Lecture 31:

Point mutations

Course 371

Lessons for life

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"Lead the way by personal example and by personal philosophy." -- Jim Rohn

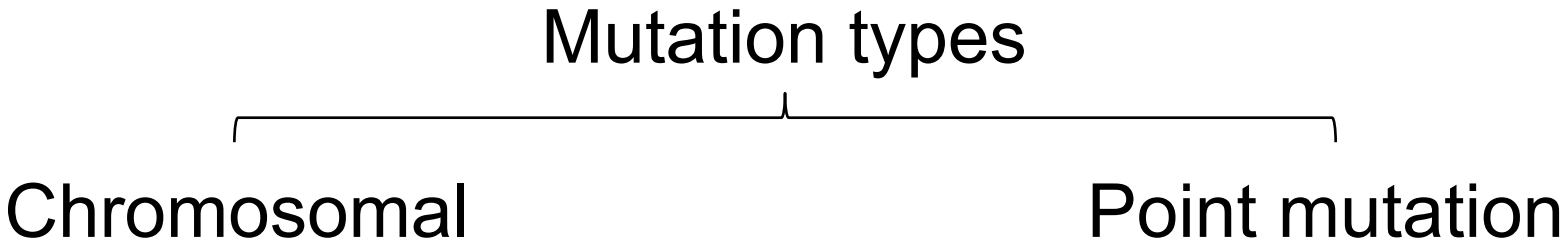
AIMS

- Understand the various point mutations that take place in DNA and the consequences of such mutations.

- Understand the terminology given for each type of point mutation.

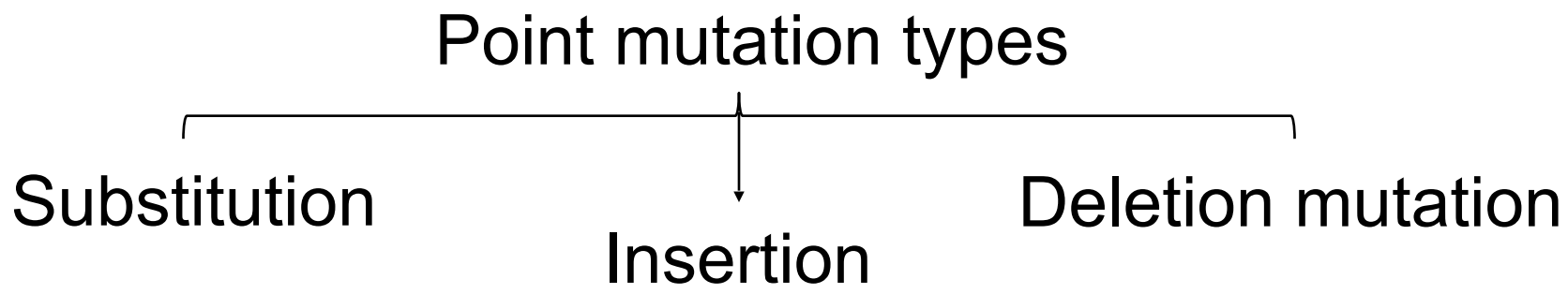
- Understand which mutation type has the least impact on protein function and structure and which has the most.

Mutations



- **Chromosomal mutations:** are mutation that involve changes to the entire chromosome or sections of it.
- Chromosomal mutations are also called **segmental mutations.**
- **Point mutations:** are changes to one or few base-pairs in the DNA in the form of substitution, deletion, or insertion.

Point mutations



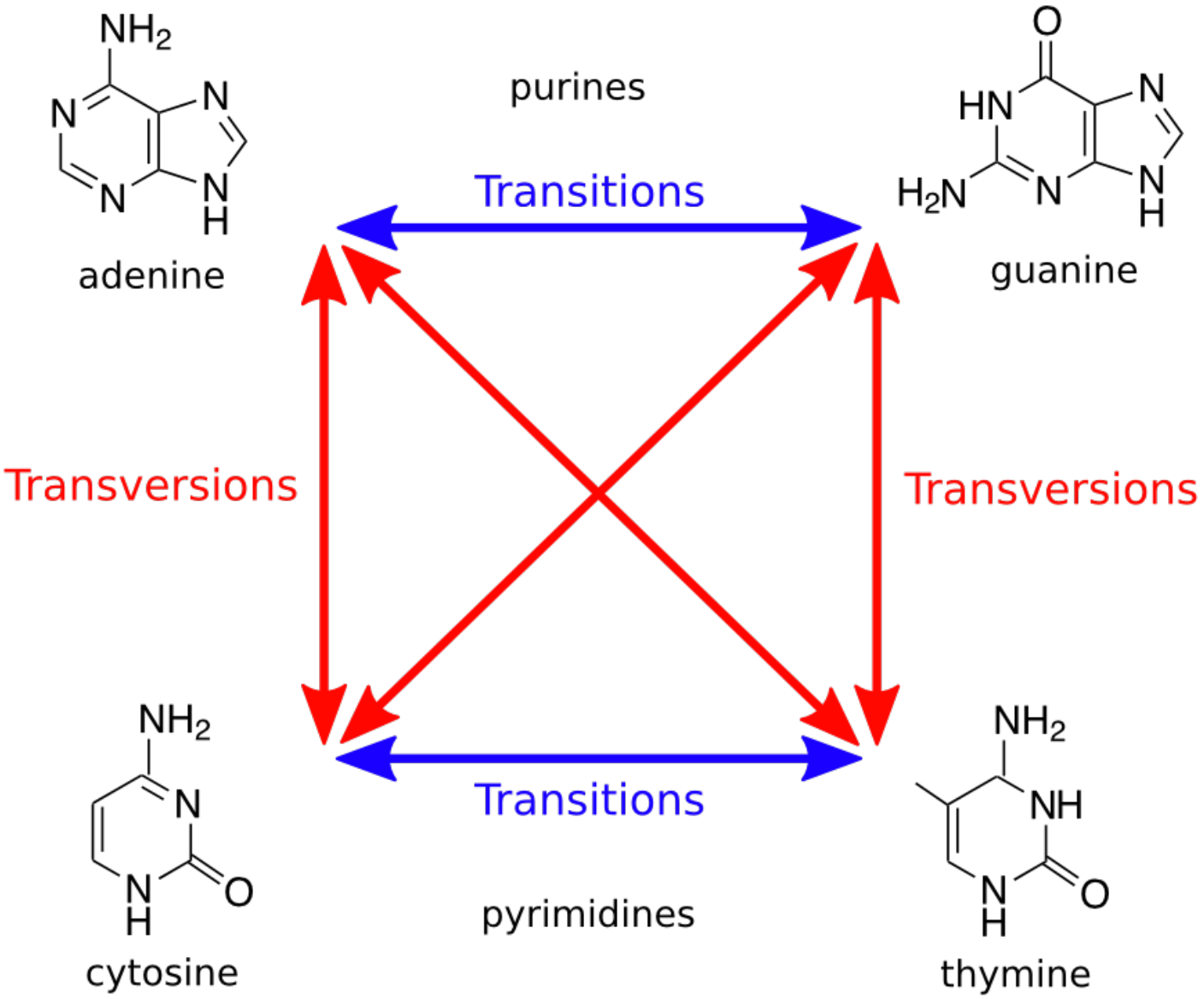
- **Substitution point mutation:** change of a nucleotide or few nucleotides from one type to another.
- **Insertion point mutation:** an insertion of one or few nucleotides in the DNA sequence.
- **Deletion point mutation:** a deletion of one or few nucleotides in the DNA sequence.

Point mutations – (1) substitutions

- Substituting (changing) a pyrimidine to a pyrimidine is called **Transition.**
- Substituting (changing) a purine to a purine is called **Transition.**
- Substituting (changing) a purine to a pyrimidine is called **transversion.**
- Substituting (changing) a pyrimidine to a purine is called **transversion.**

What does that mean?

Point mutations – (1) substitutions



Point mutations – (1) substitutions

What is the change from adenine to guanine called?

What is the change from adenine to cytosine called?

What is the change from adenine to thymine called?

What is the change from adenine to adenine called?

Point mutations – (1) substitutions

While the change from A to T is called ….., the change from T to A is called.

Where do mutations take place?

Point mutations – (1) substitutions

Point (substitution) mutations

In non-coding region

In coding region

Just a mutation
No change in protein
No functional consequences

Point mutations can take place at different localities in the genome (coding and non-coding regions).

Point mutations – (1) substitutions

- Point mutation in the non-coding region has no affects on the function or sequence of proteins.

What are some examples of non-coding regions?

- Point mutations in the non-coding region have no biological impacts on the organism and thus can be used to study genetic variation between individuals of one species or between species.

We will be focusing one point mutations in the coding regions of the genome

Point mutations – (1) substitutions

Point mutations

↓

In coding region

Synonymous mutations	Non-synonymous mutations
↓	↓
No change in amino acid	Change in amino acid

Point mutations – (1) substitutions

- Point mutations in coding region can be **synonymous or non-synonymous.**
- Synonymous mutations are also called **point mutations.**
- Synonymous mutations cause no change in the amino acid.

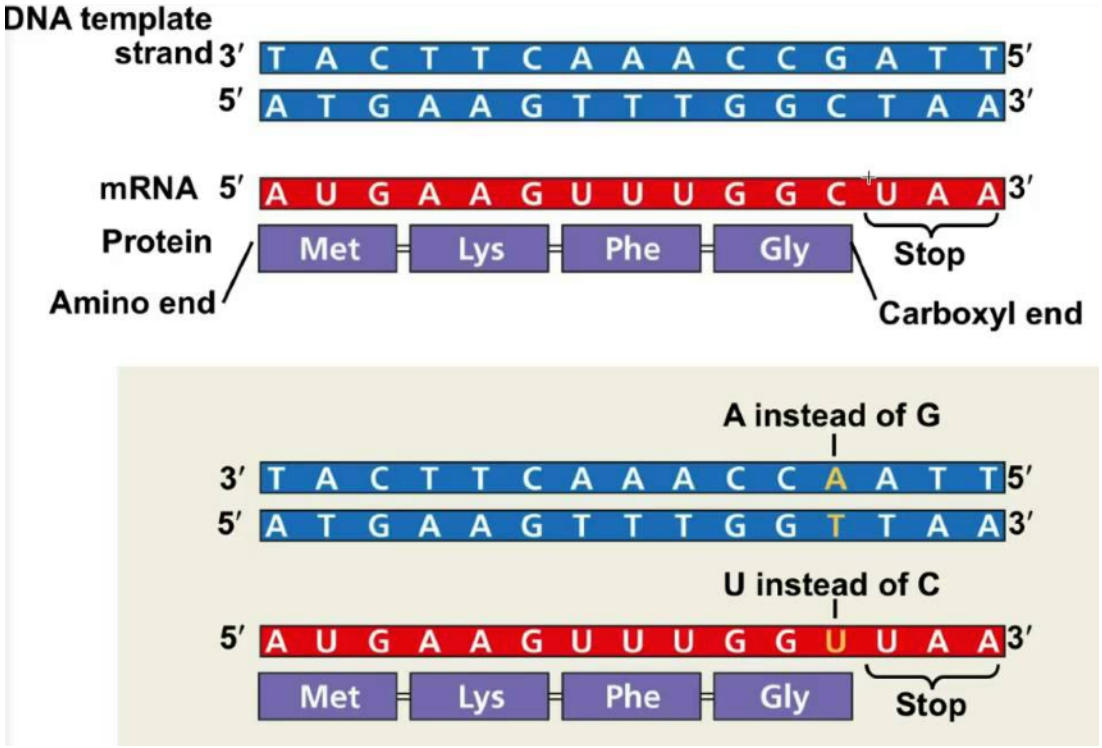
Synonymous (silent) mutations do not change amino acid

How is that?

Point mutations – (1) substitutions

Synonymous point (substitution) mutations (silent mutations)

A change in the third nucleotide of codon GGC to GGT does not change the amino acid Glycine to another one.



Point mutations – (1) substitutions

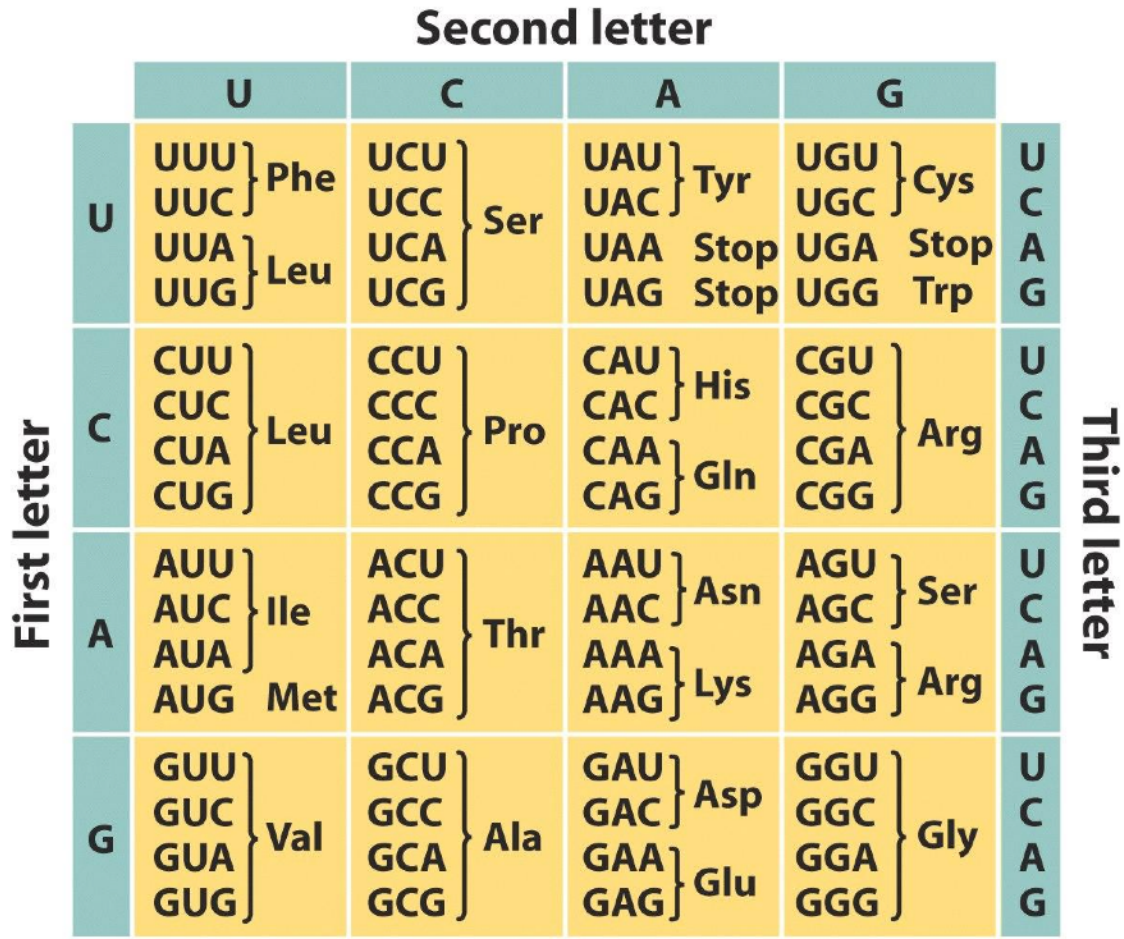
Why do synonymous (silent) mutations do not change amino acid in the coding region?

Why most silent mutations are associated with the third base in the codon?

Point mutations – in coding region

Synonymous point mutations (silent mutations)

The genetic code is degenerate



Point mutations – in coding region

Synonymous point mutations (silent mutations)

What is the effect of synonymous (silent) mutations on the function and structure of the protein?

Point mutations – (1) substitutions

Point mutations

↓

In coding region

↓

Non-synonymous mutations

Missense mutation

↓

Change an amino acid into another amino acid

Nonsense mutation

↓

Change an amino acid into a stop codon

Point mutations – (1) substitutions

- Non-synonymous point (substitution) mutations in the coding region can **change the amino acid or introduce a stop codon.**

Lets focus on missense mutations first

Point mutations – (1) substitutions

Point mutations

↓

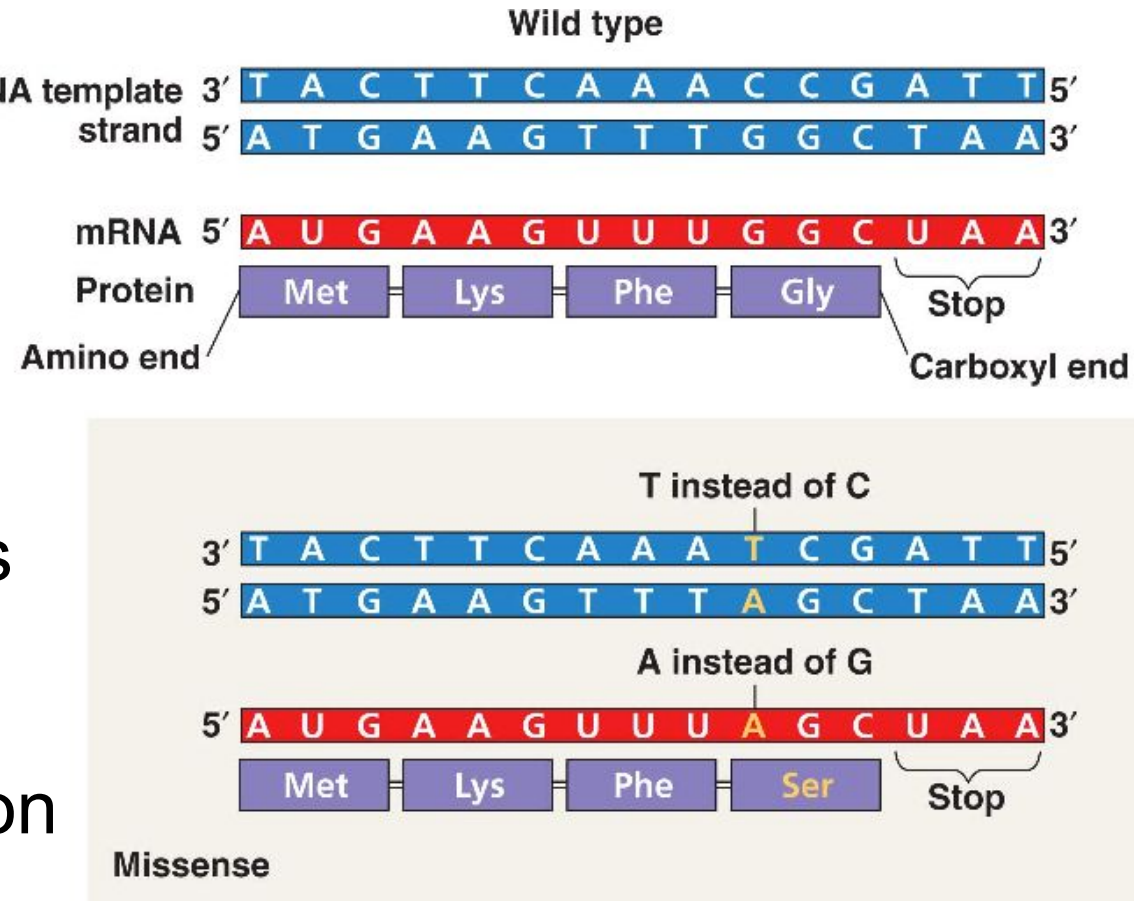
In coding region

↓

Non-synonymous mutations

↓

Missense mutation



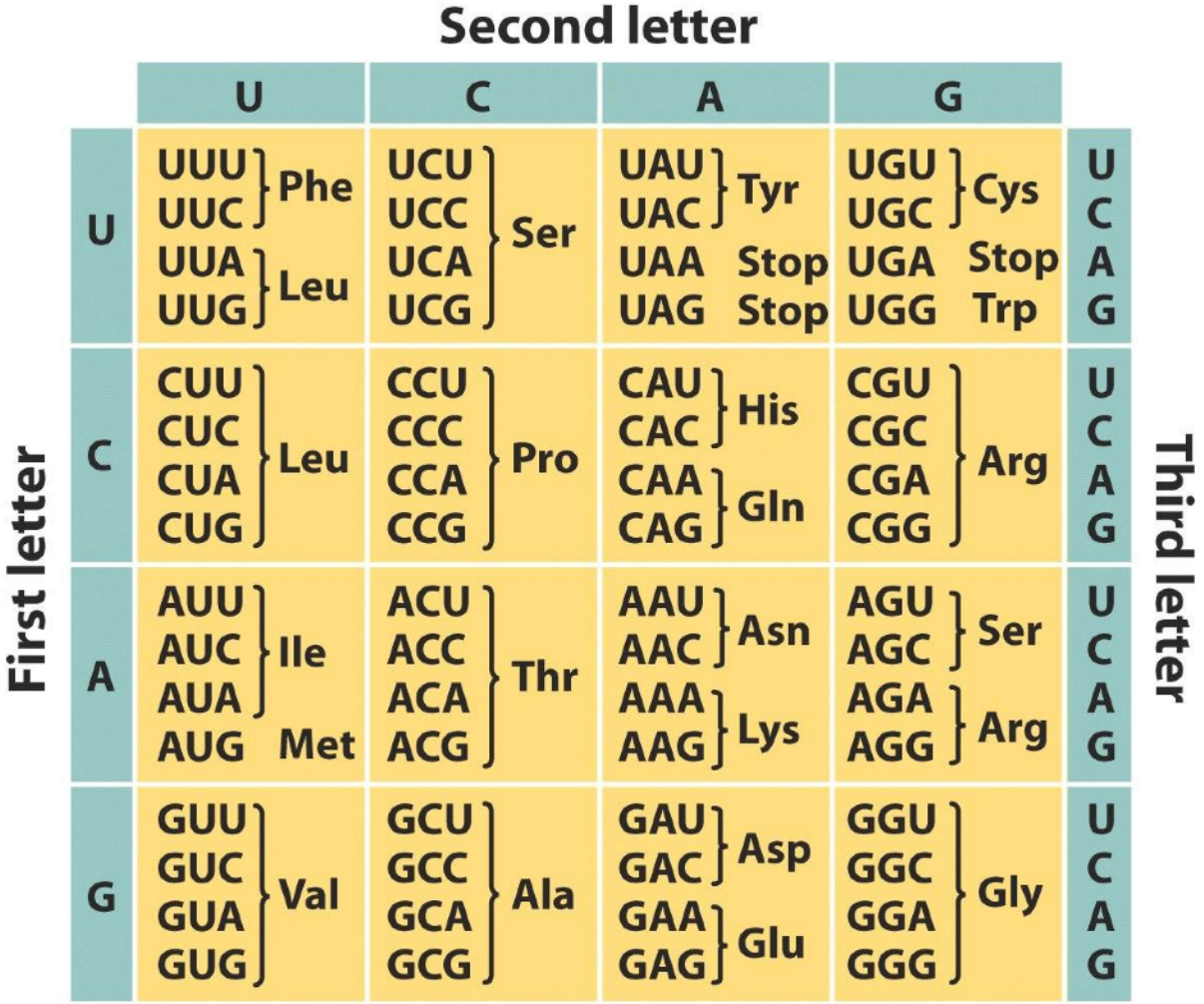
Point mutations – (1) substitutions

Missense substitutions often occurs in the 1st or 2nd base of the codon

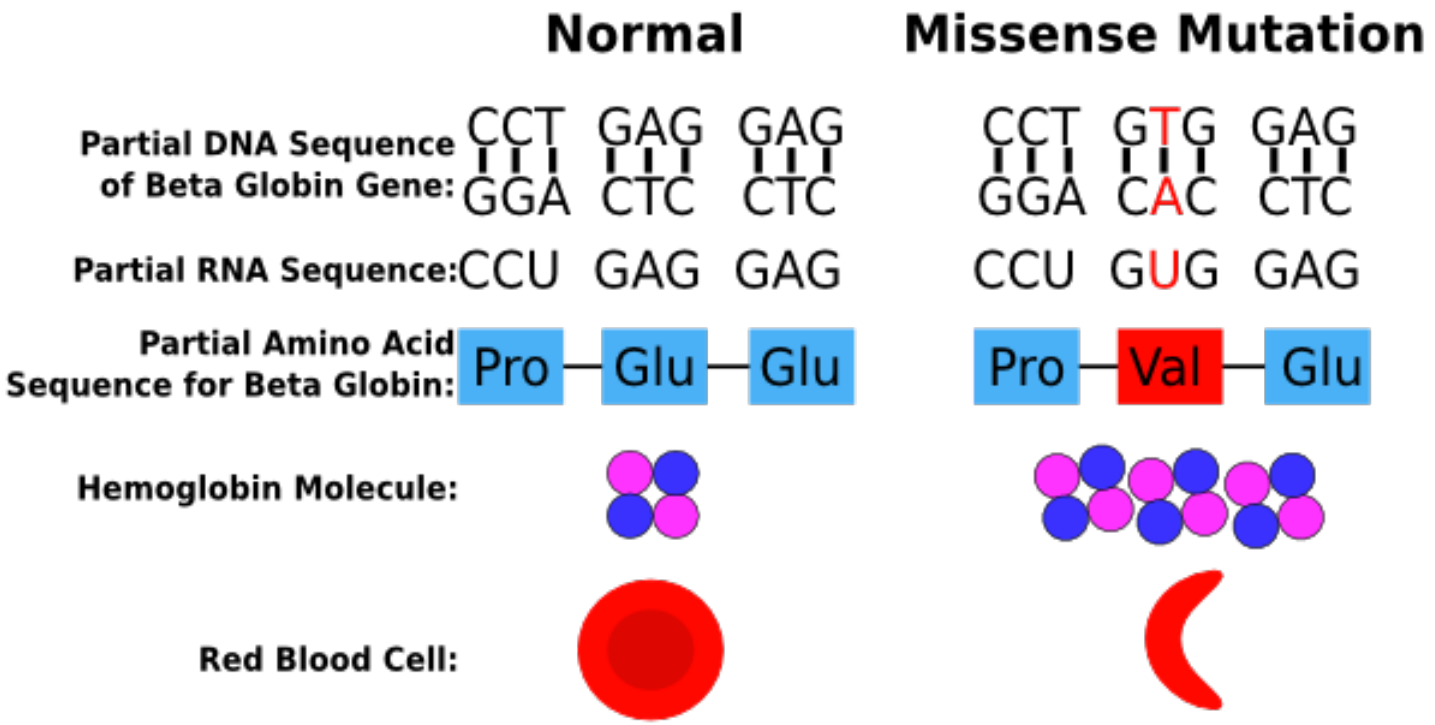
Why?

Point mutations – (1) substitutions

The degeneracy of the genetic code is associated with the 3rd base of the codon



Point mutations – (1) substitutions



- Missense mutations may alter the function of the protein by substituting an amino acid with an unfavorable one.

- Example: hemoglobin and sickle cell anemia.

Point mutations – (1) substitutions

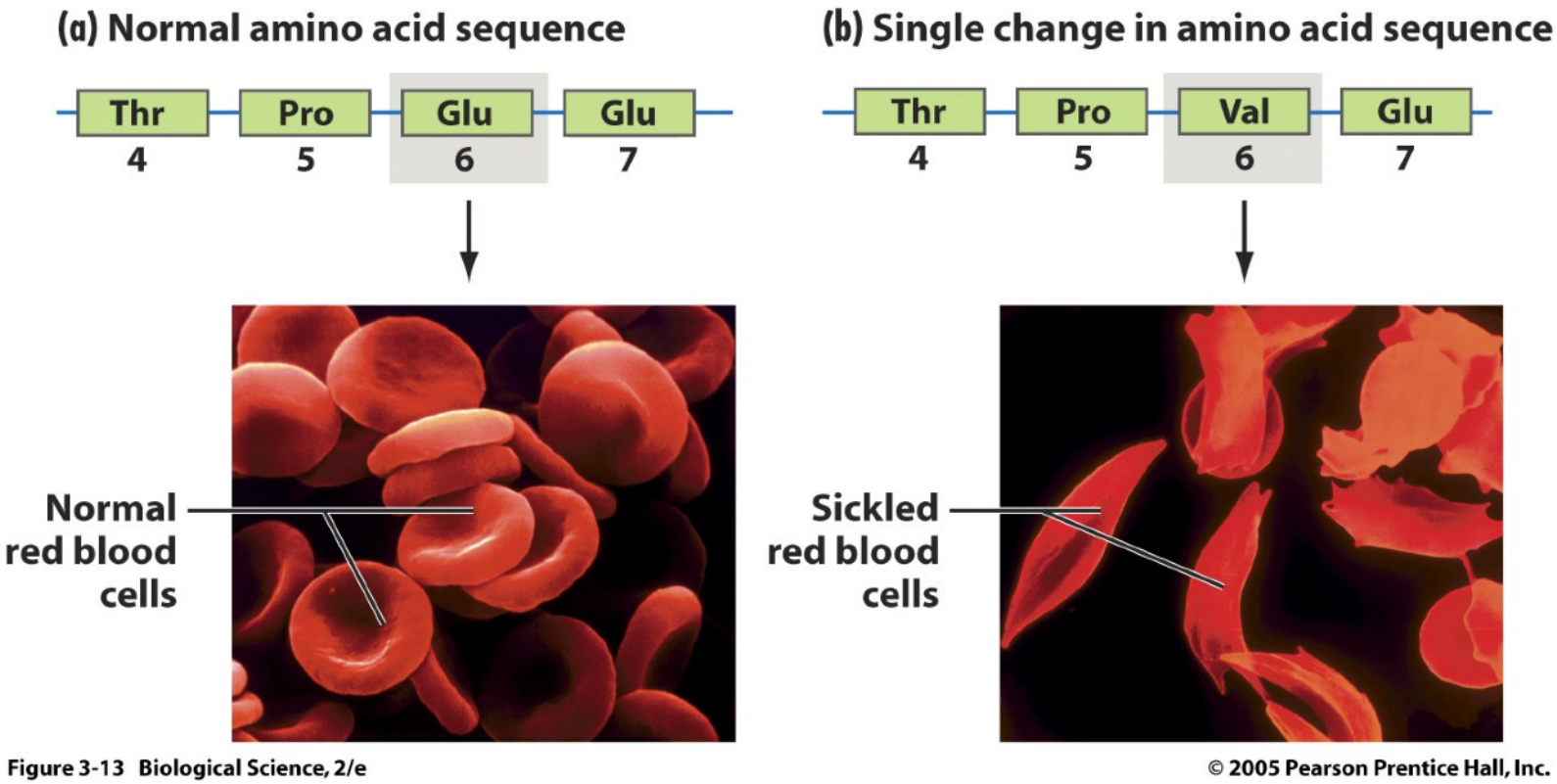


Figure 3-13 Biological Science, 2/e

A change from glutamic acid (negatively charged) to a valine (non-polar) causes a severe change in the protein function and structure.

Point mutations – (1) substitutions

Point mutations

↓

In coding region

↓

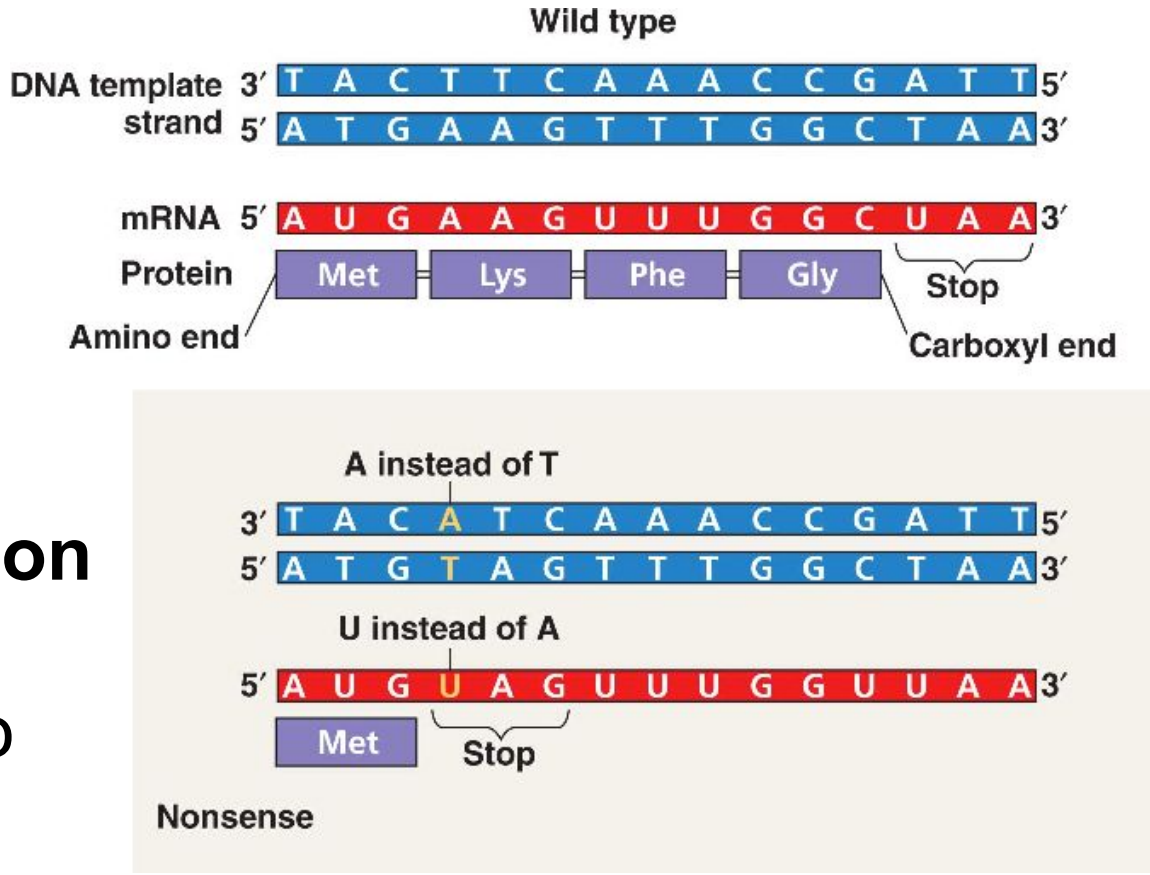
Non-synonymous mutations

↓

Nonsense mutation

↓

Change an amino acid into a stop codon

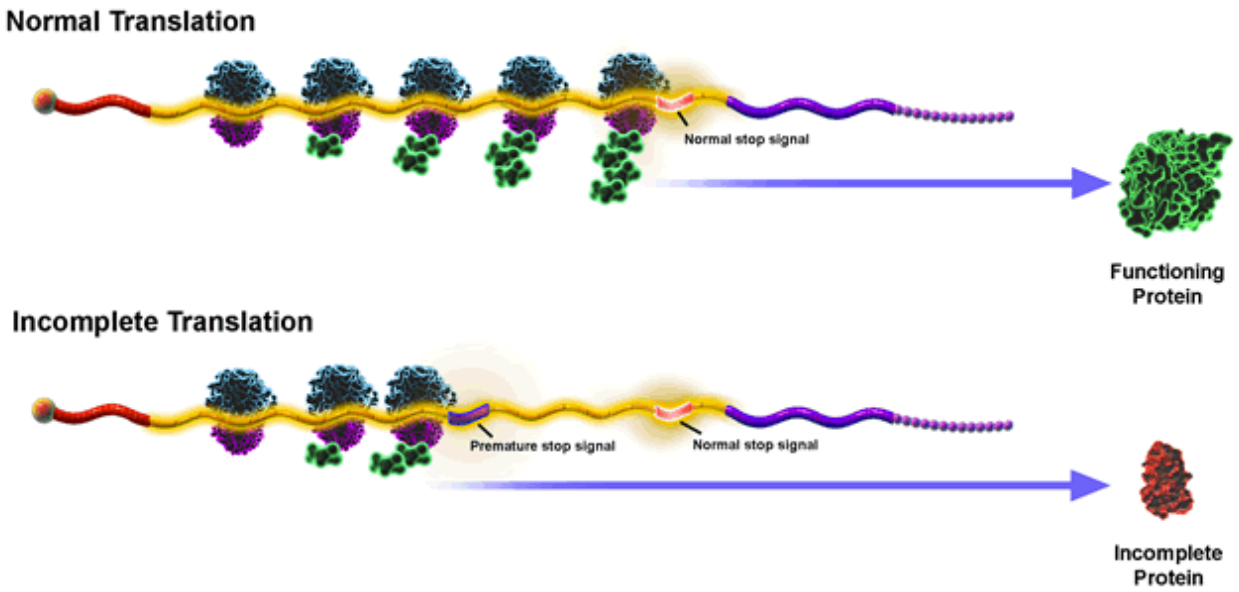


Point mutations – (1) substitutions

Nonsense mutations introduce **premature stop codon**

What happens to the protein?

Point mutations – (1) substitutions

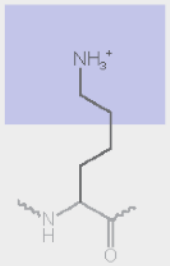
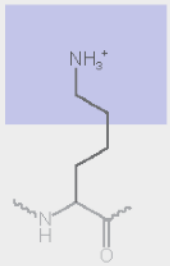
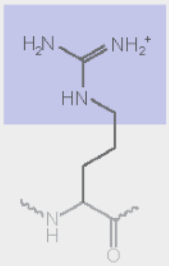
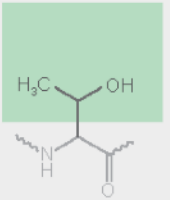


- Nonsense mutation occurs early the gene results in the truncation (shorter) of protein and loss of function (**truncated protein**).

- Nonsense mutation occurs later in the sequence of the gene results in the protein loss of function or reduction in function.

Point mutations – (1) substitutions

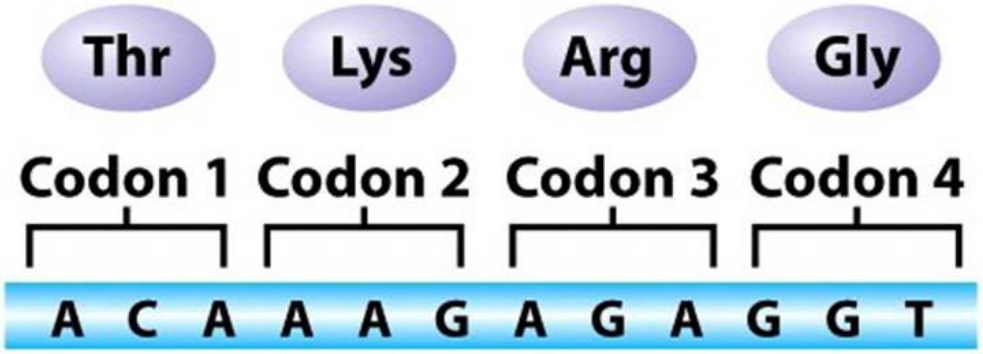
Summary of substation mutations in coding region

	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**
					

basic
polar

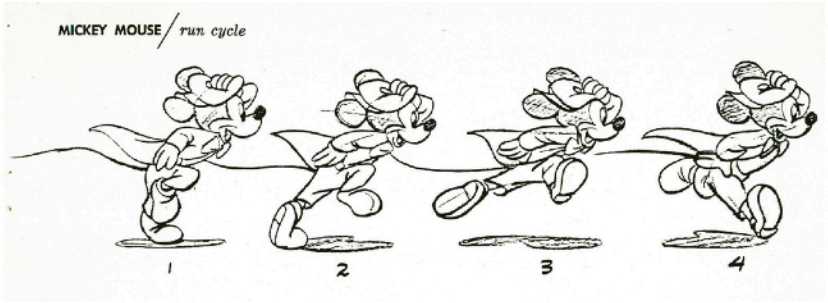
Point mutations – (2) insertion (3) deletion

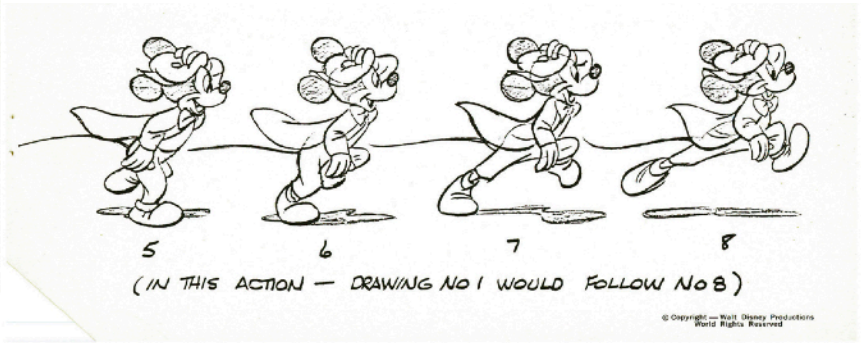
Wild-type gene



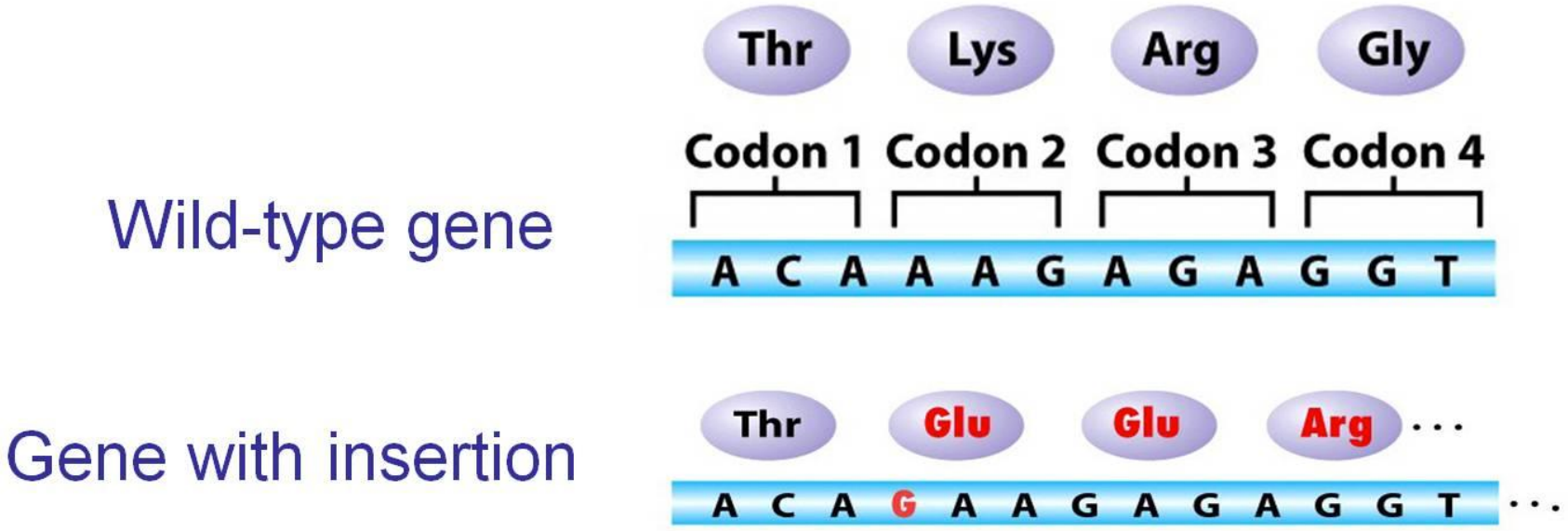
- Normal coding mRNA is called **in frame** when codons are arranged in specific sequence from start codon to stop codon.
- Insertion and deletion mutations introduce a disruption to the codon sequence called **frame-shift.**

Point mutations – (2) insertion (3) deletion





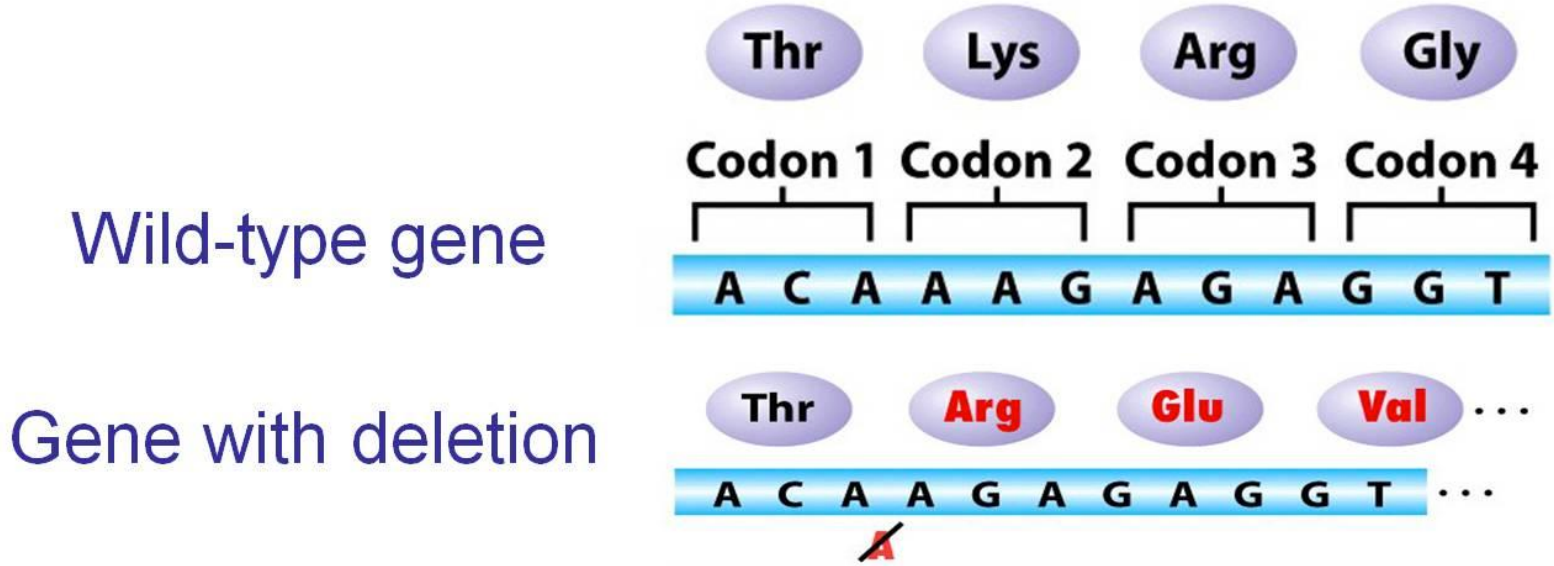
Point mutations – (2) insertion (3) deletion



- Insertion point mutations introduce a base-pair or more to the sequence of the gene which causes a **frame-shift** downstream.

- The frame-shift may result in a premature stop codon down stream or changes in amino acid sequence.

Point mutations – (2) insertion (3) deletion



- Deletion point mutations remove a base-pair or more to the sequence of the gene which causes a **frame-shift** upstream.
- The frame-shift may result in a premature stop codon down stream or changes in amino acid sequence.

Point mutations – (2) insertion (3) deletion

Is there a difference when 1 bp is inserted vs. 2 or 3?

Is there a difference when 1 bp is deleted vs. 2 or 3?

When an insertion or deletion happens and no frame-shift occurs (hint: numbers nucleotides in codon)?

Point mutations – (2) insertion (3) deletion

Frame-shift by deletion or insertion causes:

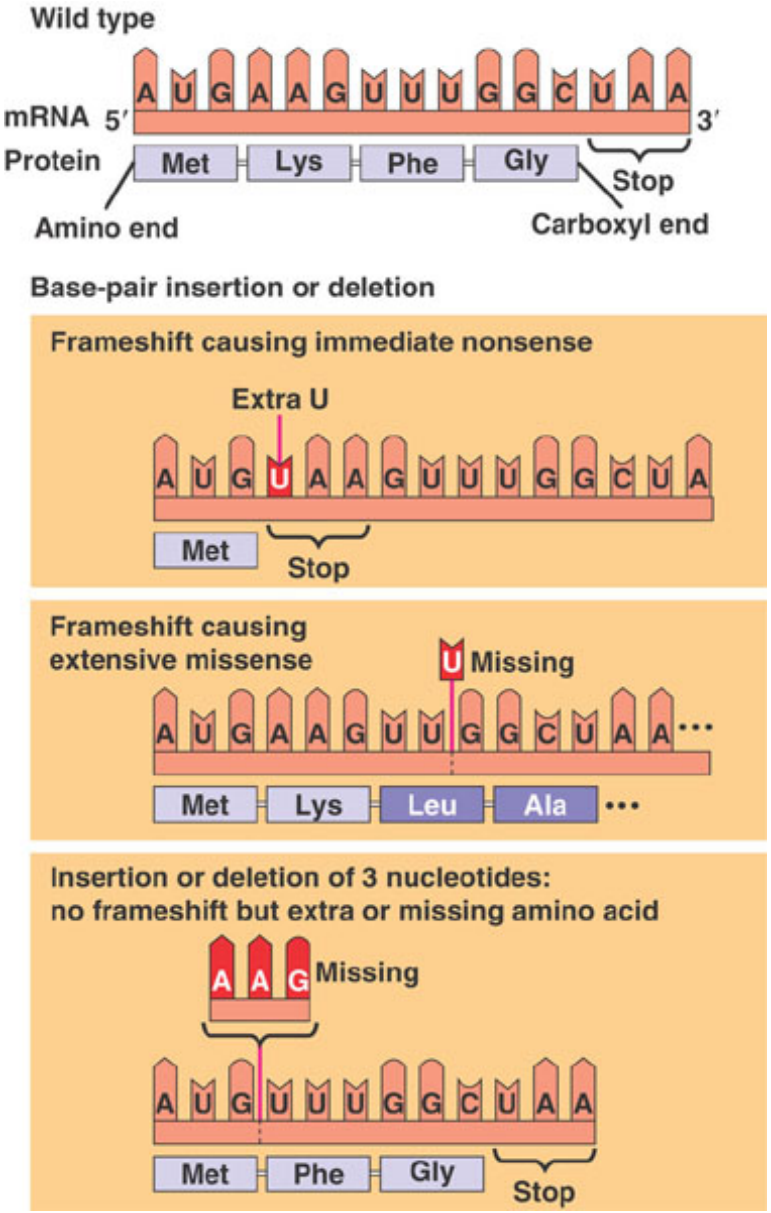
1. An immediate nonsense mutation and presence of a stop codon.

2. Causing missense mutation to downstream codons and change in all amino acids.

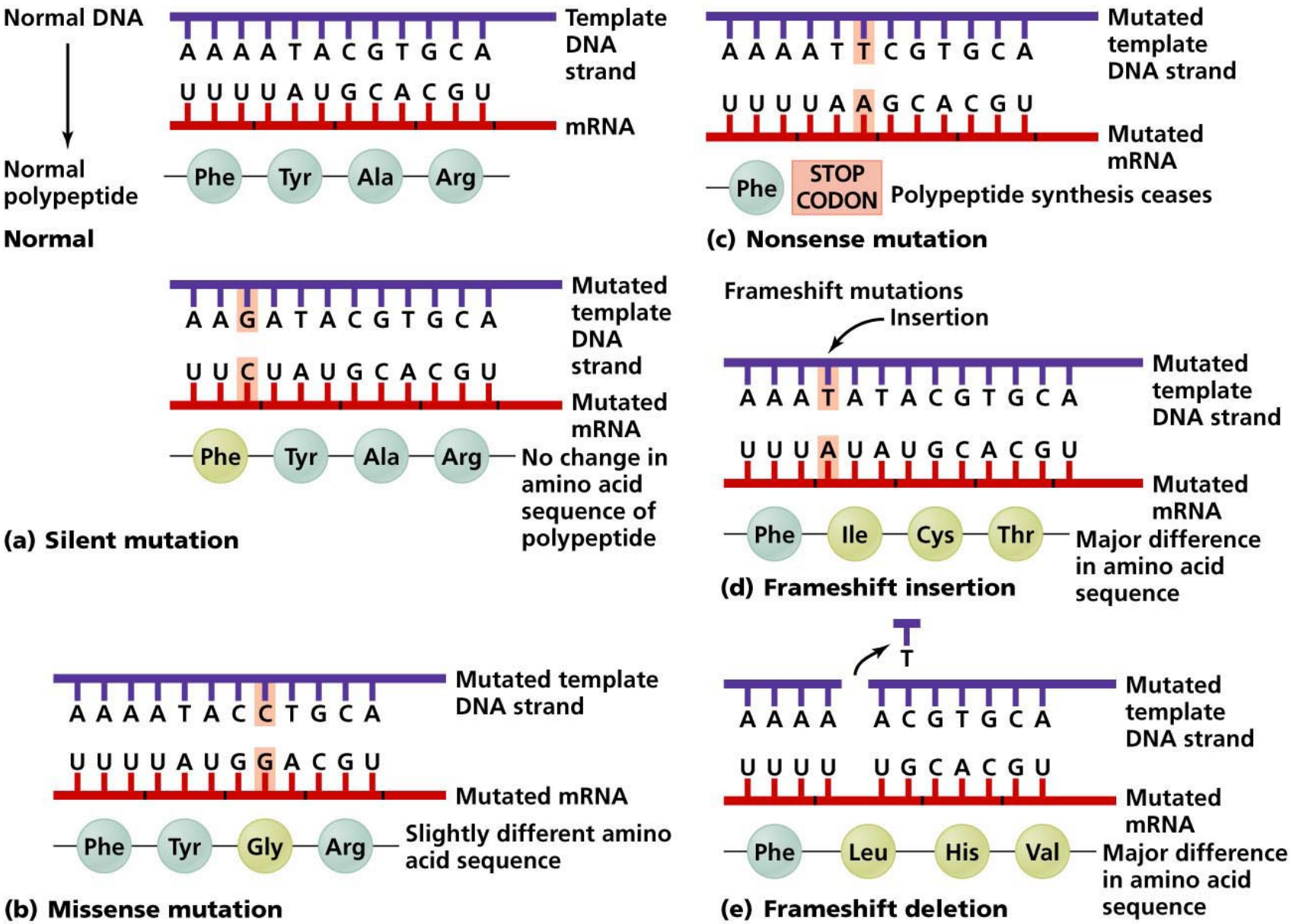
3. No frame-shift only a missing or added amino acid to the sequence.

When insertion or deletion happens with three base-pairs or multiple of three, only amino acids are added or removed

Point mutations – (2) insertion (3) deletion



Summary


Normal DNA
A A A A T A C G T G C A
Template DNA strand
U U U U A U G C A C G U
mRNA
Normal polypeptide
Phe Tyr Ala Arg
Normal
A A G A T A C G T G C A
Mutated template DNA strand
U U C U A U G C A C G U
Mutated mRNA
Phe Tyr Ala Arg
No change in amino acid sequence of polypeptide
(a) Silent mutation
A A A A T A C C T G C A
Mutated template DNA strand
U U U U A U G G A C G U
Mutated mRNA
Phe Tyr Gly Arg
Slightly different amino acid sequence
(b) Missense mutation
A A A A T T C G T G C A
Mutated template DNA strand
U U U U A A G C A C G U
Mutated mRNA
Phe
STOP CODON
Polypeptide synthesis ceases
(c) Nonsense mutation
Frameshift mutations
Insertion
A A A T A T A C G T G C A
Mutated template DNA strand
U U U A U A U G C A C G U
Mutated mRNA
Phe Ile Cys Thr
Major difference in amino acid sequence
(d) Frameshift insertion
T
A A A A A C G T G C A
Mutated template DNA strand
U U U U U G C A C G U
Mutated mRNA
Phe Leu His Val
Major difference in amino acid sequence
(e) Frameshift deletion

To know

Nonsense mutation

Transition

insertion

Point mutation

Non-coding region

Non-synonymous mutation

Premature stop codon

Missense mutation

deletion

substitution

Silent mutation

transversion

Segmental mutation

Chromosomal mutation

Frame-shift mutation

Truncated protein

Coding region

Synonymous mutation

Expectations

- You know the difference between point and segmental mutations.

- You know the various types of point mutations, the location of their occurrence, and their names.

- You know the consequences of frame-shift mutations and when they are least likely to affect protein function.

For a smile


Searching For Random Mutations
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