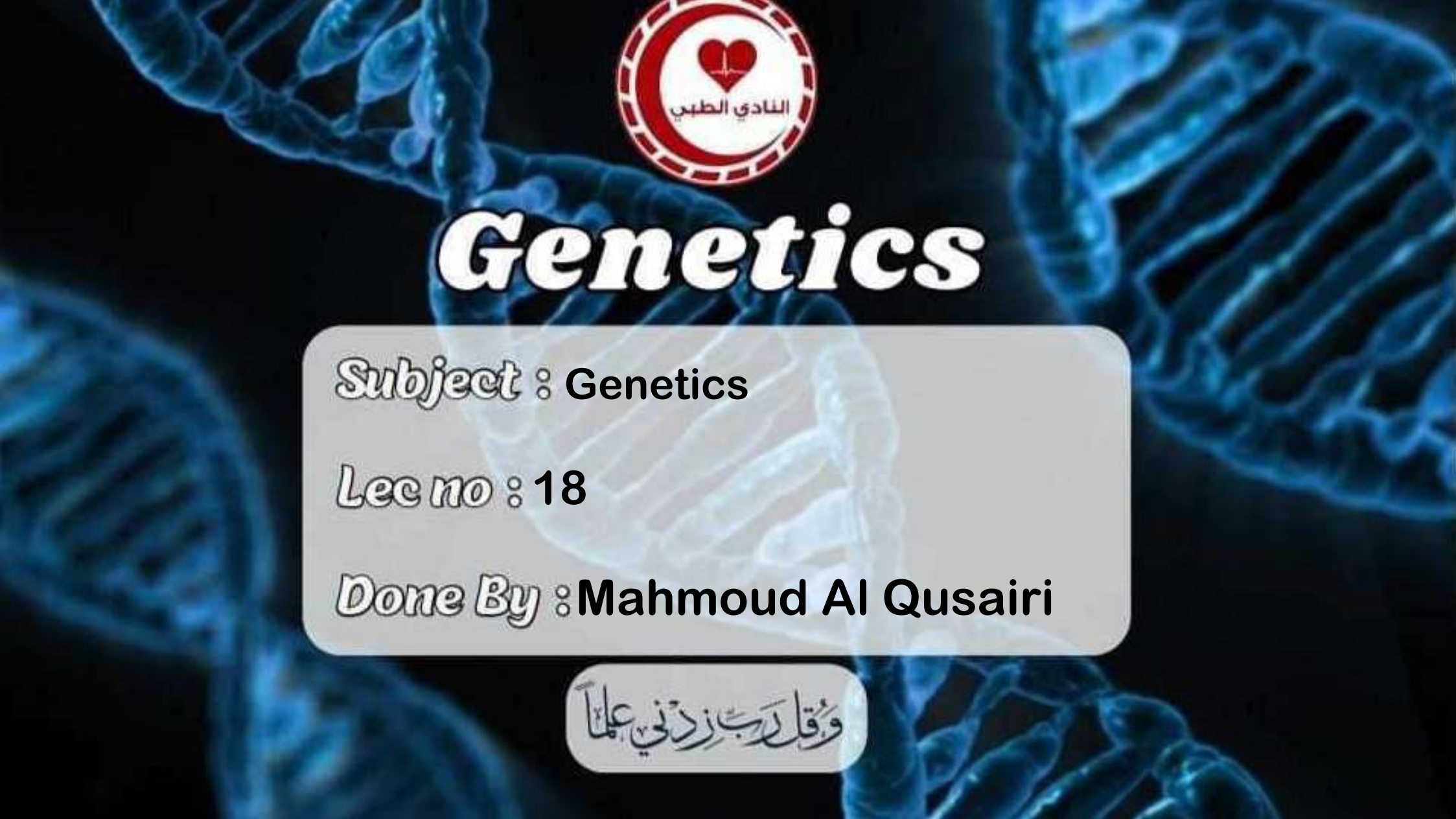


Genetics

Subject : Genetics

Lec no : 18

Done By : Mahmoud Al Qusairi

وقل رب زدني علما

Mutations

Dr. Walaa Bayoumie El Gazzar
Nebras M

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.

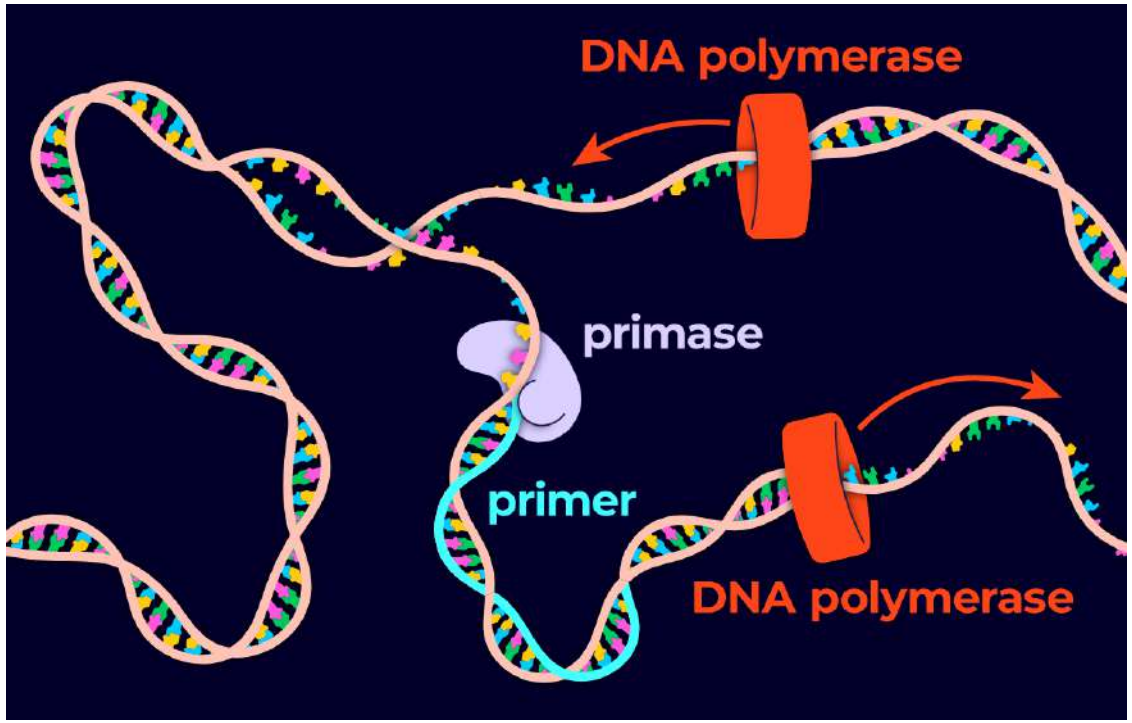
* كما نعلم أن DNA polymerase لديه proofreading activity بحيث أنه يصحح mistakes في النيوكليوتايد التي يقوم ببنائها

Causes of mutations

يحصل أخطاء أثناء عملية بناء DNA ولا يتمكن من تصحيح كل هذه الأخطاء.

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

without external interferance (external factors)

2. Spontaneous changes

ممكن تتصلّح

ممكن ما تتصلّح ← يحدث mutation

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

* كما نعلم أن DNA لا يحتوي على uracil بل يحتوي على Thymine

Spontaneous changes

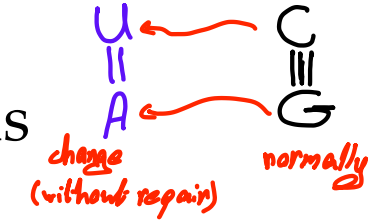
The body can detect this change and repaire it.

repaire for this change إذا لم يحدث

a) Deamination of cytosine to uracil.

هذا سيؤدي إلى تغير كبير حيث أنه كان من الطبيعي أن يرتبط (A ـ U) ولكن عند حدوث change فإن الإرتباط سيكون (A ـ U) و (G ـ C)

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.

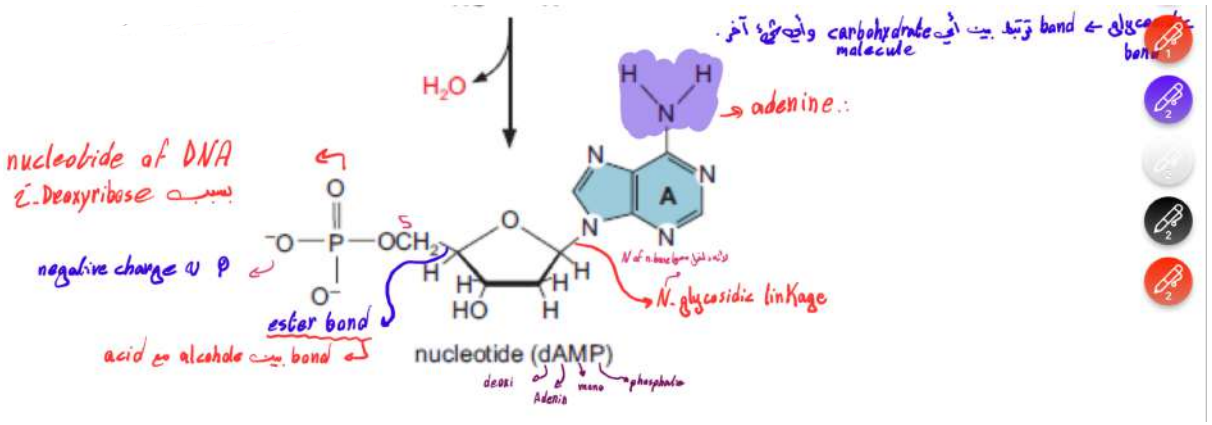


If DNA contains uracil in its structure, this type of mutation will not be detected and will not be corrected which will produce serious mutations.

* وجود Thymin بدلاً من uracil في DNA يساعد على منع تحول Cytosine إلى uracil

لكي حيث أنه يتم ملاحظته بسرعة.

Spontaneous changes



glycosidic bond يعود بسبب أن sugar phosphate backbone التي ترتبط بين purines و pyrimidines تكون (ضعيف) حيث أنه purines أقل استقرارا من pyrimidines فإن هذه bond من الممكن أن تكسر فتضع وازالتها

b) Spontaneous depurination. (Guanine / adinine) purines فقدان

Purines are less stable under normal cellular condition than pyrimidines.

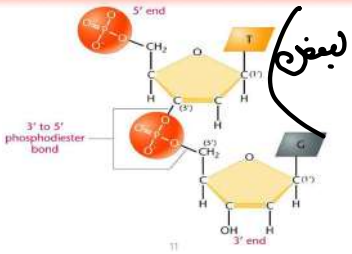
The glycosidic bonds that link **purines** to **the sugar phosphate backbone** of DNA are often broken, **if these purines are not replaced before replication**, any base may be added to complement the missing base during replication.

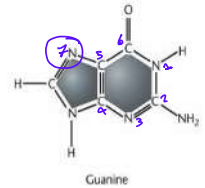
Chemical mutagens

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.

N7 of guanine بالـ CH_3 بإضافة : مثل alkyl group بيضيف.

cancer بيمكن استخدام في Alkylation
(disruption of DNA بسبب انه بيعمل)
فيمكن استخدام هذا to damage 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.

$CH_3 \rightarrow n=1 \Rightarrow C_1H_{2\times1+1} = CH_3$

- The alkyl group is attached to the guanine base of DNA, at the number 7 nitrogen atom of the purine ring.

Chemical mutagens - Cancer

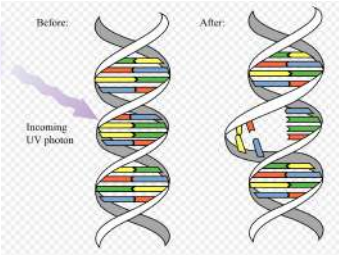
- Since cancer cells, in general, proliferate faster and with less error-correcting than healthy cells, cancer cells are more sensitive to DNA damage - such as being alkylated.

- 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

2 types of mutation

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

هذا mutation شائع

change in a single base only.

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:

كودون يتكون من 3 nucleotides يعطي a.a معين
يحدث تغير في base واحدة فيعطي a.a آخر.

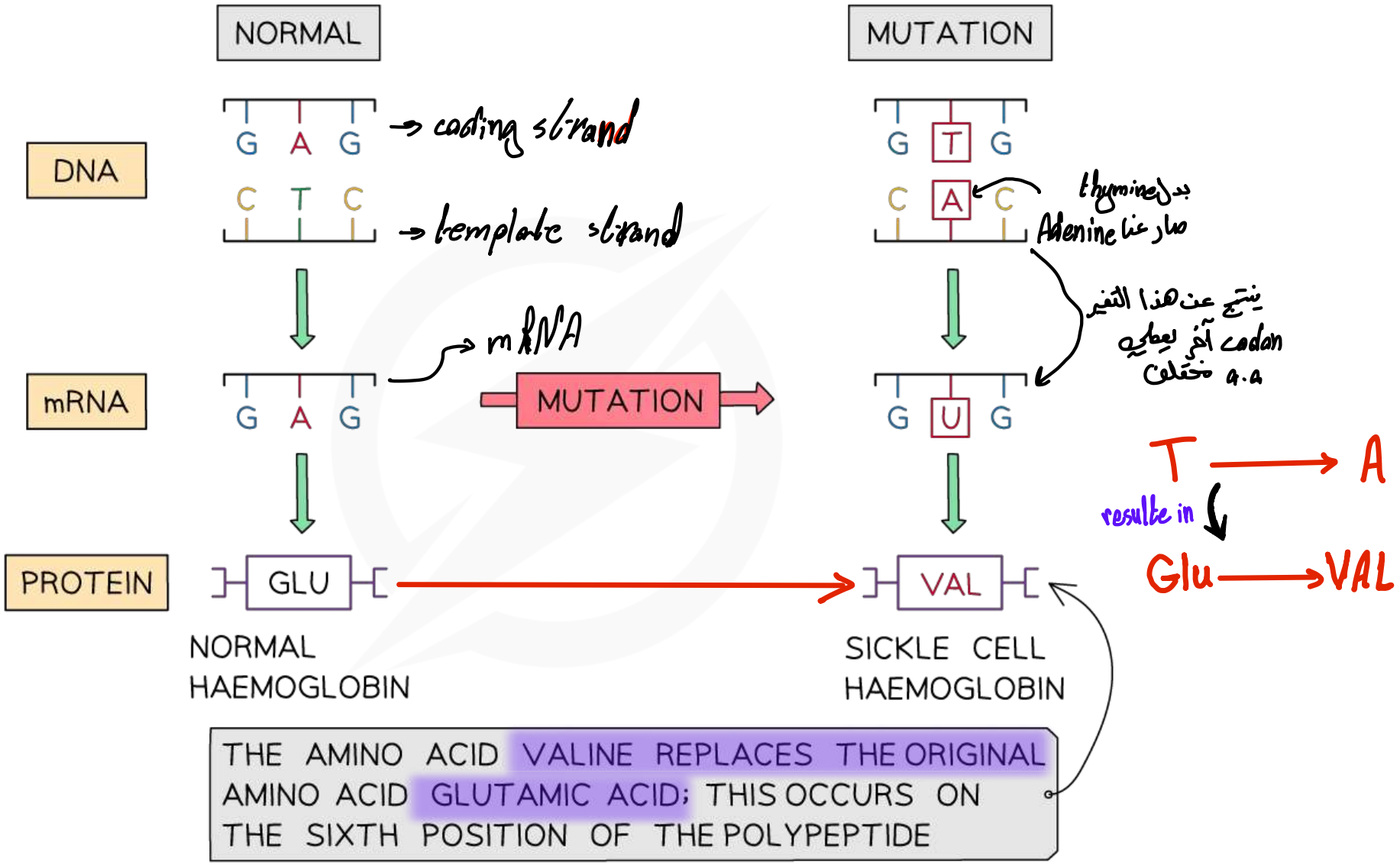
❖**Missense mutation** occurs if the resulting codon codes for a different amino acid and this leads to abnormal protein as in sickle cell anemia.

- Hemoglobin S (HbS)/sickle cell hemoglobin:

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

كي يكون فيها مشاكل وما بتكون مصنّعة بشكل جيد

بسبب تغير single nucleotide في



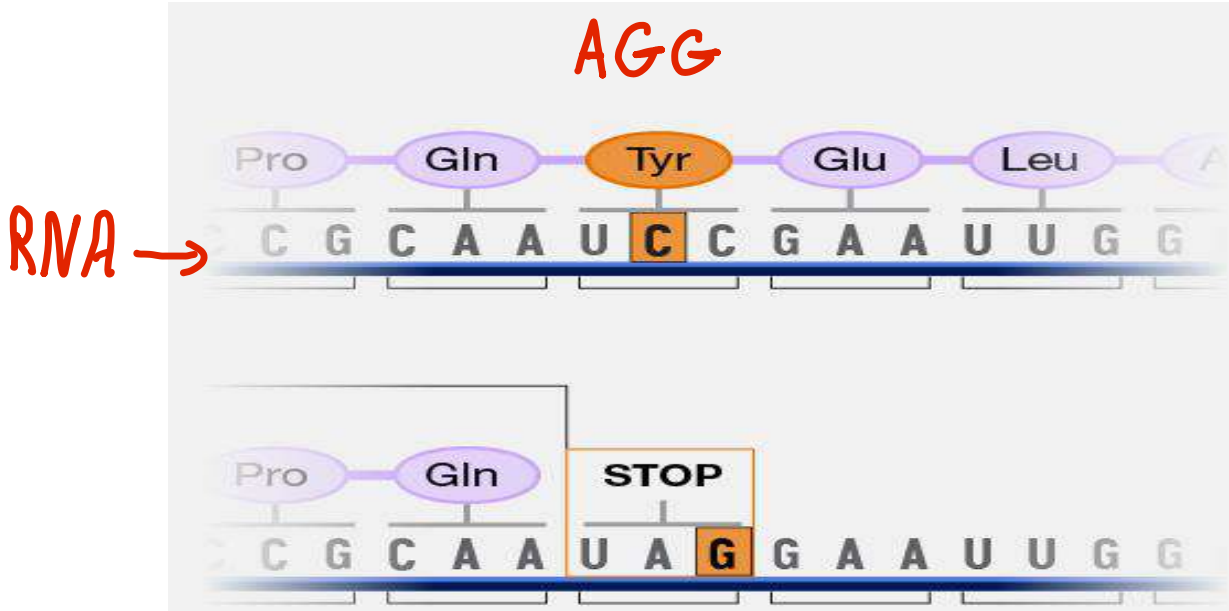
Nonsense mutation

التغير يكون على مستوى DNA ⇒

له تغير في كودون معين ينتج منه stop codon وليس a.a مختلف

فينتج non-functional protein ينتج بروتين غير مكتمل (polypeptide chains تكون أقصر من الطبيعي)

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



normal [AGG (DNA) / UCC (mRNA)]

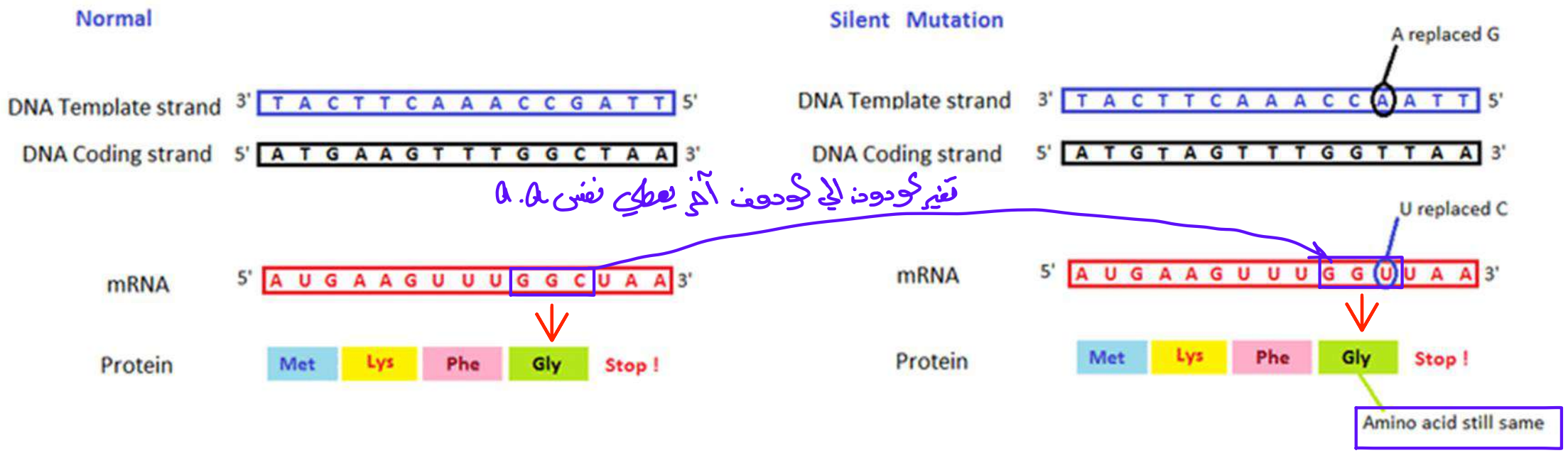
at mutation occur [ATC (DNA) / UAG (mRNA)]

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'
تغير كودون الي كودون آخر يعطي نفس a.a
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

The whole sequence incredible wrong

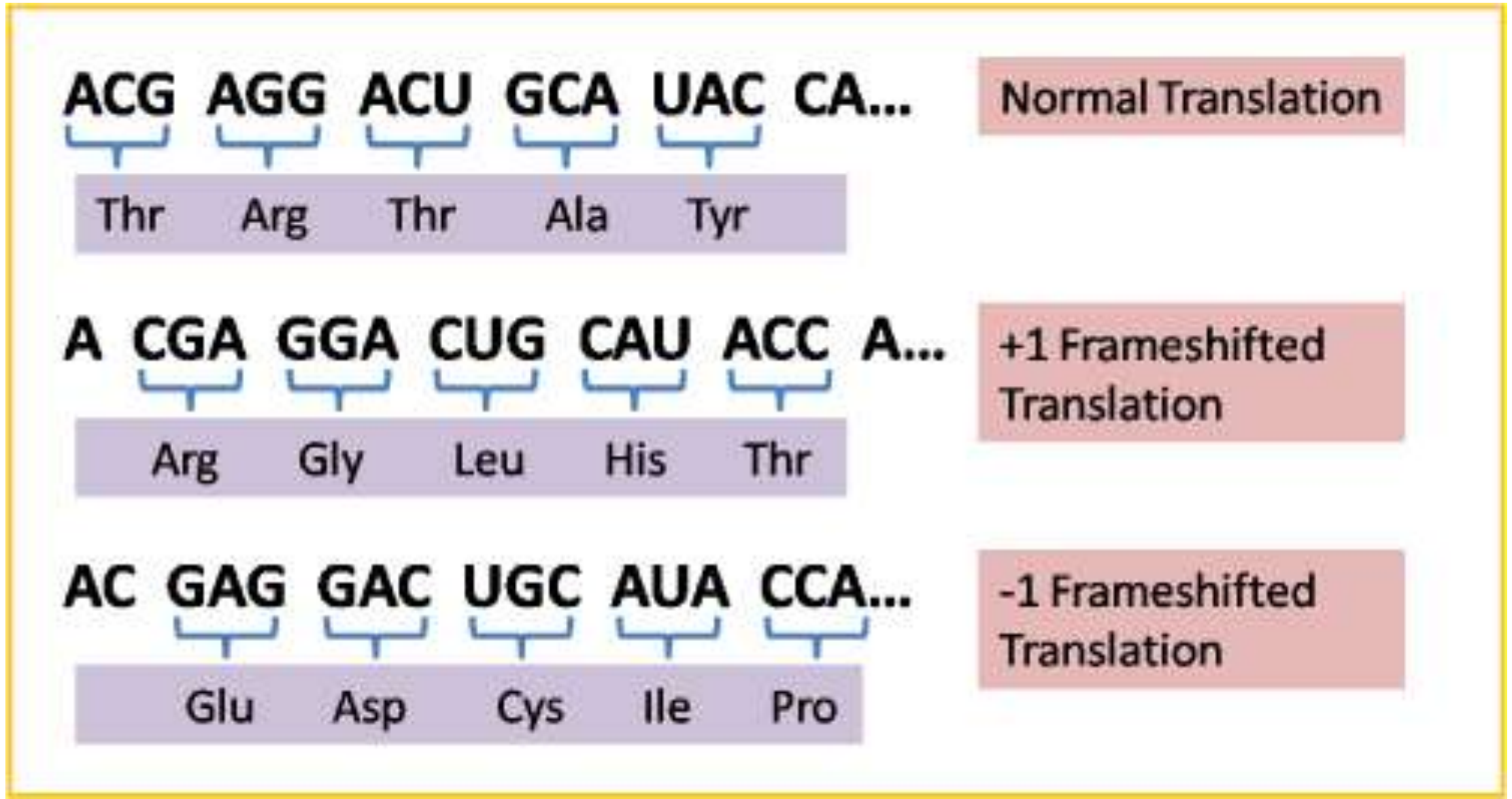
تؤثر على كل codons بعد عملية الإضافة أو الحذف

- **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.

عملية إضافة كودون منفصل لن يؤثر على بقية codons

عملية إضافة أو إزالة one amino acid

- 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

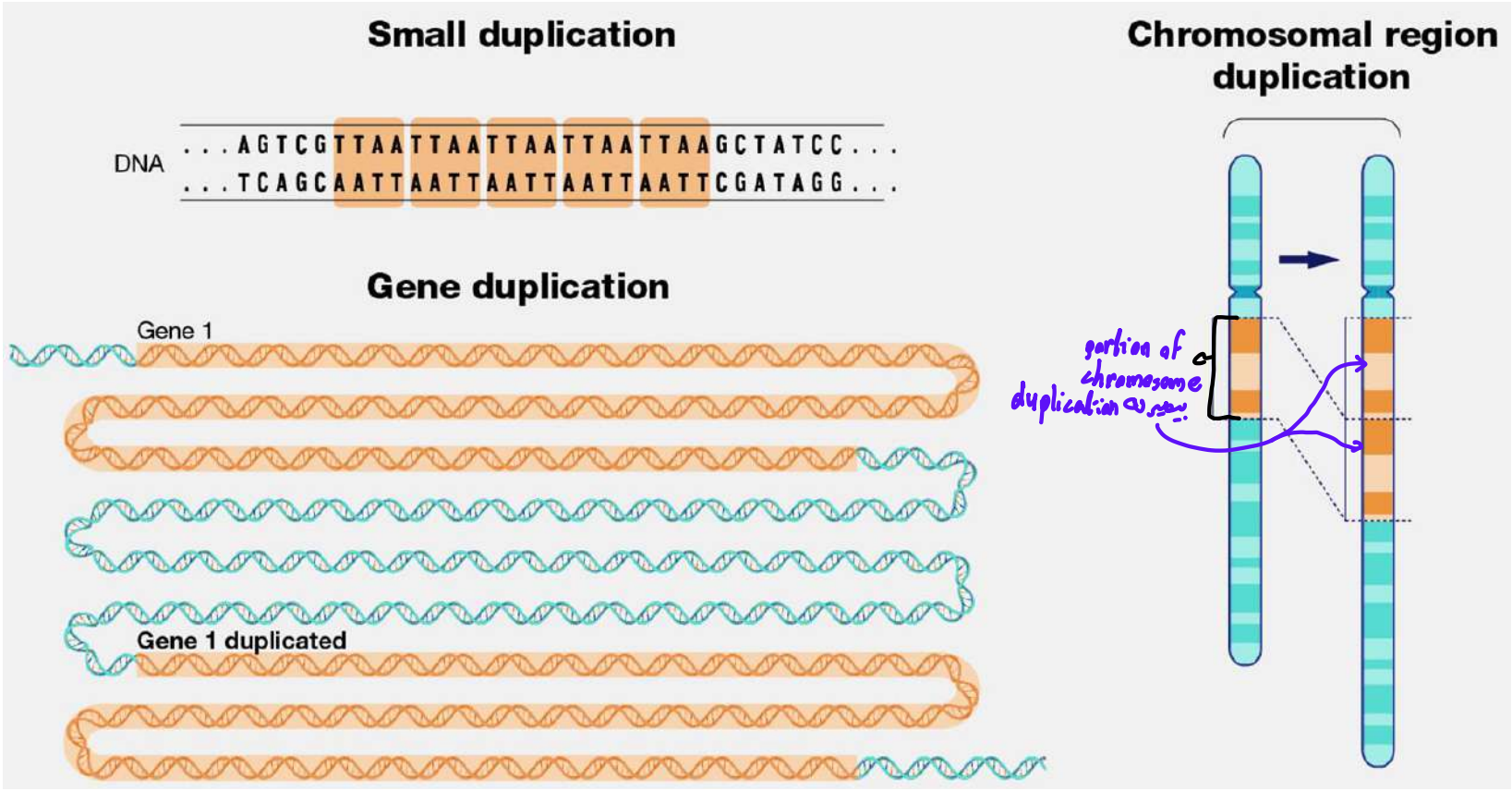
هي ما في عليها اسئلة بالامتحان

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

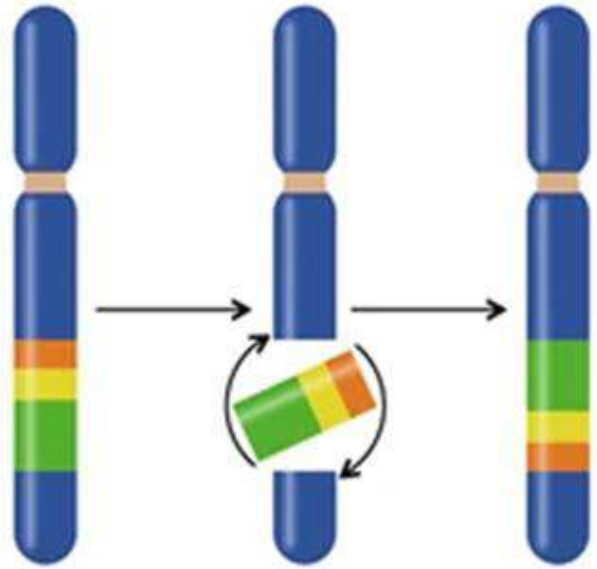
Chromosomal inversions

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

portion of chromosome has broken off
↓
turned upside down
↓
reattached
the genetic material is inverted.

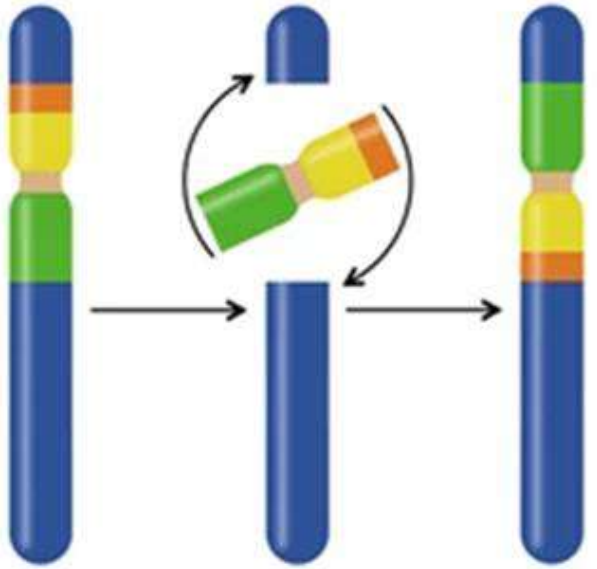
long arm على مستوى

PARACENTRIC INVERSION



centromer على مستوى

PERICENTRIC INVERSION



Chromosomal translocations

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

جزء من کروموزوم معین بحث
به transferred یک کروموزوم آخر.