GENETIC MUTATIONS

Mutations

- Mutations are defined as “a sudden genetic change in the DNA sequence that affects genetic information”.
- They can occur at the molecular level (genes) and change a single gene, or at the chromosome level and affect many genes.

- Things that can cause mutations are called “ mutagens ”.
- Known mutagens are ultraviolet light, cigarette smoking, certain chemicals like PCB’s.

The Central Dogma of Molecular Biology

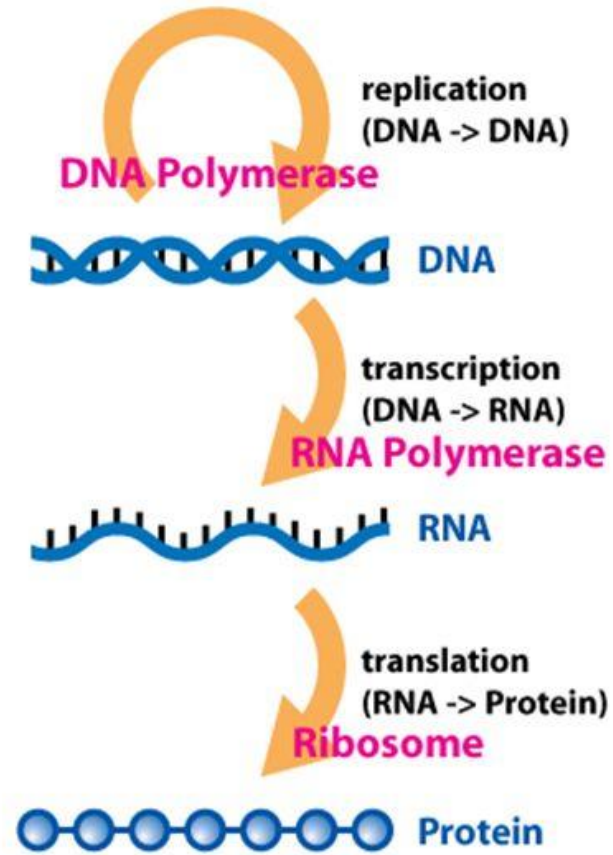
- Information is transferred from DNA to RNA to protein

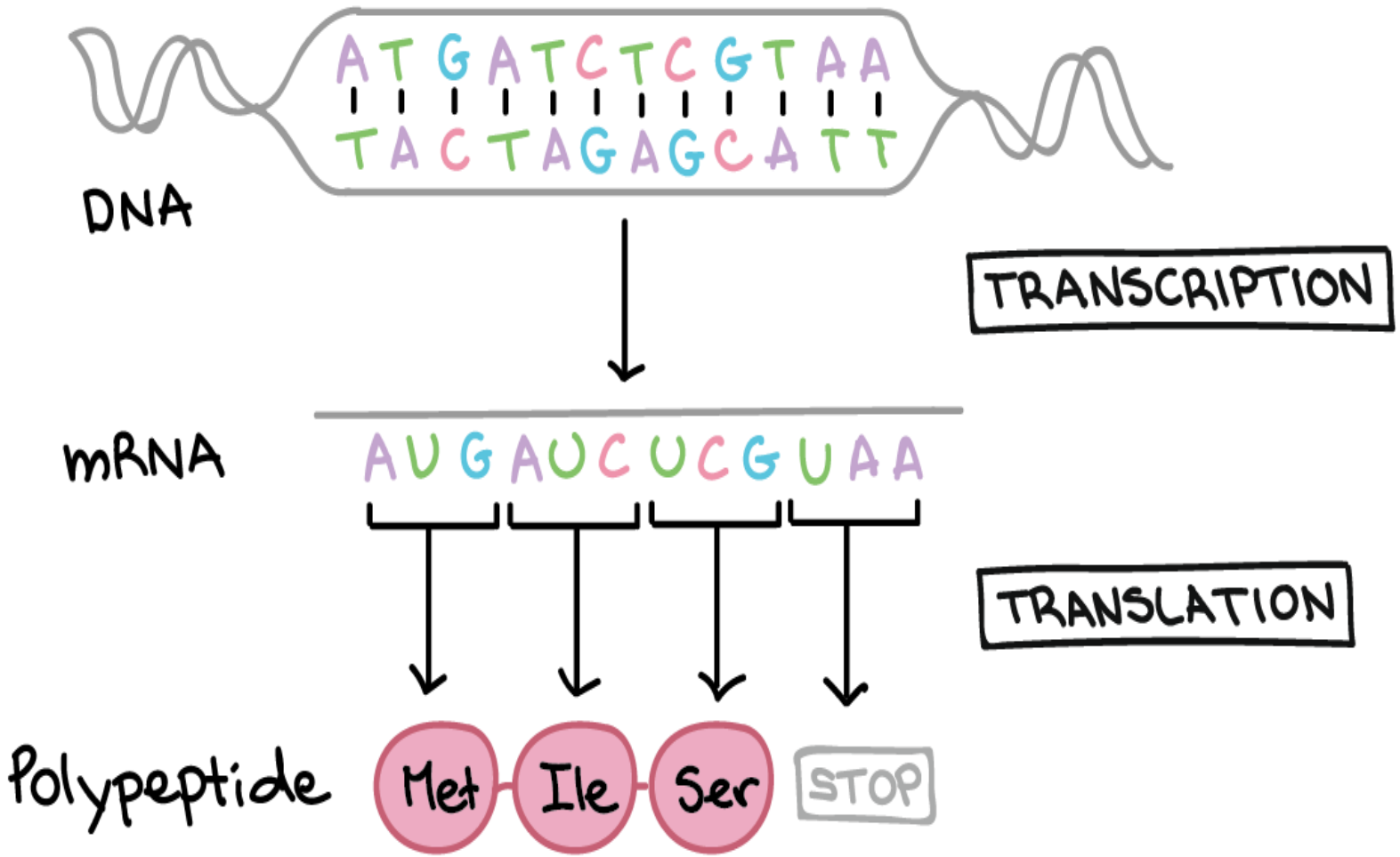
  DNA -> RNA -> Protein

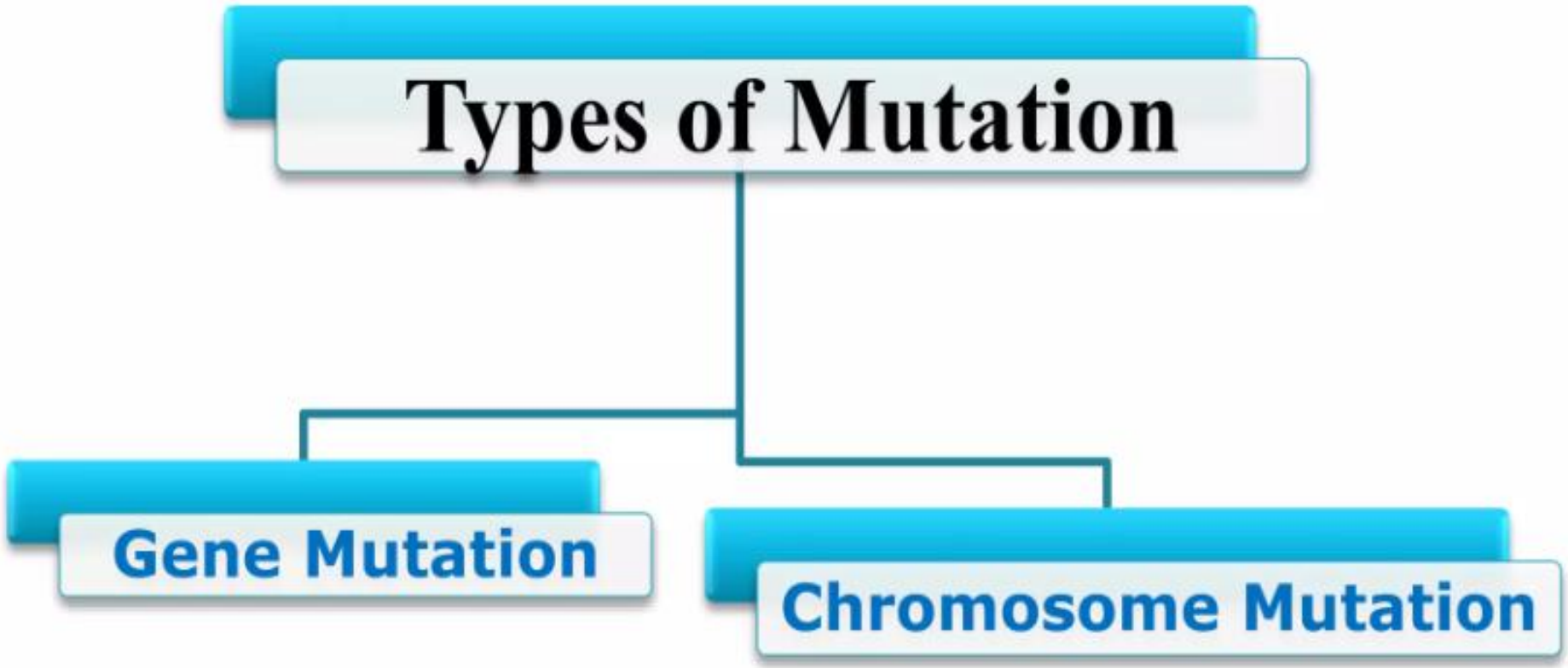
- Proteins create traits

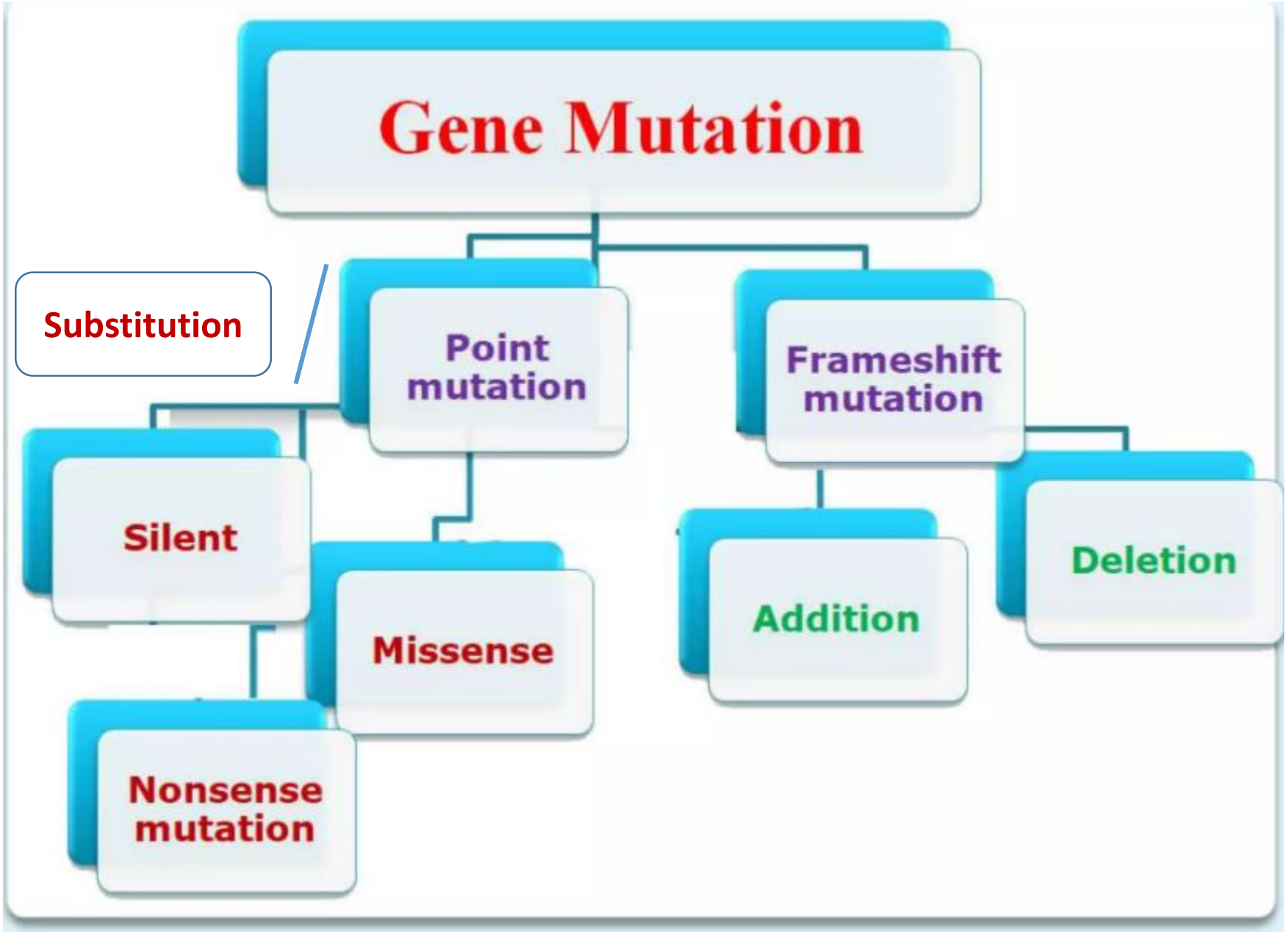
- This is called **gene expression**

- This process is found in all organisms

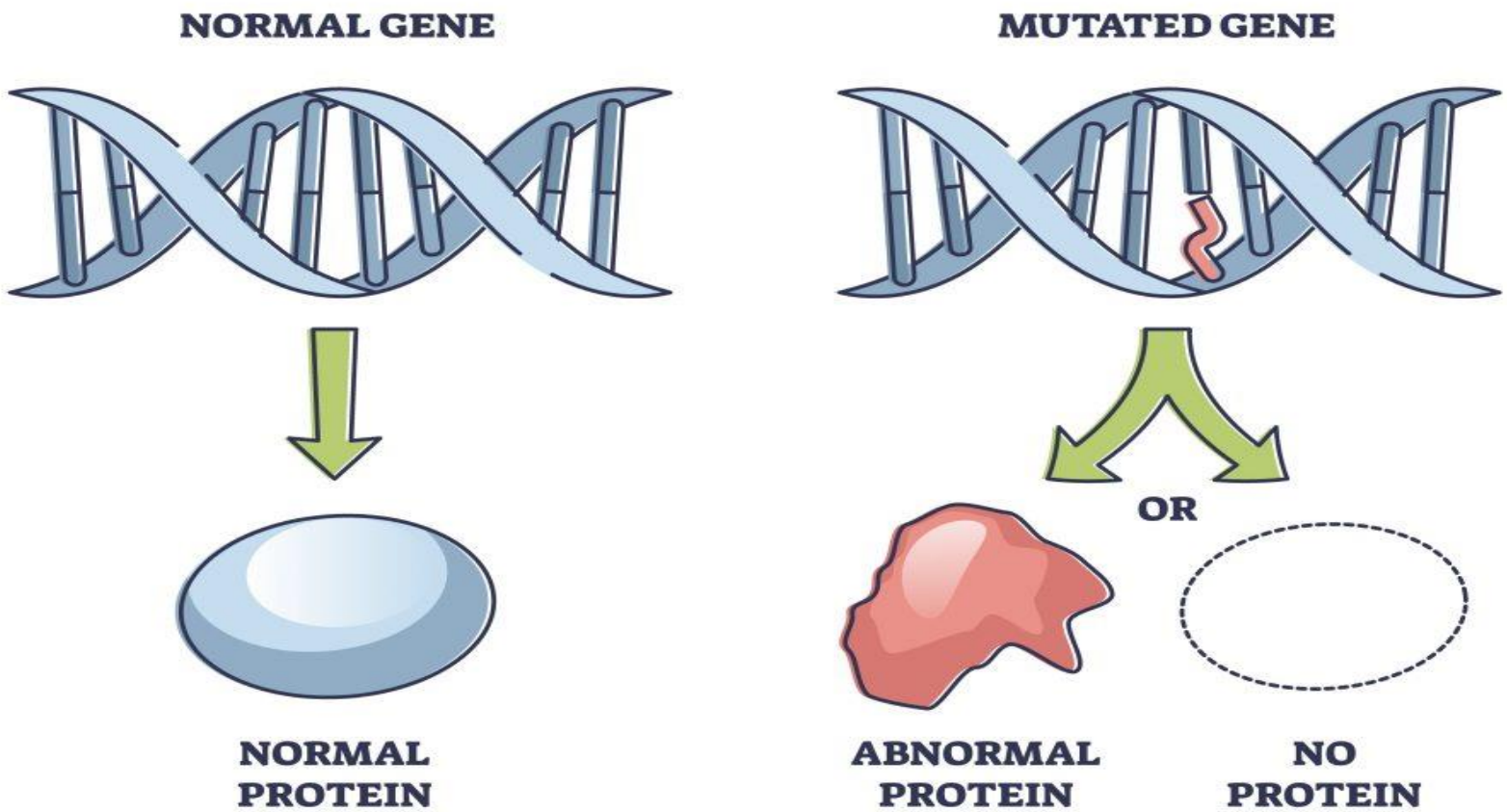



ATGATCTCGTAA
TACTAGAGCATT
DNA
TRANSCRIPTION
mRNA
AUGAUCUCGUAA
TRANSLATION
Polypeptide
Met
Ile
Ser
STOP


Types of Mutation
Gene Mutation
Chromosome Mutation


Gene Mutation
Substitution
Point mutation
Frameshift mutation
Silent
Missense
Nonsense mutation
Addition
Deletion

GENE MUTATION



GENE MUTATION: The Types

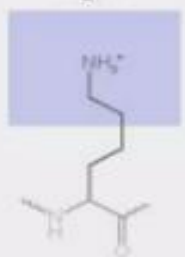
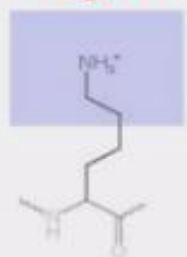
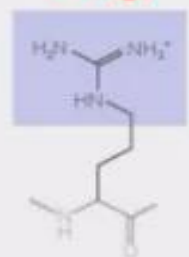
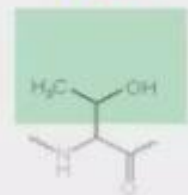
1. **Point mutations** - a one base change in DNA.

2. **Frame Shift Mutations** - the addition or deletion of **1 or more bases**. These are due to powerful mutagens; chemical or physical.

Point mutation

A point mutation or substitution is a genetic mutation where a single nucleotide base is changed, inserted or deleted from a sequence of DNA or RNA.

	No mutation	Point mutations			
		Silent	Nonsense	Missense	
				conservative	non-conservative
DNA level	TTC	TTT	ATC	TCC	TGC
mRNA level	AAG	AAA	UAG	AGG	ACG
protein level	Lys	Lys	STOP	Arg	Thr

Point Mutation

- **Missense Mutation:**

  DNA → RNA → Protein
  (Change) (Change) (Change)

- **Same/Silent Mutation:**

  DNA → RNA → Protein
  (Change) (Change) (No Change)

- **Non-Sense Mutation:**

  DNA → RNA → Protein
  (Change) (Change) (Stop)

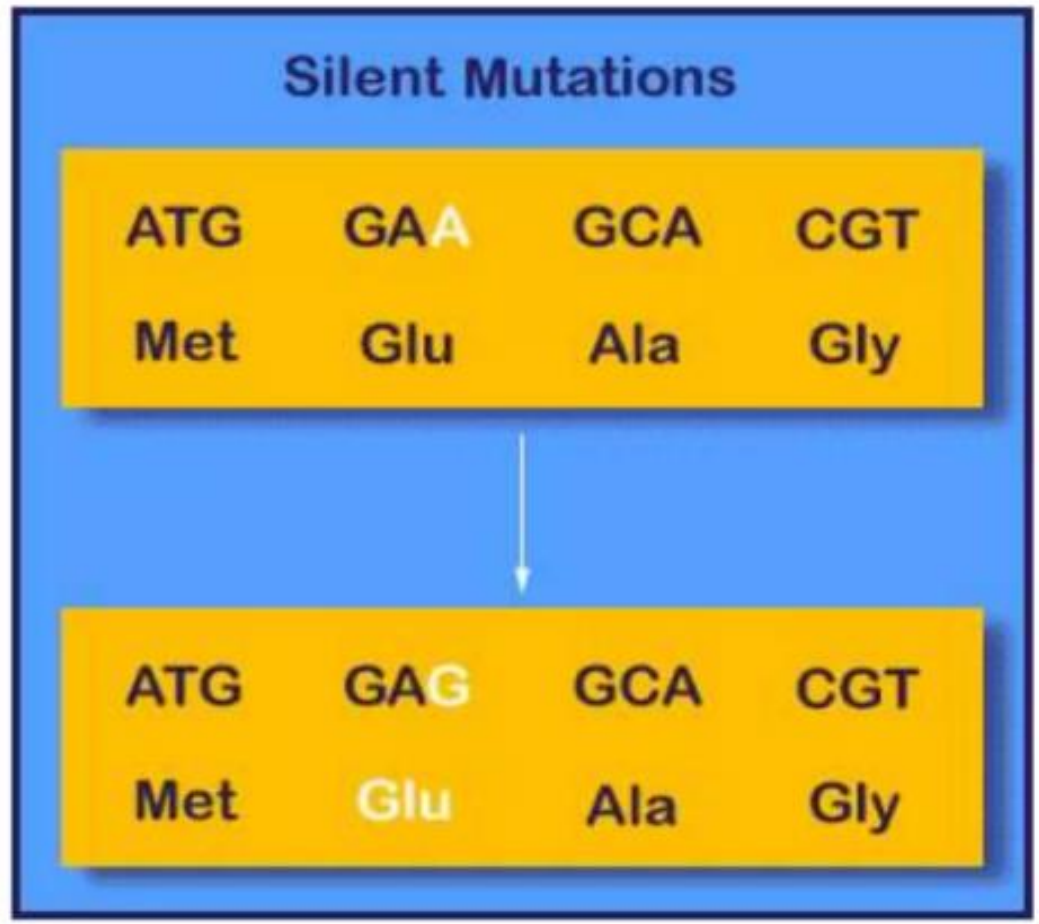
1. POINT MUTATION (PM)

3 TYPES:

- **silent mutation** - single base substitution in the 3rd base nucleotide position of a codon. This results in NO change in amino acid. Note that the first 2 letters of the genetic code are the most critical.
- **missense mutation** - single base substitution in 1st or 2nd base nucleotide position. This results in changed amino acid.
- **nonsense mutation** - single base substitutions that yield stop codon. Note: there are 3 nonsense codons in the genetic code = NO PROTEIN

PM: Silent mutation

single base substitution in the 3rd base nucleotide position of a codon. This results in NO change in amino acid. Note that the first 2 letters of the genetic code are the most critical.

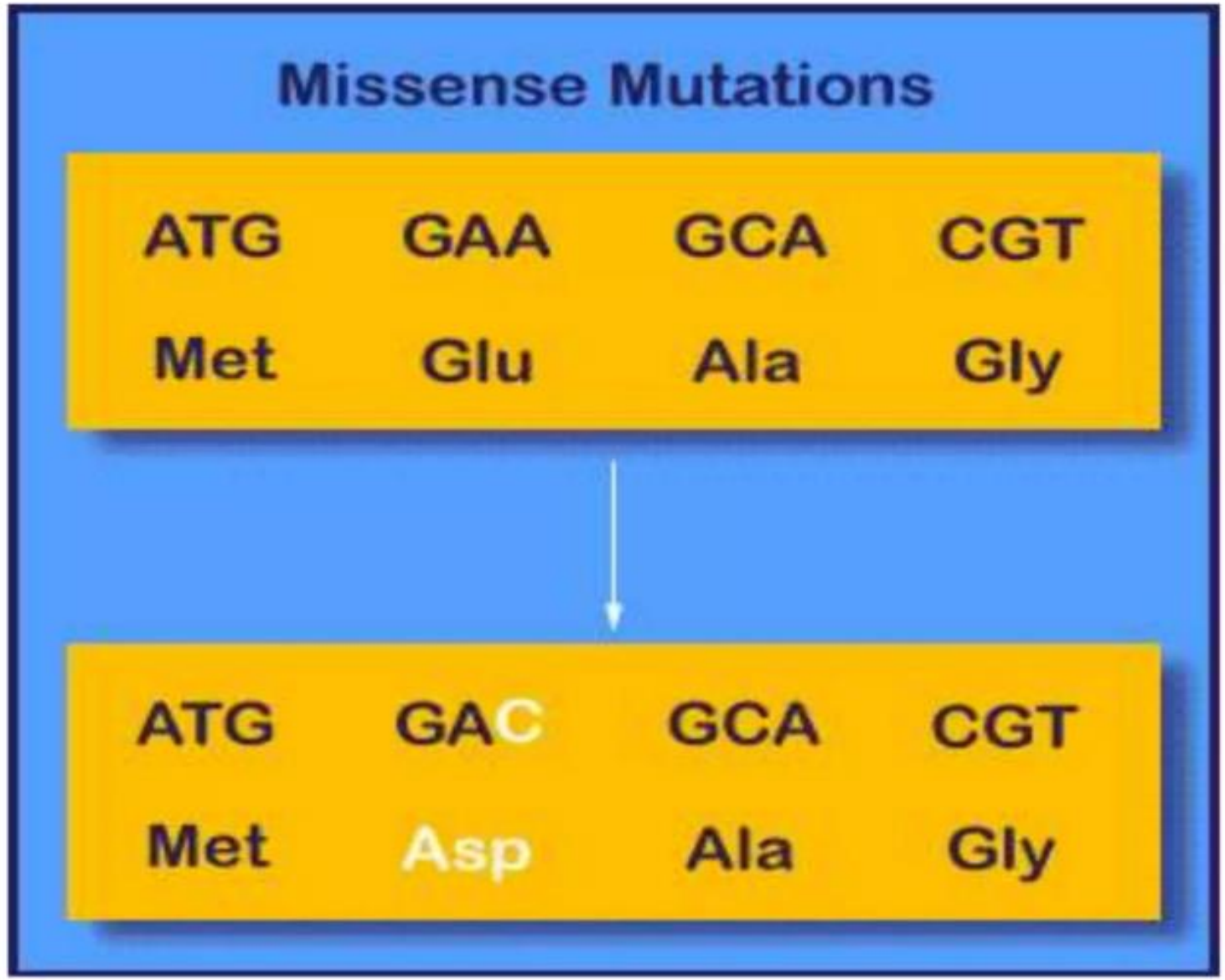


PM: Missense mutation

Single base substitution in 1st or 2nd base nucleotide position. This results in changed amino acid. This is equivalent to changing one letter in a sentence, such as this example, where we change the '**c**' in cat to an '**h**':

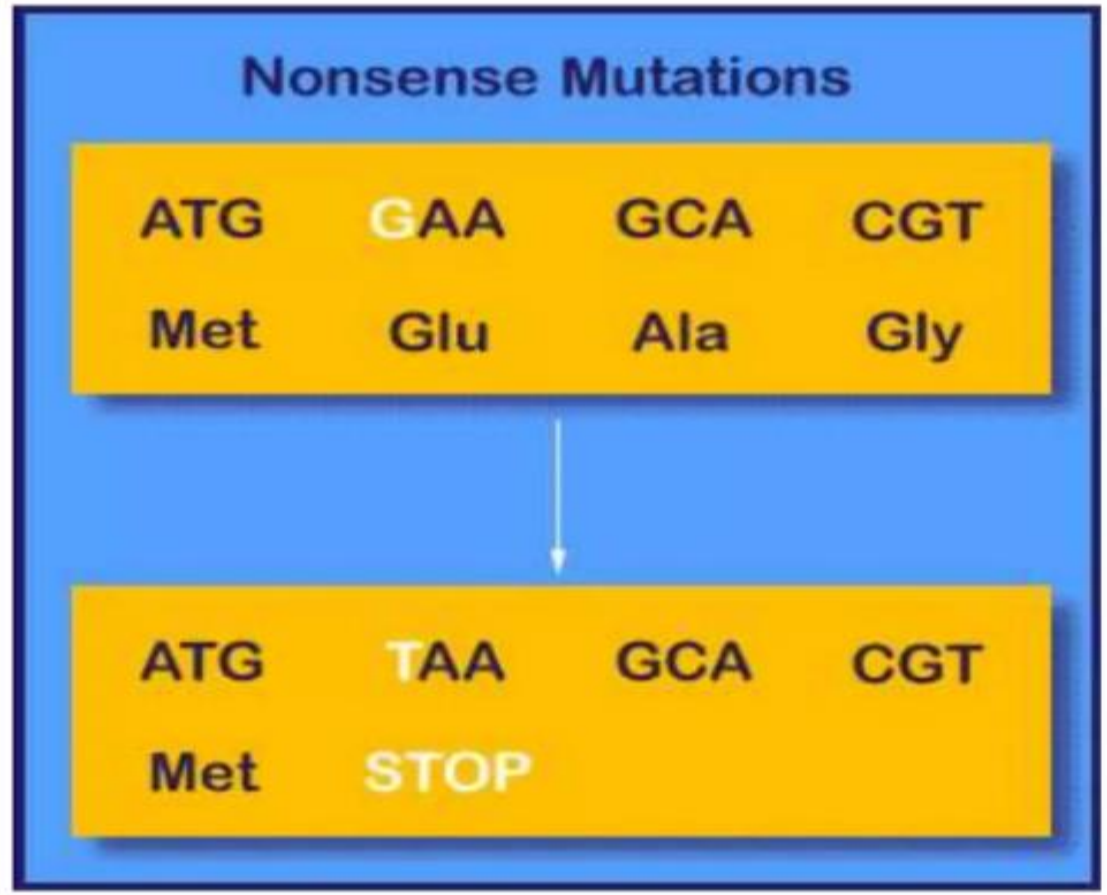
Original : The fat **c**at ate the wee rat.

Point Mutation : The fat **h**at ate the wee rat.

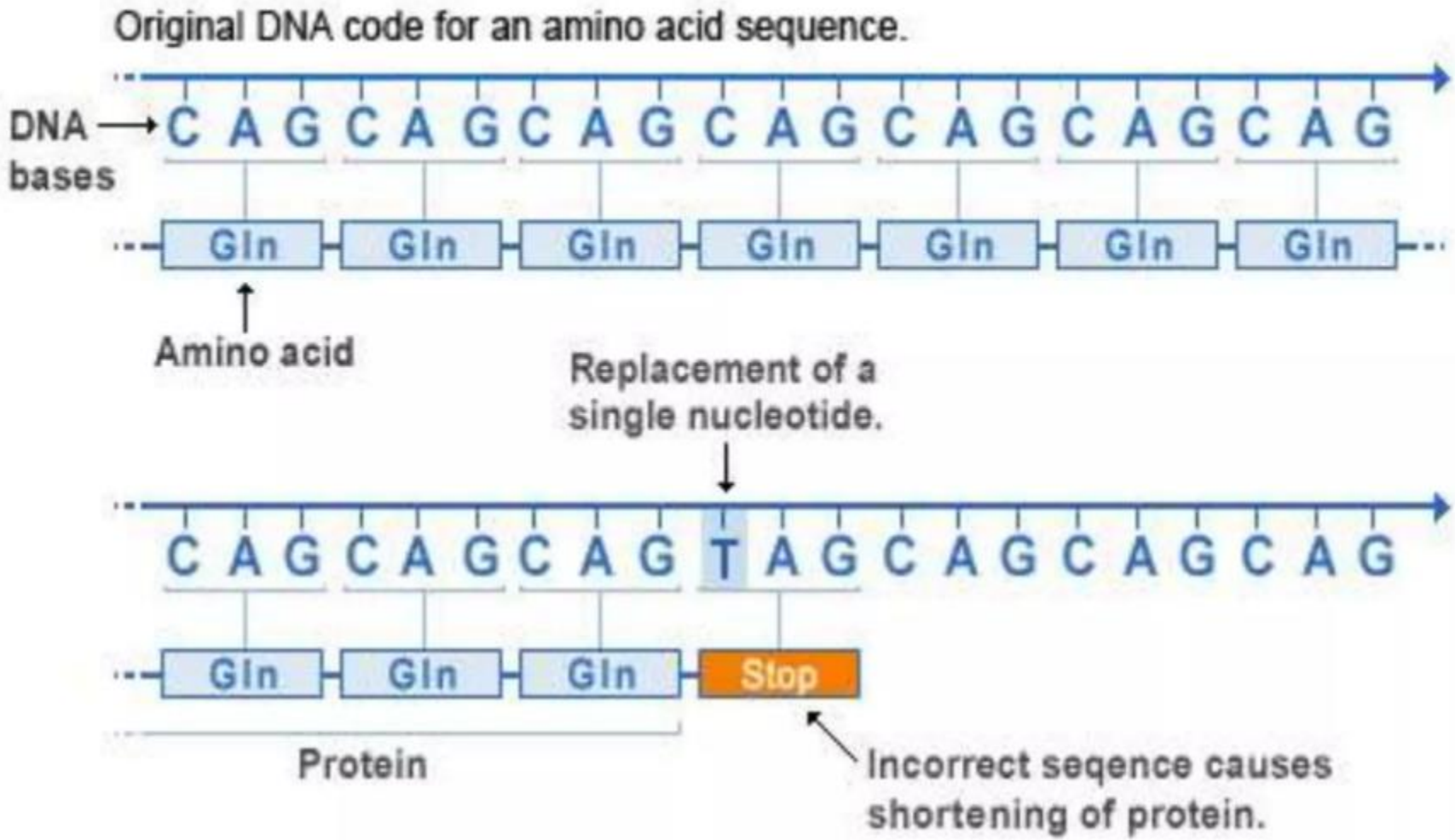

Missense Mutations
ATG GAA GCA CGT
Met Glu Ala Gly
ATG GAC GCA CGT
Met Asp Ala Gly

PM: Nonsense mutation

single base substitutions that yield/become **stop codon**. Note: there are 3 nonsense codons in the genetic code = NO PROTEIN

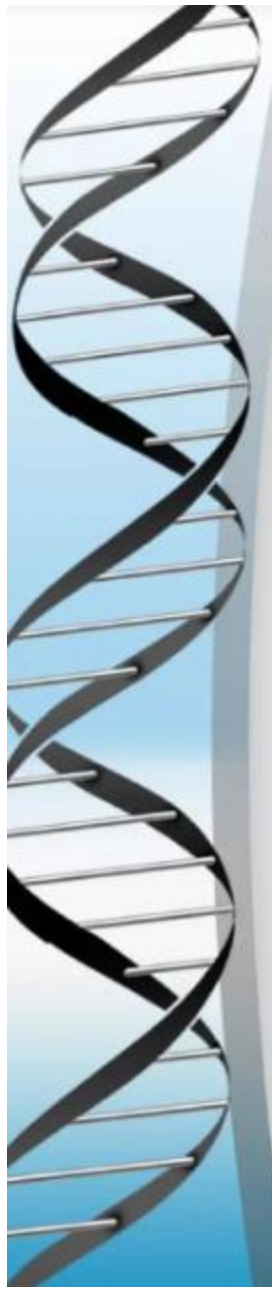


Nonsense mutation



Base Substitutions

- Single base **substitutions** are called point mutations, recall the point mutation Glu -----> Val which causes sickle-cell disease. Point mutations are the most common type of mutation and there are two types.
  - **Transition**: this occurs when a purine is substituted with another purine or when a pyrimidine is substituted with another pyrimidine.
  - **Transversion**: when a purine is substituted for a pyrimidine or a pyrimidine replaces a purine.

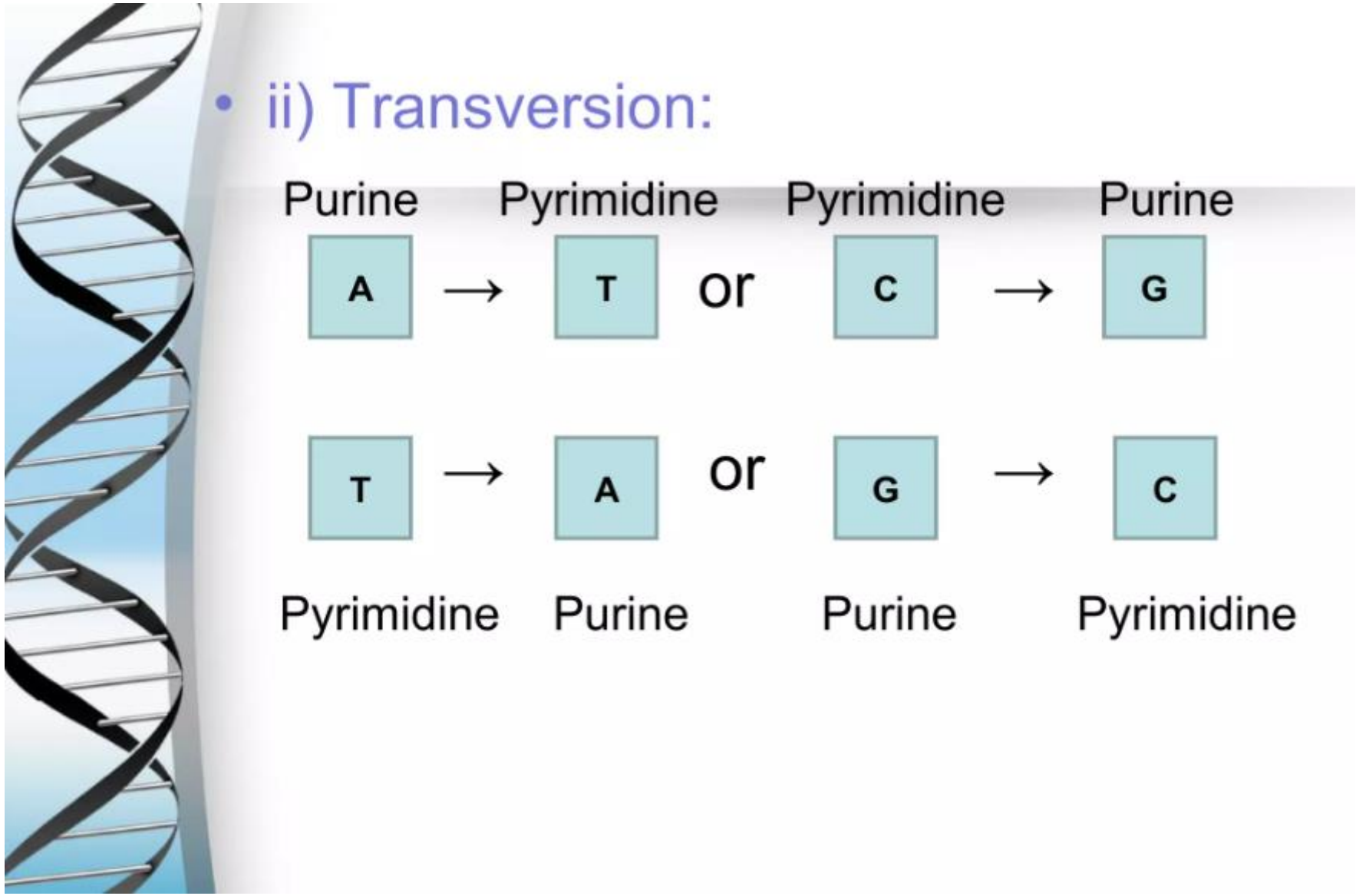


2. Base Substitution

- Replacement of one base pair by another pair in the DNA is known as base substitution.

i) Transition:

Purine	Purine		Purine	Purine
A →	G	or	G →	A
T →	C	or	C →	T
Pyrimidine	Pyrimidine		Pyrimidine	Pyrimidine



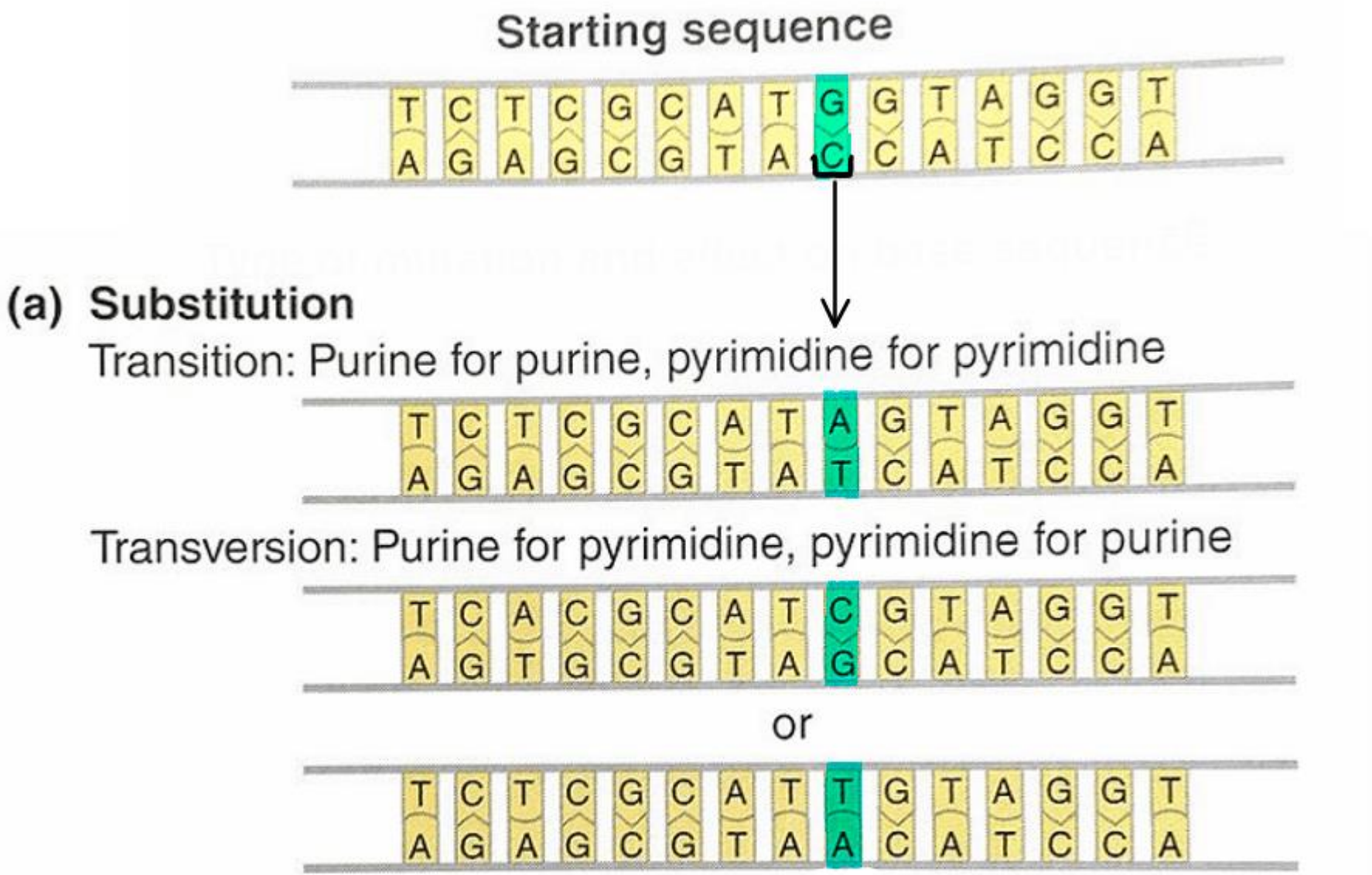
- ii) Transversion:

Purine Pyrimidine Pyrimidine Purine

A → T or C → G

T → A or G → C

Pyrimidine Purine Purine Pyrimidine


Starting sequence
T C T C G C A T G G T A G G T
A G A G C G T A C C A T C C A
(a) Substitution
Transition: Purine for purine, pyrimidine for pyrimidine
T C T C G C A T A G T A G G T
A G A G C G T A T C A T C C A
Transversion: Purine for pyrimidine, pyrimidine for purine
T C A C G C A T C G T A G G T
A G T G C G T A G C A T C C A
or
T C T C G C A T T G T A G G T
A G A G C G T A A C A T C C A

Frameshift mutation

- This type of mutation occurs when the addition or loss of DNA bases changes a gene's reading frame.
- A reading frame consists of groups of 3 bases that each code for one amino acid.
- A frameshift mutation shifts the grouping of these bases and changes the code for amino acids.
- The resulting protein is usually nonfunctional.
- Insertions, deletions, and duplications can all be frameshift mutations.

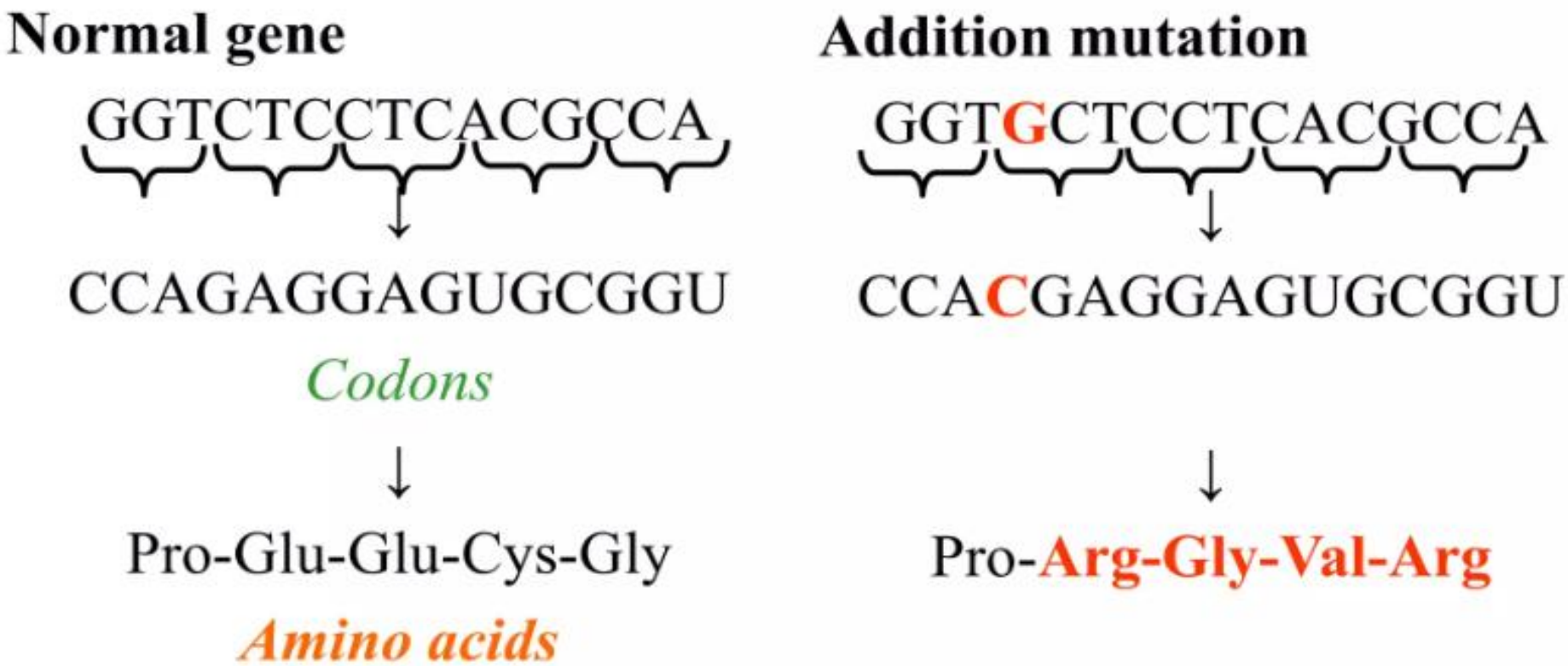
An example of a frame-shift mutation using our sample sentence is when the **'t'** from cat is **removed**, but we keep the original letter spacing:

Original : The fat cat ate the wee rat.

Frame Shift : The fat ca**a tet hew eer at**.

2. FRAME SHIFT MUTATIONS

Additions



2. FRAME SHIFT MUTATIONS

Deletion

Normal gene

GGTCTCCTCACGCCA

↓

CCAGAGGAGUGCGGU

Codons

↓

Pro-Glu-Glu-Cys-Gly

Amino acids

Deletion mutation

GGT**C/C**CTCACGCCA

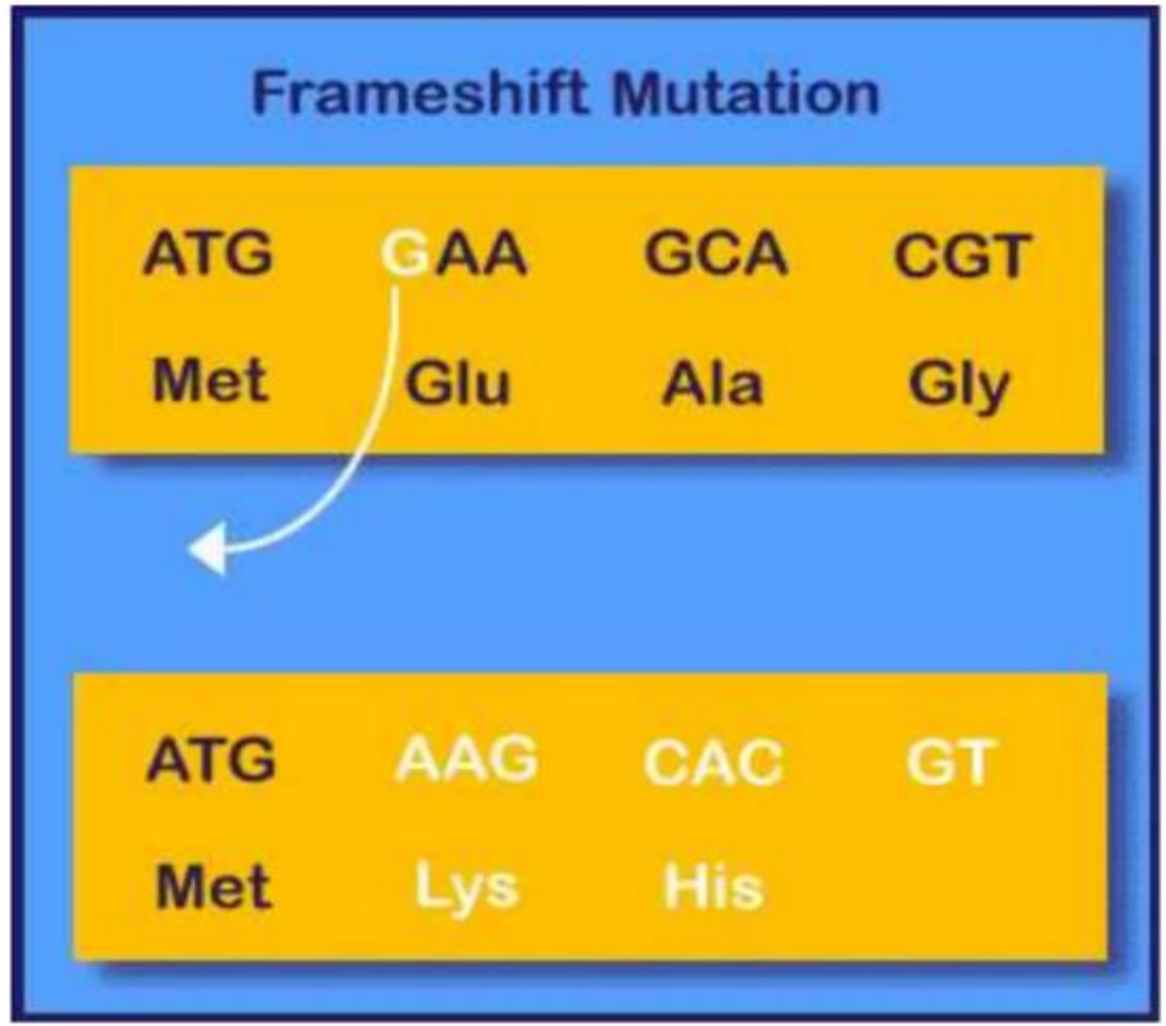
↓

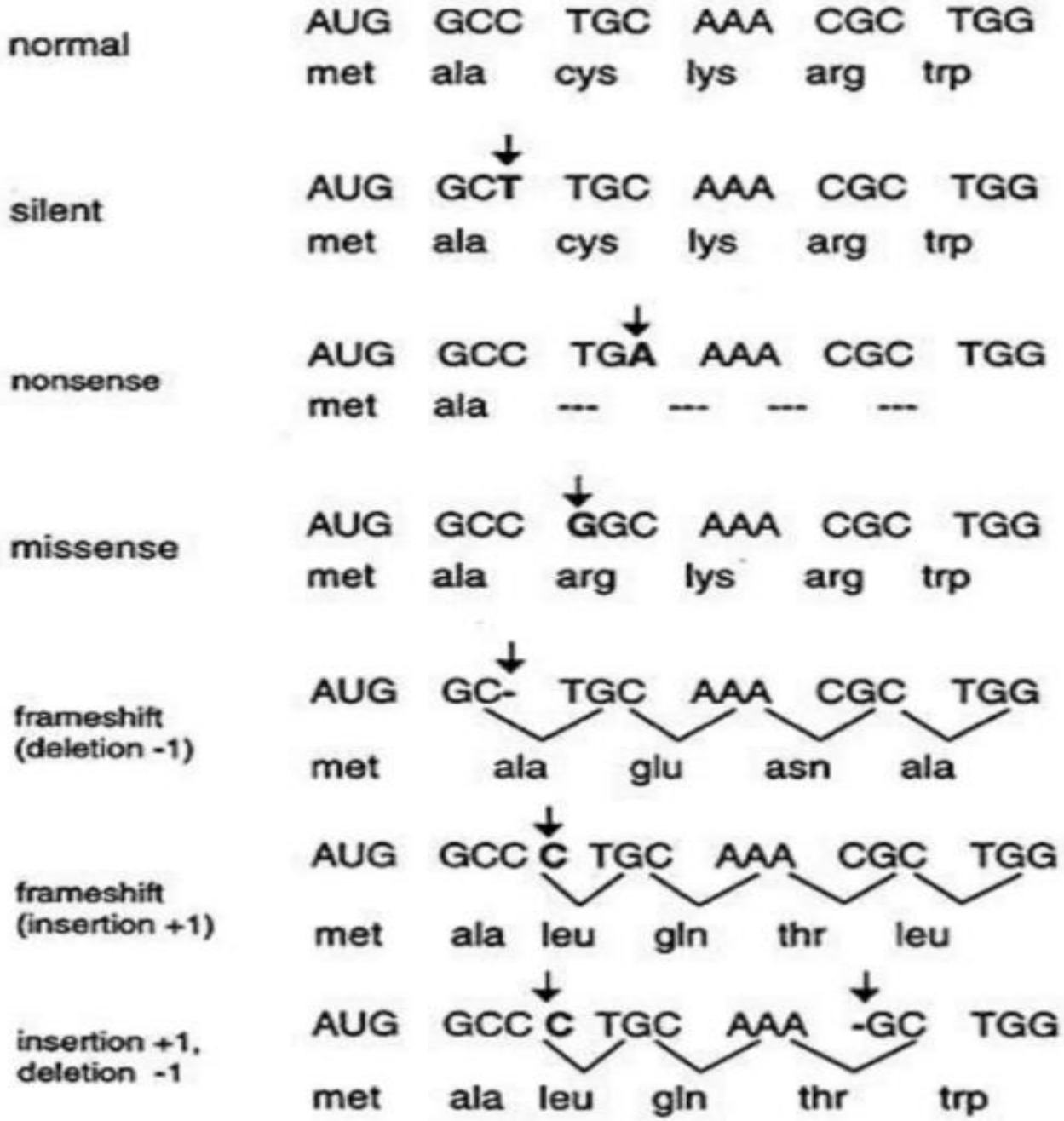
CCA**GG**GAGUGCGGU

↓

Pro-**Gly-Ser-Ala-Val**

2. FRAME SHIFT MUTATIONS




normal
AUG GCC TGC AAA CGC TGG
met ala cys lys arg trp
silent
AUG GCT TGC AAA CGC TGG
met ala cys lys arg trp
nonsense
AUG GCC TGA AAA CGC TGG
met ala --- --- --- ---
missense
AUG GCC GGC AAA CGC TGG
met ala arg lys arg trp
frameshift (deletion -1)
AUG GC- TGC AAA CGC TGG
met ala glu asn ala
frameshift (insertion +1)
AUG GCC C TGC AAA CGC TGG
met ala leu gln thr leu
insertion +1, deletion -1
AUG GCC C TGC AAA -GC TGG
met ala leu gln thr trp

Effect of Mutation

- A single mutation can have a large effect, but in many cases, evolutionary change is based on the accumulation of many mutations with small effects. Mutational effects can be beneficial, harmful, or neutral, depending on their context or location. Most non-neutral mutations are deleterious.
- In general, the more base pairs that are affected by a mutation, the larger the effect of the mutation, and the larger the mutation's probability of being deleterious.
- To better understand the impact of mutations, researchers have started to estimate distributions of mutational effects (DMEs) that quantify how many mutations occur with what effect on a given property of a biological system.
- In evolutionary studies, the property of interest is fitness, but in molecular systems biology, other emerging properties might also be of interest.
- To make things even more difficult, many mutations also interact with each other to alter their effects; this phenomenon is referred to as epistasis. However, despite all these uncertainties, recent work has repeatedly indicated that the overwhelming majority of mutations have very small effects.