Mutations

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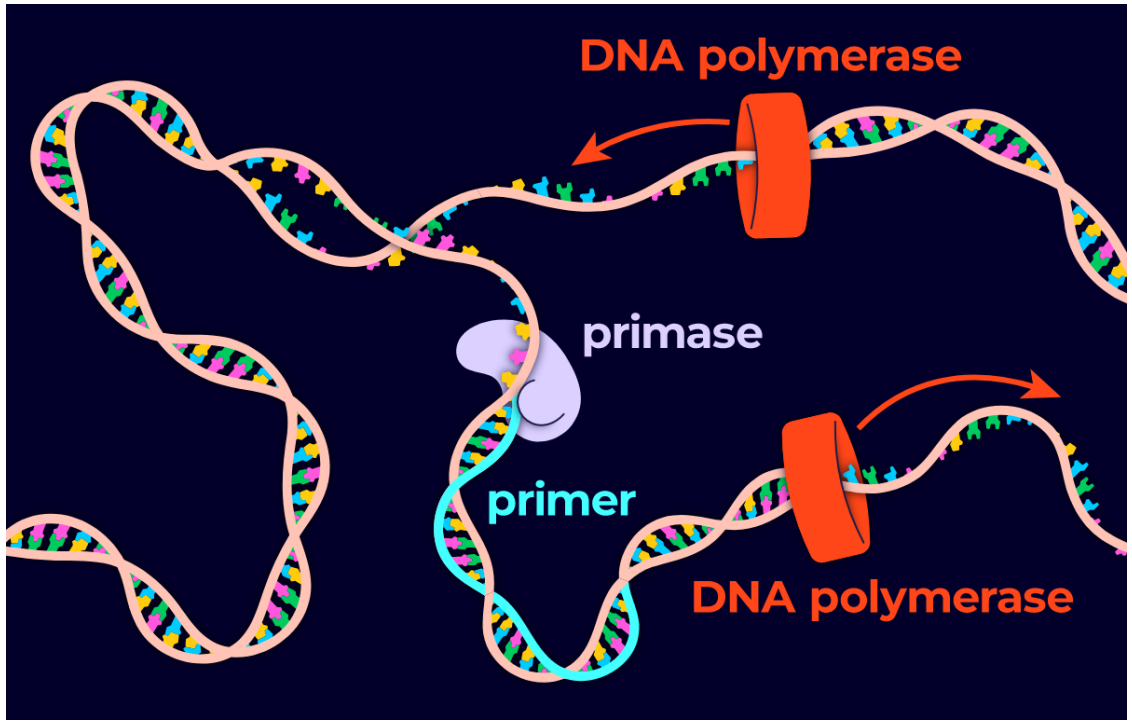
Definitions

- Mutations: Permanent changes in a DNA sequence.
- Mutagen: Physical agent or a chemical reagent that causes mutation.
- Mutagenesis: Process of producing a mutation. It may be spontaneous or induced.

Causes of mutations

1. DNA polymerase errors:

Despite of the high degree of fidelity of DNA polymerases, some mutations could occur **during DNA replication** because not all the replication errors or damage are detected and repaired by proofreading.



Causes of mutations

2. Spontaneous changes

DNA undergoes spontaneous changes that lead to mutations if they are not repaired.

Spontaneous changes

a) Deamination of cytosine to uracil.

If this is not repaired before replication, adenine pairs with the template strand containing uracil (adenine replaces guanine), this explains why DNA contains thymine but not uracil.

If DNA contains uracil in its structure, this type of mutation will not be detected and will not be corrected which will produce serious mutations.

Spontaneous changes

b) Spontaneous depurination.

Purines are less stable under normal cellular condition than pyrimidines.

The glycosidic bonds that link **purines** to **the sugar phosphate backbone** of DNA are often broken, **if these purines are not replaced before replication**, any base may be added to complement the missing base during replication.

Chemical mutagens

Many chemicals alter DNA bases or the structure of DNA

1. **Nitrous acid** (HNO_2 deaminating compound) can promote the change of guanine to xanthine; adenine to hypoxanthine and cytosine to uracil.
2. Alkylating agents such as **dimethyl sulfate**

- can cause methylation of guanine into 7 methyl guanine
- can disrupt phosphodiester bond resulting in strand break
- can interact covalently with both strands, creating intrastrand bridges.

Chemical mutagens - Cancer

- Alkylation is the transfer of an **alkyl group** from one molecule to another.
- Alkylation of DNA is used in chemotherapy to damage the DNA of cancer cells.
- An alkylating antineoplastic agent is an alkylating agent used in cancer treatment that attaches an alkyl group (C_nH_{2n+1}) to DNA.
- The alkyl group is attached to the guanine base of DNA, at the number 7 nitrogen atom of the purine ring.

Chemical mutagens - Cancer

- Since cancer cells, in general, proliferate faster and with less error-correcting than healthy cells, **cancer cells are more sensitive to DNA damage** - such as being alkylated.

- Alkylating agents are used to treat several cancers. However, they are also toxic to normal cells (cytotoxic) particularly cells that divide frequently, such as those in the gastrointestinal tract, bone marrow, testicles and ovaries, which can cause loss of fertility.

Radiation damage

- Ultraviolet including sun light and X-ray irradiation are also effective means of producing mutations.
- Radiation energy absorbed by DNA induces formation of ionized forms of bases.
- These ionized forms can not pair with the normal complementary base partner. Instead, they form atypical base pairing as the formation of dimers between adjacent pyrimidine bases e.g. thymidine dimer.

Classification of mutation types

Mutations in the structure of genes can be classified as:

1. **Large scale mutations** in chromosomal structure
2. **Small scale mutations** affecting a small gene in one or a few nucleotides

Types of Small-scale mutations

- Point mutations
- Addition or deletion of nucleotides

Point mutations

The most common type of mutations. Mutation occurs due to change in a **single** base.

- **Transition** a purine is changed into another purine or a pyrimidine is changed into another pyrimidine.

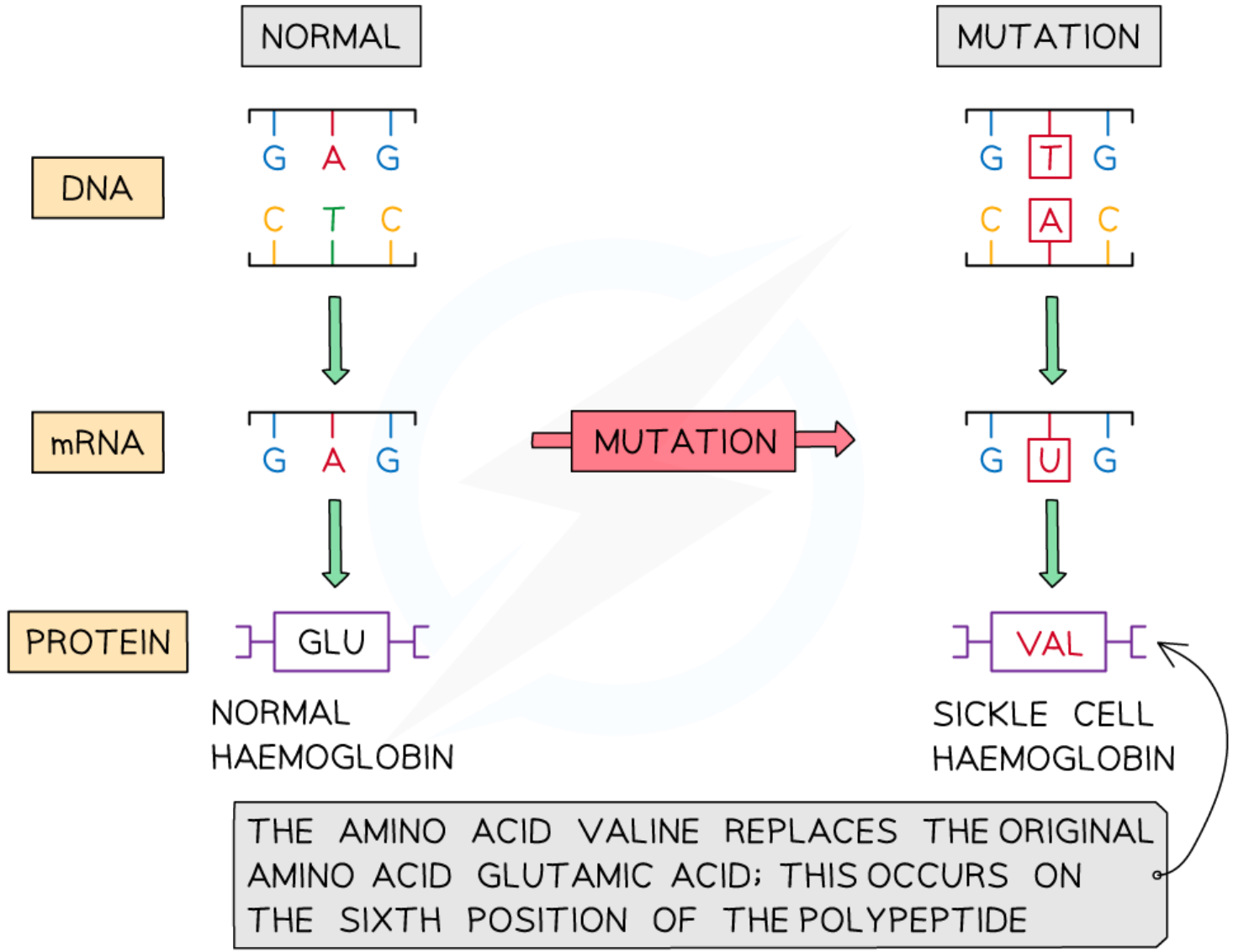
- **Transversion** a purine is replaced by a pyrimidine, or a pyrimidine is replaced by a purine.

Effects of point mutations:

❖**Missense mutation** occurs if the resulting codon codes for a different amino acid and this leads to abnormal protein as in sickle cell anemia.

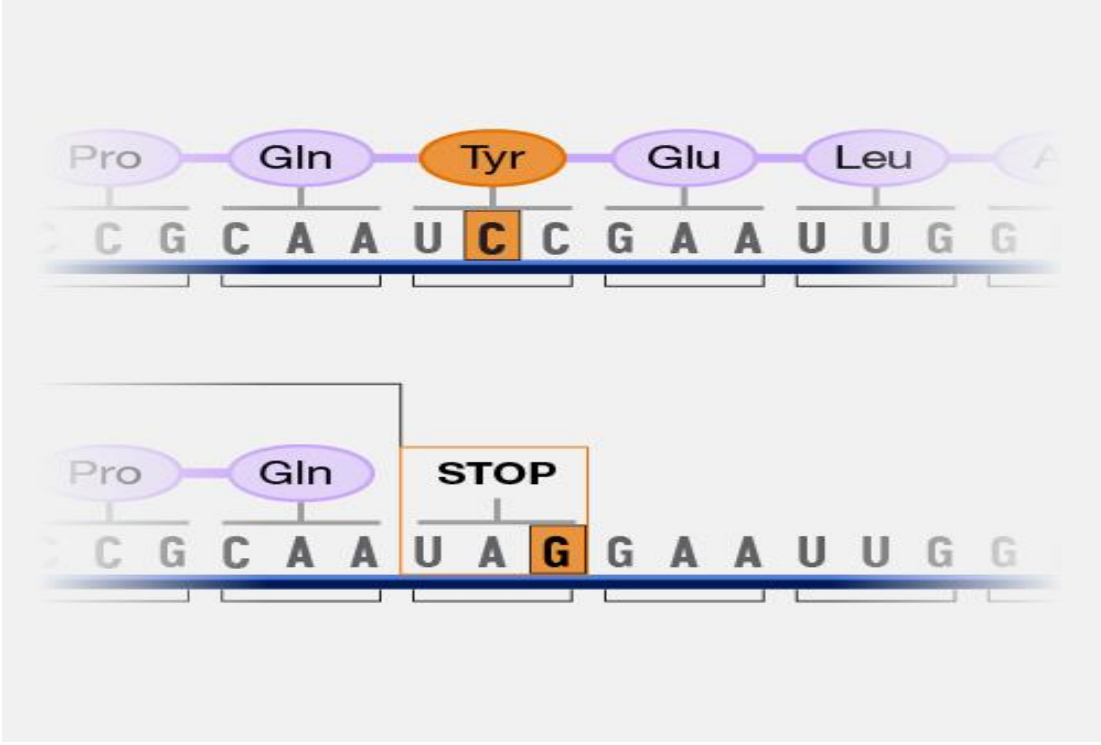
- Hemoglobin S (HbS)/sickle cell hemoglobin:

  Genetic disease caused by replacement of glutamic acid in the 6th position of beta chain by valine.



Nonsense mutation

- Will result in stop codon with premature termination of the translated polypeptide which is usually nonfunctional e.g. thalassemia's.

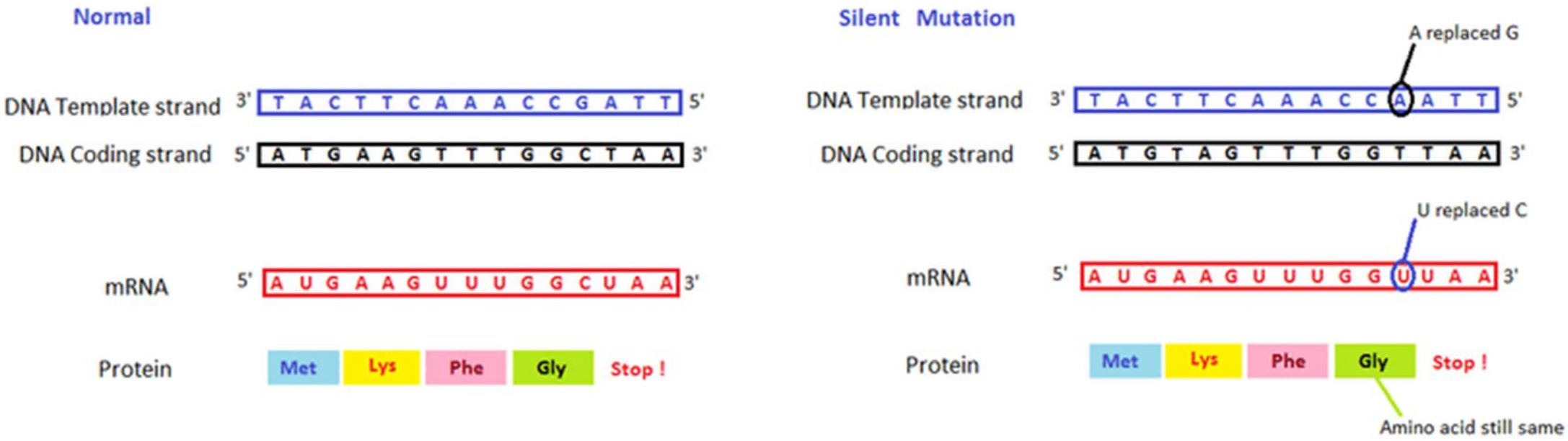


Silent mutation

This occurs if the **resulting codon** still **codes for the same amino acid** due to degeneracy of the code.

If the mutation affects nonessential DNA or if it has a negligible effect on the function of a gene, it is known as a **silent mutation**.

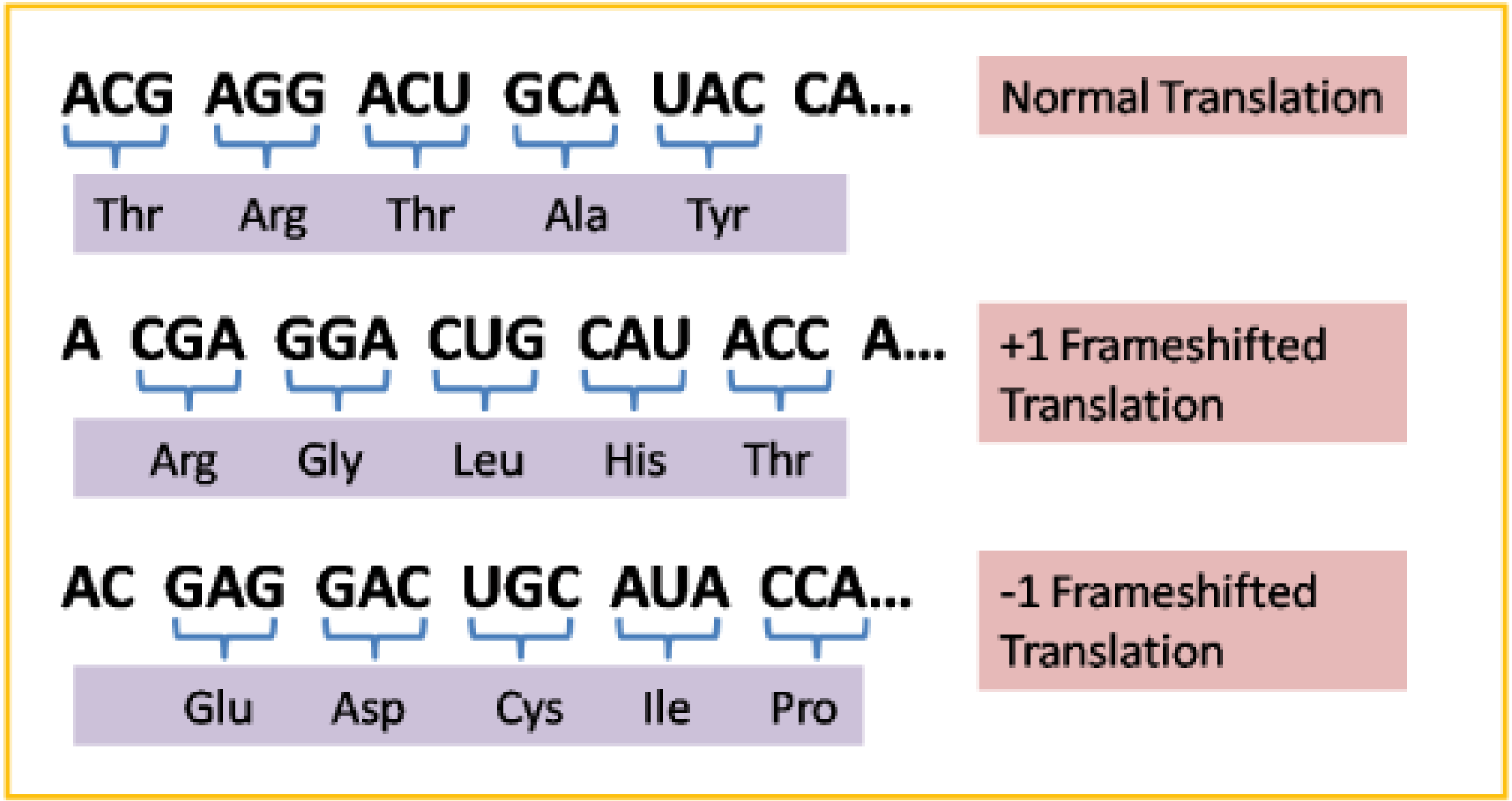
A gene mutation that causes **no detectable change** in the biological characteristics of the gene product.


Normal
DNA Template strand
3' T A C T T C A A A C C G A T T 5'
DNA Coding strand
5' A T G A A G T T T G G C T A A 3'
mRNA
5' A U G A A G U U U G G C U A A 3'
Protein
Met
Lys
Phe
Gly
Stop !
Silent Mutation
A replaced G
DNA Template strand
3' T A C T T C A A A C C A A T T 5'
DNA Coding strand
5' A T G T A G T T T G G T T A A 3'
U replaced C
mRNA
5' A U G A A G U U U G G U U A A 3'
Protein
Met
Lys
Phe
Gly
Stop !
Amino acid still same

Addition or deletion of nucleotides

- **Addition** or **deletion** of **one** or **two nucleotides**: this results in a **frame shift mutation**, leading to a change in all codons after the addition or deletion.
  - This usually results in the production of a non-functional gene product.

- Addition or deletion of **3 nucleotides**: this leads to **addition** or **deletion** of **one amino acid** to the peptide chain.
  - **The reading frame is not changed**. Such mutation is less severe than the frame shift mutation.

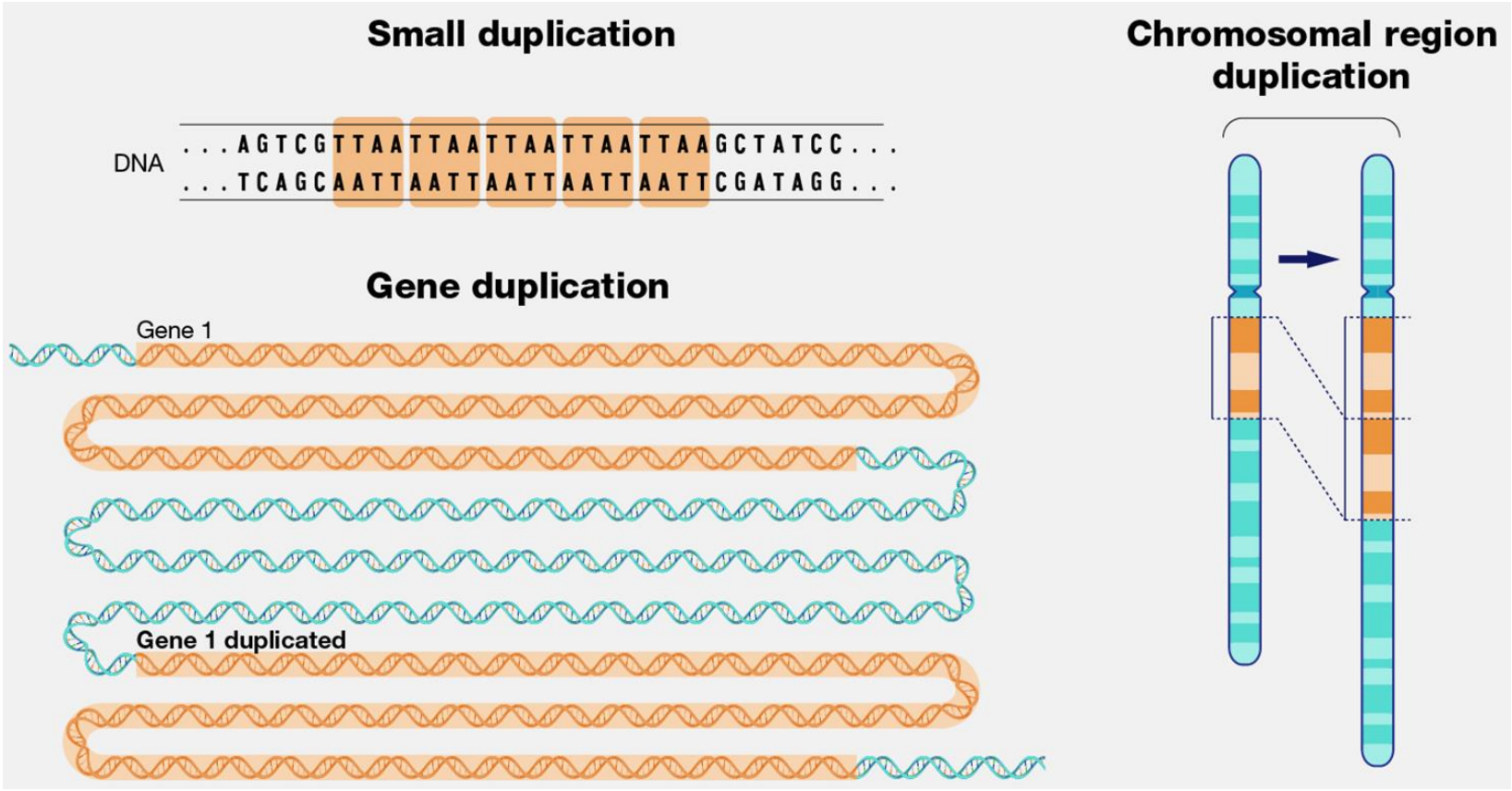

ACG AGG ACU GCA UAC CA...
Thr Arg Thr Ala Tyr
Normal Translation
A CGA GGA CUG CAU ACC A...
Arg Gly Leu His Thr
+1 Frameshifted Translation
AC GAG GAC UGC AUA CCA...
Glu Asp Cys Ile Pro
-1 Frameshifted Translation

Types of Large-scale mutations

- Chromosomal **duplications**
- Chromosomal **deletions**
- Chromosomal **inversions**
- Chromosomal **translocations**

Chromosomal duplication

A portion of the chromosome is duplicated, resulting in extra genetic material.

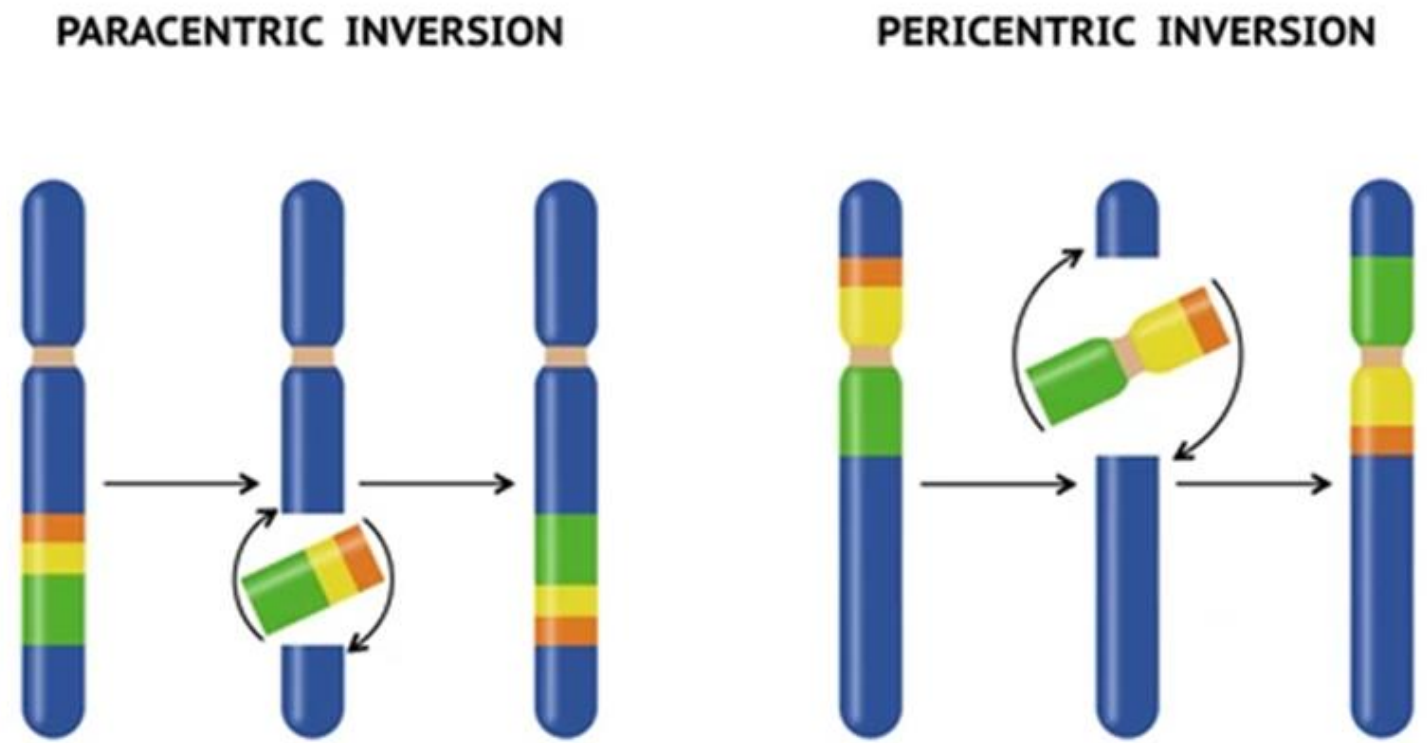


Chromosomal deletions

A portion of the chromosome is missing or deleted

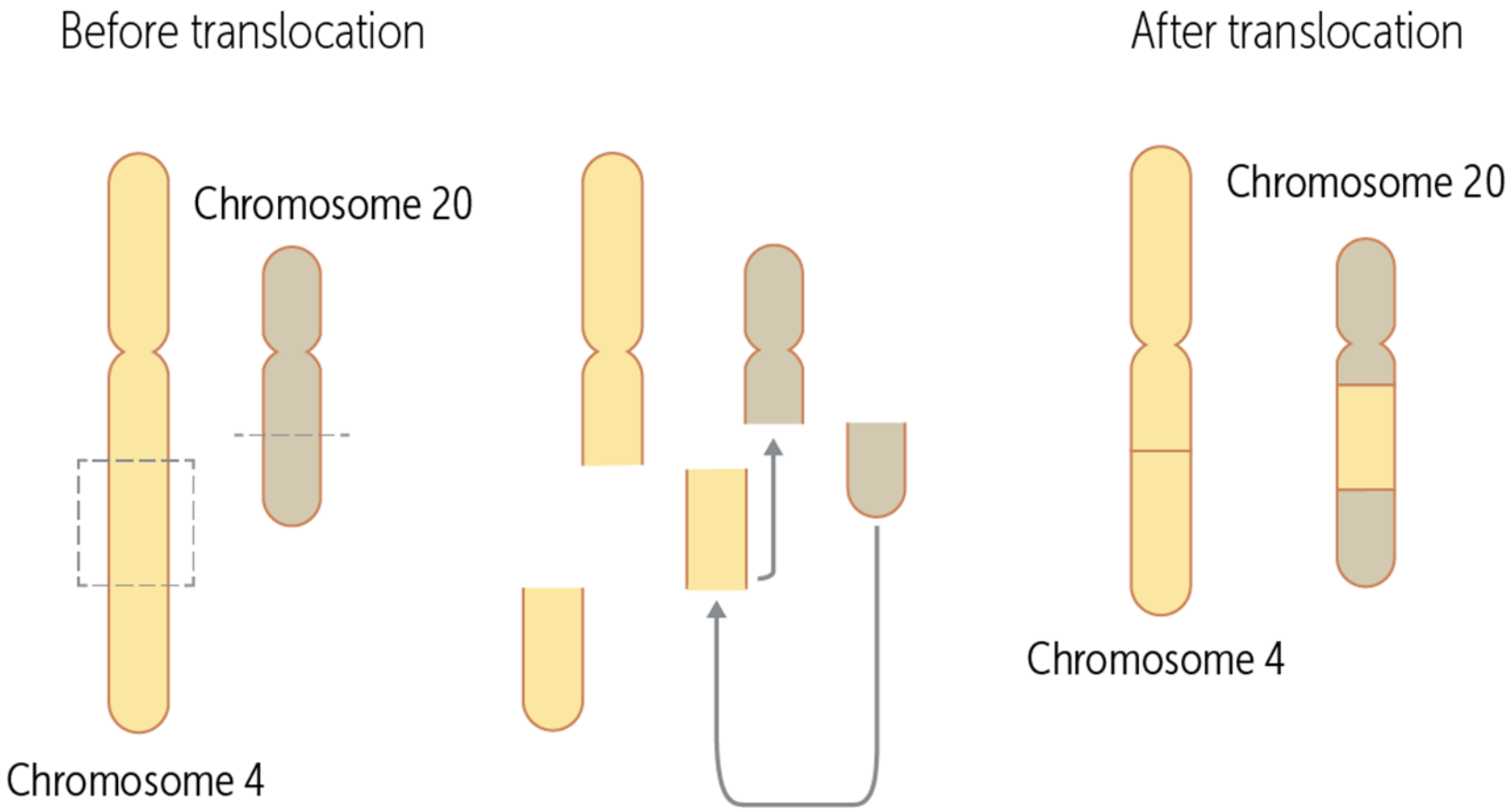
Chromosomal inversions

- A portion of the chromosome has broken off, turned upside down, and reattached, therefore the genetic material is inverted.



Chromosomal translocations

- A portion of one chromosome is transferred to another chromosome.



Manifestations of Mutations

A. Lethal Mutations

- The alteration is incompatible with life of the cell or the organism. For example, mutation producing alpha-4 Hb is lethal, and so the embryo dies.

B. Silent Mutations

- Alteration at an insignificant region of a protein may not have any functional effect.

Manifestations of Mutations

C. Beneficial Mutations

- Although rare, beneficial spontaneous mutations are the basis of evolution.

- Such beneficial mutants are artificially selected in **agriculture**. Normal maize is deficient in tryptophan. Tryptophan rich maize varieties are now available for cultivation.

- Microorganisms often have antigenic mutation. These are beneficial to micro-organisms (but of course, bad to human beings).

Manifestations of Mutations

D. Carcinogenic Effect

- The mutation **may not be lethal** but may alter the regulatory mechanisms.

- Such a mutation in a **somatic cell** may result in **uncontrolled cell division leading to cancer**.

- Any substance causing increased rate of mutation can also increase the probability of cancer. **Thus, all carcinogens are mutagens.**