MUTATIONS

- A mutation is any change in the sequence of DNA in a genome, OR
- A mutation is a permanent change in the DNA sequence of a gene
- Mutations in a gene's DNA sequence can alter the amino acid sequence of the protein encoded by the gene.

- Mutations range in size from a single DNA building block (DNA base) to a large segment of a chromosome.

- Mutations can be beneficial, neutral, or harmful for the organism, but mutations do not "try" to supply what the organism "needs."

- In this respect, mutations are random—whether a particular mutation happens or not is unrelated to how useful that mutation would be.

How does mutation happens?

- Like words in a sentence, the DNA sequence of each gene determines the amino acid sequence for the protein it encodes.

- The DNA sequence is interpreted in groups of three nucleotide bases, called **codons.**

- Each codon specifies a single amino acid in a protein.

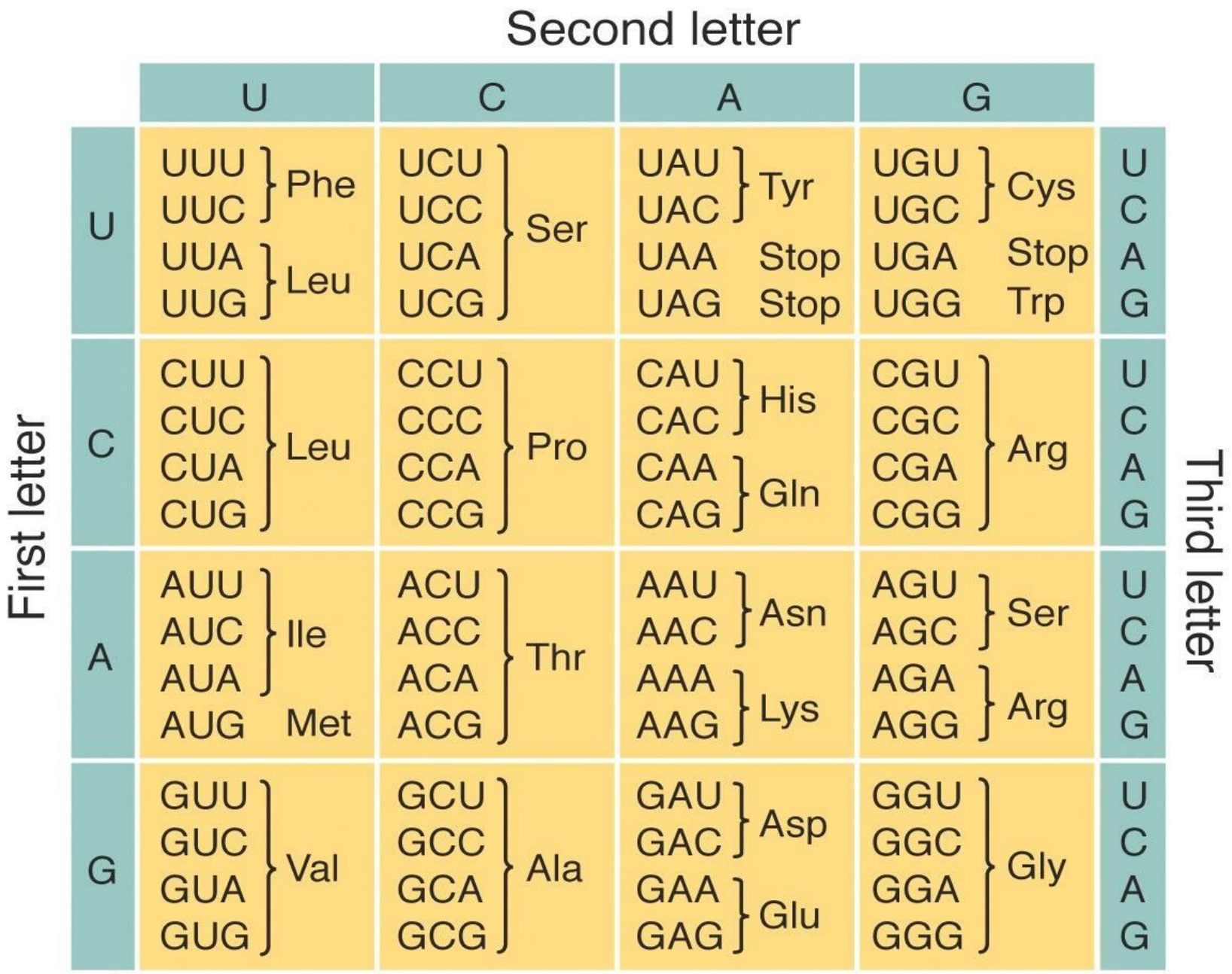
THE GENETIC CODE

- The set of rules that determine how a nucleotide sequence is converted into the amino acid sequence of proteins.

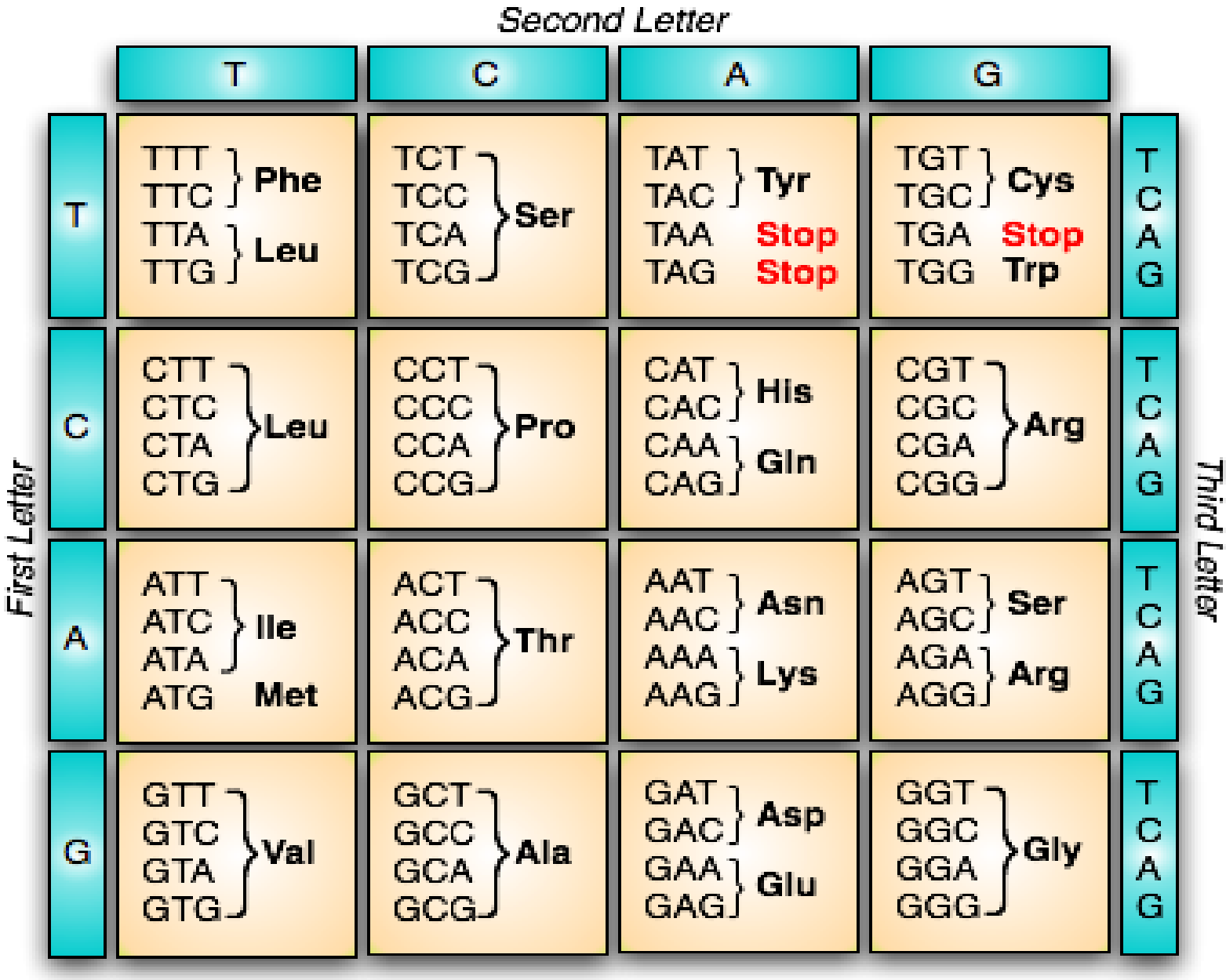
OR

- The rules by which the nucleotide sequence of a gene is translated into the amino acid sequence of a protein.

THE GENETIC CODE



THE GENETIC CODE



Mutate a sentence

- We can think about the DNA sequence of a gene as a sentence made up of entirely three-letter words.

- In the sequence, each three-letter word is a codon, specifying a single amino acid in a protein.

- Considering a sentence like:

Thesunwashotbuttheoldmandidnotgethishat.

- If you were to split this sentence into individual three-letter words, you would probably read it like this:

The sun was hot but the old man did not get his hat.

This sentence represents a gene.

The sun was hot but the old man did not get his hat.

- Each letter corresponds to a nucleotide base, and each word represents a codon.

What will happen if you shifted the three-letter "reading frame?"

We will end having the following:

T hes unw ash otb utt heo ldm and idn otg eth ish at.

Or

Th esu nwa sho tbu tth eol dma ndi dno tge thi sha t.

- From the three “reading frames” shown above, ONLY ONE can be translated into an understandable sentence i.e.,

The sun was hot but the old man did not get his hat.

- In the same way, only one three-letter reading frame within a gene codes or specify for the correct protein.

- Now, back to the original sentence of:

Thesunwashotbuttheoldmandidnotget hishat.

- Let us mutate the reading frame of this sentence by inserting or deleting letters within the sentence.

What happens?

Generation of Mutations (Mutagenesis)

- In general, the appearance of a new mutation is a rare event.

- Most mutations that were originally studied occurred spontaneously i.e., they are historically recognized in nature from an unknown source.

- This class of mutation is termed **spontaneous mutations**.

- This class of mutations represent only a small number of all possible mutations.

- But to understand biological systems further, geneticists/scientists can create new mutations by treating organisms with a mutagenizing agent or a **mutagen**.

- These mutations are called **induced mutations**.
- Mutations can be induced by several methods.
- Three general approaches are used to generate mutations are **radiation**, **chemical** and **transposon insertion**.

- The first induced mutations were created by treating Drosophila with X-rays.

- In addition to X-rays, gamma rays and fast neutron bombardment have also been used.
- These treatments can induce **point mutations** (changes in a single nucleotide) or deletions (loss of a chromosomal segment).

- Chemical mutagens work mostly by inducing **point mutations**.

- Point mutations occur when a single base pair of a gene is changed.

- These changes are classified as **transitions** or **transversions**.

- Transitions occur when a purine is converted to a purine (**A to G or G to A**) or a pyrimide is converted to a pyrimidine (**T to C or C to T**).

- A transversion results when a purine is converted to a pyrimidine or a pyrimidine is converted to a purine

- Two major classes of chemical mutagens which are routinely used are;

- **alkylating agents** and **base analogs**. Each has a specific effect on DNA.

- Alkylating agents [such as ethyl methane sulphonate (EMS) and ethyl ethane sulphonate (EES)] can mutate both replicating and non-replicating DNA

- By contrast, a base analog (e.g.,5-bromouracil) only mutate DNA when the analog is incorporated into replicating DNA.

- Each class of chemical mutagen has specific effects that can lead to transitions, transversions or deletions.

- Scientists are now using the power of transposable elements to create new mutations.

- Transposable elements are mobile pieces of DNA that can move from one location in a genome to another.

- Often when they move to a new location, the result is a new mutant.

- The mutant arises because the presence of a piece of DNA in a wild type gene disrupts the normal function of that gene

- Among the mutations that affect the function of a protein (gene), some allow the protein to be **active** at the organism's **normal temperature** but **inactive** at either **higher** or **lower** temperatures.

- The former are **temperature-sensitive** (**Ts**) mutations and the latter are **cold-sensitive** mutations

- Usually, a gene fails to function at a higher temperature, but functions normally at a low temperature.

- Such mutations are called temperature-sensitive (*heat-sensitive*).

- *Cold-sensitive* mutants on the other hand function normally at higher temperatures, but fail to function at a reduced temperature.

- Not all mutations in DNA lead to a detectable change in the phenotype.

- Mutations without any apparent effect are called silent mutations.

Classes of Mutations

- We can divide mutations into two general classes.

- These are **Point mutations** and **Rearrangement mutations** or **Chromosomal mutations**.

- This causes a corresponding change in the protein that the gene produces.
- A rearrangement mutation on the other hand affects a large region.
- The simplest type of rearrangements are **insertions** of additional material or **deletions** of a stretch of the gene.

Point Mutation

- When a single base in the nucleotide sequence is replaced by another, then it is known as point mutation.
- Point mutations also include insertion and/or deletion of a single base in the DNA strand.
- Usually, they are caused due to error in DNA replication.
-

- At times, it occurs after exposure to mutagens like heat and radiation.

- Point mutations can be either **transitions** or **transversions**.

- In the former case, a purine base (adenine or guanine) is substituted by another purine or

- A pyrimidine base (cytosine or thymine) is replaced by another pyrimidine.

- In transversion type of point mutations, purine is substituted by pyrimidine or vice versa.

- Transition point mutation is more common than transversion type.

- The effects of point mutation can vary depending upon the site of mutation on the gene.

- If point mutation occurs in the coding sequence of DNA or exon, then the protein coded by the altered gene is changed.

- A point mutation can be reversed by another point mutation, in which the nucleotide is changed back to its original state

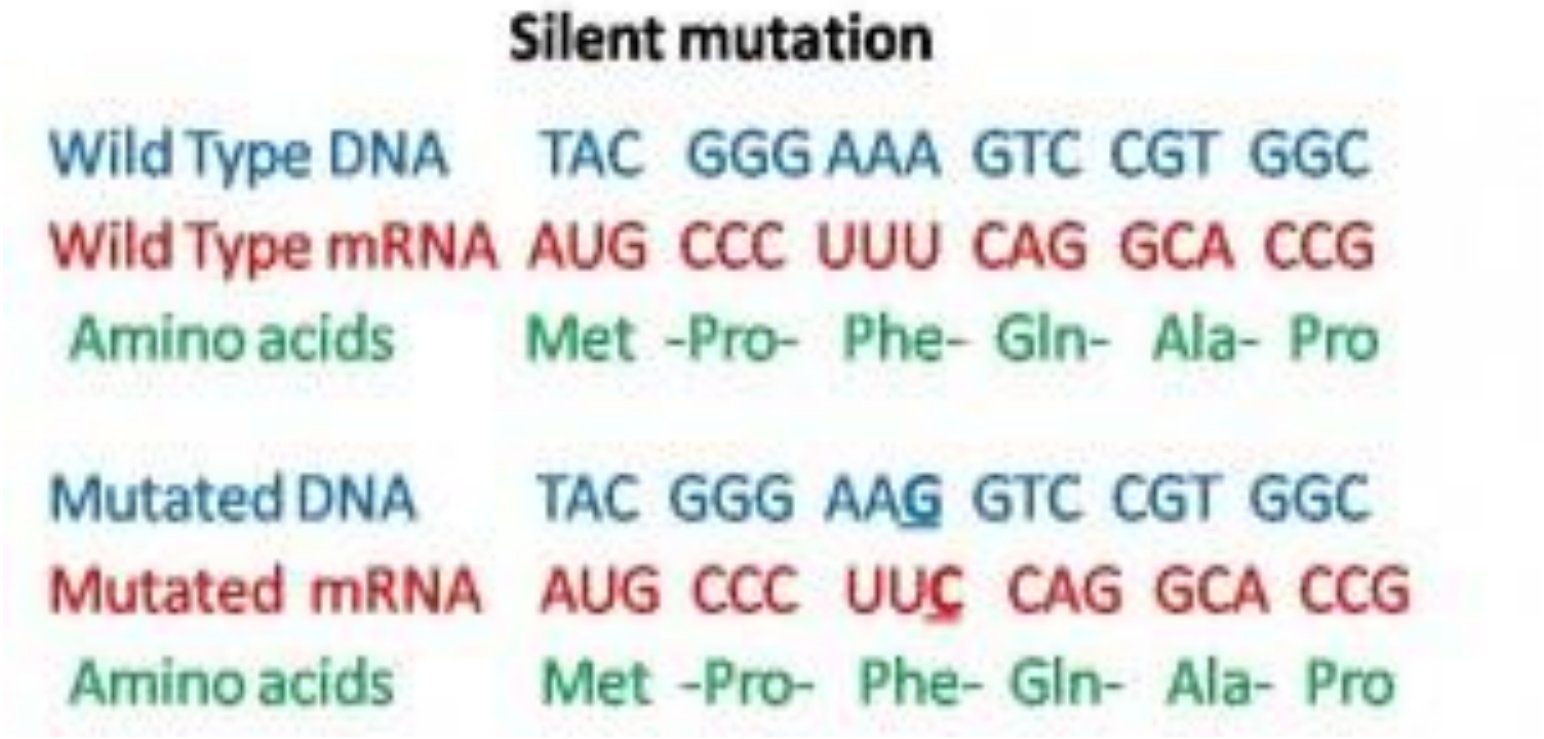
- Point mutations that occur within the protein coding region of a gene may be classified into **three** kinds, depending upon what the erroneous codon codes for:

- **Silent mutations**: which code for the same (or a sufficiently similar) **amino acid.**

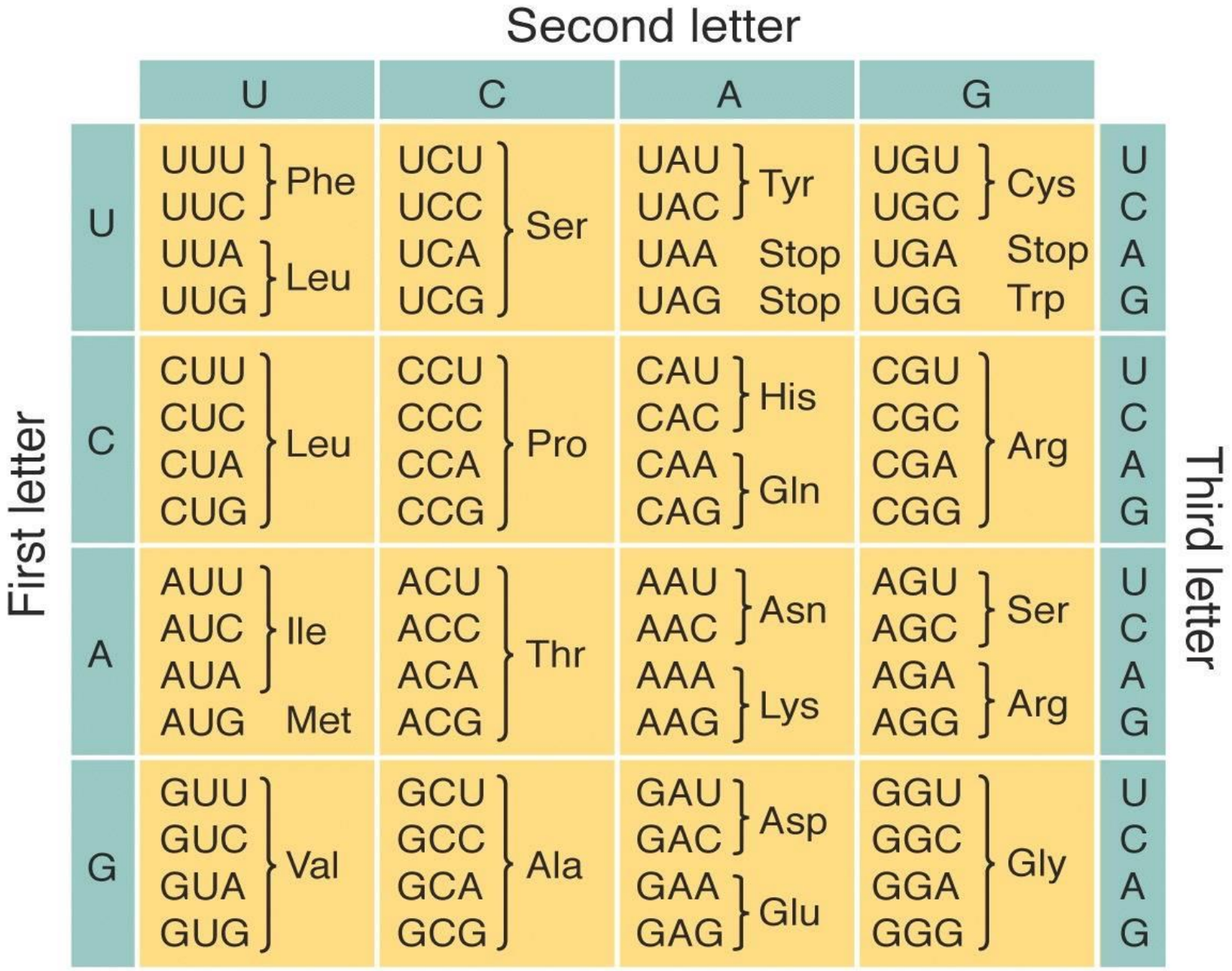
- **Missense mutations**: which code for a different amino acid.

- **Nonsense mutations**: which code for a stop and can truncate the protein.

Silent Mutation



THE GENETIC CODE



- Such mutations are said to be silent because they cause no change in their product and cannot be detected without sequencing the gene (or its mRNA)

Silent mutation

Wild Type DNA	TAC GGG AAA GTC CGT GGC
Wild Type mRNA	AUG CCC UUU CAG GCA CCG
Amino acids	Met -Pro- Phe- Gln- Ala- Pro
Mutated DNA	TAC GGG AA**G** GTC CGT GGC
Mutated mRNA	AUG CCC UU**C** CAG GCA CCG
Amino acids	Met -Pro- Phe- Gln- Ala- Pro

Missense mutations

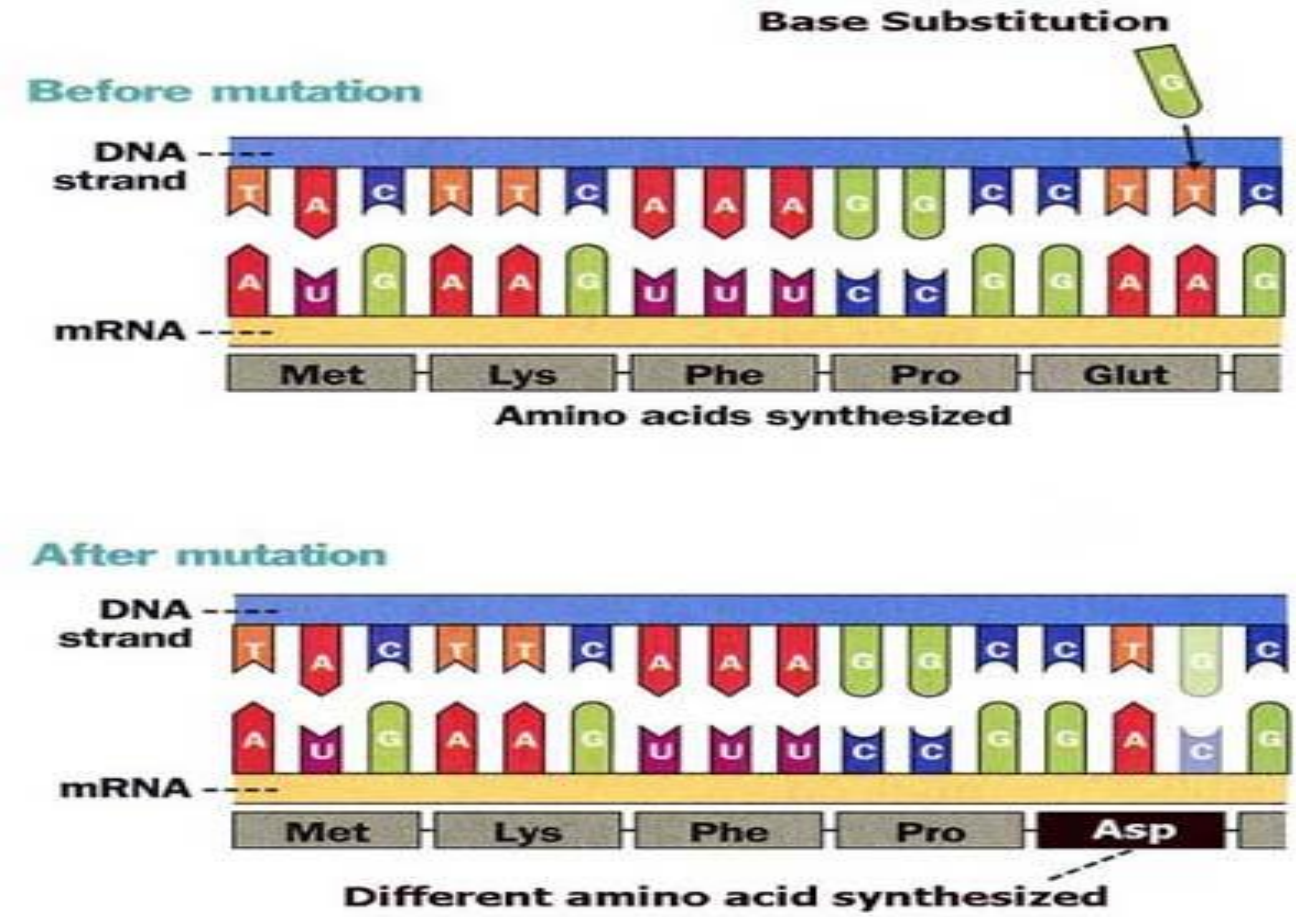
- Missense mutation is a genetic change that results in the substitution of one amino acid in protein for another. Or

- It is a mutation in which a codon specifying one amino acid is altered so as to specify a different amino acid.

- It is missense because the resulting codon has the "wrong sense" for an amino acid.)

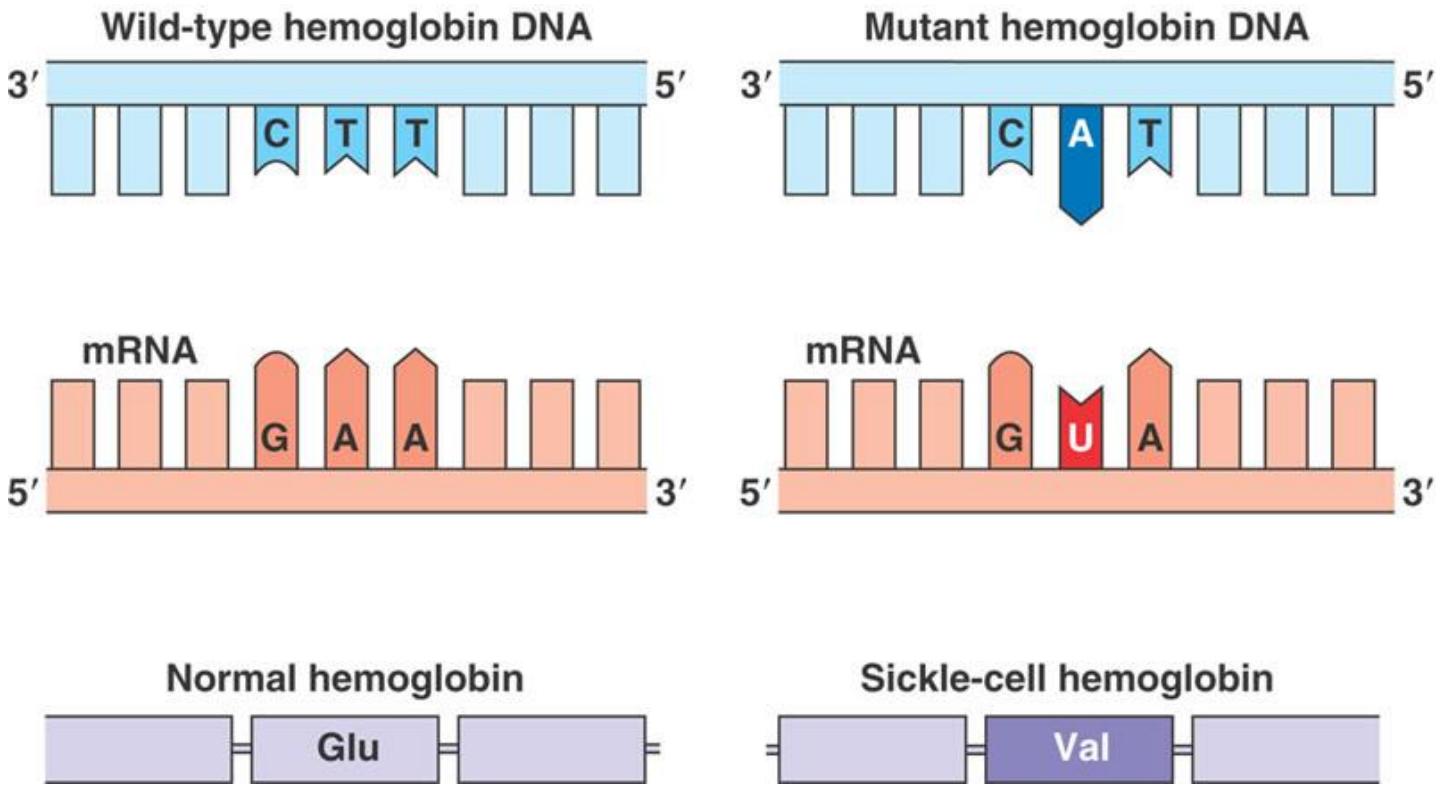
- A missense mutation is a "readable" genetic message although its "sense" (its meaning) is changed.

- This is in contrast to a nonsense mutation which has no meaning except to halt the reading of the genetic message.

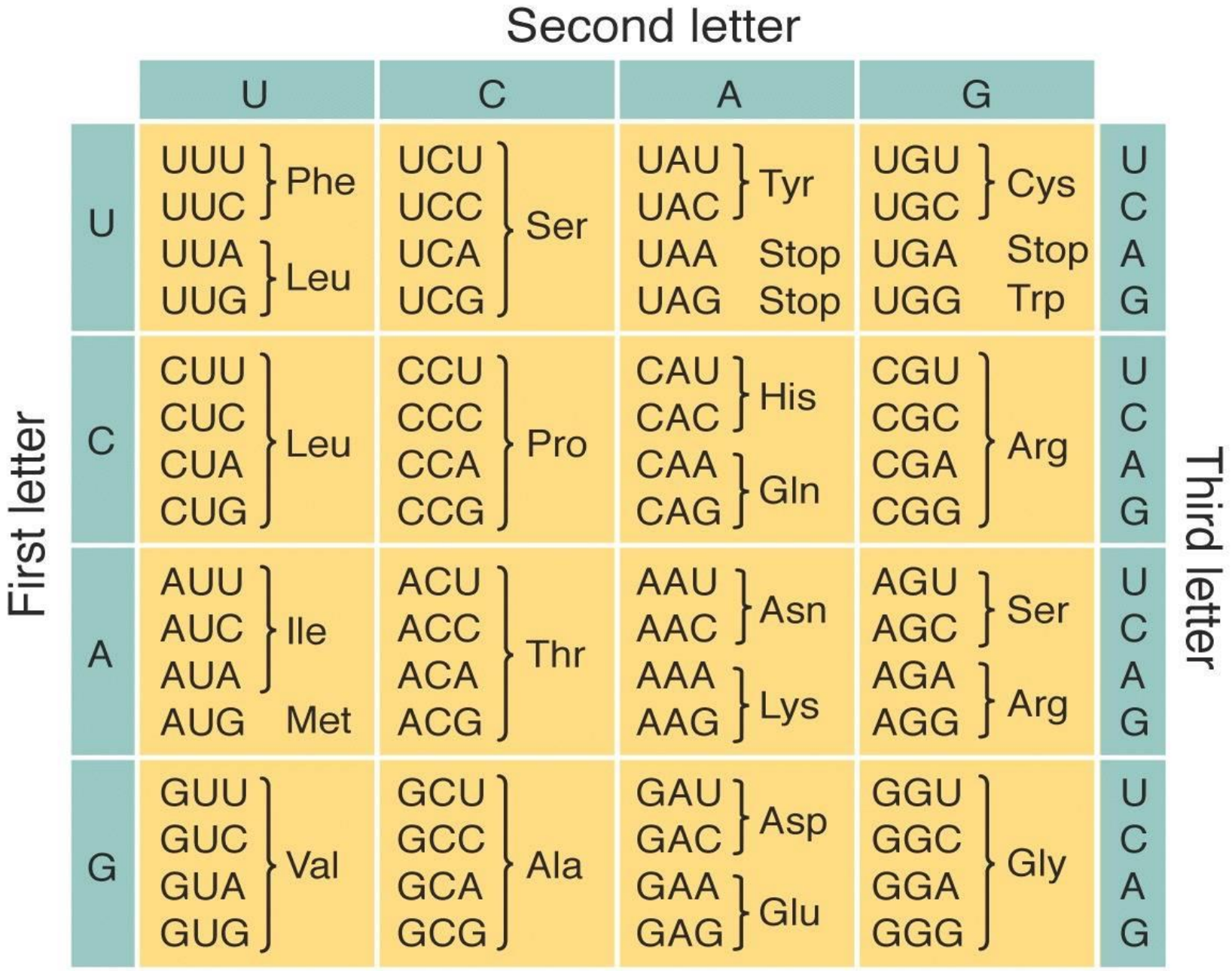

Base Substitution
Before mutation
DNA strand
T A C T T C A A A G G C C T T C
A U G A A G U U U C C G G A A G
mRNA
Met Lys Phe Pro Glut
Amino acids synthesized
After mutation
DNA strand
T A C T T C A A A G G C C T G C
A U G A A G U U U C C G G A C G
mRNA
Met Lys Phe Pro Asp
Different amino acid synthesized

- The first missense mutation discovered in humans was found to be responsible for sickle hemoglobin, the molecular basis of sickle cell trait and sickle cell anemia.

- The mutation causes an amino acid change from **glutamic acid** to **valine**, converting normal adult hemoglobin (hemoglobin A) to sickle hemoglobin (hemoglobin S) as shown below.


Wild-type hemoglobin DNA
3′
5′
C
T
T
Mutant hemoglobin DNA
3′
5′
C
A
T
mRNA
5′
3′
G
A
A
mRNA
5′
3′
G
U
A
Normal hemoglobin
Glu
Sickle-cell hemoglobin
Val

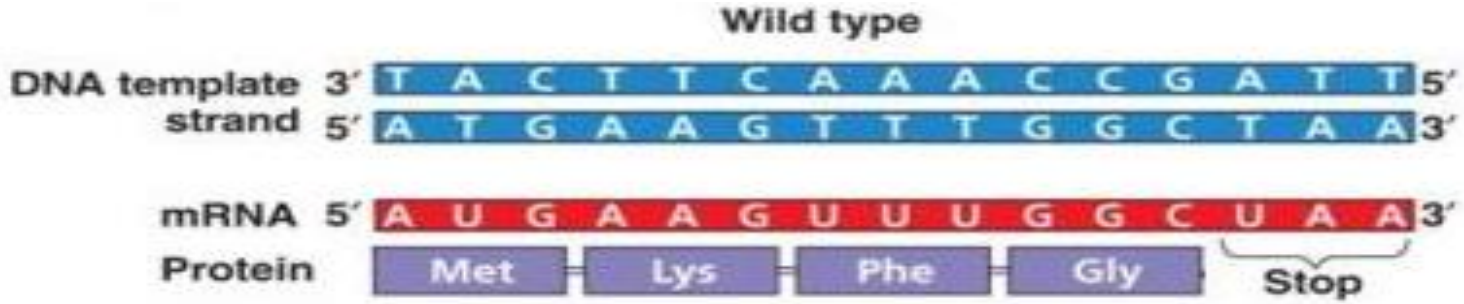
THE GENETIC CODE

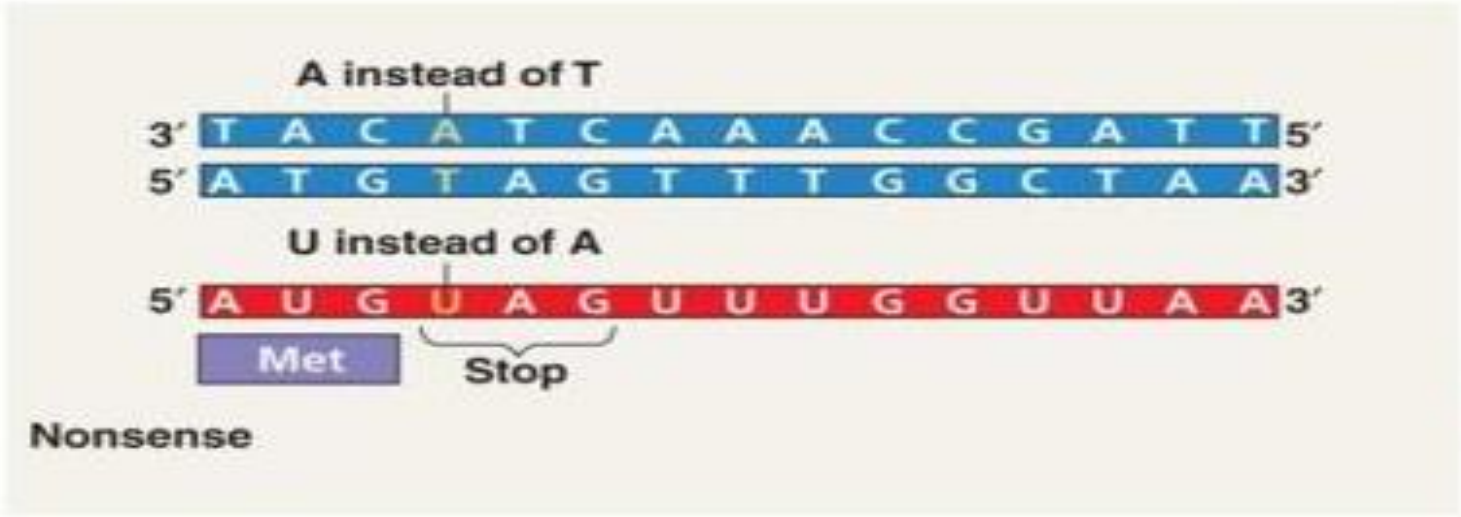


Nonsense Mutations

- Nonsense mutation is a change in a base in the DNA that prematurely stops the translation of messenger RNA (mRNA) resulting in a polypeptide (protein) chain that ends prematurely.

- This results in a protein product that is truncated and incomplete and usually nonfunctional.

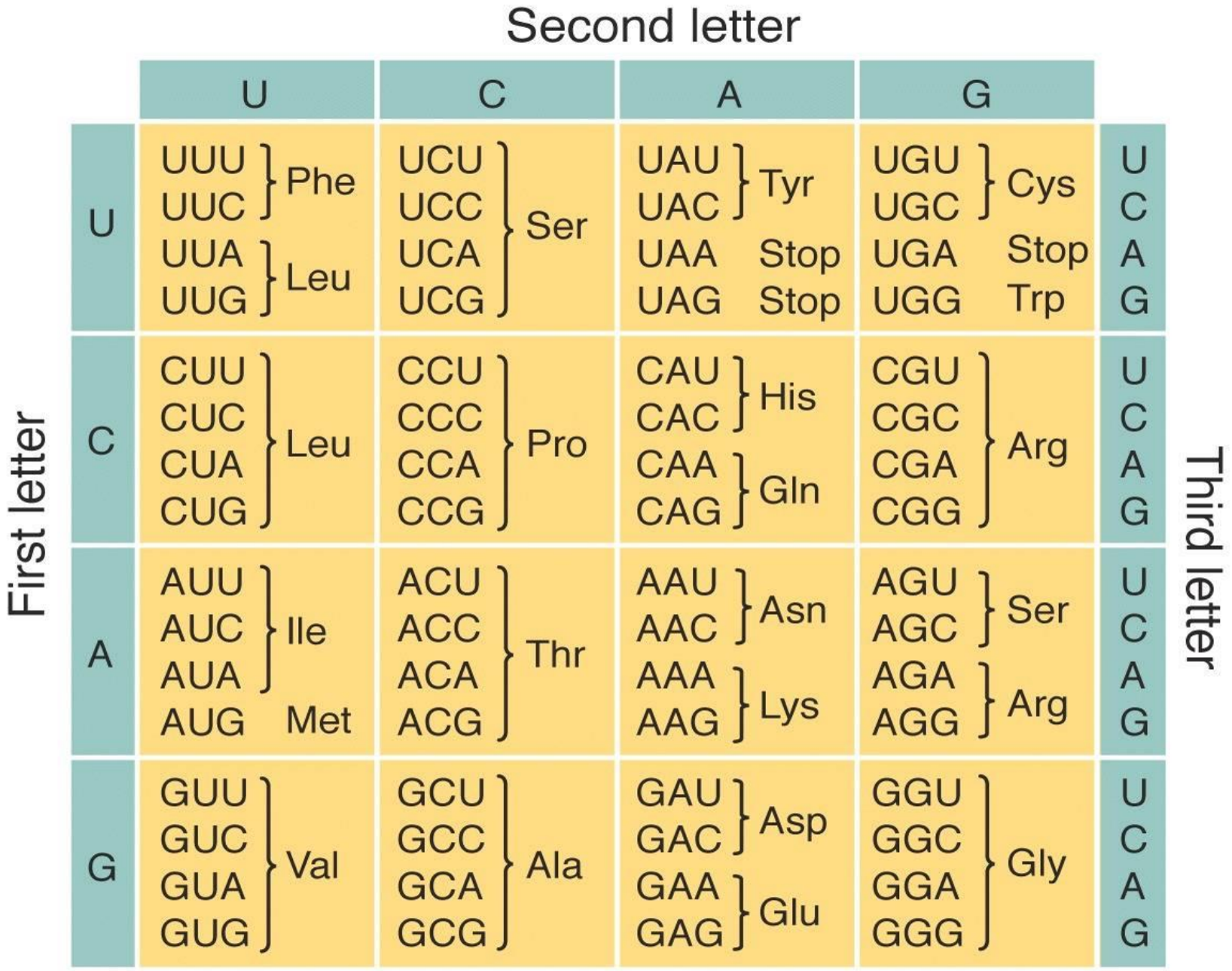

Wild type
DNA template strand
3′ T A C T T C A A A C C G A T T 5′
5′ A T G A A G T T T G G C T A A 3′
mRNA 5′ A U G A A G U U U G G C U A A 3′
Protein
Met
Lys
Phe
Gly
Stop


A instead of T
3′ T A C A T C A A A C C G A T T 5′
5′ A T G T A G T T T G G C T A A 3′
U instead of A
5′ A U G U A G U U U G G U U A A 3′
Met
Stop
Nonsense

- The nonsense mutation converts a codon that encodes an amino acid into a **stop codon**, i.e., a that specifies the termination of translation.

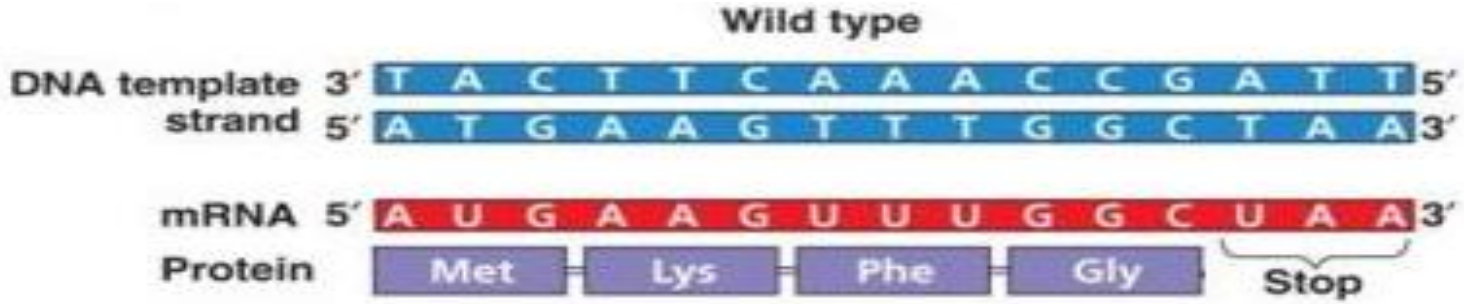
- There are three nonsense codons (**UAG**, **UAA**, and **UGA**) in mRNA (see the Genetic Code).
- One of them comes normally at the end of each polypeptide (see above slide).

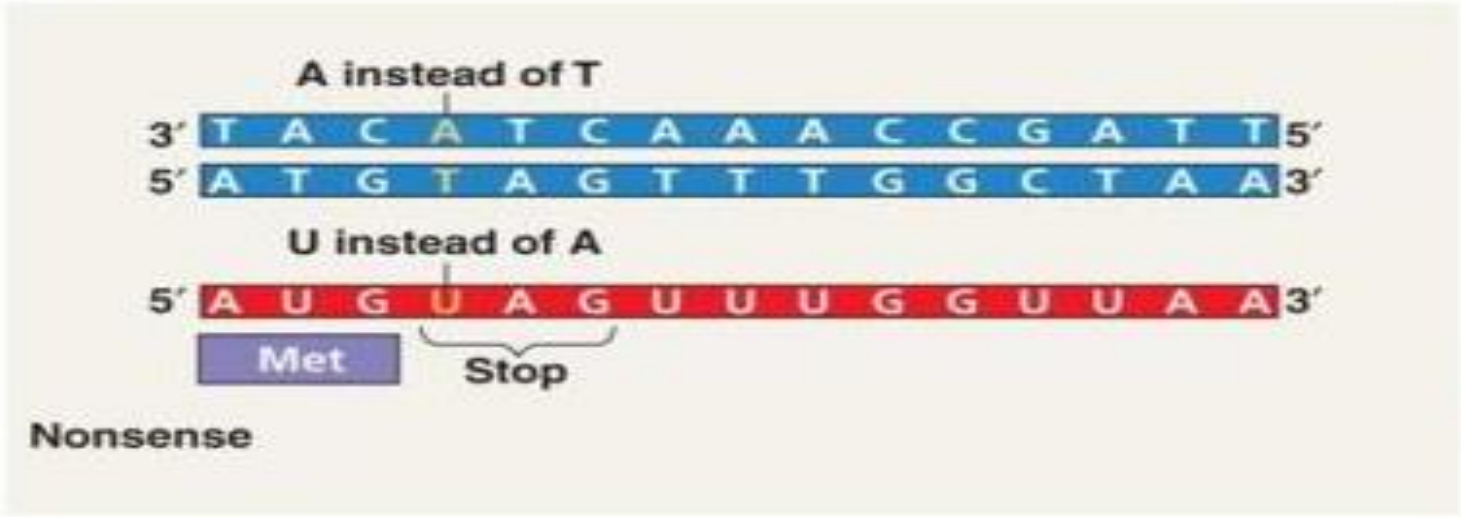
THE GENETIC CODE



- Three codons in the genetic code tell the cell to stop adding amino acids to a protein because the end of the gene has been reached.

- In a nonsense mutation, a codon that stands for an amino acid mutates to one of these three stop codons.


Wild type
DNA template strand
3′ T A C T T C A A A C C G A T T 5′
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


A instead of T
3′ T A C A T C A A A C C G A T T 5′
5′ A T G T A G T T T G G C T A A 3′
U instead of A
5′ A U G U A G U U U G G U U A A 3′
Met
Stop
Nonsense

- The term "nonsense mutation" is used because the stop codon has "no sense" for an amino.

- **Cystic fibrosis** is a disease caused by a nonsense mutation.

- It is a genetic disorder that affects most critically the lungs, and also the pancreas, liver, and intestine.

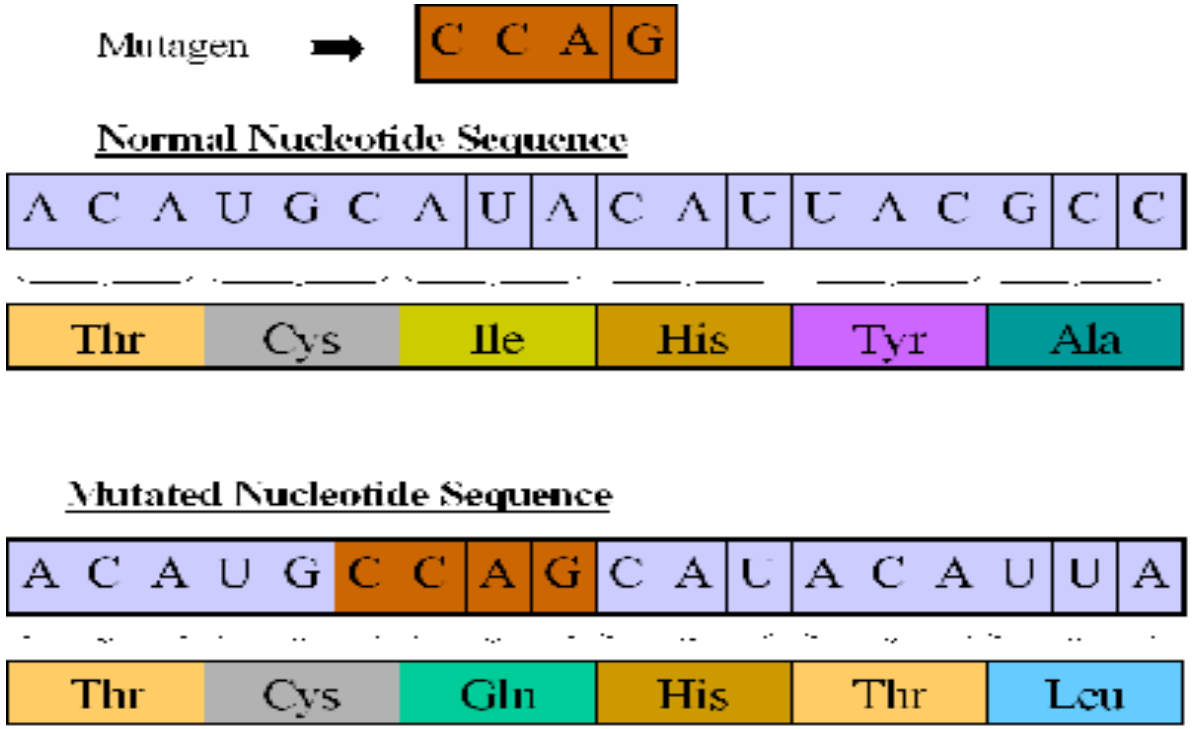
- The signs and symptoms of cystic fibrosis are poor growth and poor weight gain despite a normal food intake, frequent chest infections, and coughing.

Frameshift Mutation

- A mutation in a DNA chain that occurs when the number of nucleotides inserted or deleted is not a multiple of three; OR

- It is a type of mutation in which a number of nucleotides not divisible by three is inserted into or deleted from a coding sequence.

- This therefore will make every codon beyond the point of insertion or deletion (downstream) read incorrectly during translation.



- A frameshift mutation will in general cause the reading frame of the codons after the mutation to code for different amino acids.

- The frameshift mutation will also alter the first stop codon ("UAA", "UGA" or "UAG") encountered in the sequence.

- The polypeptide which is being created could be abnormally short or abnormally long, and will most likely not be functional.

- Frameshift mutations can be caused by **intercalating agents**.

- These are chemical agents that insert between adjacent base pairs (like inserting between the rungs of a ladder).

- The intercalation causes a conformational change in the double helix, so that when replication occurs, the aberrant conformation causes small deletions or insertions to occur in the newly synthesized DNA.

Difference between Point and Frameshift Mutations

- A **point mutation** is where a **single letter is the only thing changed** in the DNA sequence.

- Lets say your phone number (or DNA code) was 483-183**9** and you mistakely told someone that your phone number was 483-183**5**.

- that one digit is enough to make that person dial the wrong number (or cause a mutation in DNA.)

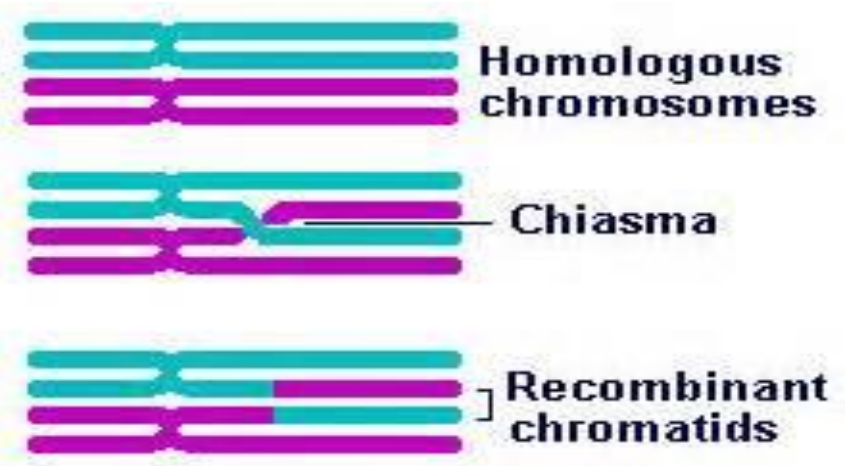
- For example suppose your DNA sequence was ACT **G**CT, a point mutation would just be a change in one of those bases (or letters), so it could end up like : ACT **A**CT.

- A **frameshift mutation** on the other hand is generally much more serious and will cause a change all the way down (downstream) a DNA sequence, making each codon a different sequence, not just in one point or base like a point mutation.

TRANSFER OF GENETIC MATERIAL

- Sometimes when two pieces of DNA come into contact with each other, sections of each DNA strand will be exchanged.

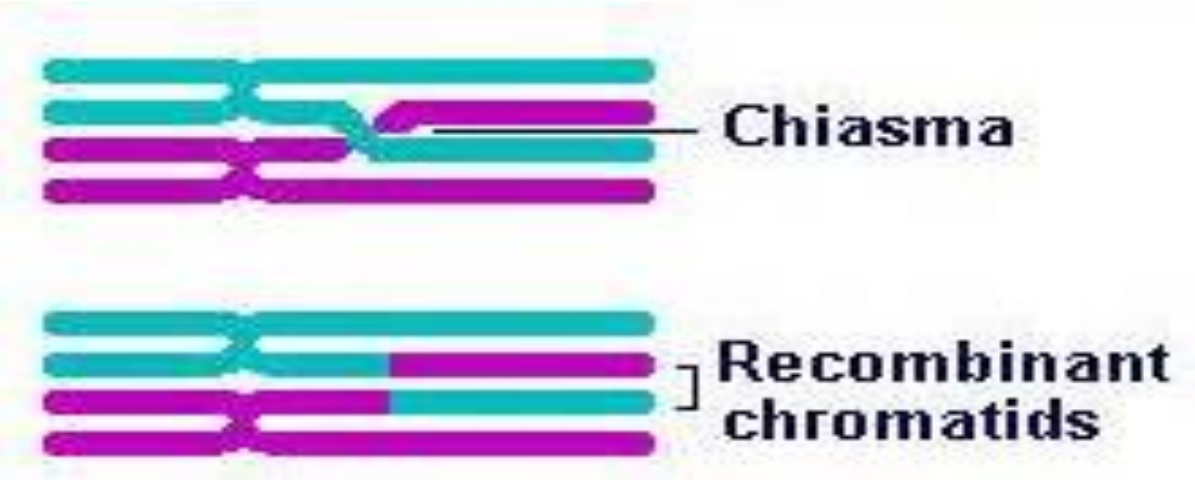
- This is usually done through a process called crossing over in which the DNA breaks and is attached on the other DNA strand leading to the transfer of genes and possibly the formation of new genes.



- Genetic recombination is the transfer of DNA from one organism to another.

- The transferred donor DNA may then be integrated into the recipient's nucleoid by various mechanisms.

- In the case of homologous recombination, homologous DNA sequences having nearly the same nucleotide sequences are exchanged by means of breakage and reunion of paired DNA segments.



- Genetic information can be transferred from organism to organism through vertical transfer (from a parent to offspring) or through horizontal transfer methods such as **transformation**, **transduction** or **conjugation**.

- Bacterial genes are usually transferred to members of the same species but occasionally transfer to other species can also occur.

❖Bacterial transformation