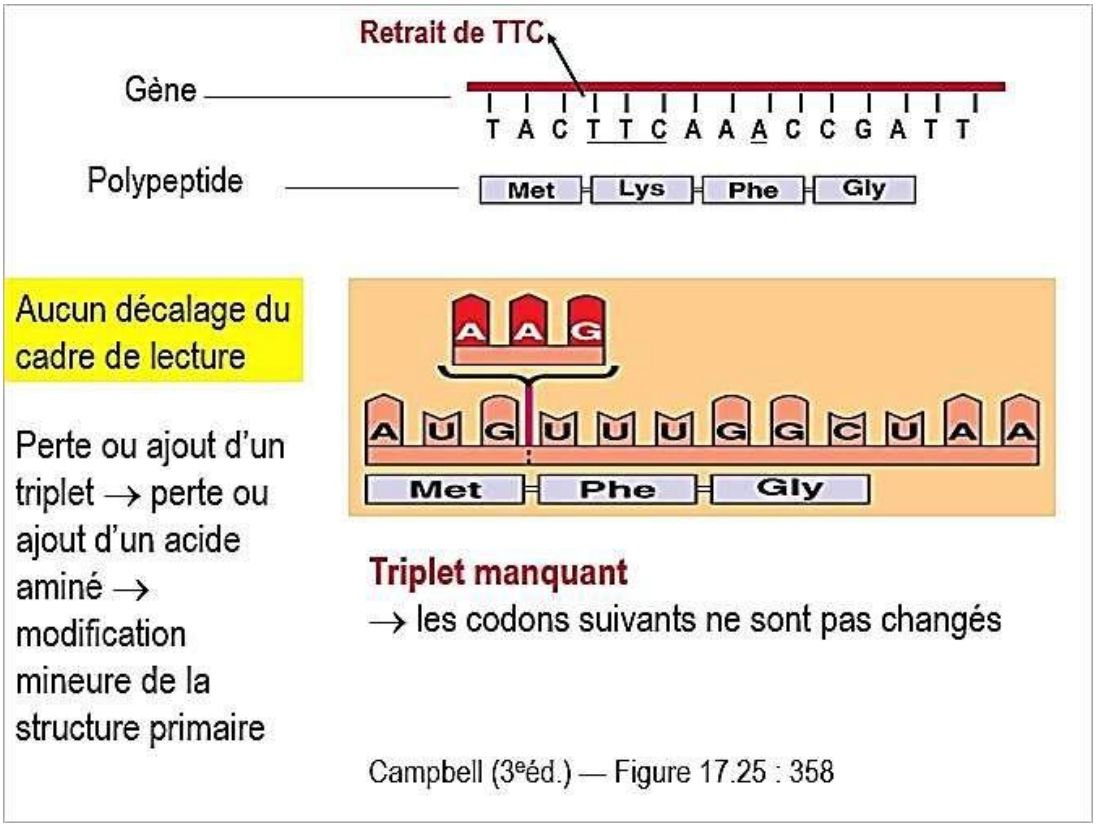

A surnuméraire
A manquant
T A C T T C A A A C C G A T T
Gène
Met Lys Phe Gly
Polypeptide
Décalage du cadre de lecture
Non-sens immédiat par insertion → coupure de la structure primaire (ici, complètement disparue)
A U G U A A G U U U G G C U A A
Met
Codon d'arrêt
U surnuméraire → lecture des codons décalée d'une base → le premier codon lu est un codon d'arrêt
Décalage du cadre de lecture
Long faux-sens par délétion → modification importante de la structure primaire
U
A U G A A G U U G G C U A A ...
Met Lys Leu Ala ...
U manquant → lecture des codons décalée d'une base → les nouveaux codons mettent en place de «mauvais a.a.».
Campbell (3eéd.) — Figure 17.25 : 358



Aucun décalage du cadre de lecture

Perte ou ajout d'un triplet → perte ou ajout d'un acide aminé → modification mineure de la structure primaire

Triplet manquant

→ les codons suivants ne sont pas changés

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