Why should I learn this?

Amyotrophic Lateral Sclerosis (ALS)

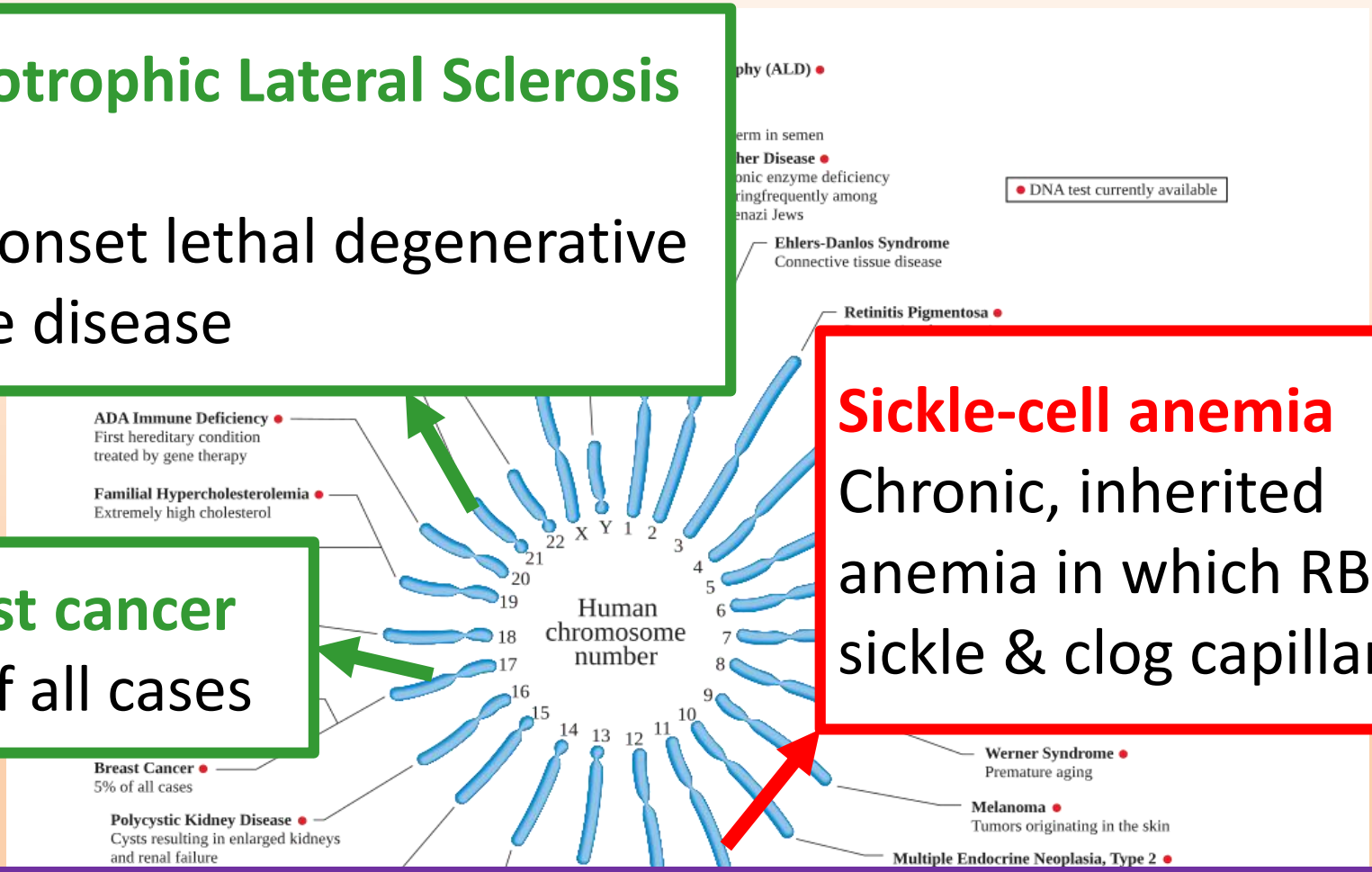
Late-onset lethal degenerative nerve disease

Sickle-cell anemia

Chronic, inherited anemia in which RBCs sickle & clog capillaries

Breast cancer

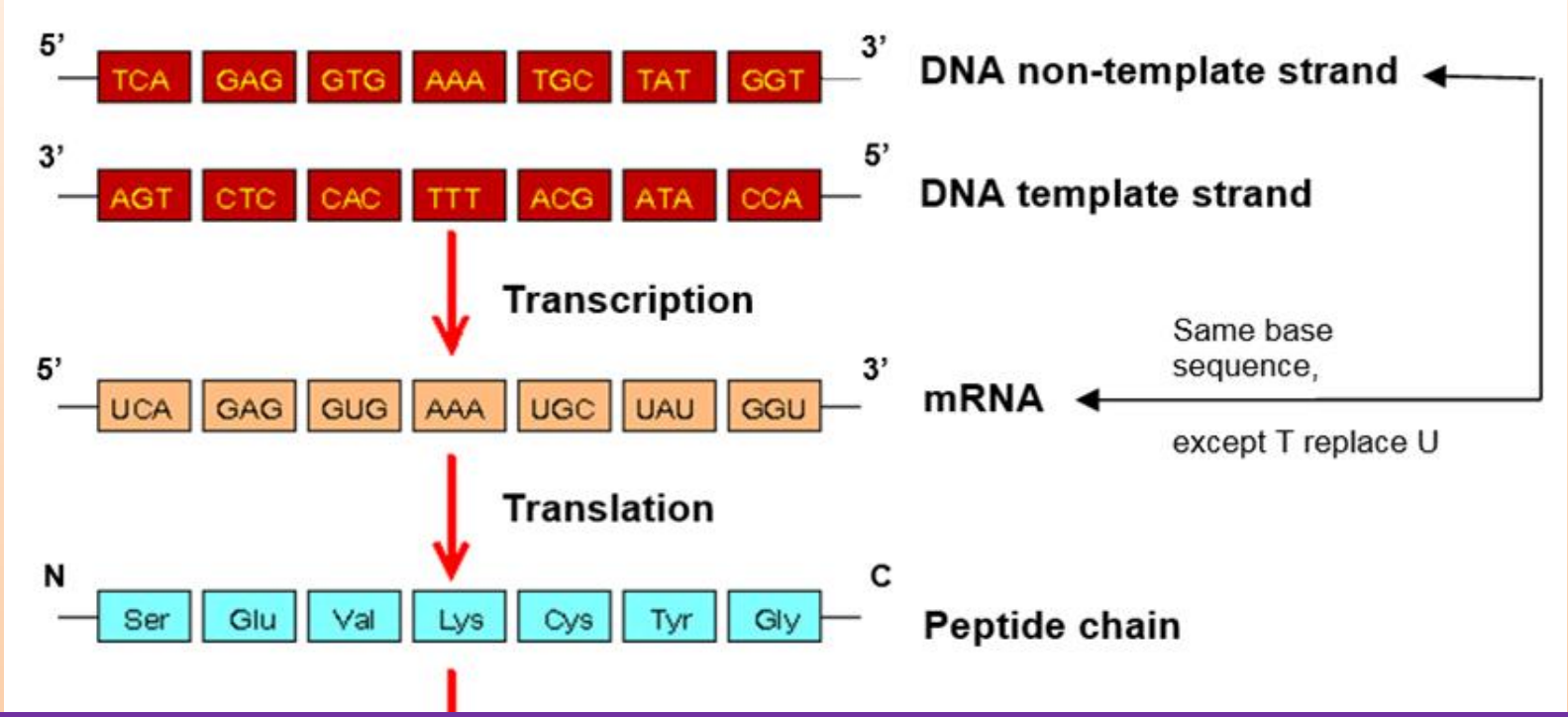
5% of all cases



Understand the basis for genetic diseases

What you have learnt …

- **Central Dogma & the Genetic Code**



What happens when DNA is altered?

Learning Objectives

- 2(d)
  Explain what is meant by the terms **gene mutation** and chromosomal aberration.
  For gene mutation, knowledge of how substitution, addition and deletion could change the amino acid sequence (including frameshift) is required.

  2(e)
  Explain how gene mutations can result in diseases (including sickle cell anaemia).

Mutation

Definition:

Gene

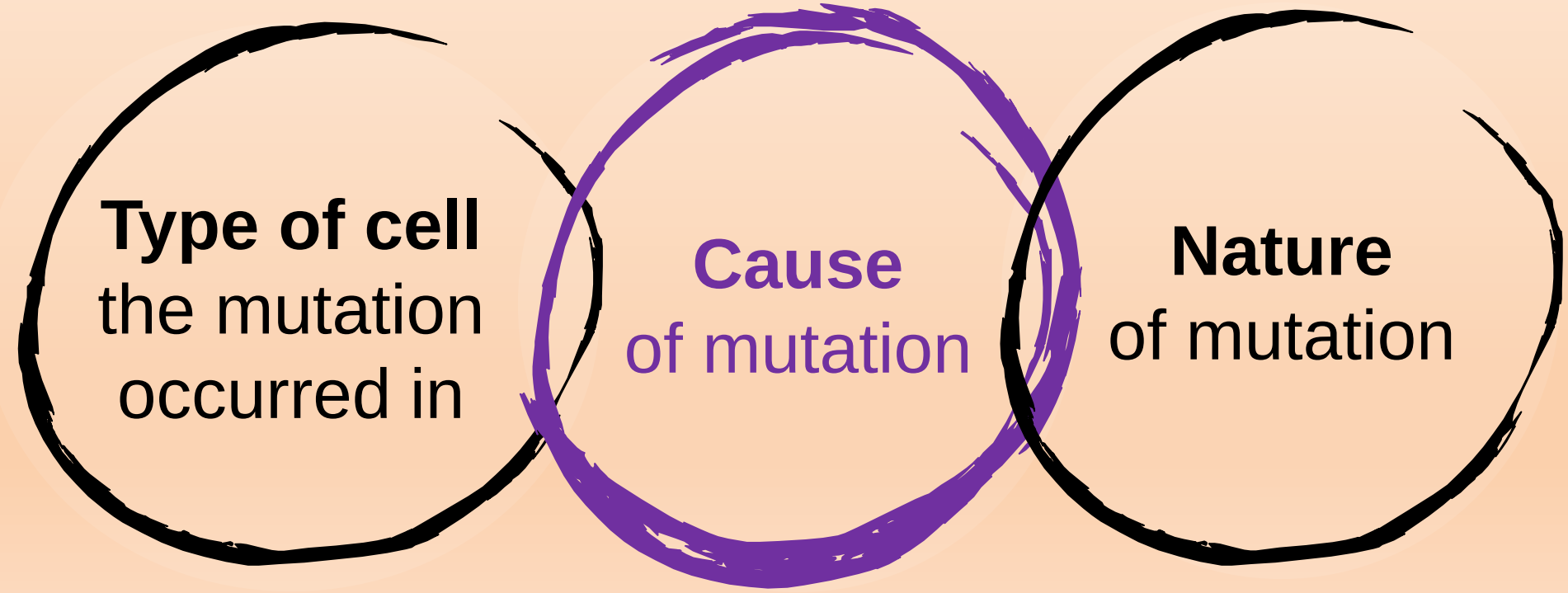
Chromosome

- Change in the sequence, amount or structure of the **DNA** of an organism.

Not in notes

Mutation

- There are several ways to classify the types of mutations, by:



Type of mutation

Somatic

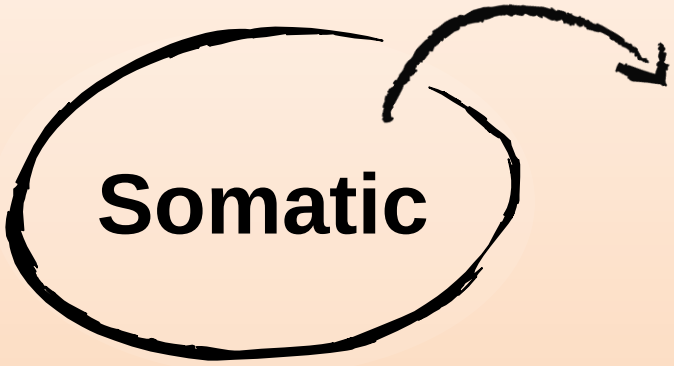
Occurred in **somatic cells** - cells other than germ line cells.

Germline

Occurred in the specialized cells that give rise to gametes

Spermatogonia / oogonia

Type of mutation

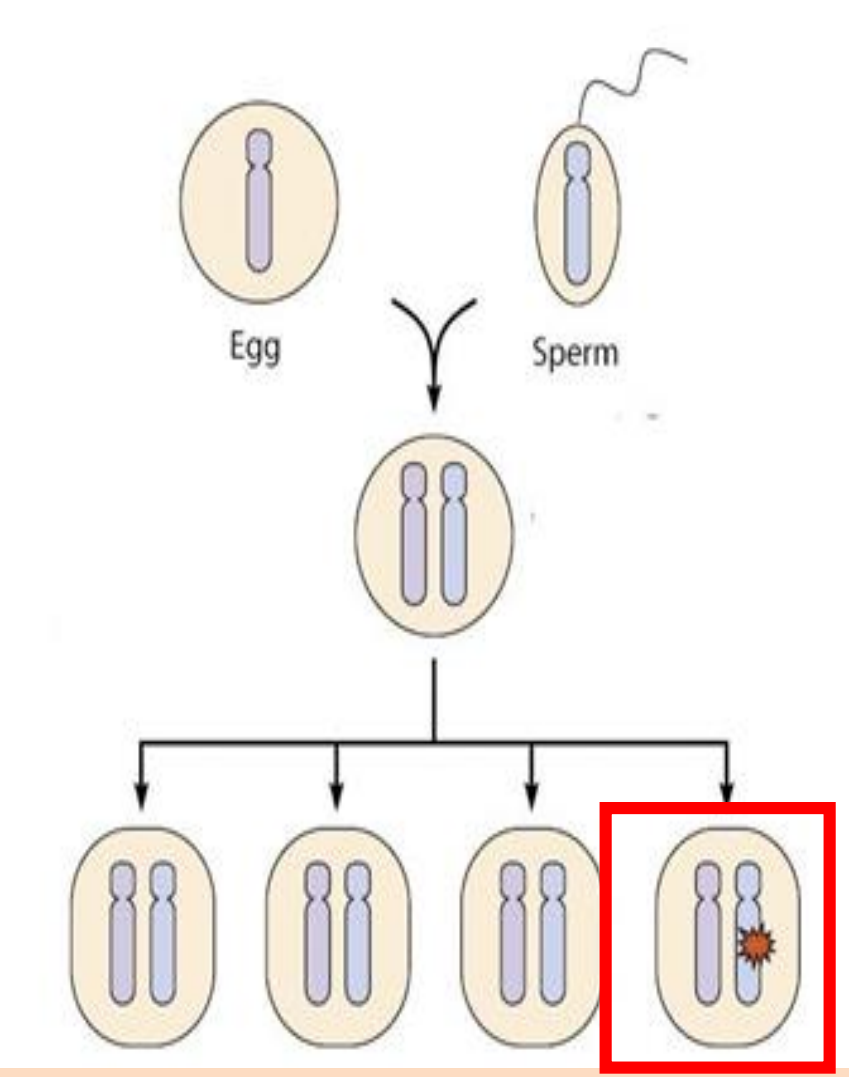


Mutations are passed on to the daughter cells after mitosis, i.e. remains in same organism.

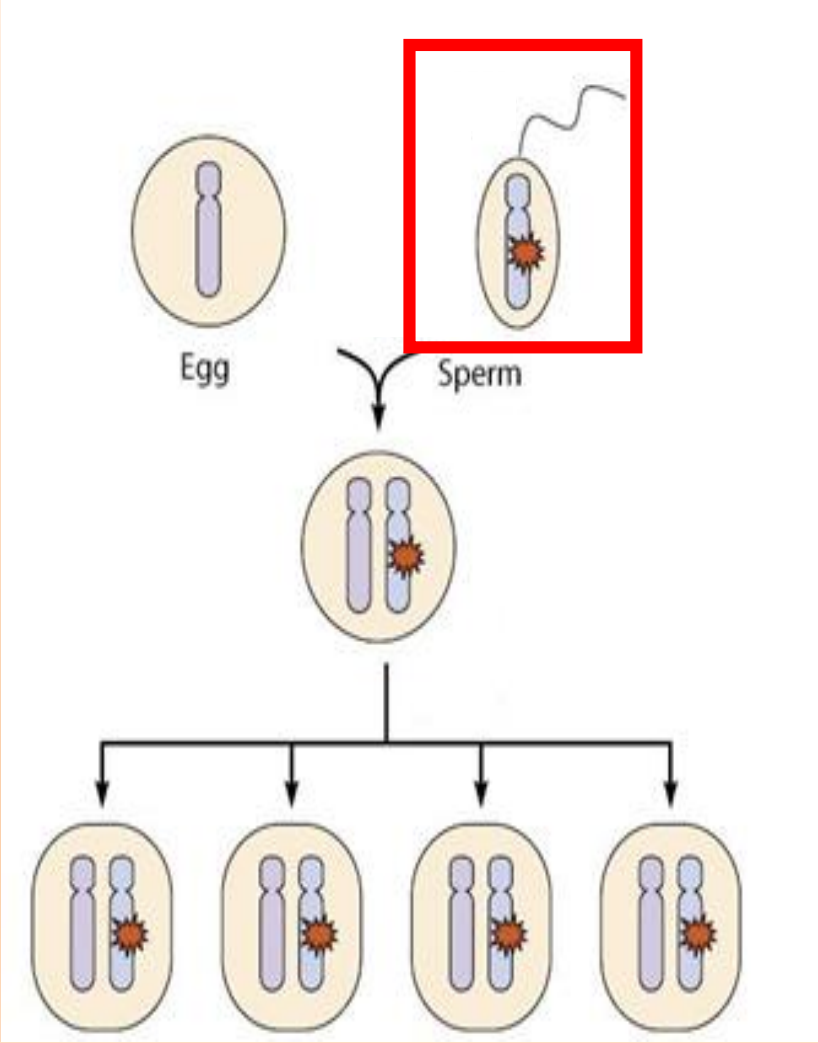
A gamete with the mutation passes it on to the new offspring at fertilization

Not in notes

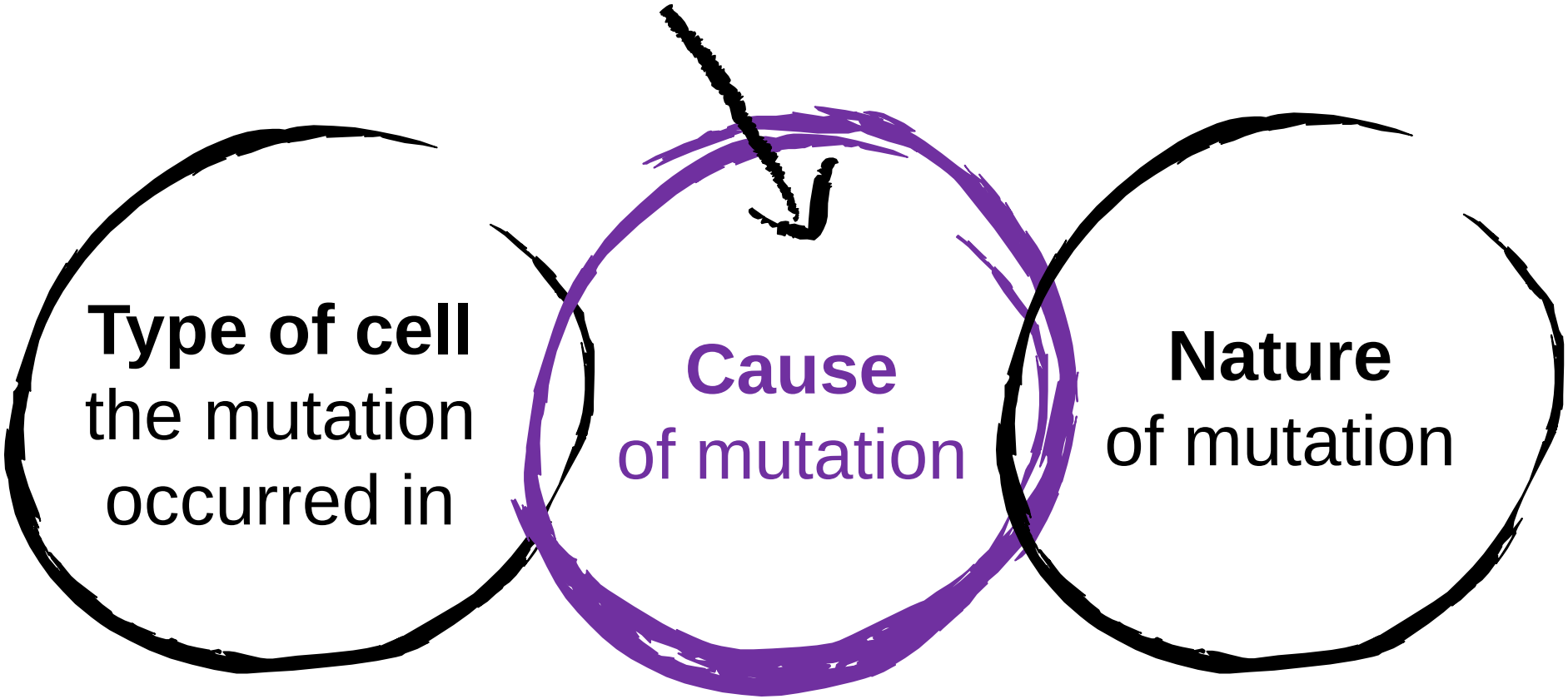
Somatic mutations



Germ-line mutations



Mutation

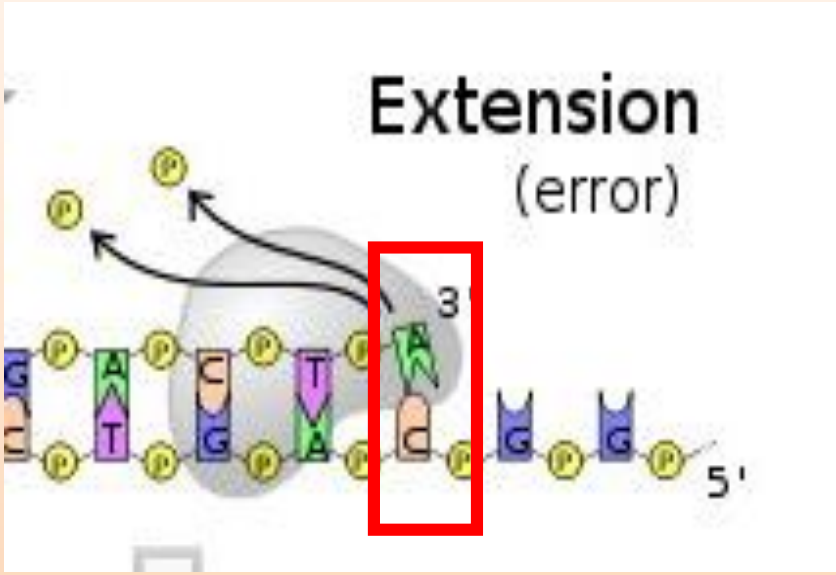

Type of cell the mutation occurred in
Cause of mutation
Nature of mutation

Cause of mutation

Spontaneous

Happen naturally.
No specific agents are associated.

e.g. errors during DNA replication, recombination or repair



DNA Pol's error rate of 1/100,000,000 bp
= ~0.6 to 1 mutation per replication of human genome

Cause of mutation

Spontaneous

Happen naturally.
No specific agents are associated.

e.g. errors during DNA replication, recombination or repair

Induced

Result from the influence of extraneous factors.

e.g. mutagens

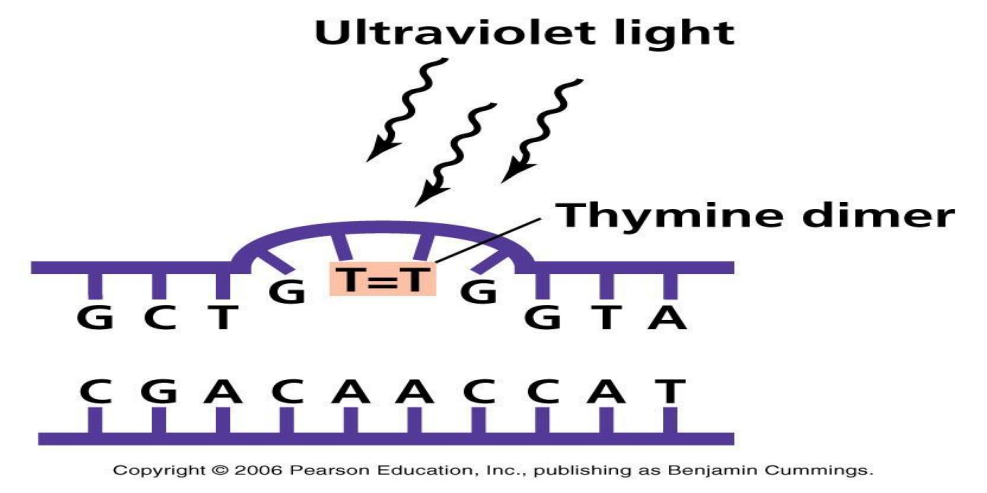
Mutagens

Agents that bring about a permanent alteration to the physical composition of DNA/gene, such that the genetic message is changed.

PG 37

Types of Mutagens

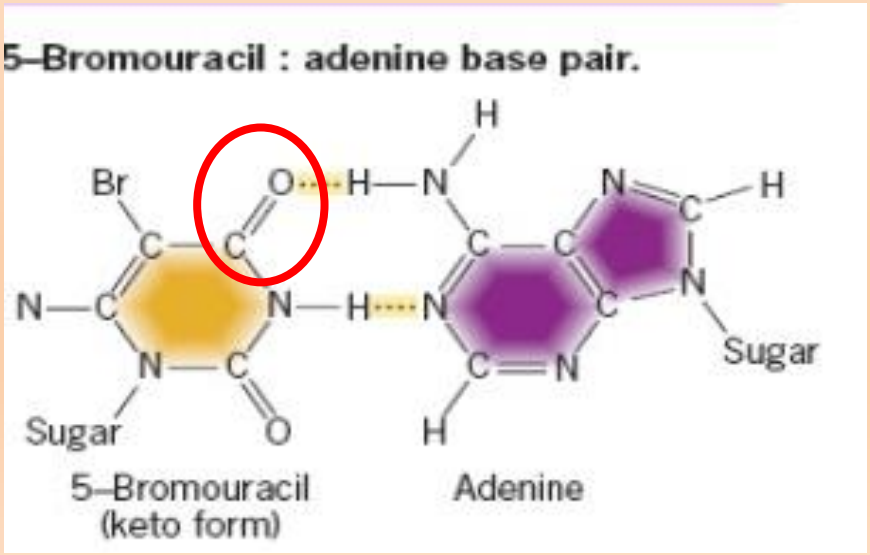
i. **Ionizing radiation**, such as X-rays, UV and gamma rays

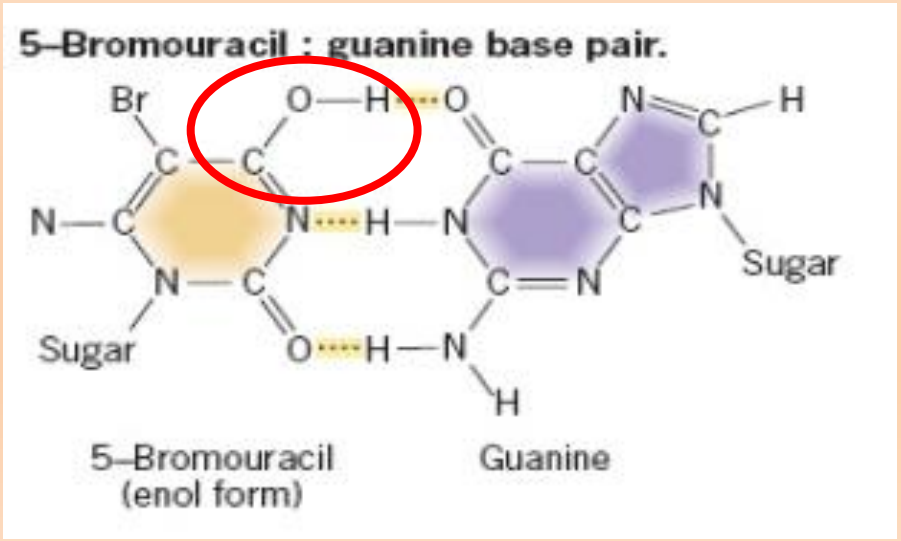


ii. **Chemical substances** such as formaldehyde, **colchicine***, mustard gas.

Types of Mutagens

iii. **Base mutagens** – chemicals that are **structurally similar** to the normal DNA bases **BUT** base-pair incorrectly during **DNA replication**

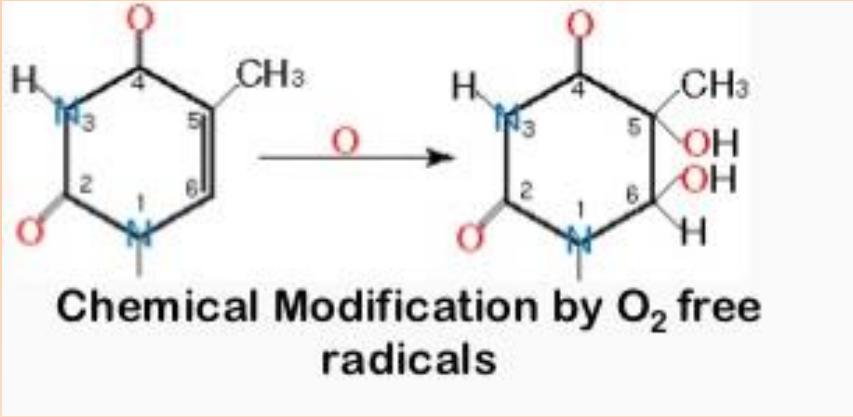




Types of Mutagens

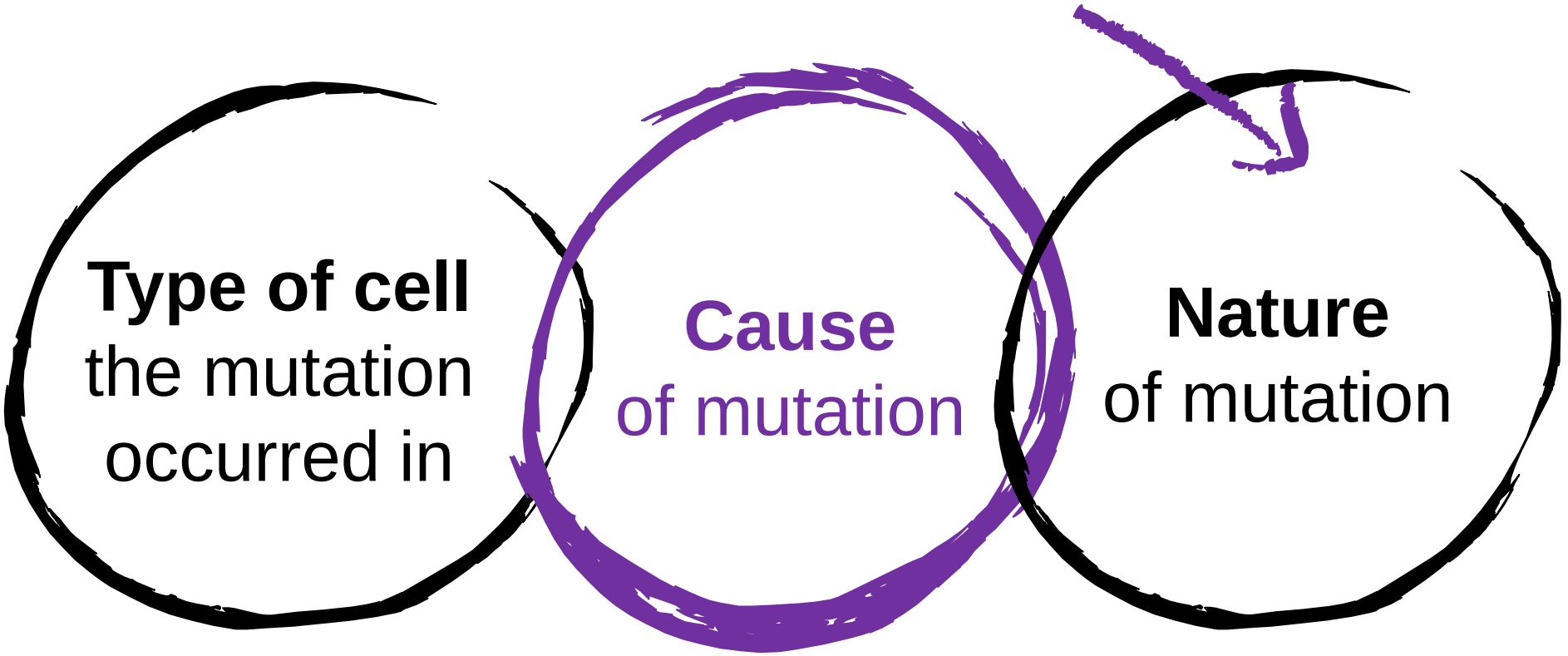
iv. Other chemical mutagens can also **interfere with DNA replication** by:

- inserting themselves into the DNA and distorting the double helix.
- chemically modifying bases, which changes their base-pairing properties.



Chemical Modification by O_2 free radicals

Mutation

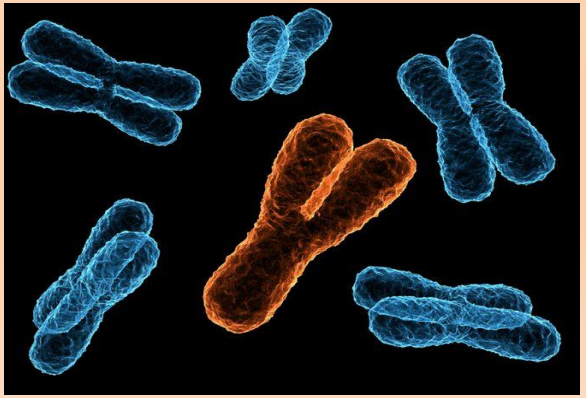

Type of cell the mutation occurred in
Cause of mutation
Nature of mutation

Nature of mutations

Mutations

Gene mutation
(new alleles of a gene formed)

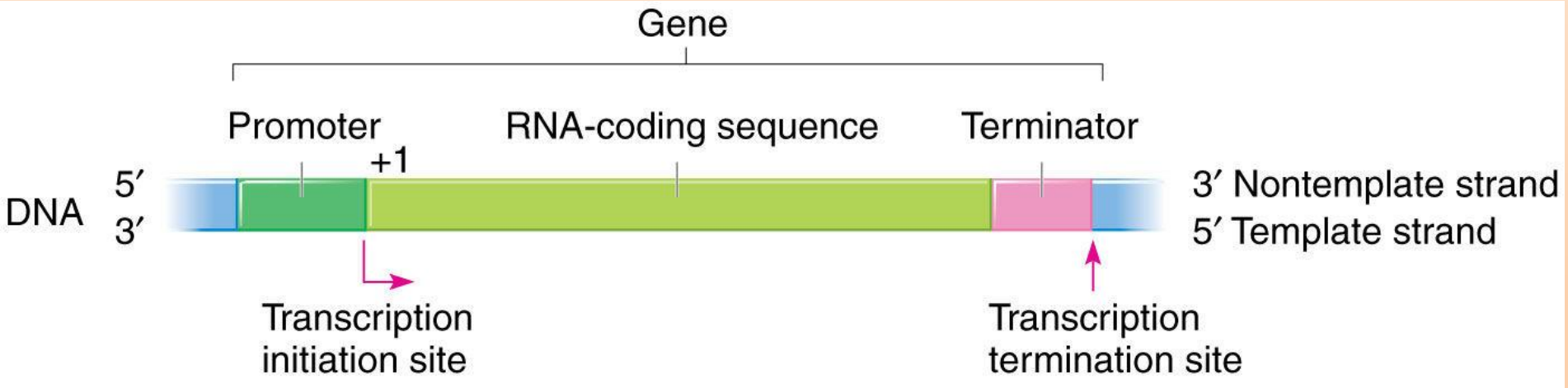
Chromosomal Aberration
(Change in number of copies of existing alleles OR reshuffling of existing alleles)

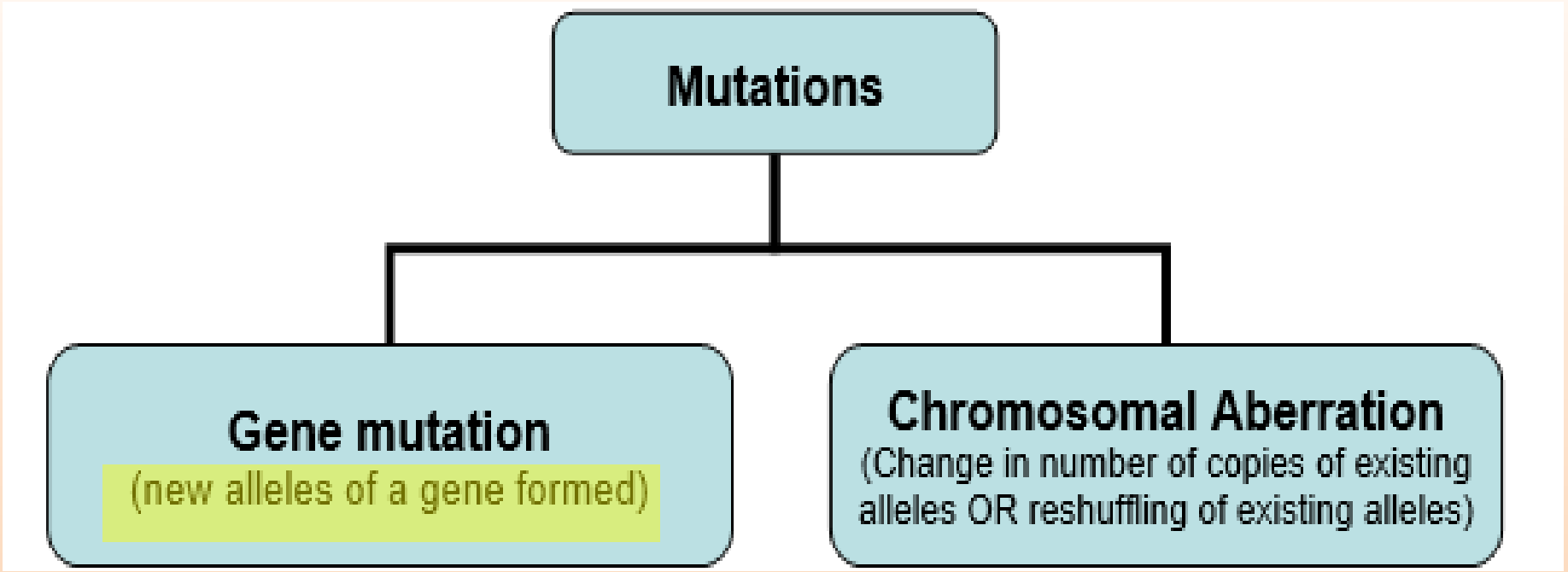


Not in Notes

RECAP: What is a gene?

- A specific sequence of **nucleotides** along a DNA molecule which **codes** for a specific sequence of **amino acids** in a polypeptide chain.

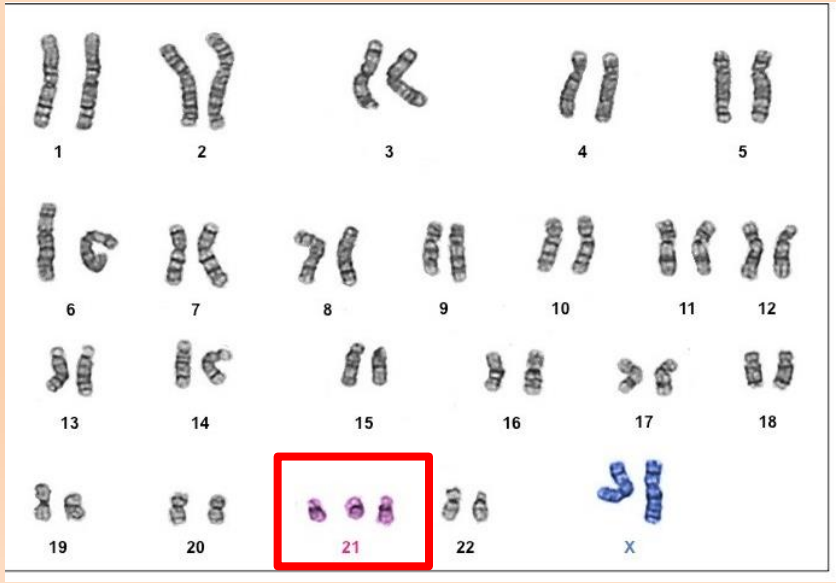




While drastic effects of mutations are often emphasized in **diseases** such as cancer, mutations are actually the **source of allele variation** & play a role in **evolution**

1) Chromosomal aberration

- A change in the **number or structure** of chromosomes
- **Several gene loci** are involved
- Effect: Change in number of copies of alleles / reshuffling of alleles
- Case study : Trisomy 21



2) Gene mutation

- A change in the **nucleotide / base sequence** of a gene
- A single gene locus is involved
- May involve a **change in one or more bases**

2) Gene mutation

Effect: Formation of new alleles

Change in **DNA sequence**

may Δ → **amino acid sequence** in polypeptide

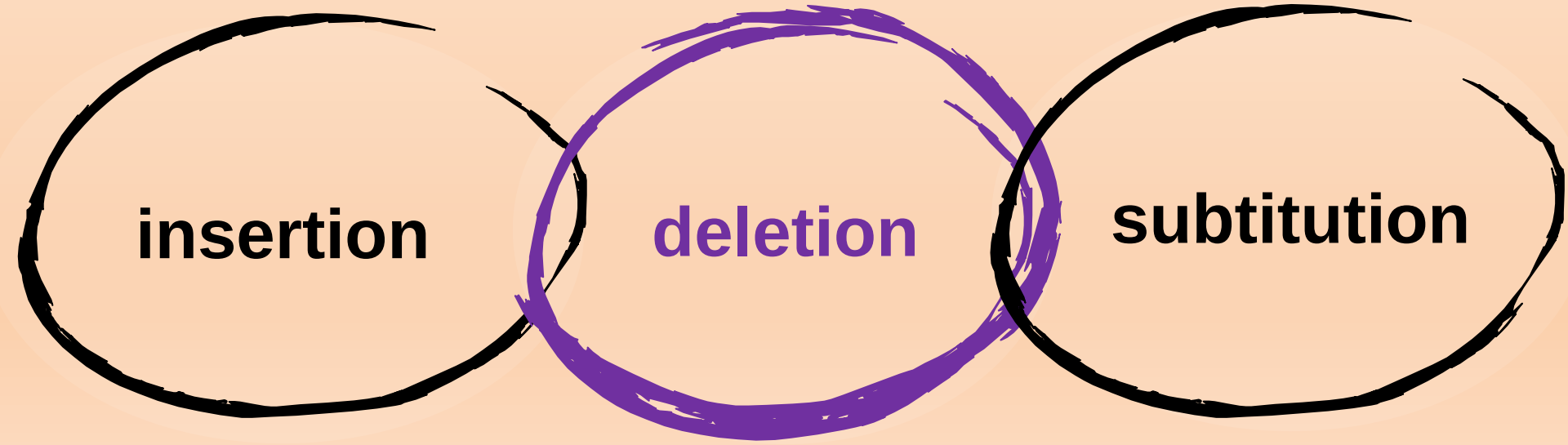
may Δ → properties of the protein

may Δ → phenotype of organism

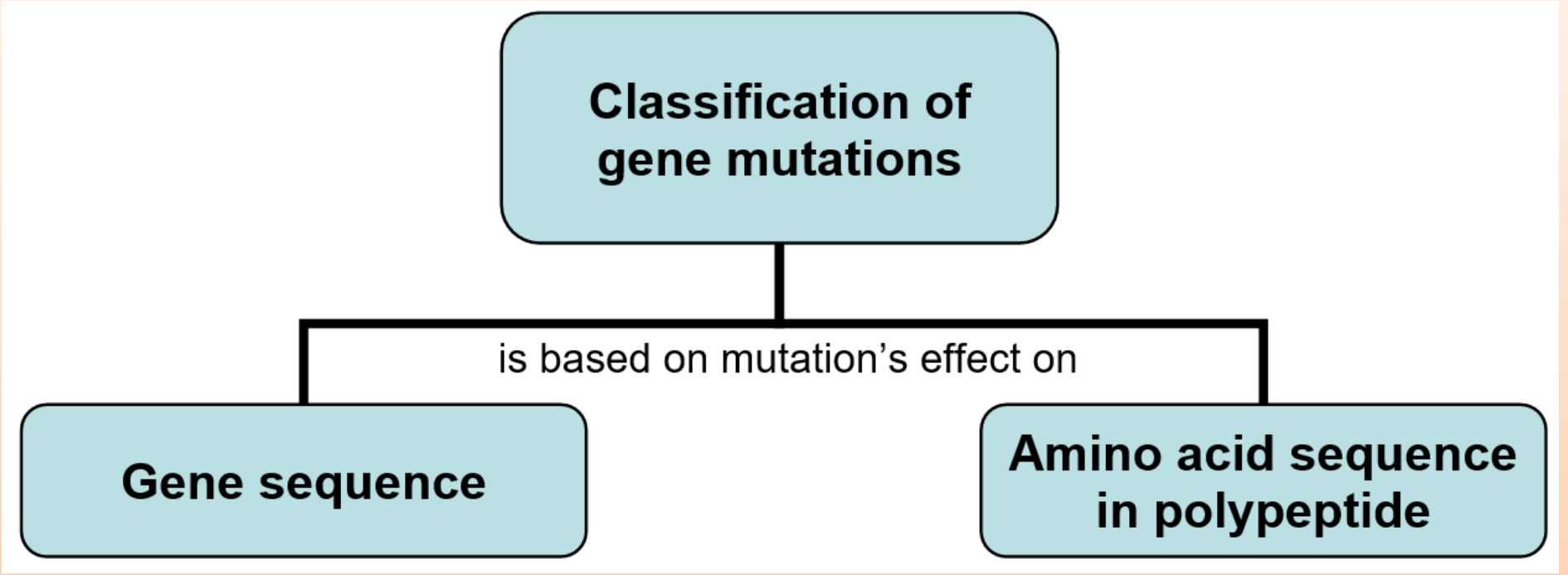
2) Gene mutation

Point Mutation:

- Involves changes in just **1 base pair** of the gene
- Can be:



Types of gene mutations



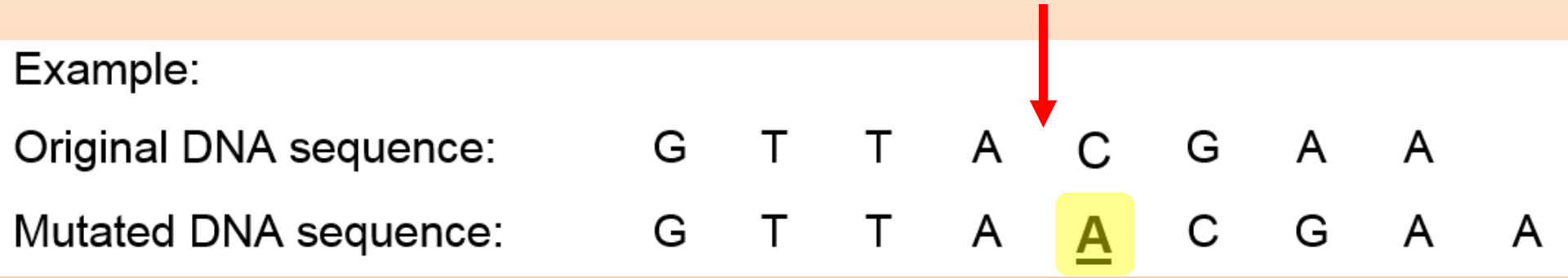
1. Insertion
2. Deletion
3. Substitution
4. Inversion

1. Silent
2. Neutral
3. Missense
4. Nonsense
5. Frameshift

1) Insertion

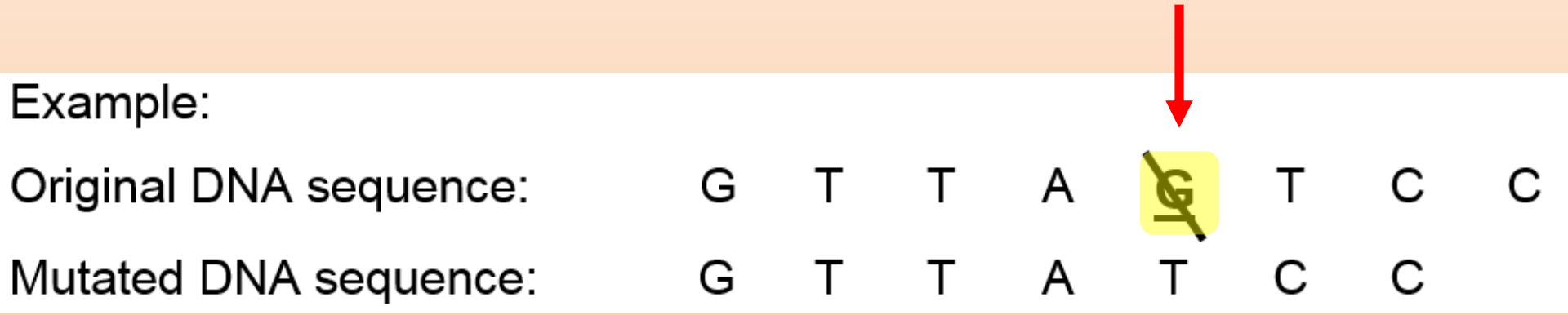
- Or called '**Addition**'
- One or more nucleotides are **added** into the sequence

Example:



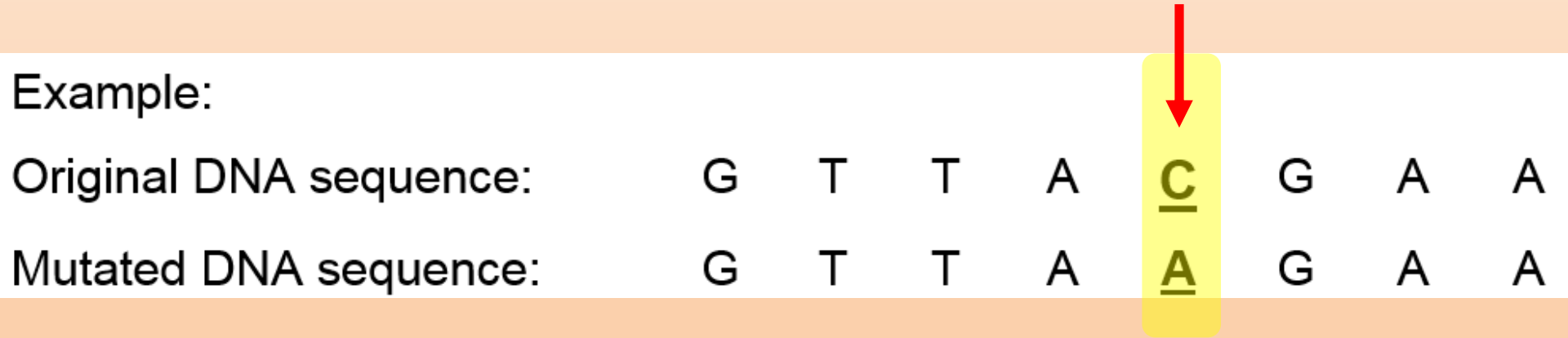
2) Deletion

- One or more nucleotides are **removed** from the sequence



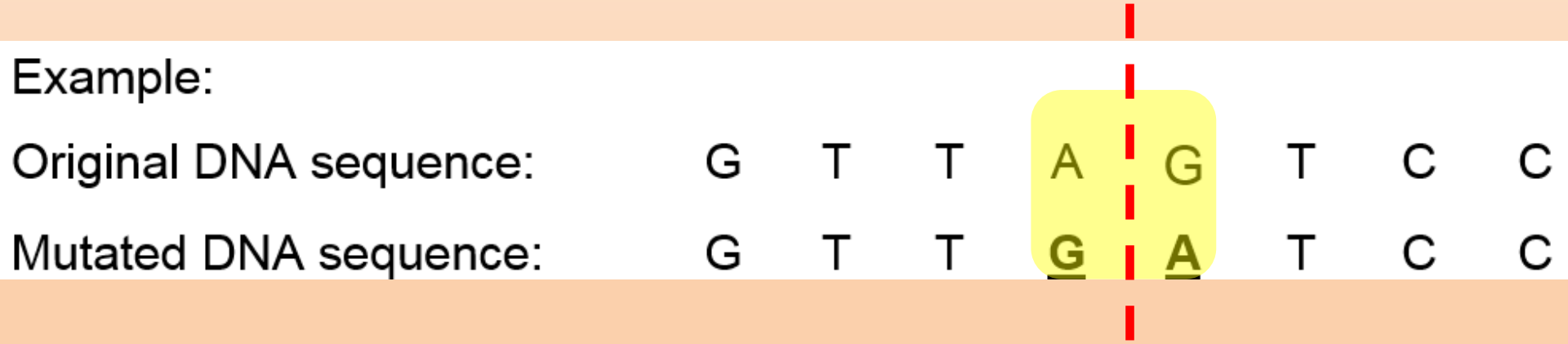
3) Substitution

- One nucleotide in the sequence is **replaced** by another nucleotide

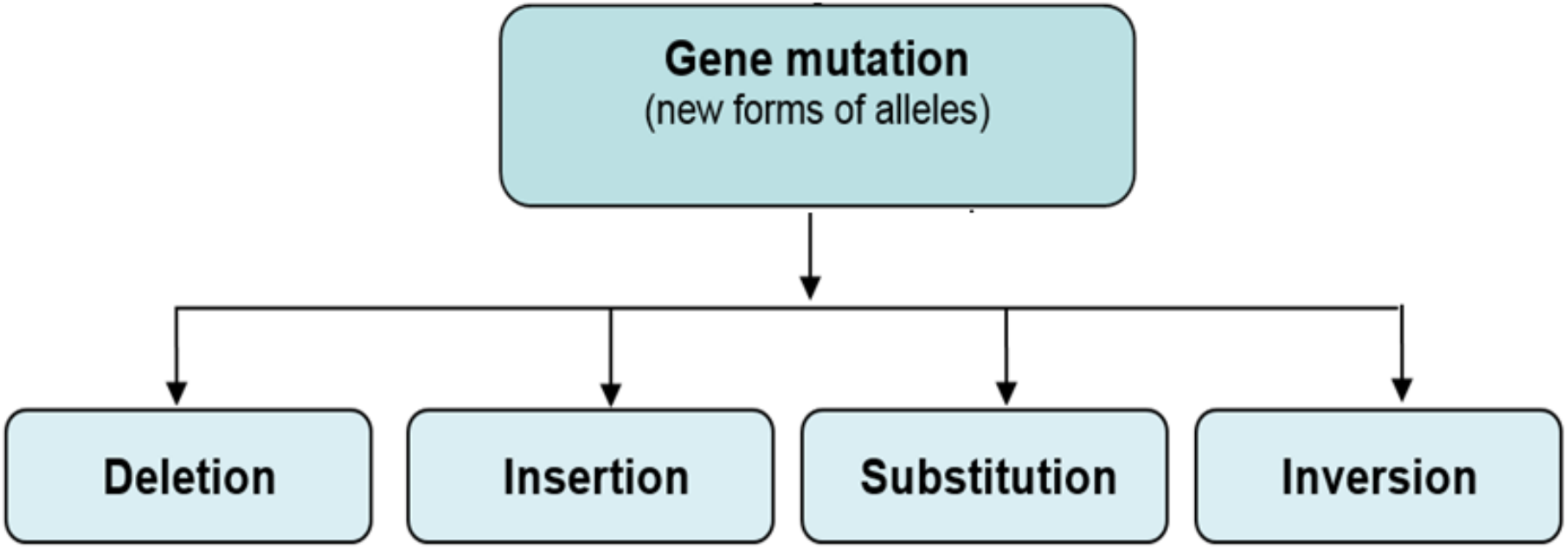


4) Inversion

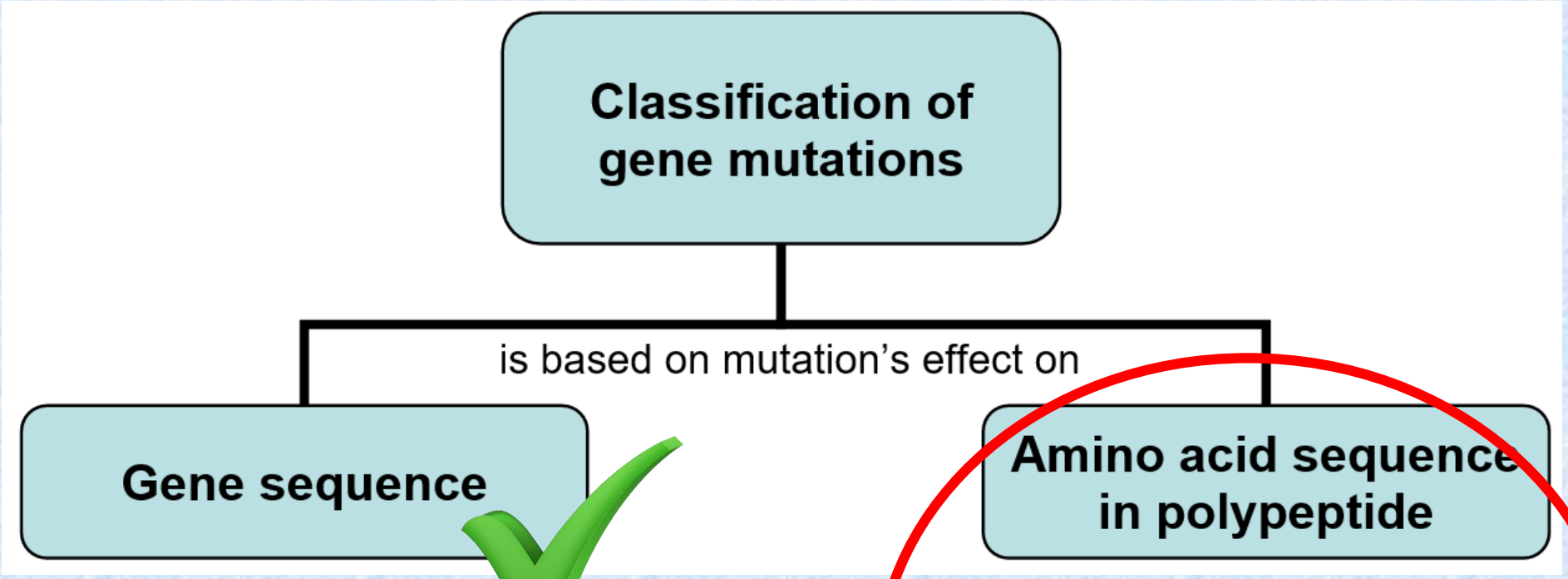
- Several nucleotides are **inverted (or switch positions)** from the sequence



Consolidate (1 min)



Types of gene mutations



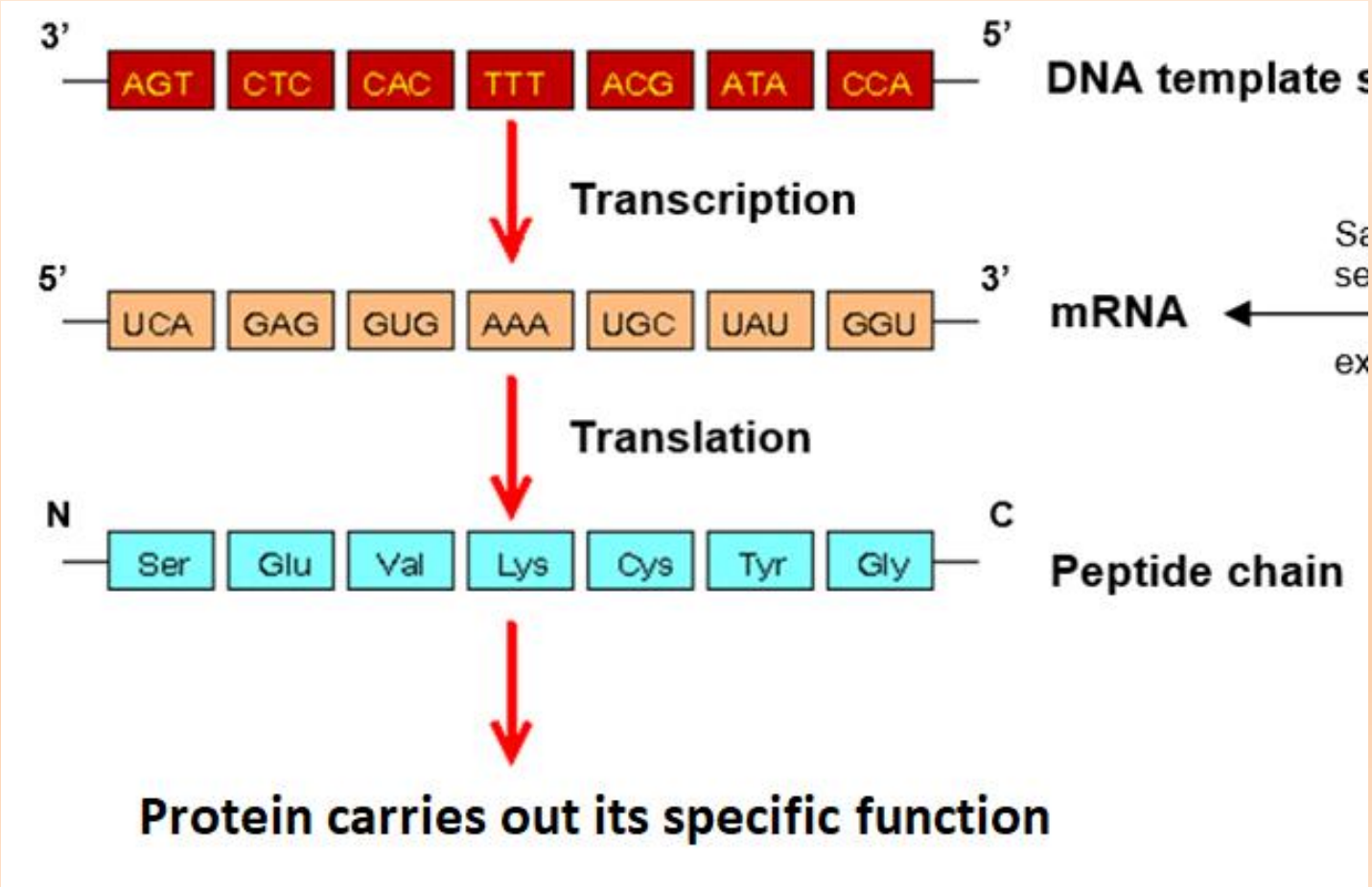
1. Insertion
2. Deletion
3. Substitution
4. Inversion

1. Silent
2. Neutral
3. Missense
4. Nonsense
5. Frameshift

Not in Notes

Question 1

Will a change in DNA sequence **always** result in a change in its **protein's primary structure**?



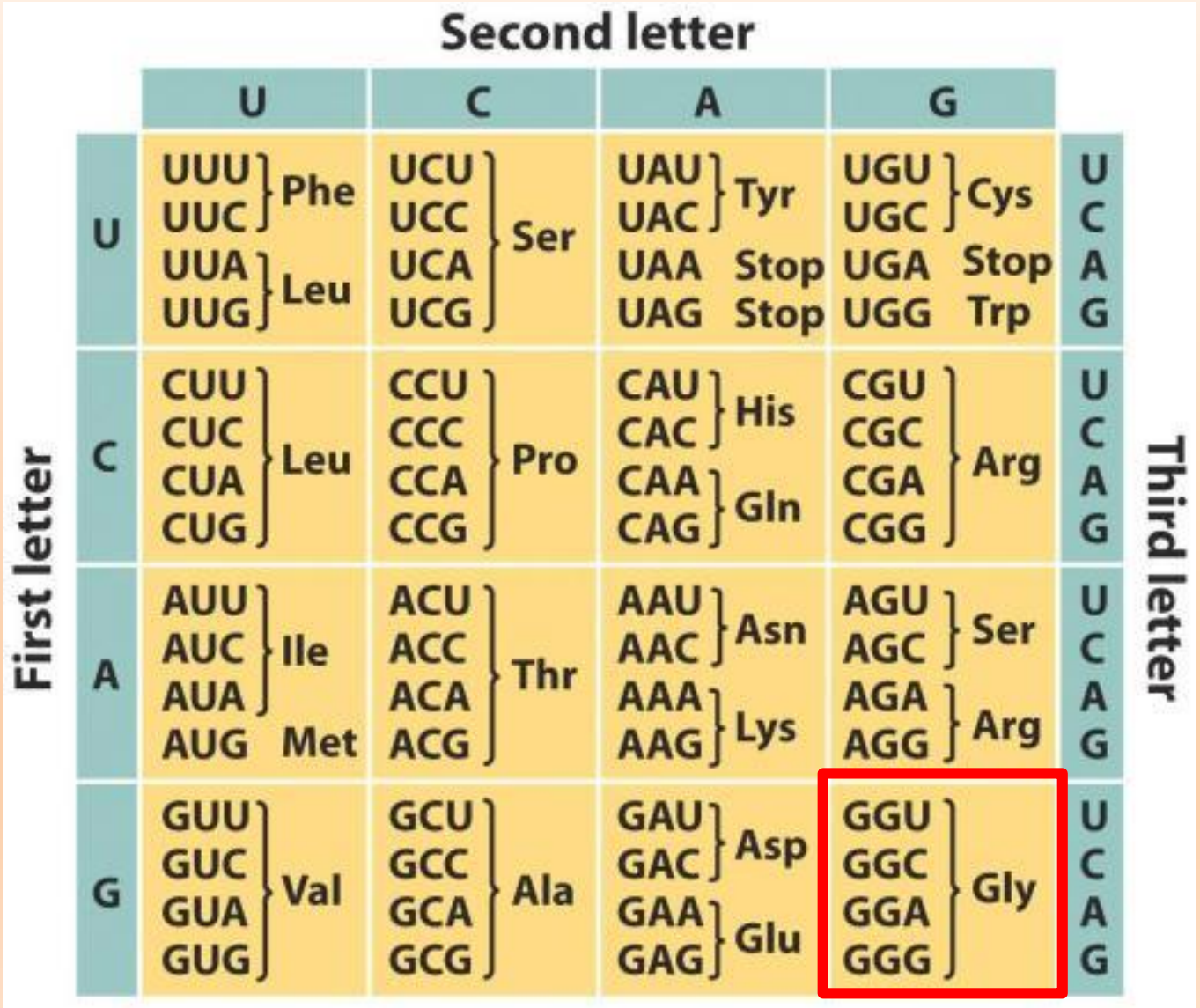
1) Silent mutations

- Refer to mutations that do **not** change the amino acid sequence of a protein.

- **Reason**: The **altered** codon still codes for the **same amino acid** due to the **degeneracy of the genetic code**.

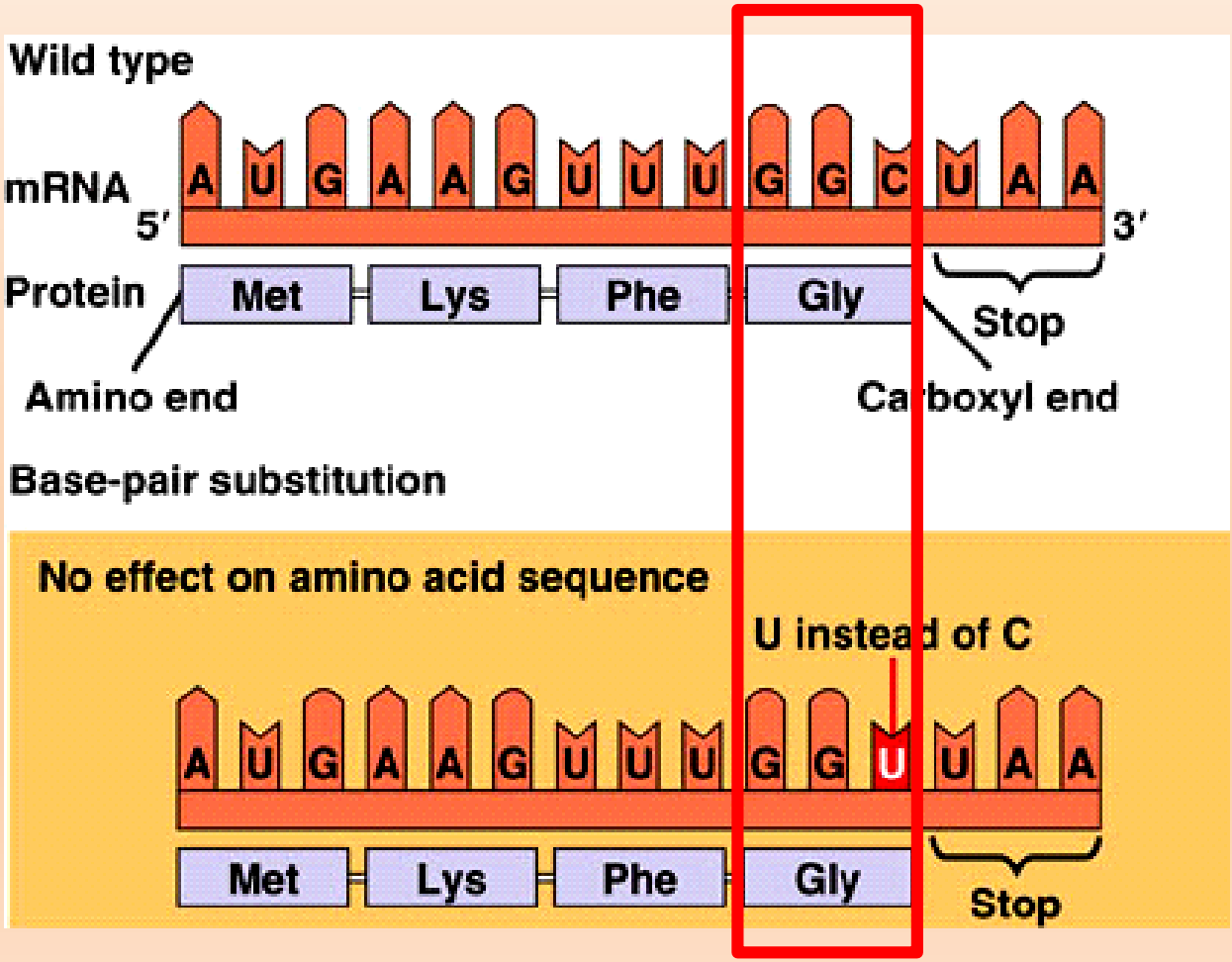
Not in Notes

Genetic Code Table



1) Silent mutations

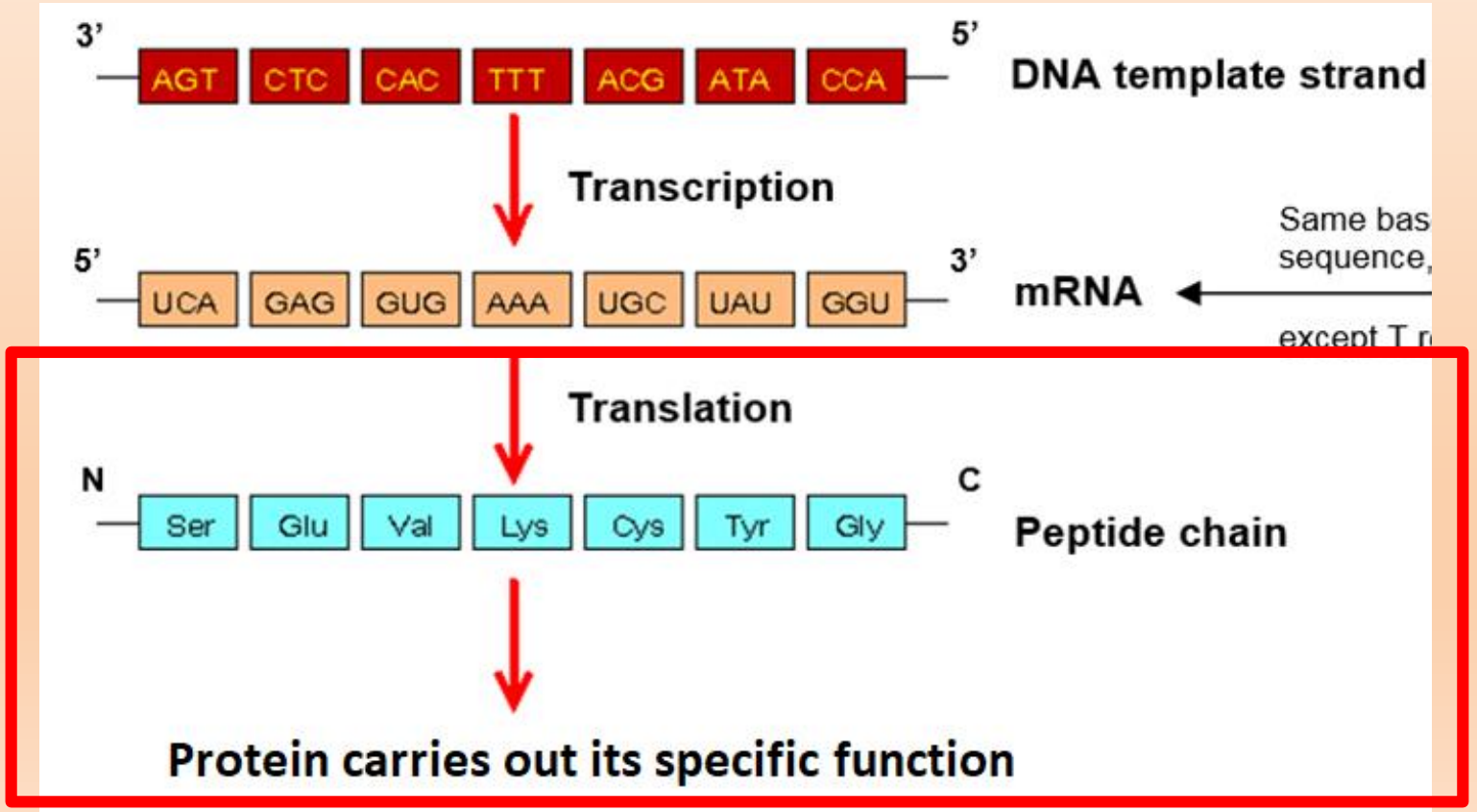
- By base substitution



Not in Notes

Question 2

Will a change in primary structure **always** result in a change in its **protein's functional properties**?



2) Neutral mutations

- Refers to mutations that **alter the normal codon** **BUT** has **no effect on the property & function** of the encoded protein.

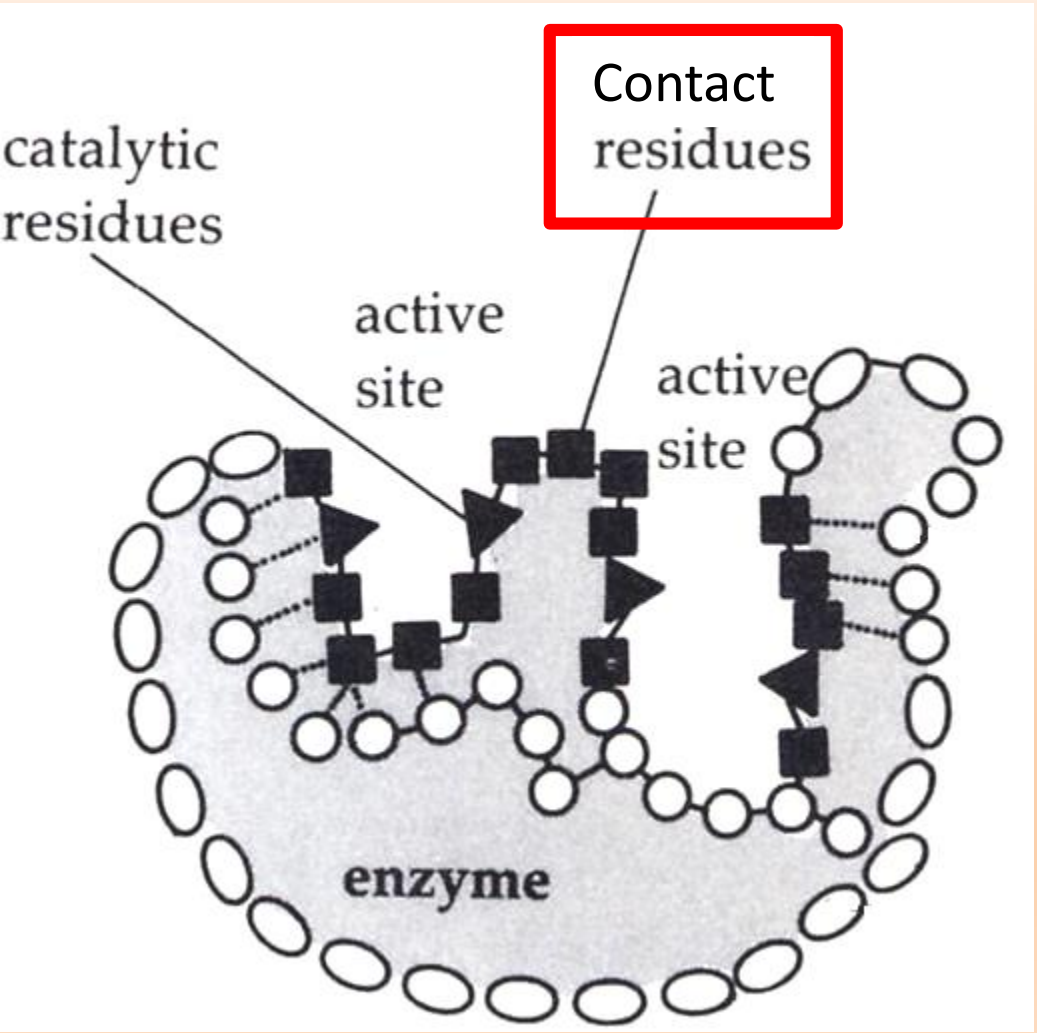
- Generally by base **substitution.**

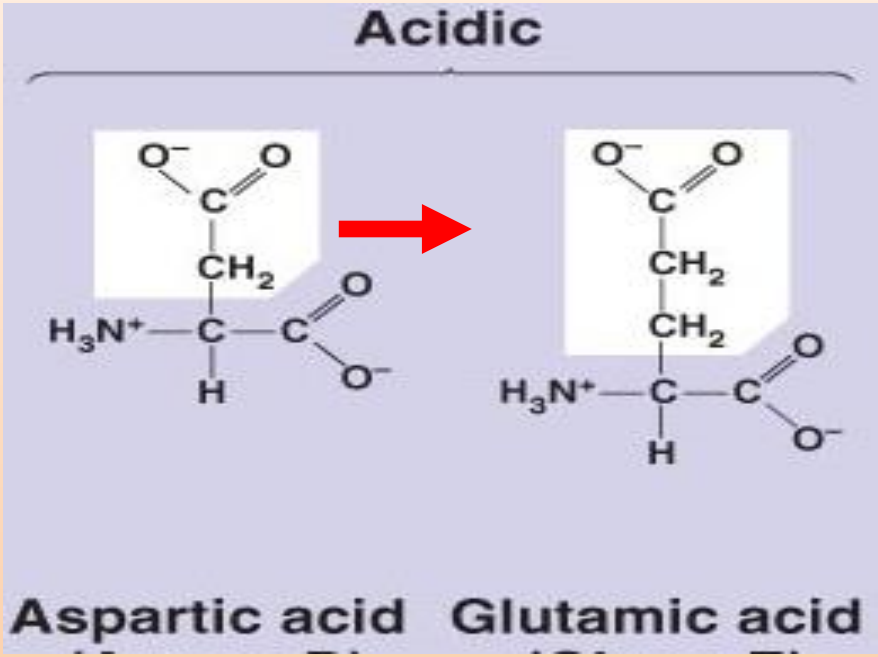
2) Neutral mutations

- Two possible instances:
  a) The altered codon encodes for a **different amino acid**
  BUT this amino acid's **R-group has similar chemical properties** as that of original amino acid.

Not in Notes

e.g. enzyme





2) Neutral mutations

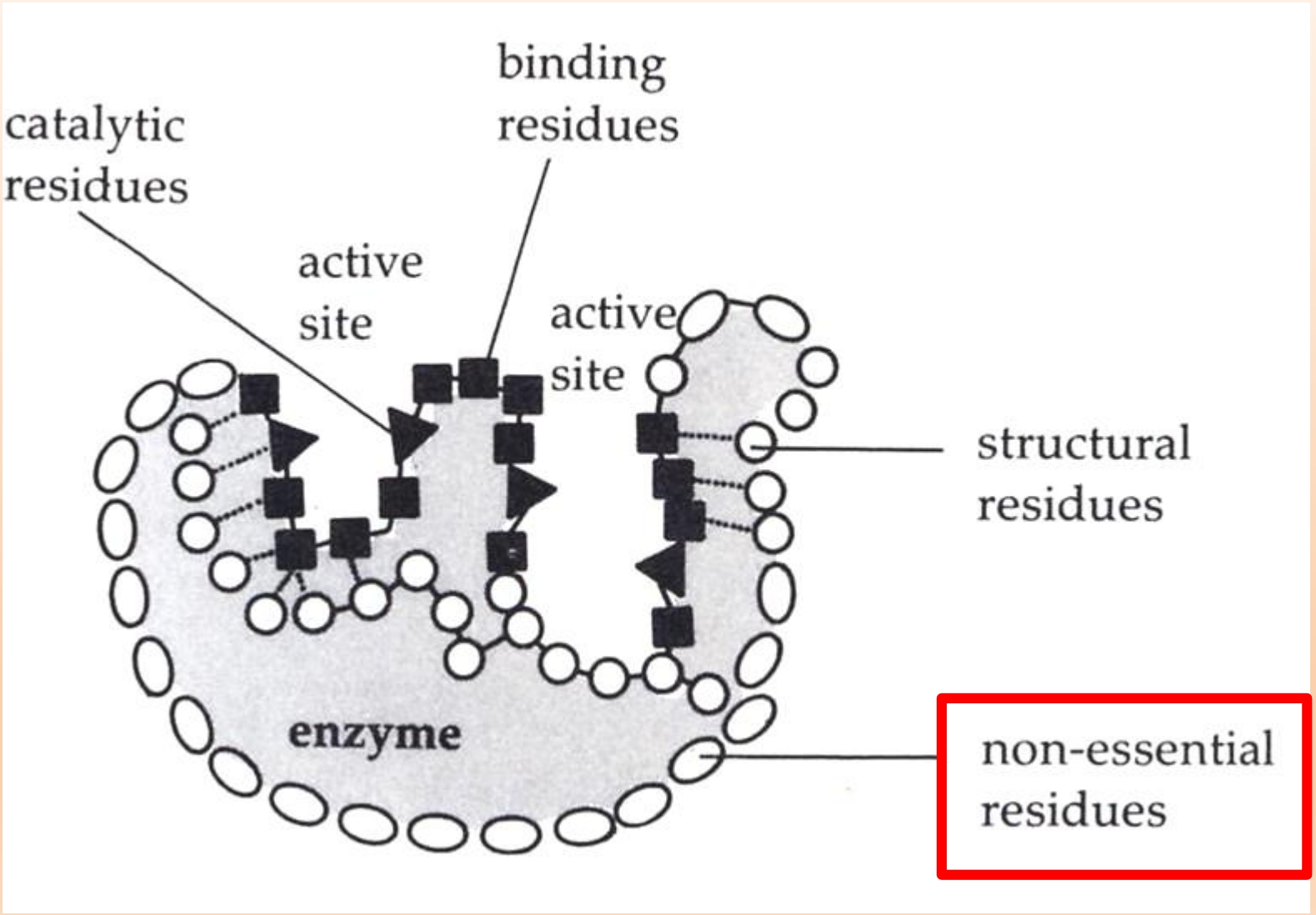
Two possible instances:

b) The altered codon encodes for a **different amino acid**

BUT it is found in a region of the protein where the **exact sequence** of amino acids is **NOT essential to the protein's function**.

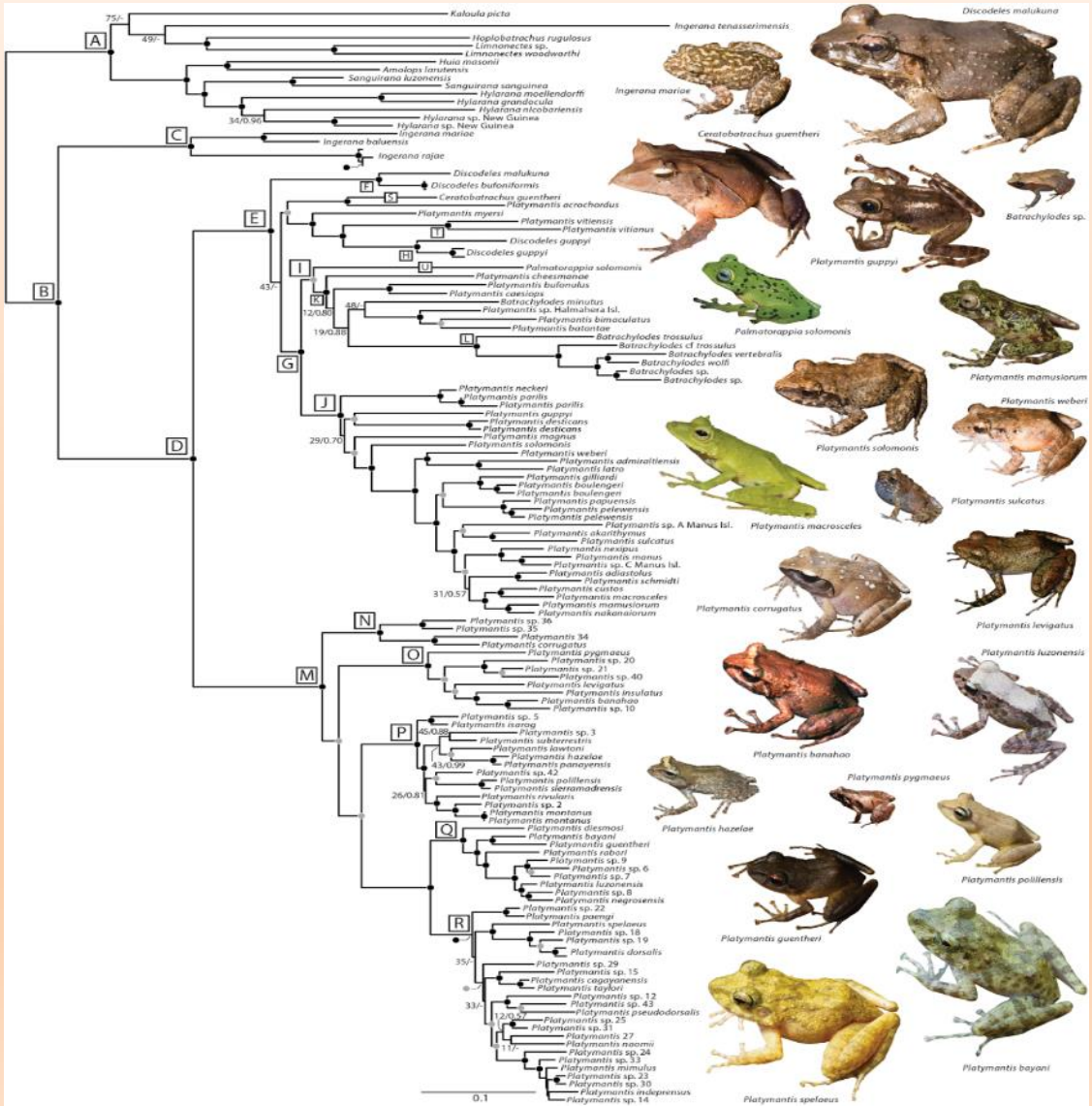
Not in Notes

E.g. enzyme



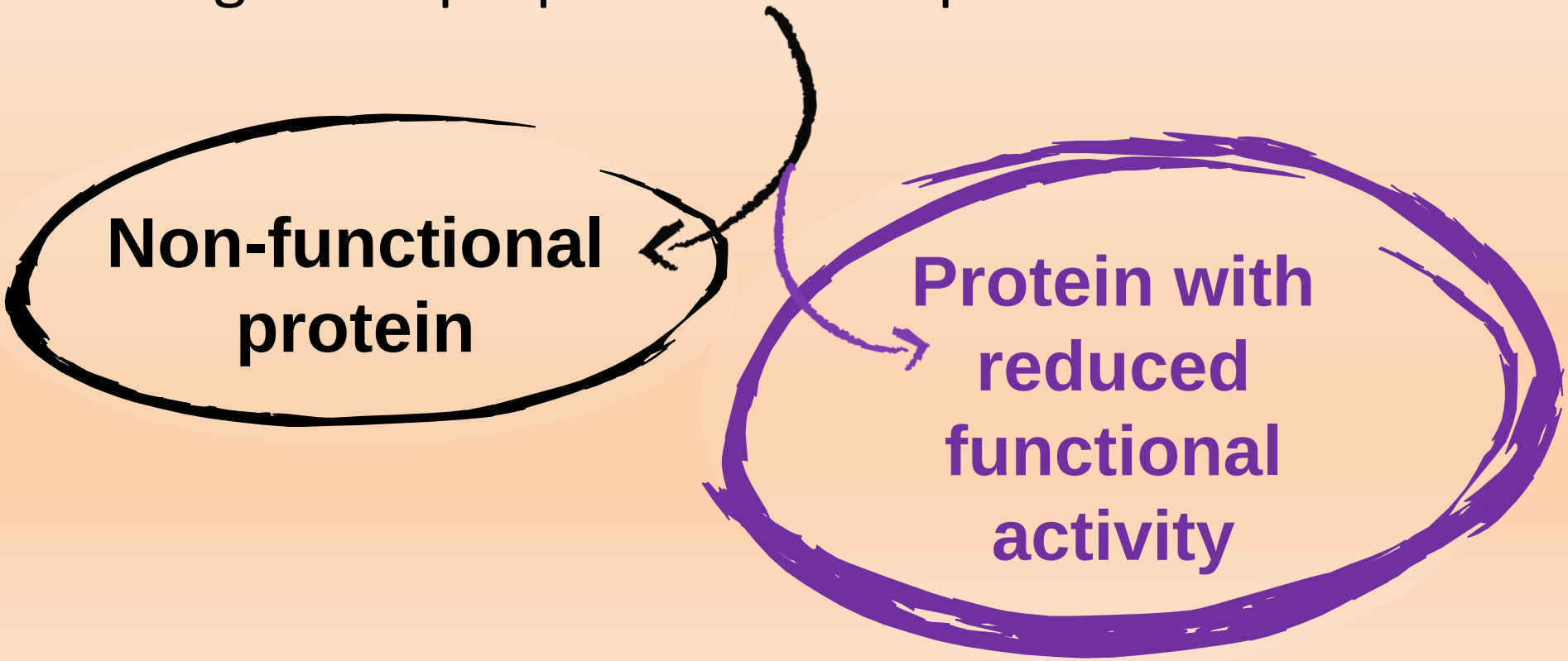
2) Neutral mutations

Play an important role in **molecular evolution**



3) Missense mutations

The altered codon encodes for a **different amino acid** which has **different chemical properties** → changes the properties of the protein



3) Missense mutations

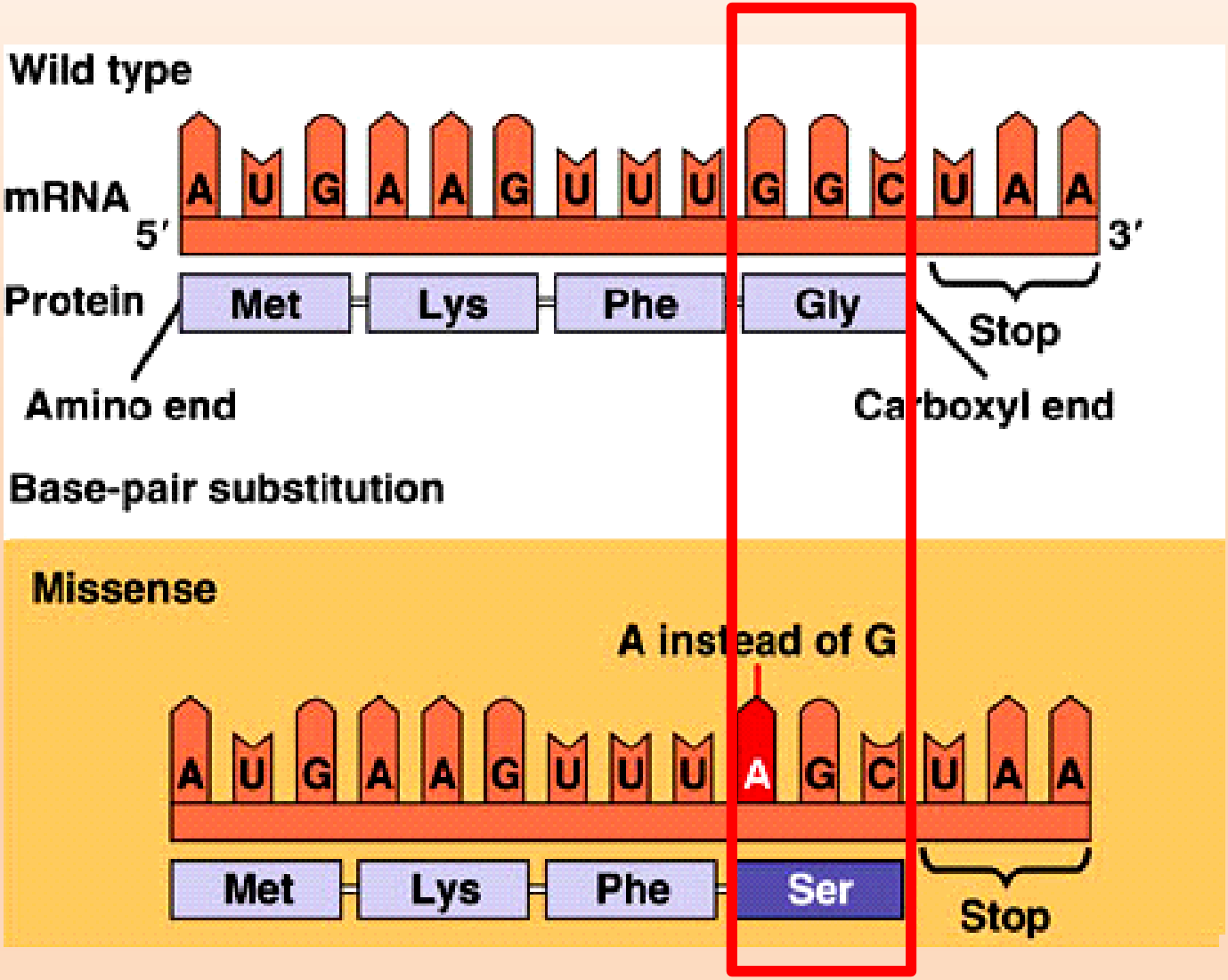
- By base **substitution**

e.g. **sickle-cell anaemia**

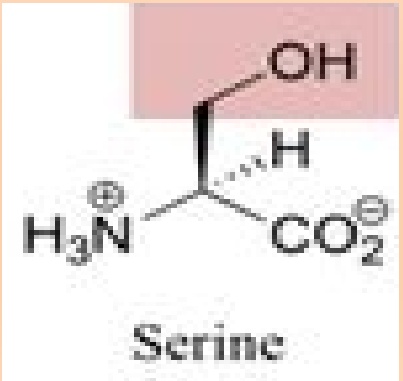
To insert into notes

- Can also occur or by **insertion** or **deletion** of bases in multiples of three (i.e. one or more codons)

3) Missense mutations



non-polar



polar

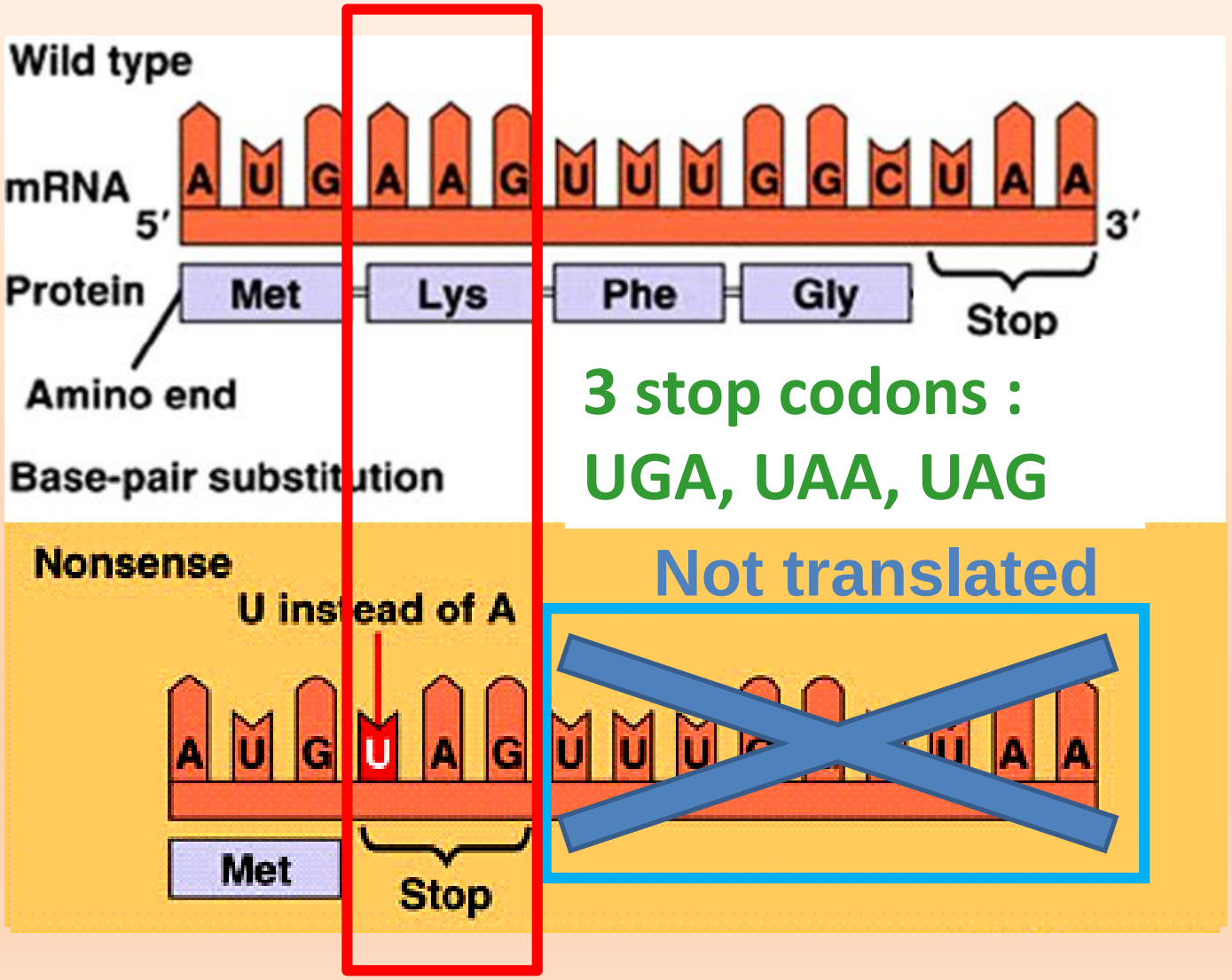
4) Nonsense mutations

shortened

- Refer to mutations that result in a **truncated** protein.
- The altered codon encodes for a **stop codon** which results in the **premature termination** of translation.

- Resulting polypeptide would be **shorter** than the polypeptide encoded by the normal gene and it is usually **non-functional.**
- By base substitution, insertion or deletion.

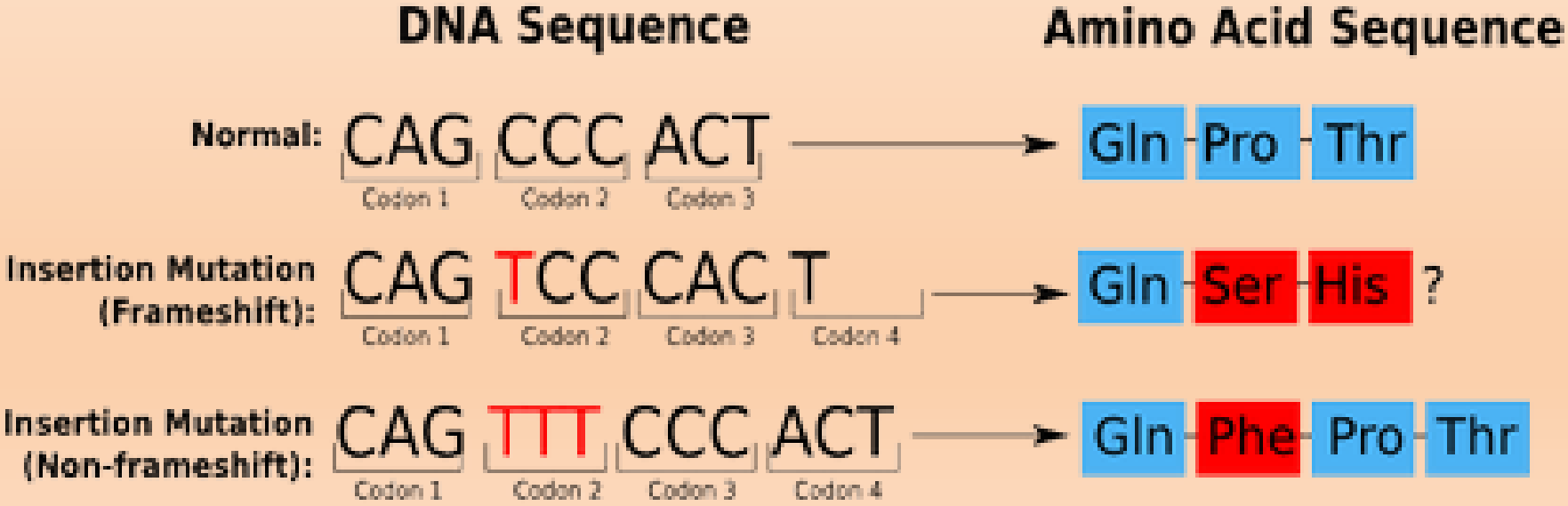
4) Nonsense mutations



5) Frameshift mutations

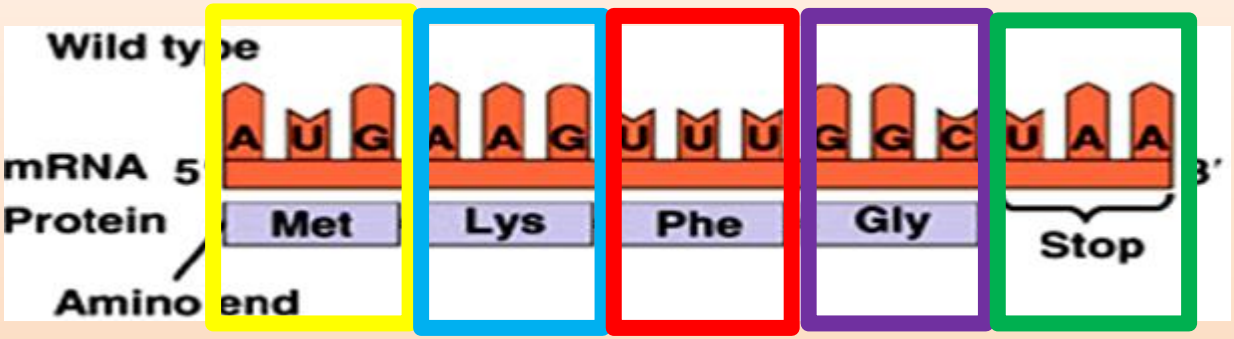
Mutations that cause the triplet **reading frame** of mRNA to be shifted

By (1 or 2) base insertion or deletion.



Not in notes

5) Frameshift mutations



Reading frame *(noun)*

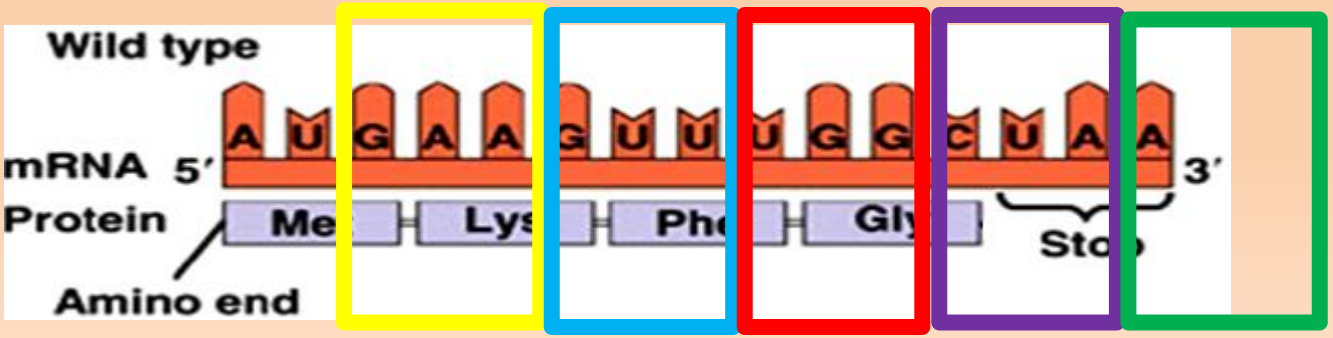
The grouping of three successive bases of DNA that constitutes the codons for the amino acids encoded by the DNA.

5) Frameshift mutations

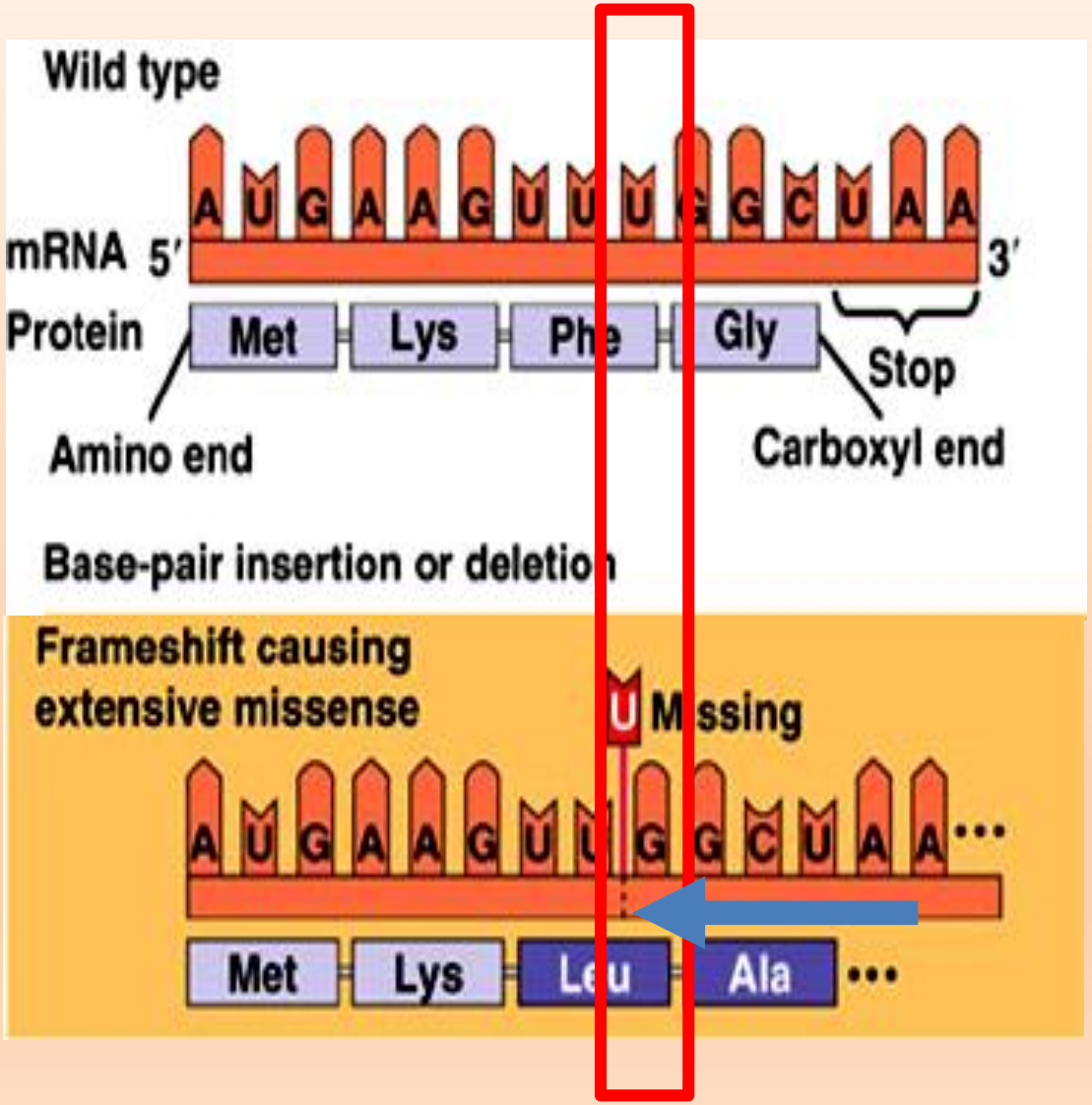
- As mRNA is read as a series of nucleotide **triplets** during translation,

in non-multiples of 3 base pairs

- base **insertion** or **deletion** in the gene causes a catastrophic effect as ribosomes now read incorrect triplets on the mRNA from the point of insertion/deletion.

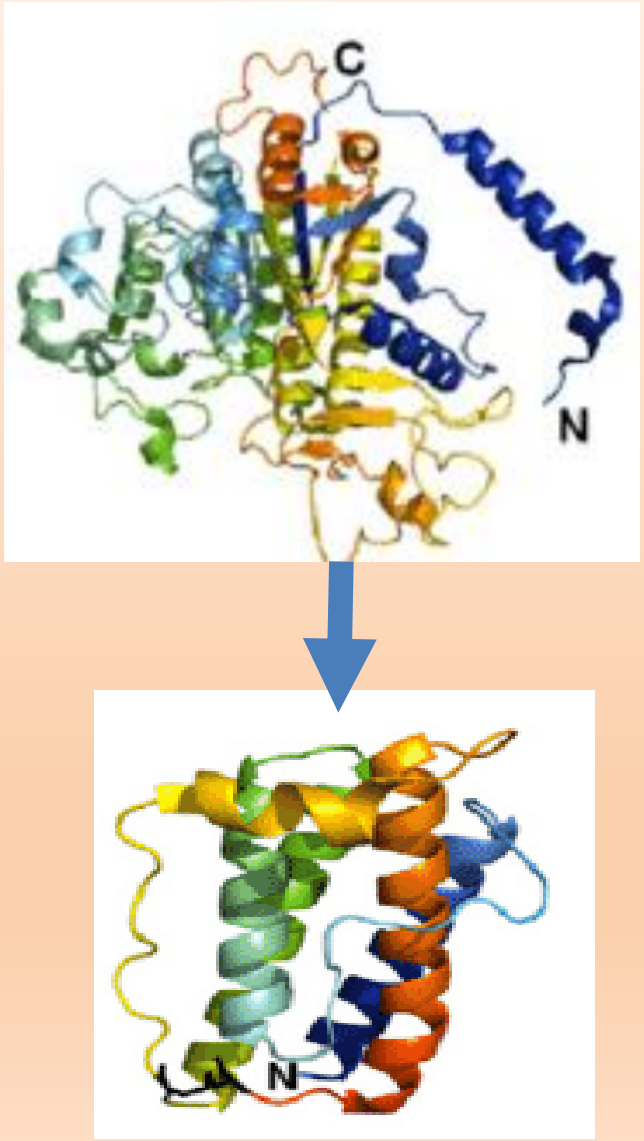


5) Frameshift mutations



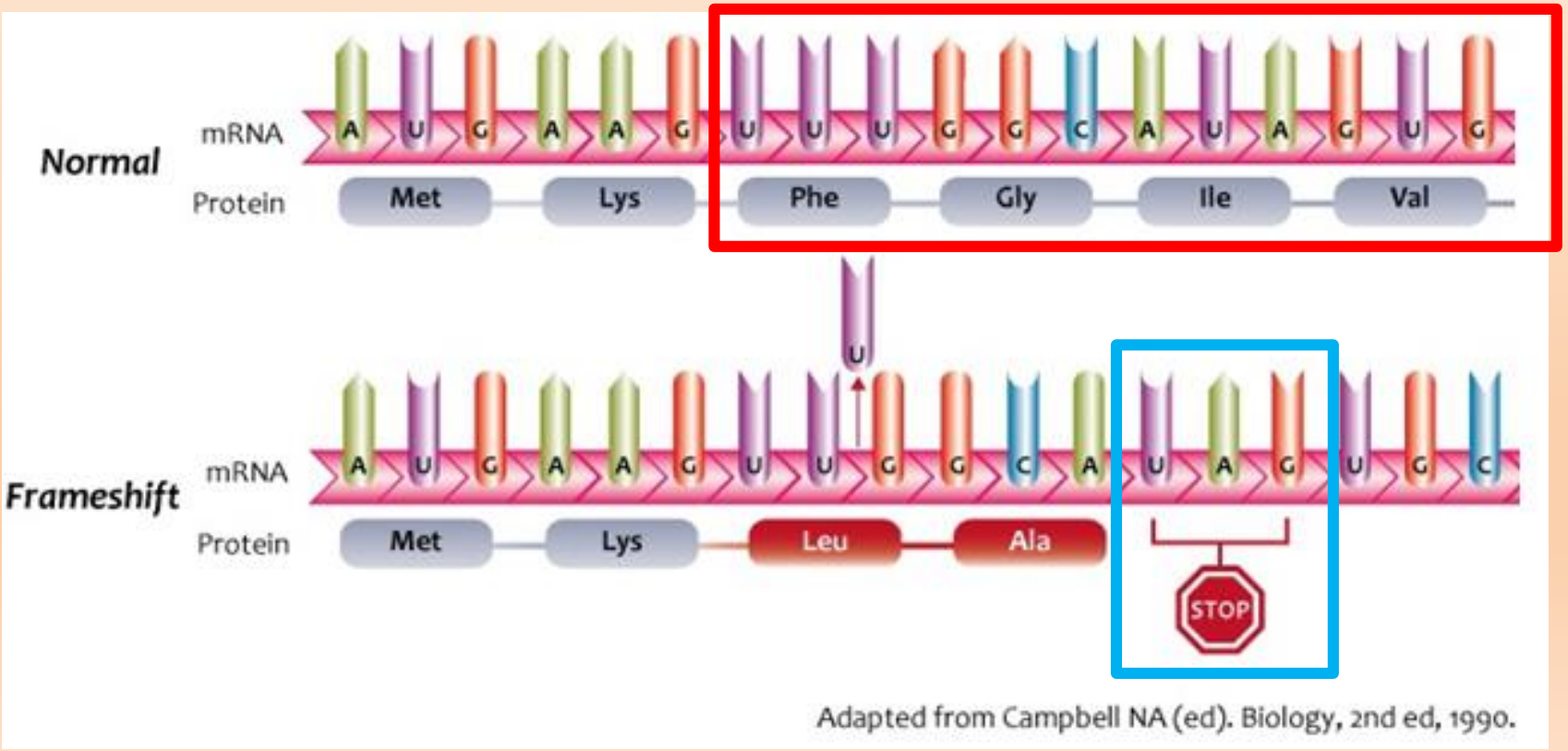
5) Frameshift mutations

- **Effect 1** = The **protein** specified by the new codons is **most likely <u>non-functional</u>**
- *unless the frameshift is very near the end of the gene.*

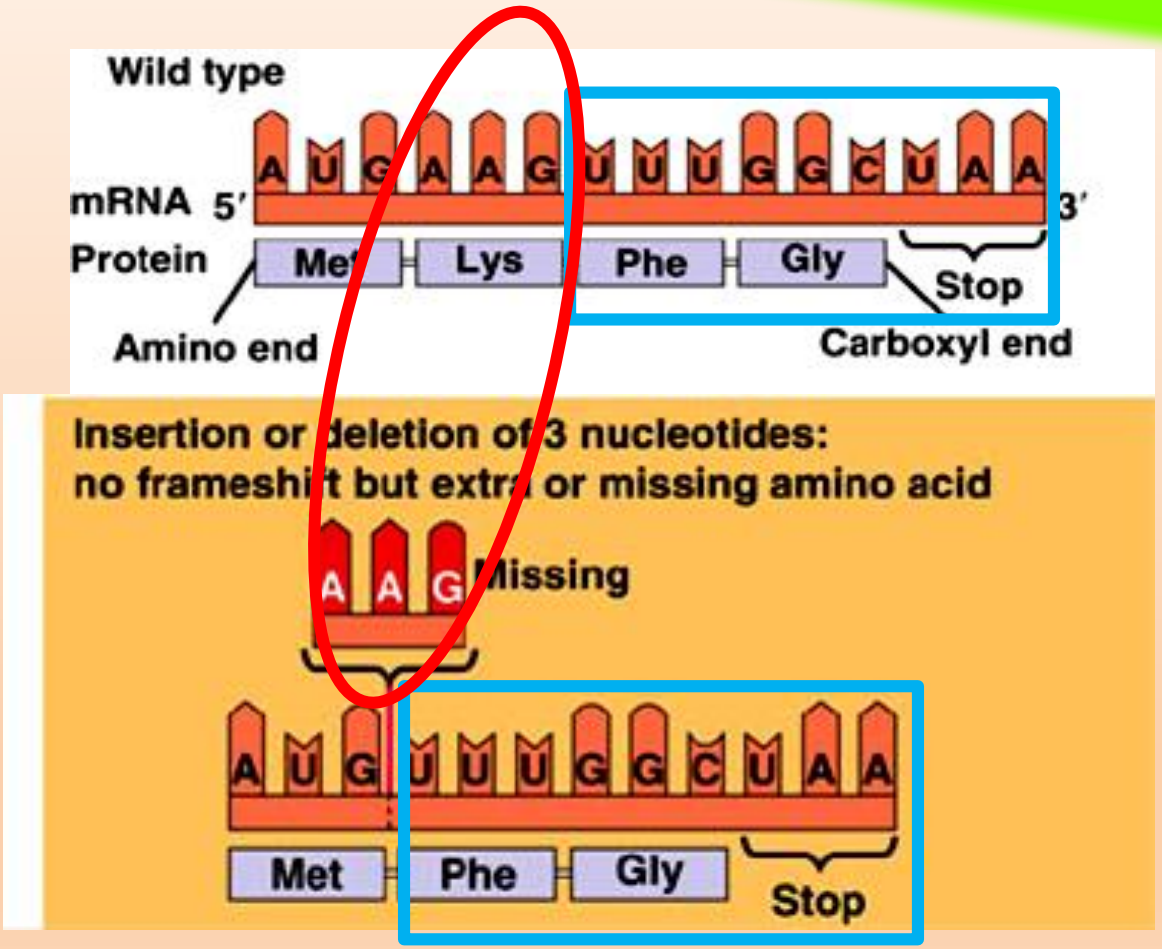


5) Frameshift mutations

Effect 2: Frameshifts **often** create **new stop codons**, thus generating **nonsense mutations,** leading to premature termination of translation.



Important



Effects of **deleting/inserting** **3 consecutive nucleotides** are not as severe because only **one or two amino acid** is removed/added.

Not in Notes

Consolidate

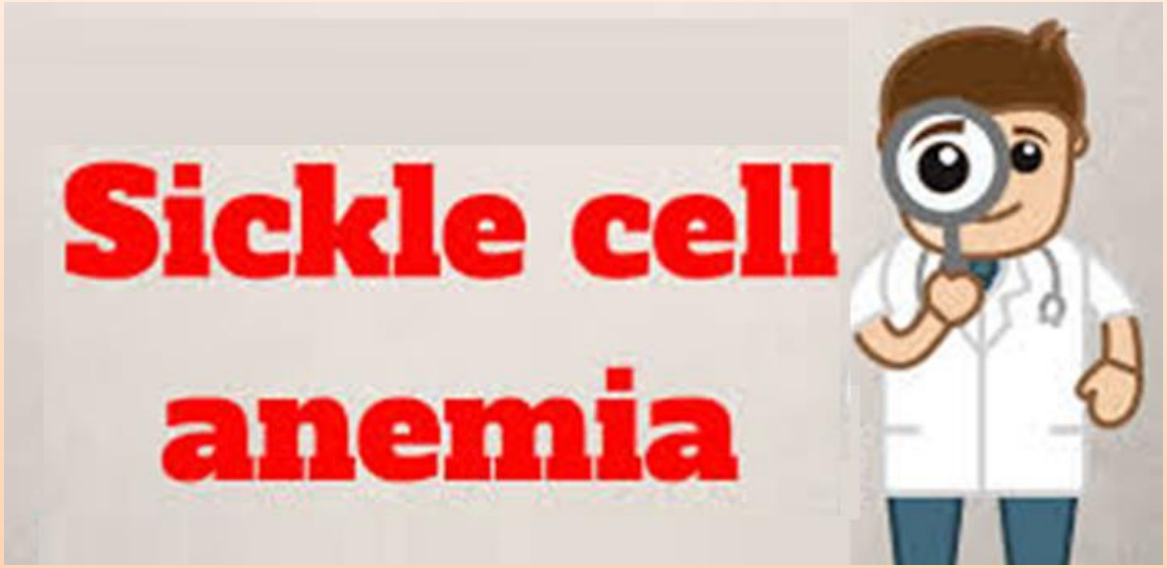
New protein encoded by mutated gene [CLUE]	Gene Mutation (Effect on polypeptide)
A) A very very different protein	**Frameshift**
B) A truncated protein	**Nonsense**
C) Non - / less functional protein	**Missense**
D) Protein with different primary structure, but same function	**Neutral**
E) Exactly the same protein	**Silent**

Summary

- 2(l)
  Explain what is meant by the terms **gene mutation** and chromosomal aberration.
  For gene mutation, knowledge of how substitution, addition and deletion could change the amino acid sequence (including frameshift) is required.

2(m)
Explain how gene mutations can result in diseases (including sickle cell anaemia).

Case study: Genetic Disease



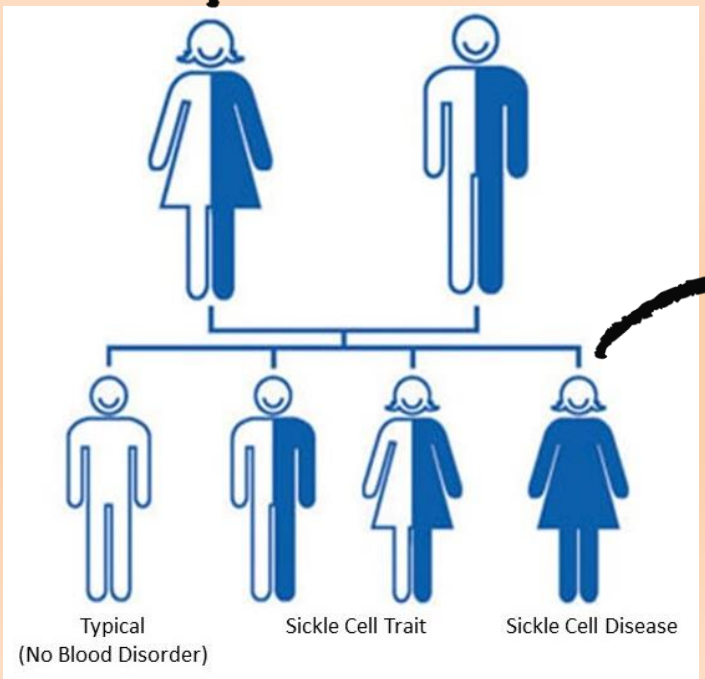
Base substitution & Missense mutation

Case study : sickle cell anaemia

- A **homozygous recessive** disorder
- **2 copies** of the defective allele needed for manifestation of the disease

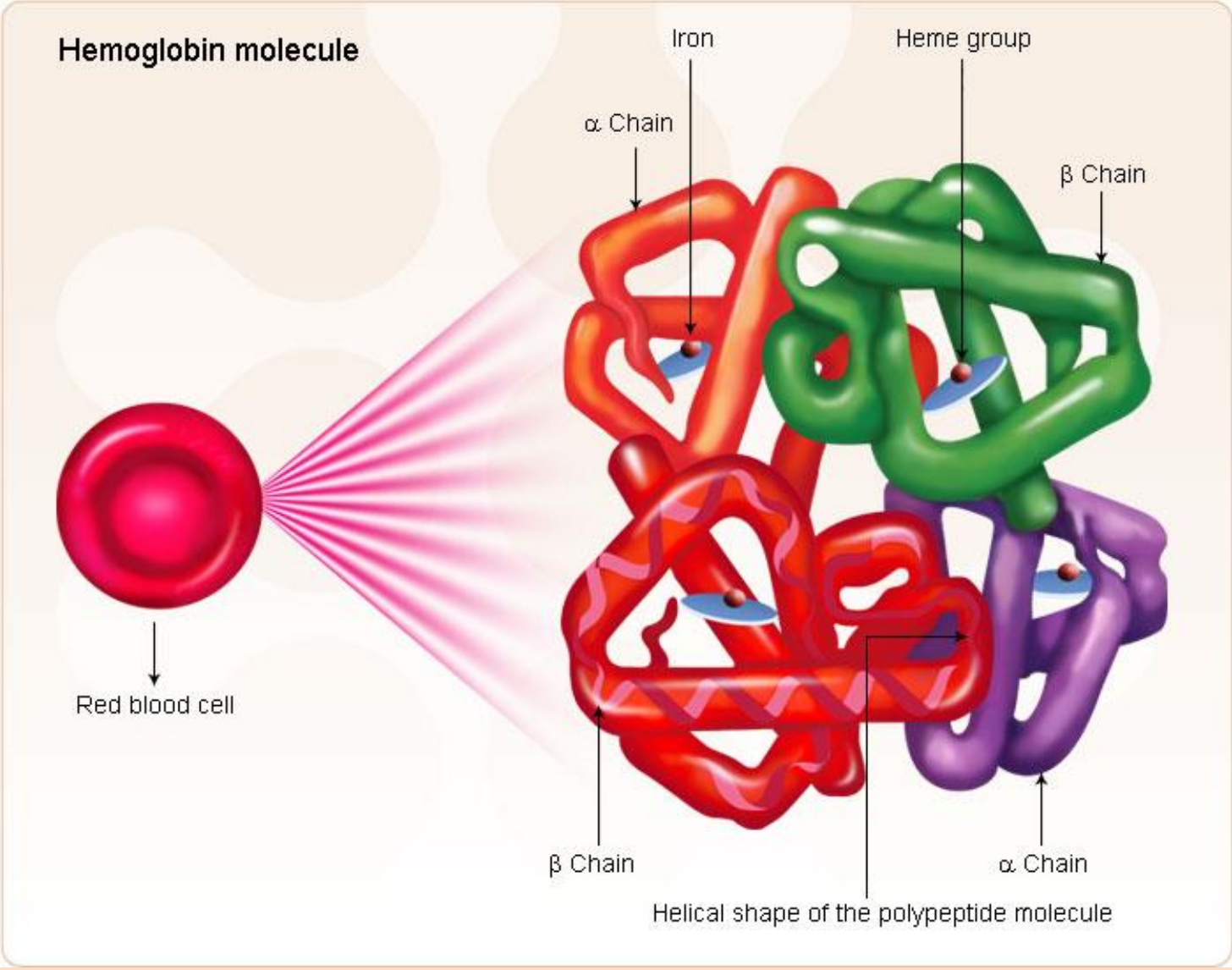
HbA HbS

HbA HbS



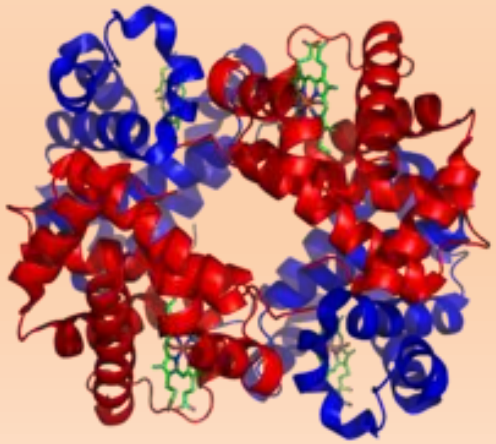
HbS HbS

RECAP - haemoglobin



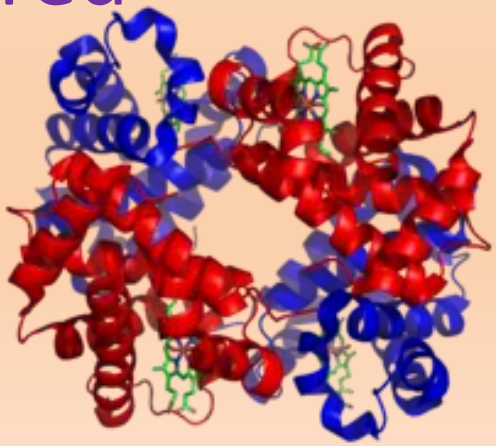
Case study : sickle cell anaemia

- The major form of haemoglobin (**HbA**) has a **quaternary** structure
- contains 2 identical α-chains + 2 identical β-chains.
- The α and β-chains are encoded by **two different genes** found on two different chromosomes.
  - **α chain** : 141 a.a. (Chr 16)
  - **β chain** : 146 a.a. (Chr 11)

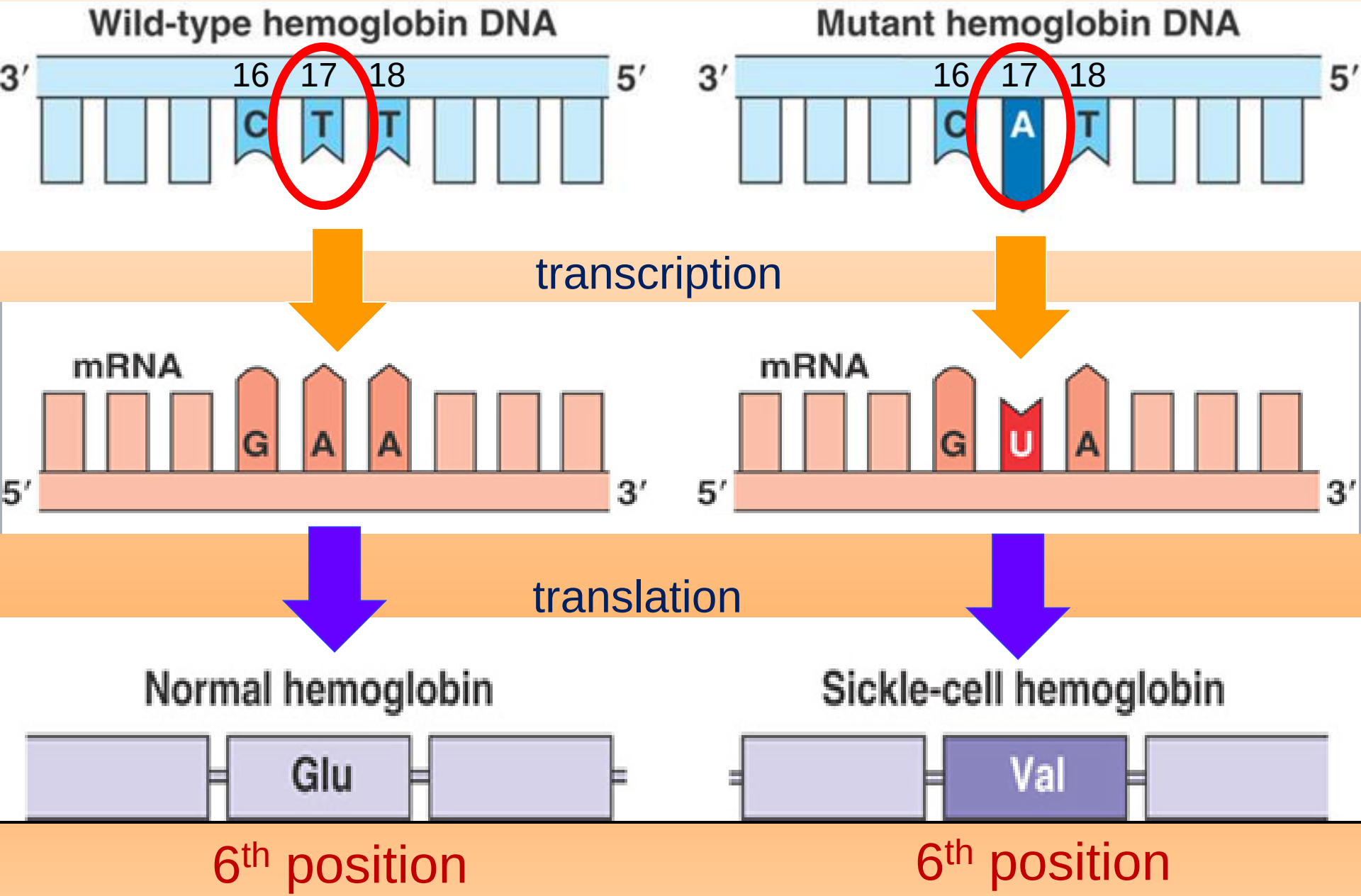


Case study : sickle cell anaemia

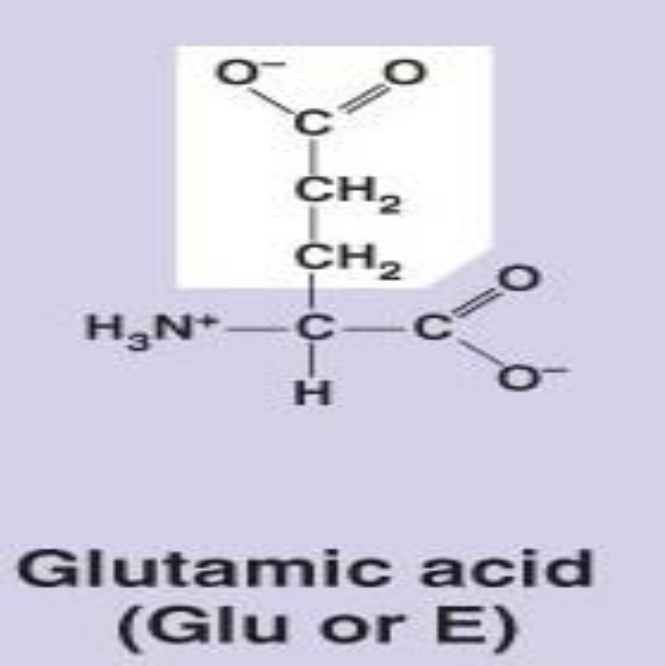
- Sickle-cell anaemia patients have altered haemoglobin known as haemoglobin S, **HbS**
- **α chains** of HbA & HbS are identical but for
- **the gene coding for β chain** in HbS, a **single base substitution** occurred



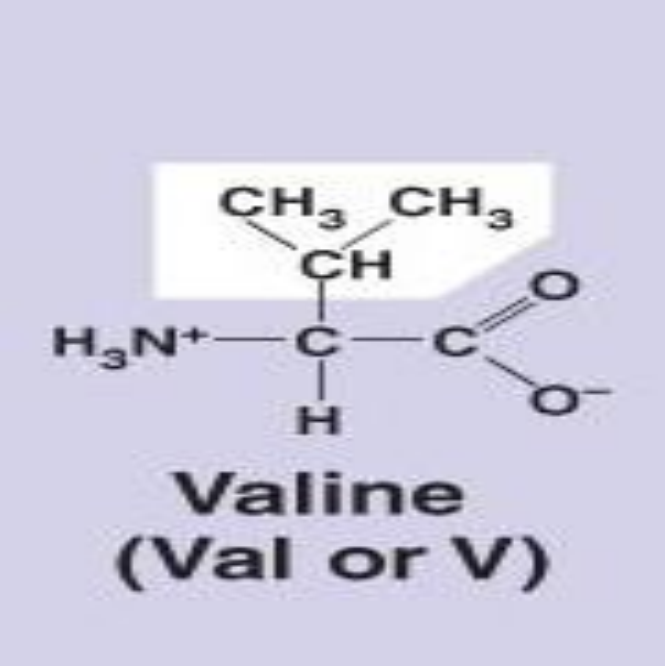
Gene coding for β chain



Case study : sickle cell anaemia



Acidic, hydrophilic



Non-polar, hydrophobic

Case study : sickle cell anaemia

Tertiary structure of haemoglobin changes as the **R groups** of valine **form different interactions** with other amino acids

Case study : sickle cell anaemia

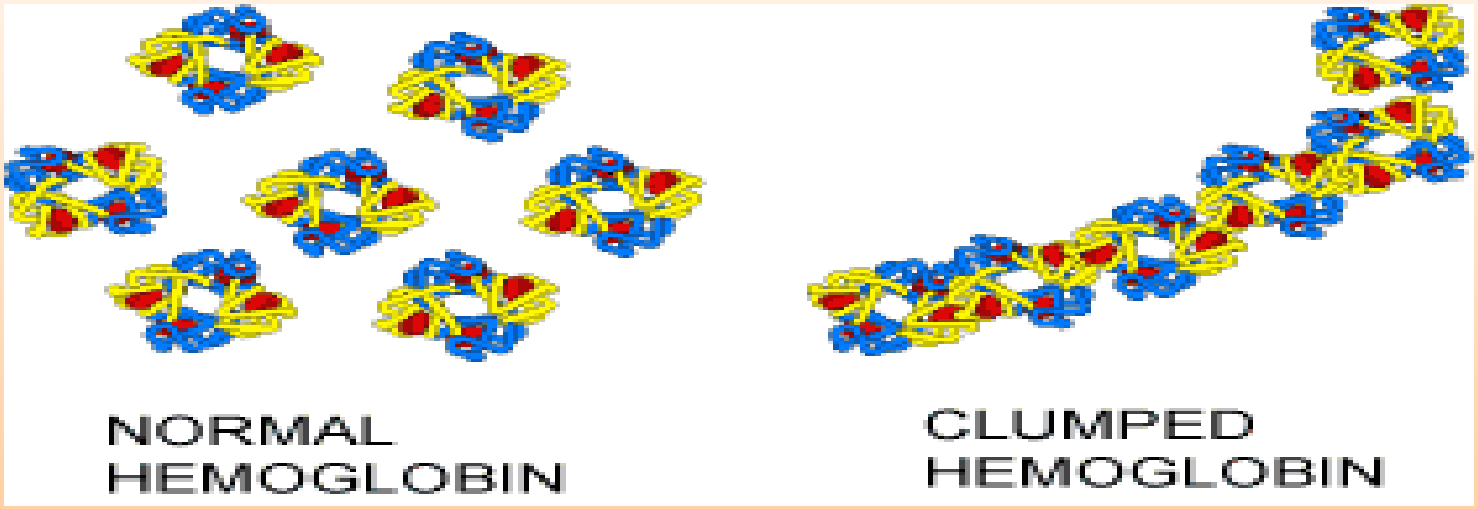
At low oxygen concentrations

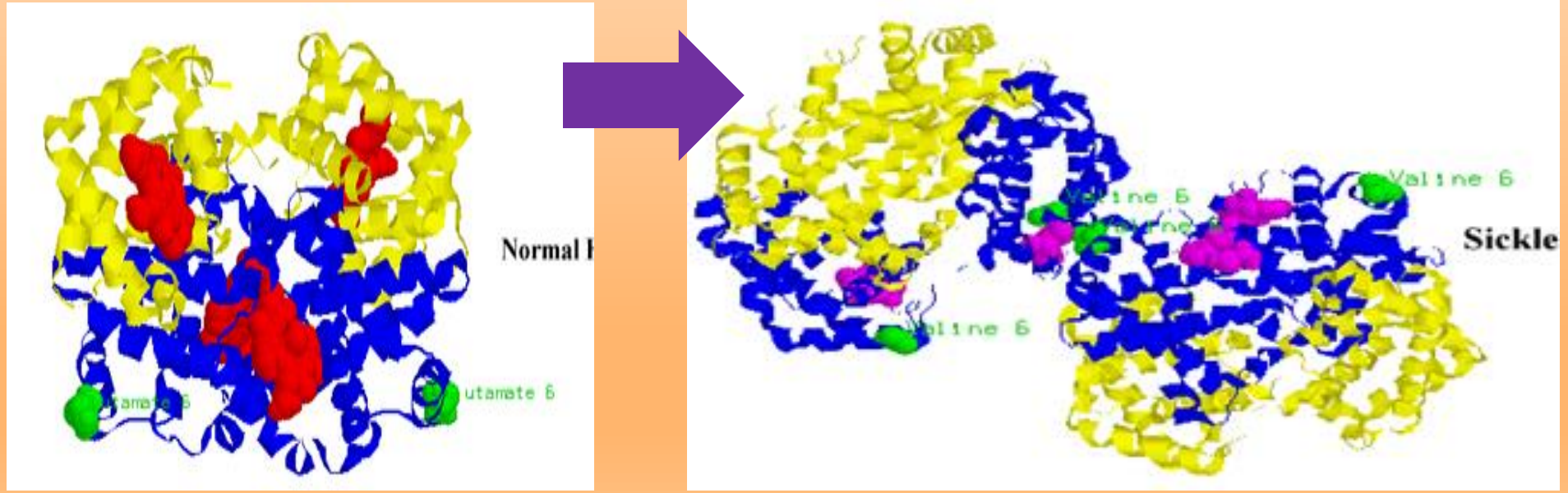
→ **solubility** of deoxygenated HbS decreases

→ HbS molecules stick to each other via their **hydrophobic regions** [valine]

→ **Polymerization** of HbS into **long fibres** inside RBCs

Not in notes





HbA

HbS

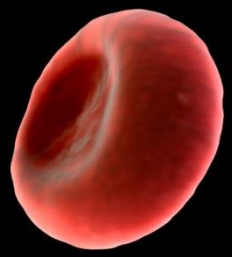
Polymerisation of HbS

https://www.youtube.com/watch?v=-1_qkwQkB_c

Case study : sickle cell anaemia

Long fibres of abnormal haemoglobin **deform** red blood cells into sickle shape

Normal O_2 concentration
Circular, biconcave shape red blood cells

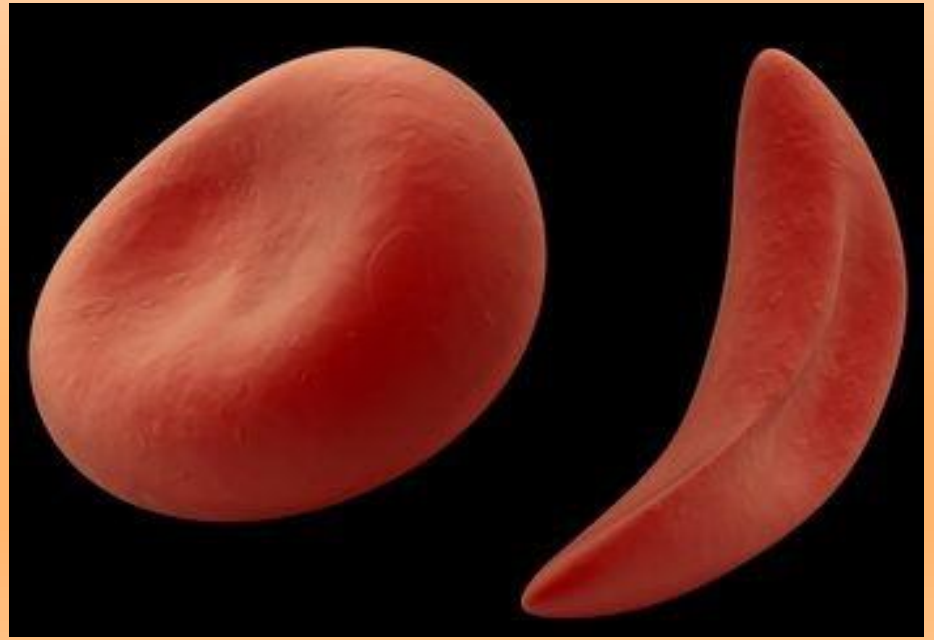


→

Low O_2 concentration
Sickle-shaped red blood cells

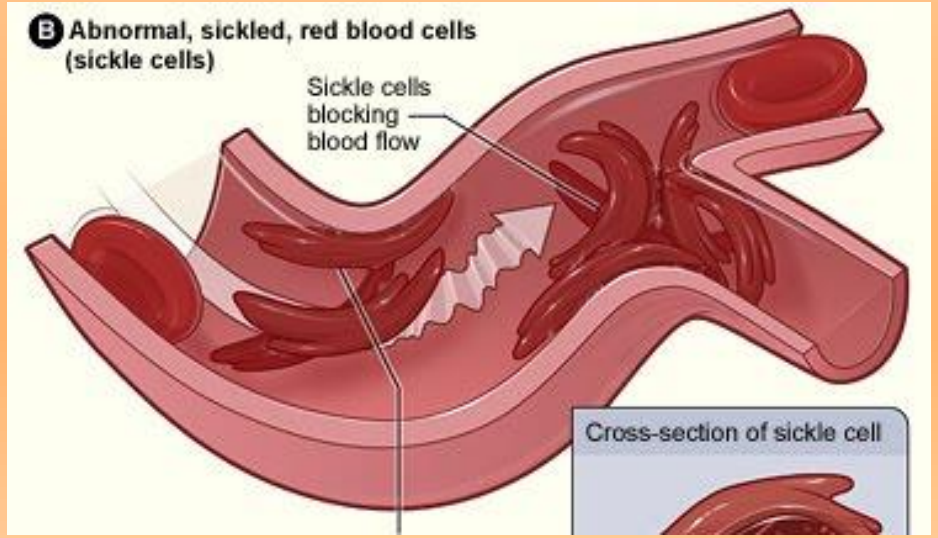
Case study : sickle cell anaemia

- **Consequence 1**: Sickle-shaped red blood cells are **ineffective** in transporting oxygen



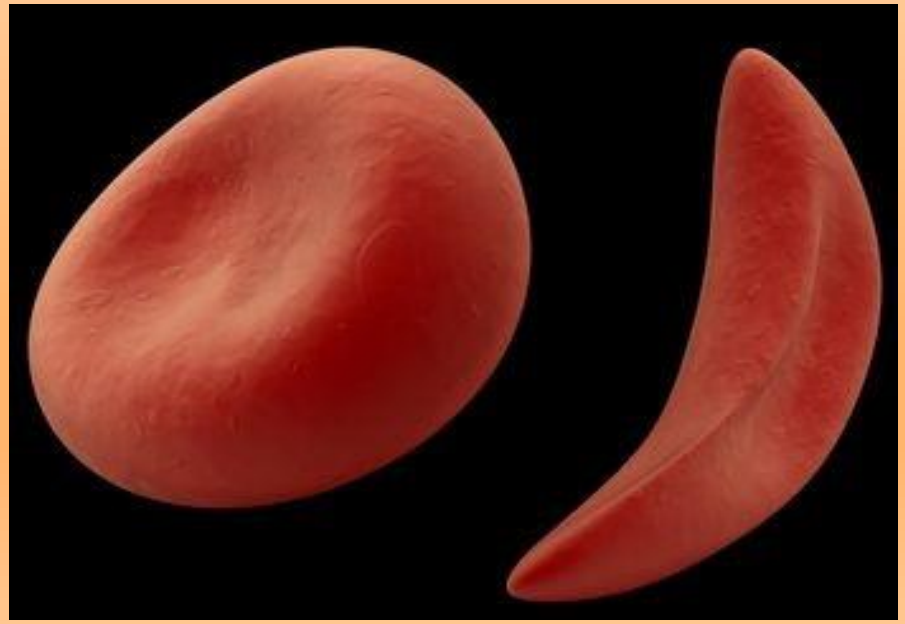
Case study : sickle cell anaemia

- **Consequence 2**: Due to their shape, sickled-shaped red blood cells **clump** to one another and **clog** small capillaries;
- **Obstructing blood flow** -> symptoms such as physical weakness, pain or organ damage



Consequences of sickle cell anaemia

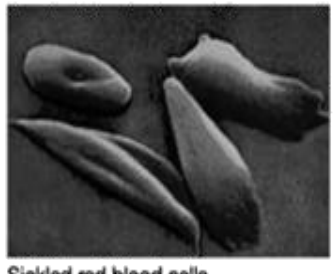
- **Consequence 3**: Sickle-shaped RBCs have a shorter lifespan and haemolyse readily,
- => resulting in **anaemia**



Not in Notes

Comparison Table

Features	Normal condition	Sickle-cell anaemia
Gene coding for β-globin chain	… T …	… A …
Resultant codon on mRNA	… GAA …	… GUA …
Resultant amino acid residue	Glutamic acid	Valine
Resultant haemoglobin	Haemoglobin *A*	Haemoglobin *S*
Solubility of haemoglobin	Soluble	Less soluble
At low oxygen concentration	Remains soluble	Forms rigid fibres
Appearance of red blood cell	Circular biconcave shape	Sickle shape



Summary

- 2(l)
  Explain what is meant by the terms **gene mutation** and chromosomal aberration.
  For gene mutation, knowledge of how substitution, addition and deletion could change the amino acid sequence (including frameshift) is required.

For chromosomal aberration, knowledge of numerical aberration (including aneuploidy, as in the case of trisomy 21, i.e. Down syndrome) and structural aberration (including translocation, duplication, inversion and deletion) is required.

- 2(m)
  Explain how gene mutations can result in diseases (including sickle cell anaemia).