Medical Genetics

Lecture #8

Mutations

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Lecture Outline

- Causes of Mutations
- Types of Mutations
- Consequences of Mutations

Learning Objectives:

At the end of this lecture, the student is expected to

- Know what mutations are
- Know the causes of Mutations
- Know the different types of mutations and their clinical relevance
- Appreciate the biological and clinical significance of Mutations

Synopsis

- **Mutations** are permanent changes in the primary nucleotide sequence of DNA regardless of its functional significance.
- Mutations are the bases of genetic diseases.
- They occur spontaneously during cell division or are caused by **mutagens** such as radiation, viruses, & chemicals.
- Can occur in germ line cells (sperm or oocytes) or in somatic cells or during embryogenesis.
- **Germline mutations** can be passed from one generation to the next & thus cause inherited disease.
- **Somatic mutations** do not cause hereditary disease but they may cause cancer & some congenital malformations.

TABLE 5.1 Alternative definitions for mutation and polymorphism

	Mutation	Polymorphism
Formal definition	Any DNA sequence change, without regard to whether it has functional consequences OR The process by which a DNA sequence is altered	Any sequence variant present at a frequency of 1% or higher in a population, whether or not it has functional consequences
Other common usage	A DNA change that has functional consequences, i.e., a change that causes a phenotype	Benign sequence variants (those that do not affect phenotype) even if the frequency is unknown or less than 1%

Causes of Mutations

Radiation

UV Radiation
Both natural sunlight and tanning beds

X-Rays
Medical, dental, airport security screening

Chemicals

Cigarette Smoke
Contains dozens of mutagenic chemicals

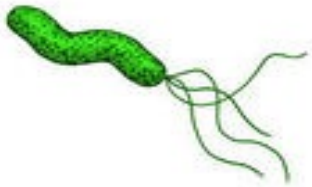
Benzoyl Peroxide
Common ingredient in acne products

Nitrate & Nitrate Preservatives
In hot dogs and other processed meats

Barbecuing
Creates mutagenic chemicals in foods

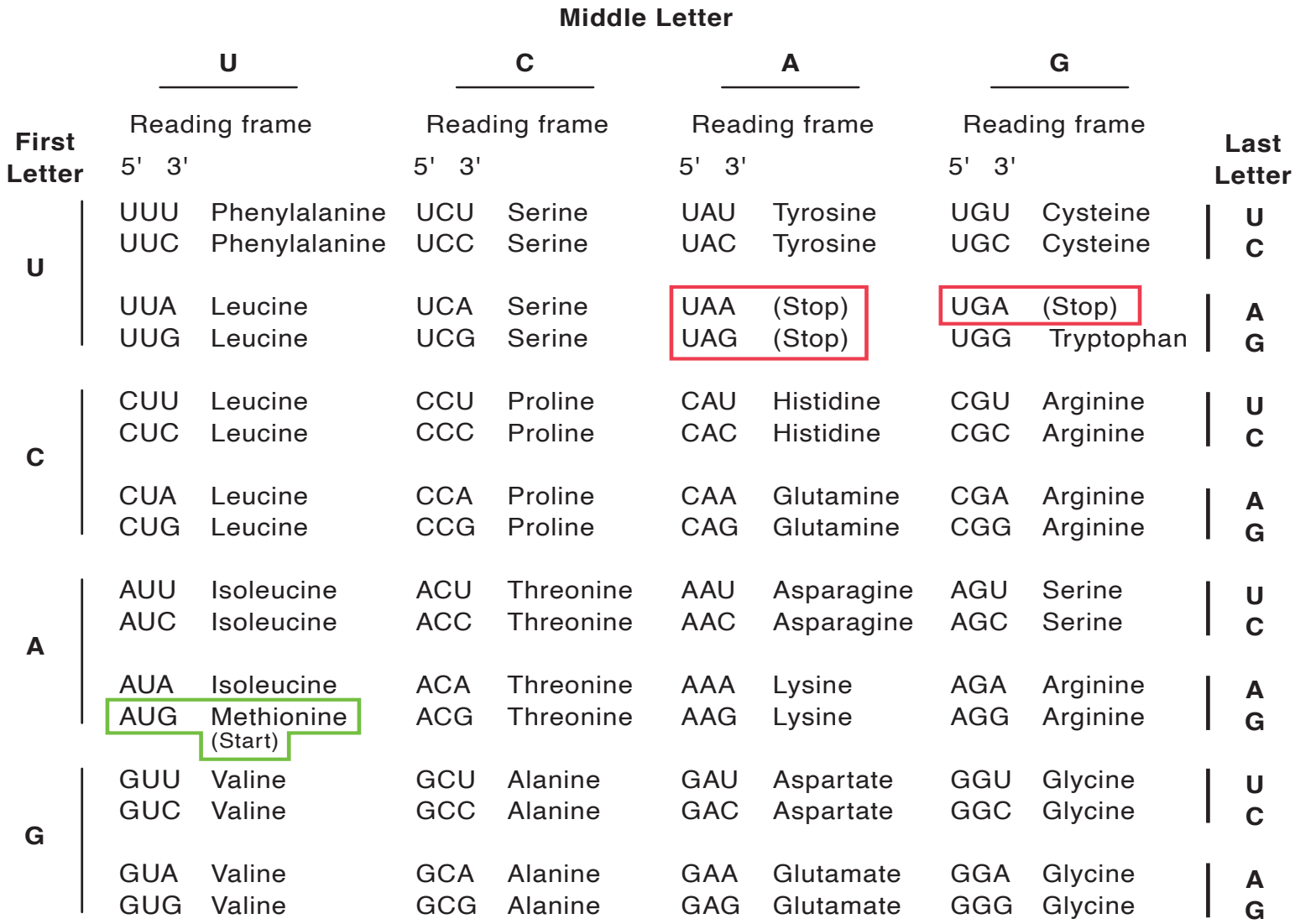
Infectious Agents

Human Papillomavirus (HPV)
Sexually transmitted virus



Helicobacter pylori
Bacteria spread through contaminated food

The Genetic Code (An overview)



First Letter	Middle Letter U (Reading frame 5' 3')		Middle Letter C (Reading frame 5' 3')		Middle Letter A (Reading frame 5' 3')		Middle Letter G (Reading frame 5' 3')		Last Letter
U	UUU	Phenylalanine	UCU	Serine	UAU	Tyrosine	UGU	Cysteine	U
	UUC	Phenylalanine	UCC	Serine	UAC	Tyrosine	UGC	Cysteine	C
	UUA	Leucine	UCA	Serine	UAA	(Stop)	UGA	(Stop)	A
	UUG	Leucine	UCG	Serine	UAG	(Stop)	UGG	Tryptophan	G
C	CUU	Leucine	CCU	Proline	CAU	Histidine	CGU	Arginine	U
	CUC	Leucine	CCC	Proline	CAC	Histidine	CGC	Arginine	C
	CUA	Leucine	CCA	Proline	CAA	Glutamine	CGA	Arginine	A
	CUG	Leucine	CCG	Proline	CAG	Glutamine	CGG	Arginine	G
A	AUU	Isoleucine	ACU	Threonine	AAU	Asparagine	AGU	Serine	U
	AUC	Isoleucine	ACC	Threonine	AAC	Asparagine	AGC	Serine	C
	AUA	Isoleucine	ACA	Threonine	AAA	Lysine	AGA	Arginine	A
	AUG	Methionine (Start)	ACG	Threonine	AAG	Lysine	AGG	Arginine	G
G	GUU	Valine	GCU	Alanine	GAU	Aspartate	GGU	Glycine	U
	GUC	Valine	GCC	Alanine	GAC	Aspartate	GGC	Glycine	C
	GUA	Valine	GCA	Alanine	GAA	Glutamate	GGA	Glycine	A
	GUG	Valine	GCG	Alanine	GAG	Glutamate	GGG	Glycine	G

Classifications of Mutations

- Mutations can be classified into the following three categories based on the extent of the genetic damage:
    - Genome Mutation
    - Chromosomal Mutation
    - Gene Mutation

Genome Mutations

- Are due to chromosome mis-segregation.
- Are gain or loss of one or more or whole chromosomes.
- Are exemplified by aneuploidy & polyploidy.
- Are often incompatible with survival.

Chromosome Mutations

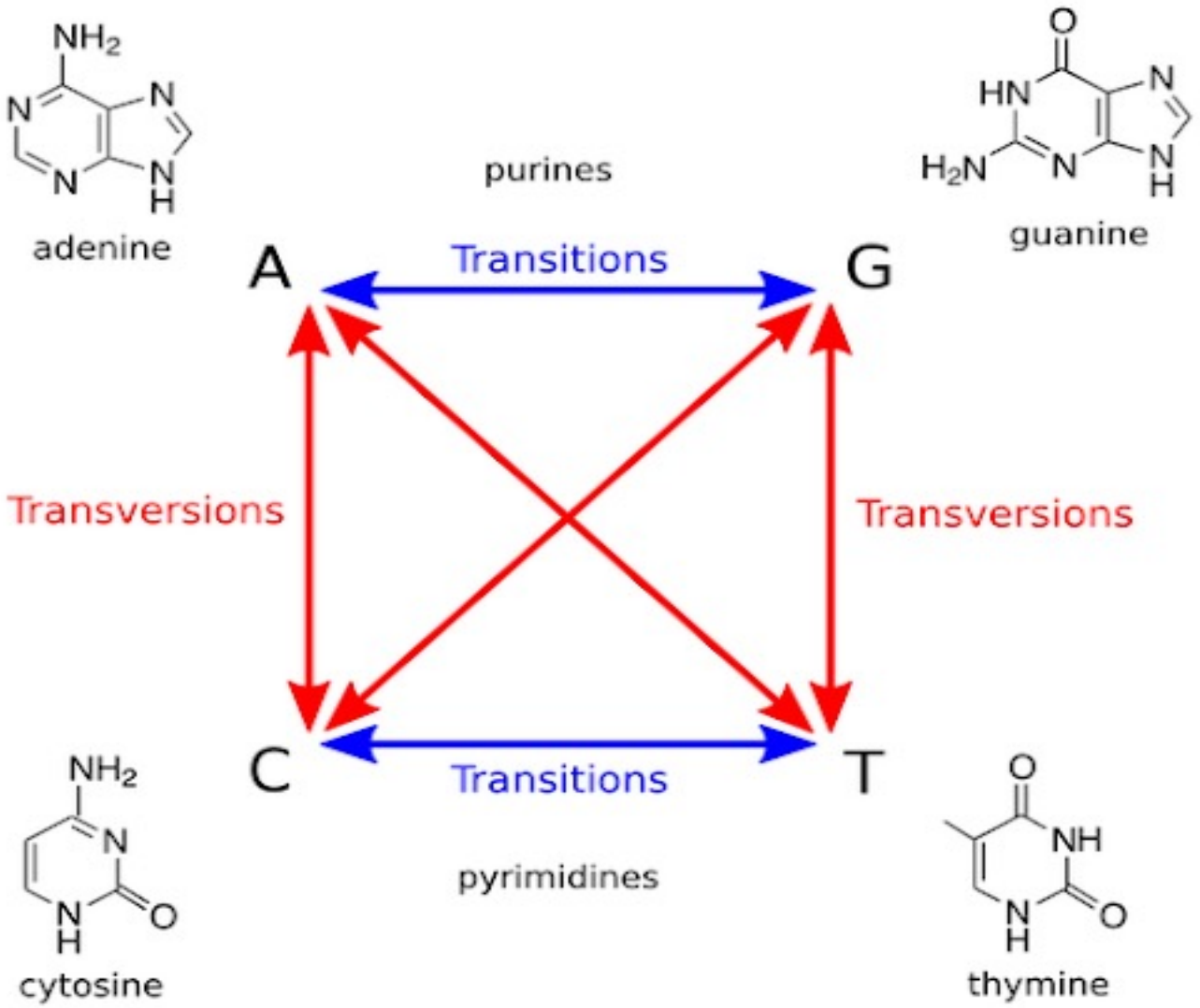
- Are due to rearrangement of genetic material in a chromosome which results in structural changes in the chromosome.
- Are exemplified by translocations.
- Are infrequently transmitted because most are incompatible with survival

Gene Mutations

- Cause most of the hereditary diseases.
- May affect a single base (more common) or they may affect a larger portion of a gene.
- Have the following types:
  - 1. Point Mutations
  - 2. Frame shift mutations
  - 3. Expansions of repeat sequences
  - 4. Unequal Crossing over

Point Mutations

- Are also called Single-base substitutions Mutations
- **Are the substitution of one base for another.**
- If one purine [A or G] or pyrimidine [C or T] is replaced by the other, the substitution is called a **transition**.
- If a purine is replaced by a pyrimidine or vice versa, the substitution is called a **transversion**.


adenine
purines
guanine
A
Transitions
G
Transversions
Transversions
C
Transitions
T
pyrimidines
cytosine
thymine

Point Mutations..,

- Point mutations includes the following types:-
    - 1. Silent mutations
    - 2. Missense mutations
    - 3. Nonsense mutations
    - 4. Neutral Mutations

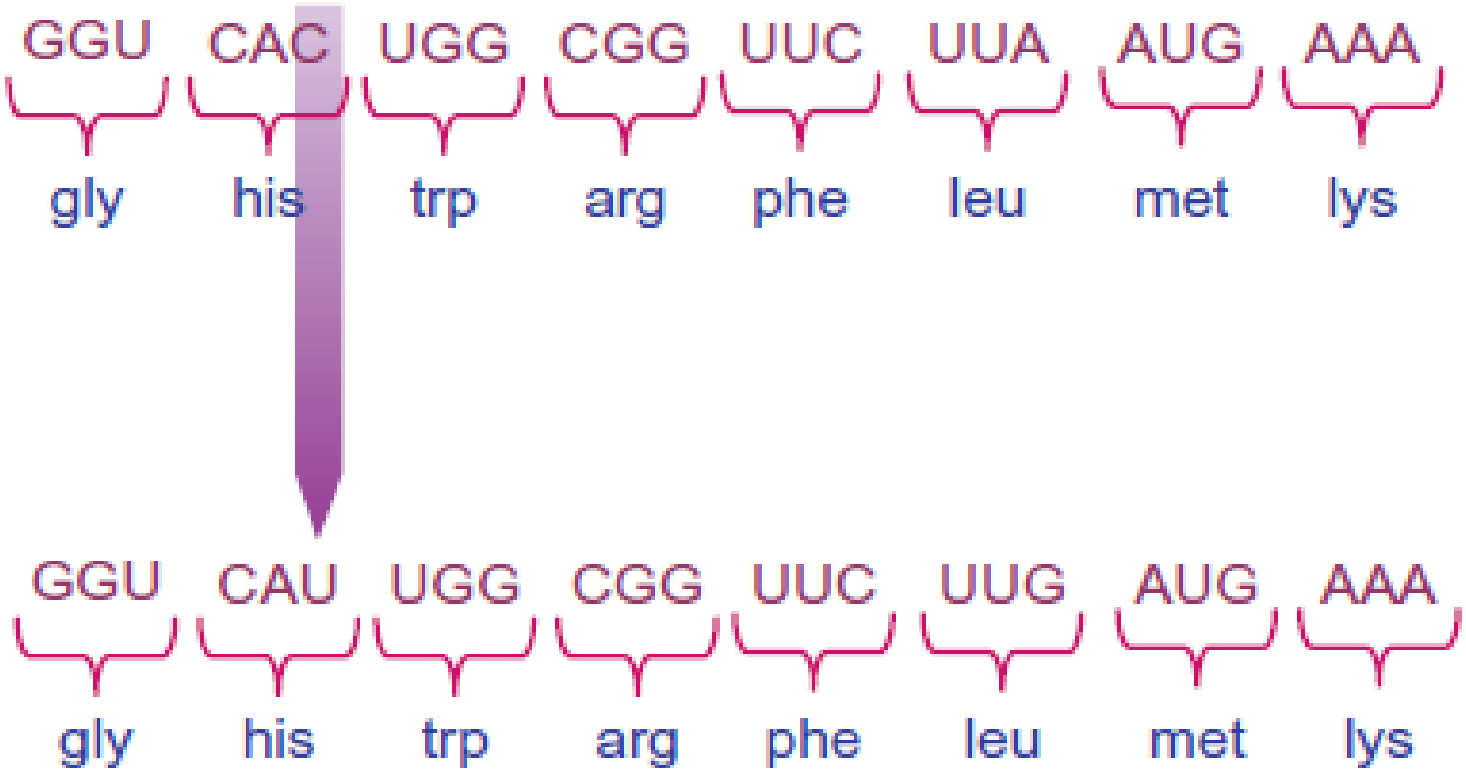
Silent Mutation

- **Silent Mutation** is a point mutation where a change in one base result in a codon which codes for the same amino acid in the protein.
- This is due to the **redundancy** of the genetic code, i.e. for each of the 20 amino acids; there is more than one codon from the 64 codons formed by the four nucleotide bases.
- For example, the change of the codon UUU which codes for phenylalanine to UUC (i.e. the replacement of U by C) is a silent mutation because the new codon (UUC) also codes the same amino acid (phenylalanine).

Silent Mutation.,

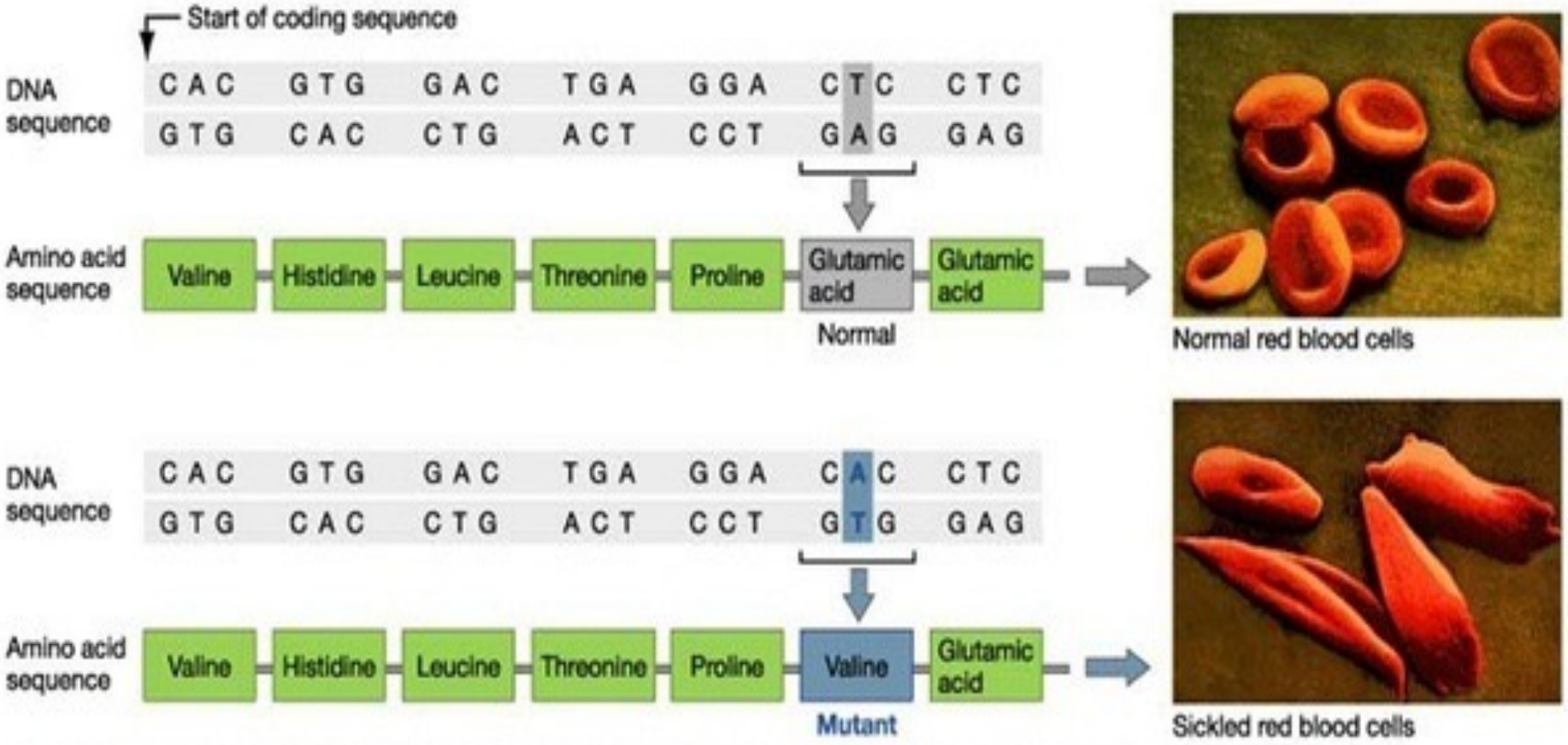
- Such mutations are said to be silent (or synonymous) because they cause no change in their product and cannot be detected without sequencing the gene (or its mRNA).
- Therefore, the character of the protein would not change and nothing results **but** there are proteins formed by DNA sequence that are variable among individuals although the protein is the same.
- This variation forms the bases for DNA finger printing used to identify individuals like the original finger prints.

A SILENT MUTATION



Missense Mutations

- A **Missense Mutation** Changes the codon for one amino acid to the codon for another amino acid.
- Is exemplified by the mutation which causes sickle cell anemia.
- The replacement of A by T at the 17^{th} nucleotide of the gene for the beta chain of hemoglobin changes the codon GAG (for glutamic acid) to GTG (which encodes valine).
- Thus the 6^{th} amino acid in the chain becomes valine instead of glutamic acid.



The change in amino acid sequence causes hemoglobin molecules to crystallize when oxygen levels in the blood are low. As a result, red blood cells sickle and get stuck in small blood vessels.

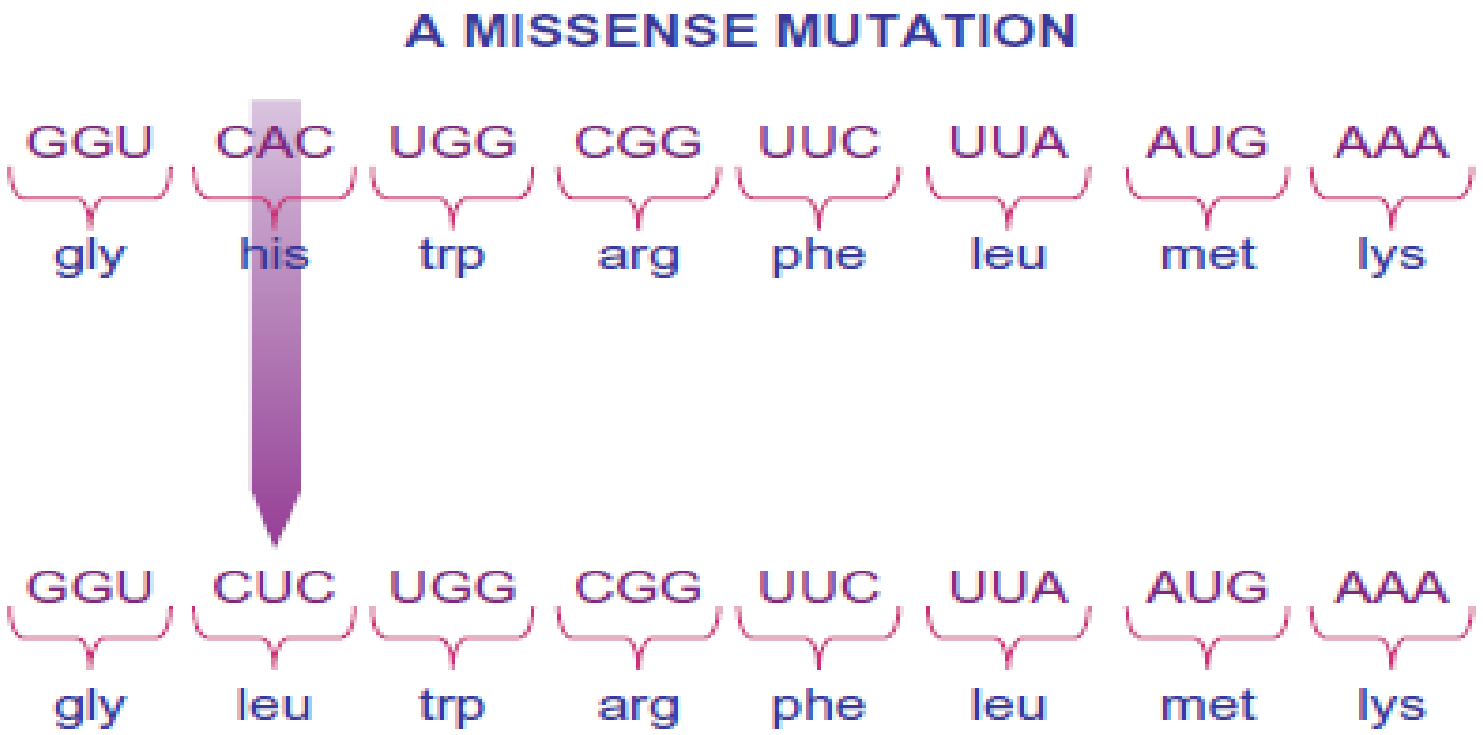


FIGURE 5.8 A missense mutation. A single base change in the mRNA due to a base change mutation in the DNA results in the incorporation of a different amino acid, leucine in place of histidine.

Non-sense Mutation

- A **Non-sense Mutation** Changes the codon for an amino acid to a stop codon, leading to termination of translation of the mRNA transcript & a truncated protein.
- Is exemplified by the mutation which causes β – thalassemia.
- In this, a substitution of U for C in the codon 39 of the β globin chain of hemoglobin (i.e. the change of CAG to UAG) converts the codon for glutamine to a stop codon.
- This results in premature termination of the β globin gene translation. i.e. protein synthesis stops at the 38^{th} amino acid. This results in short peptide which is rapidly degraded leading to the absence of β-globin chains. This leads to βo – thalassemia.

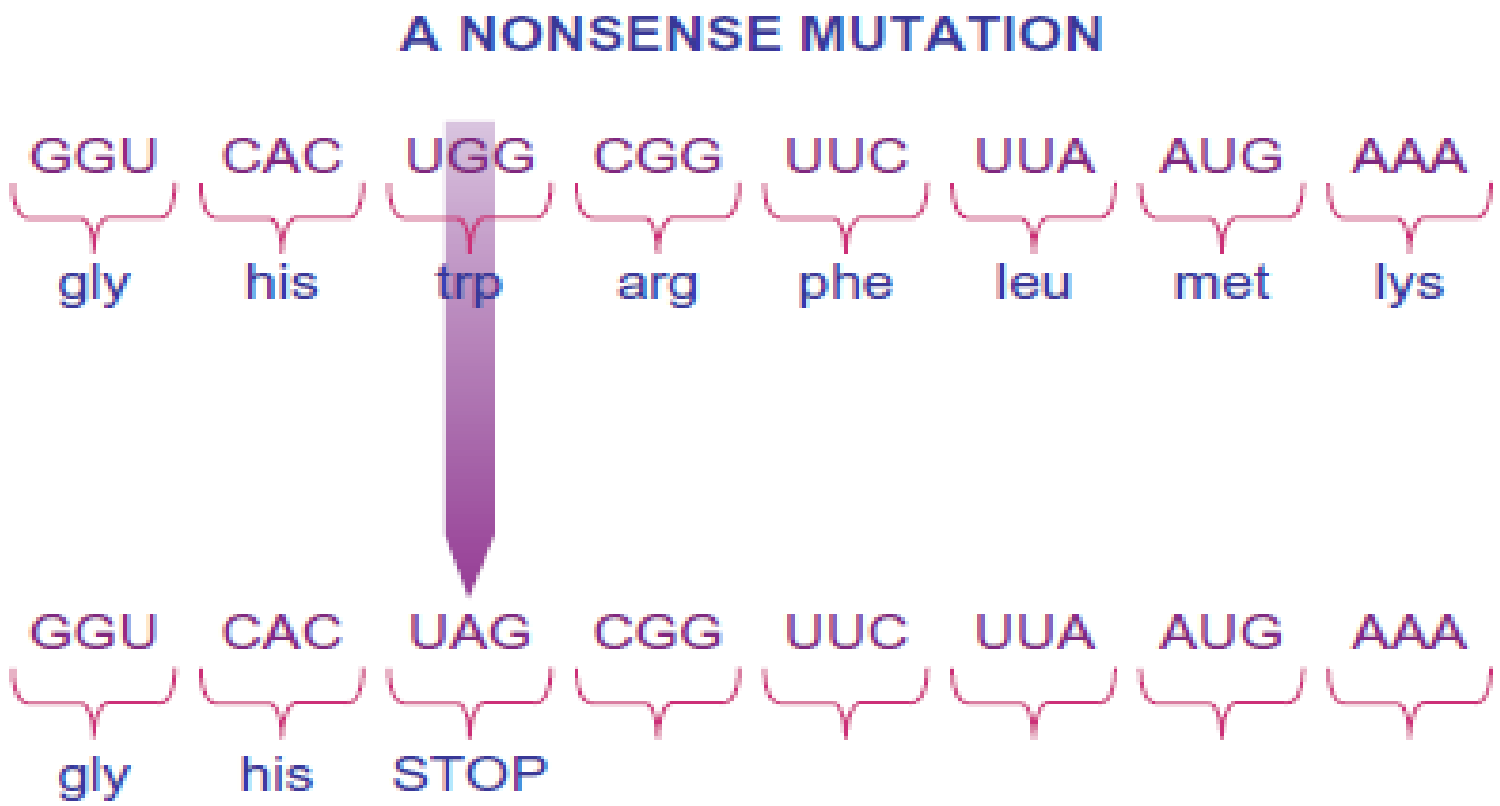


FIGURE 5.9 A nonsense mutation. A single base change in the mRNA due to a base change mutation in the DNA results in production of a stop signal that tells the ribosome to stop adding amino acids to the growing protein chain.

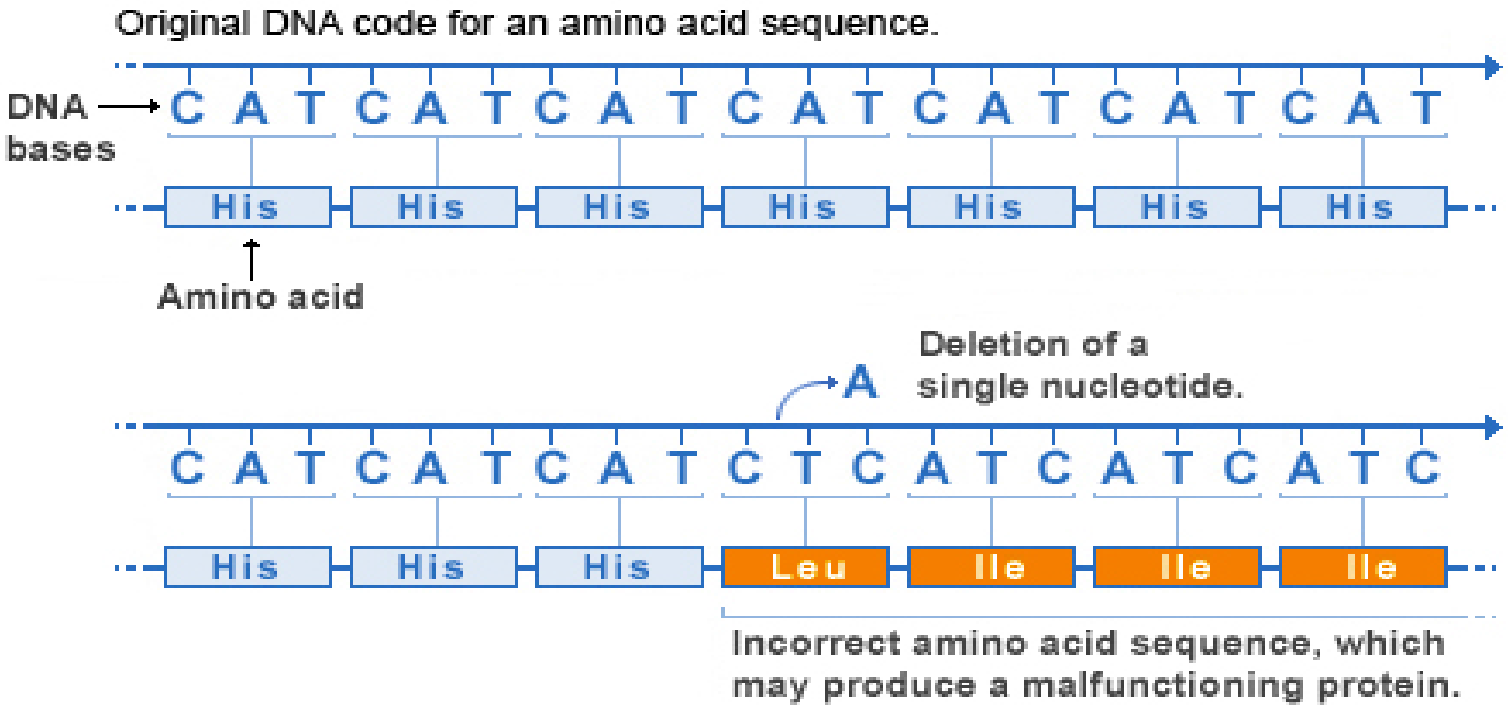
Neutral Mutation

- A **Neutral Mutation** changes the codon for one amino acid to the codon for another amino acid and the new codon codes for another amino acid that is physically and chemically similar (not identical) to the normal one
- The function of the new polypeptide chain is unaffected
- Produces no disease state.

Frameshift Mutations

- AKA Additional / deletion mutations:
- Addition or deletion of one single base (or more than one nucleotide base) cause a gain or loss of one single nucleotide base shift in the reading frame of the trios "codons" changing the whole codons from the point of mutation onwards creating a completely new type of protein or sometimes creates a termination code in the center of the molecule.

Deletion mutation



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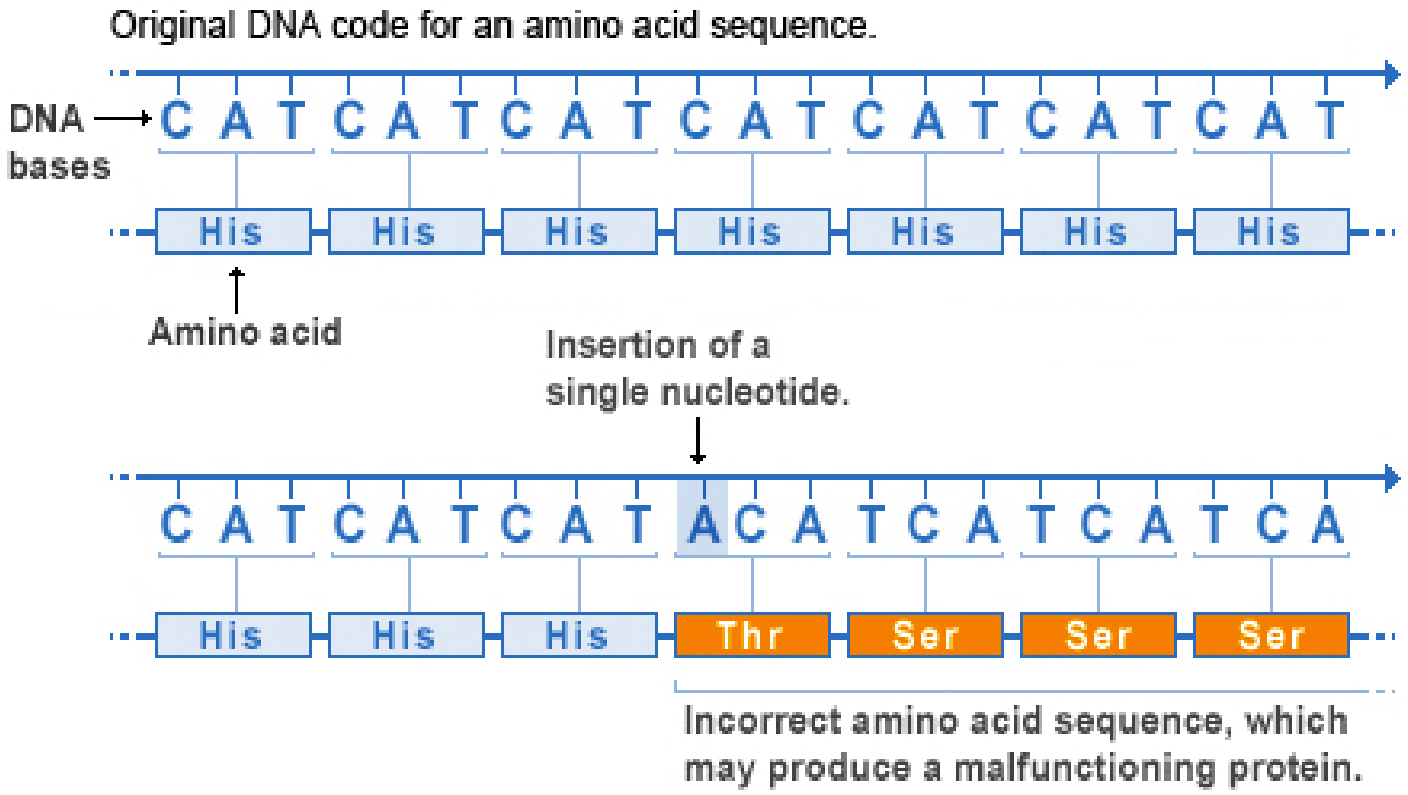
In this example, one nucleotide (adenine) is deleted from the DNA code, changing the amino acid sequence that follows.

Insertion mutation



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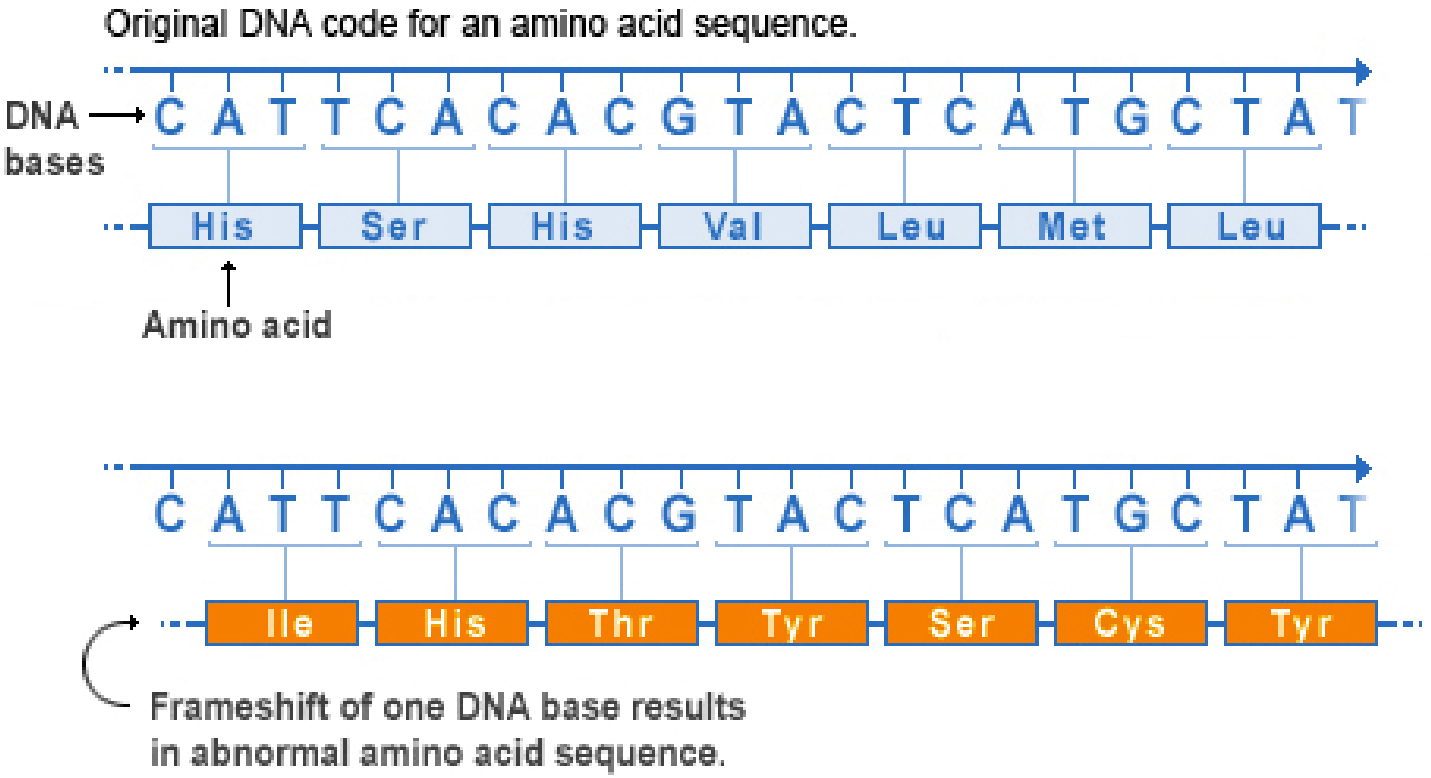
In this example, one nucleotide (adenine) is added in the DNA code, changing the amino acid sequence that follows.

Frameshift mutation



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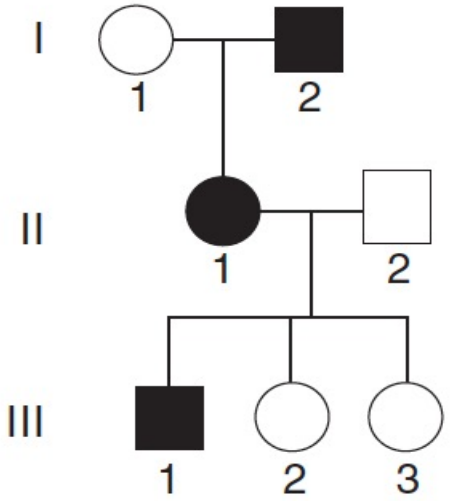
A frameshift mutation changes the amino acid sequence from the site of the mutation.

Trinucleotide Repeat Mutations

- AKA Expansion of repeat sequences
- Show expansion of a sequence of 3 nucleotides.
- Normally, 3 nucleotides are repeated 20-30 times.
- Trinucleotide repeat mutation is when there is expansion of these normally repeated sequences to more than 100 repeats. The increase leads to disease.

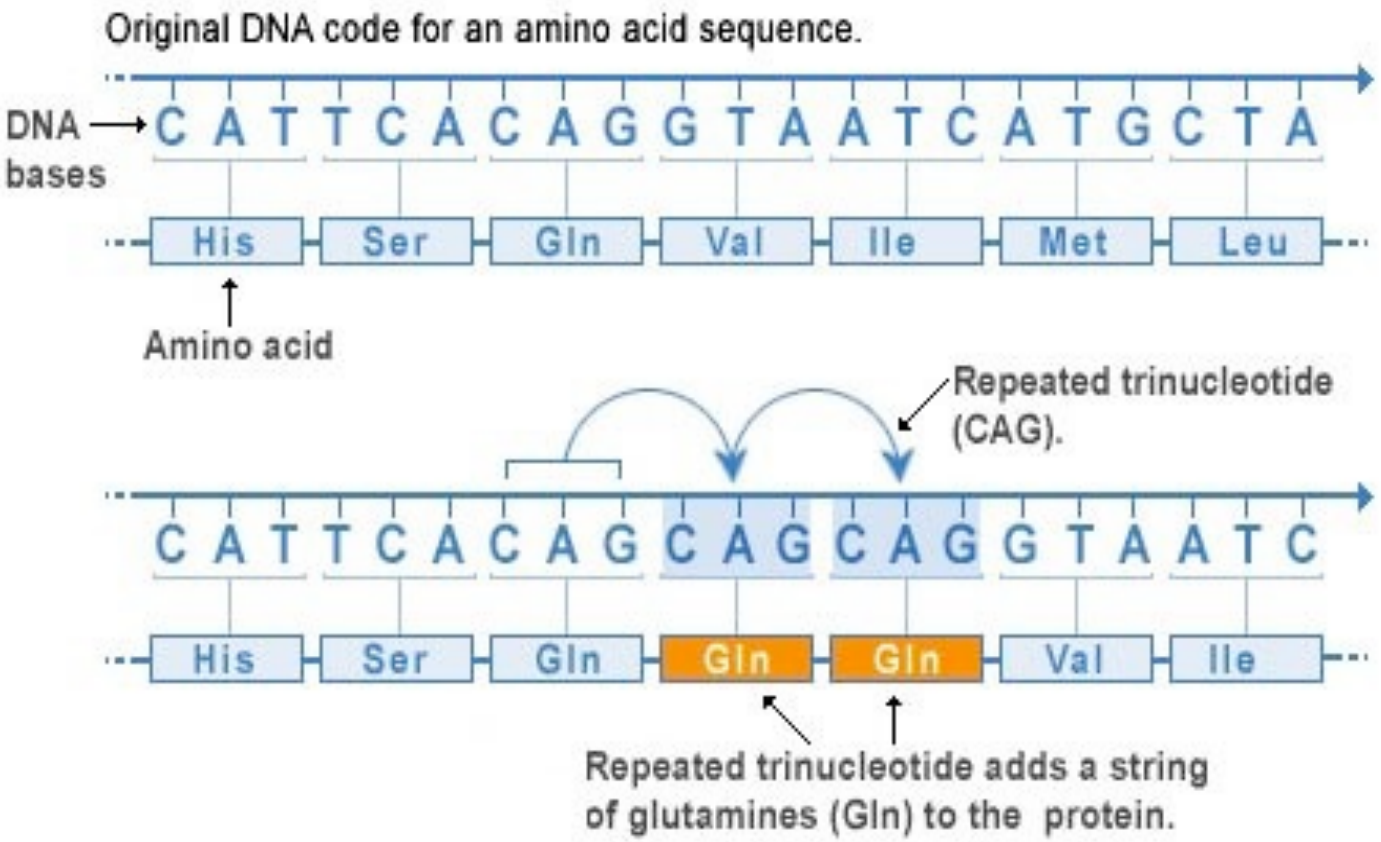
Myotonic Dystrophy



Pedigree	Age of onset	Phenotype	Number of copies of GAC mRNA repeat
I	Older adulthood	Mild forearm weakness, cataracts	50–80
II	Mid-adulthood	Moderate limb weakness	80–700
III	Childhood	Severe muscle impairment, respiratory distress, early death	700+

Figure 12.10 **Expanding genes explain anticipation.** In some disorders, symptoms that worsen from one generation to the next—termed *anticipation*—have a physical basis: The gene is expanding as the number of repeats grows.

Repeat expansion mutation



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In this example, a repeated trinucleotide sequence (CAG) adds a series of the amino acid glutamine to the resulting protein.

Unequal Crossing Over

- Usually during crossing over at meiosis, the chromosomes align themselves side by side.
- This process should be very precise that one allele would be in front of its brother allele and even the bases are matched to each other in number and type.
- So, when there is a crossing over and exchange of chromosomal segments, no disturbance occurs in the newly formed chromosomes or genes, but if the alignment is improper, then the alleles are pushed away for a certain degree.

Unequal Crossing Over.,

- This case takes place in sites of the DNA where there are grouping of genes of similar DNA structure with very slight variation so one gene is mistaken for a different gene as being its allele and if crossing over occurs, a defect will result leading to the formation of two unbalanced homologues, one containing duplicated sequences and the other deleted sequences.
- Repeated rounds of unequal crossing over cause the homogenization of the two sequences.
- With the increase in the duplicates, unequal crossing over can lead to dosage imbalance in the genome and can be highly deleterious.

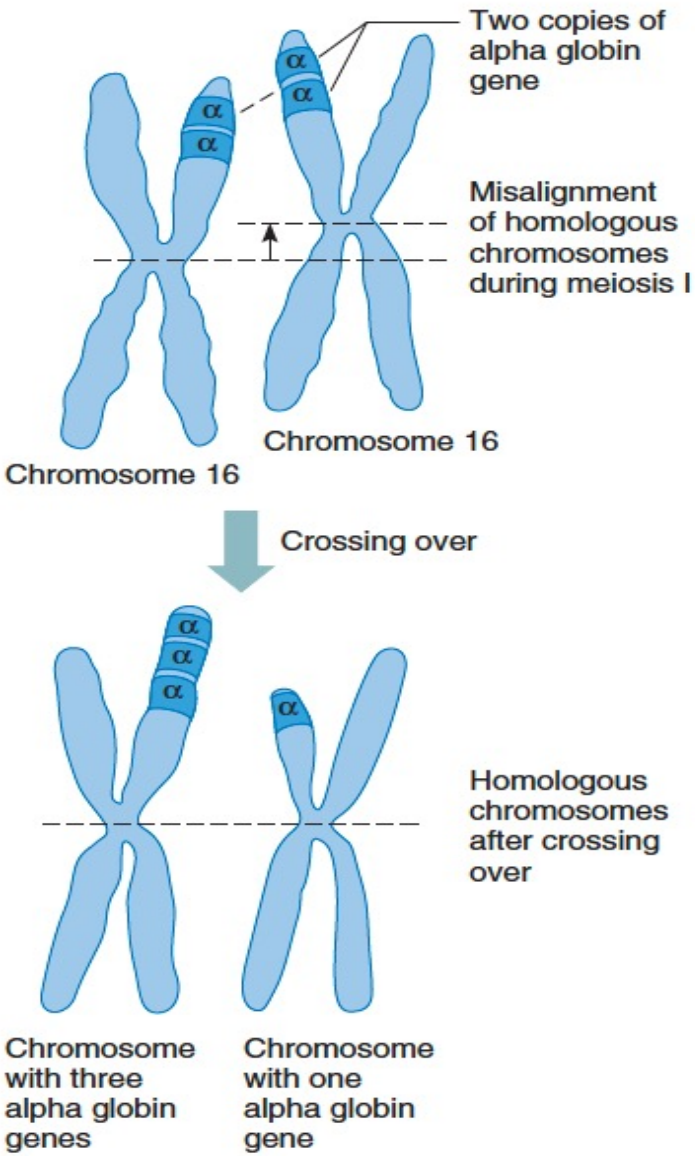
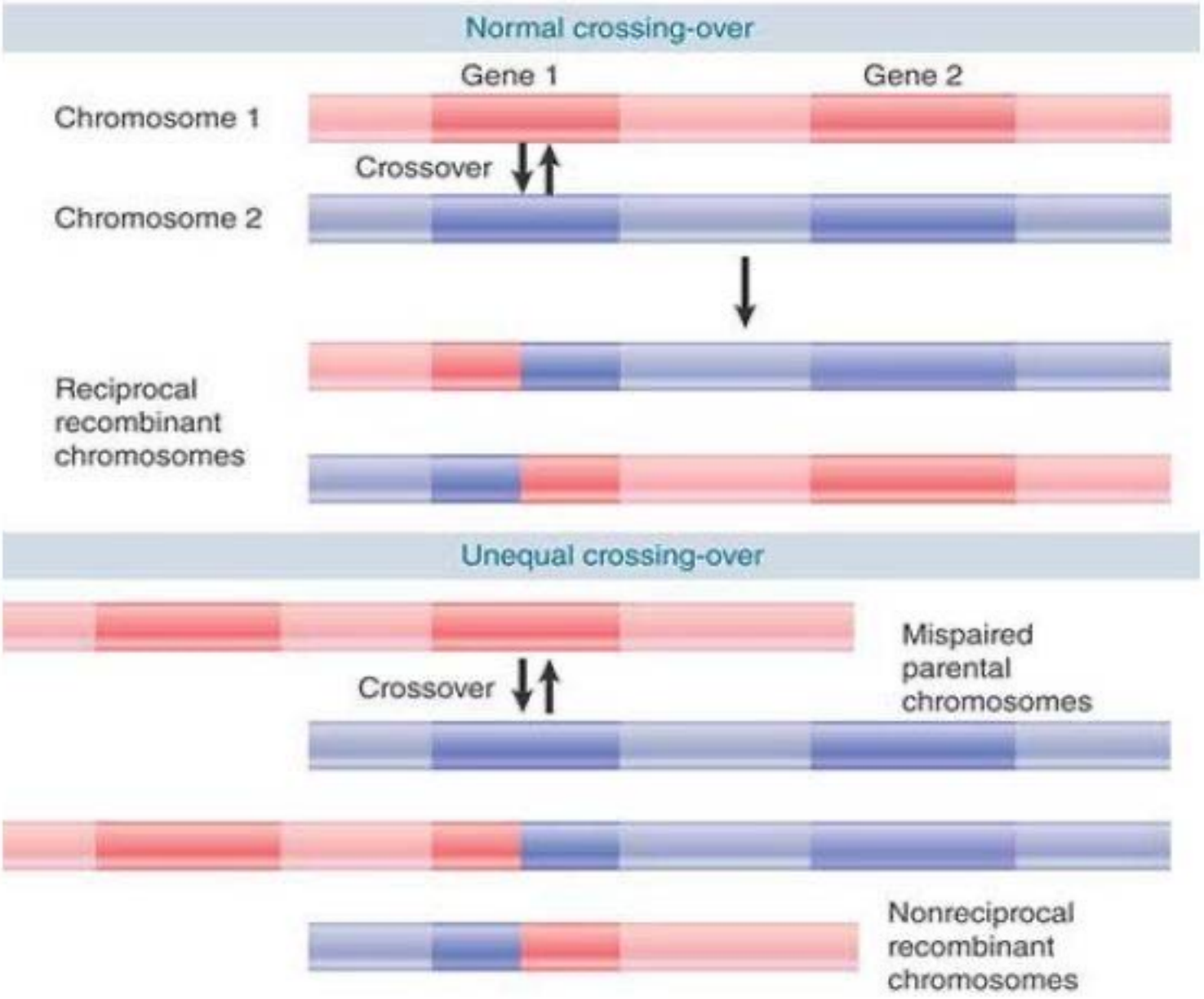


Figure 12.7 **Gene duplication and deletion.** The repeated alpha globin genes are prone to mutation by mispairing during meiosis.


Normal crossing-over
Gene 1
Gene 2
Chromosome 1
Crossover
Chromosome 2
Reciprocal recombinant chromosomes
Unequal crossing-over
Crossover
Mispaired parental chromosomes
Nonreciprocal recombinant chromosomes

Consequences of Mutations

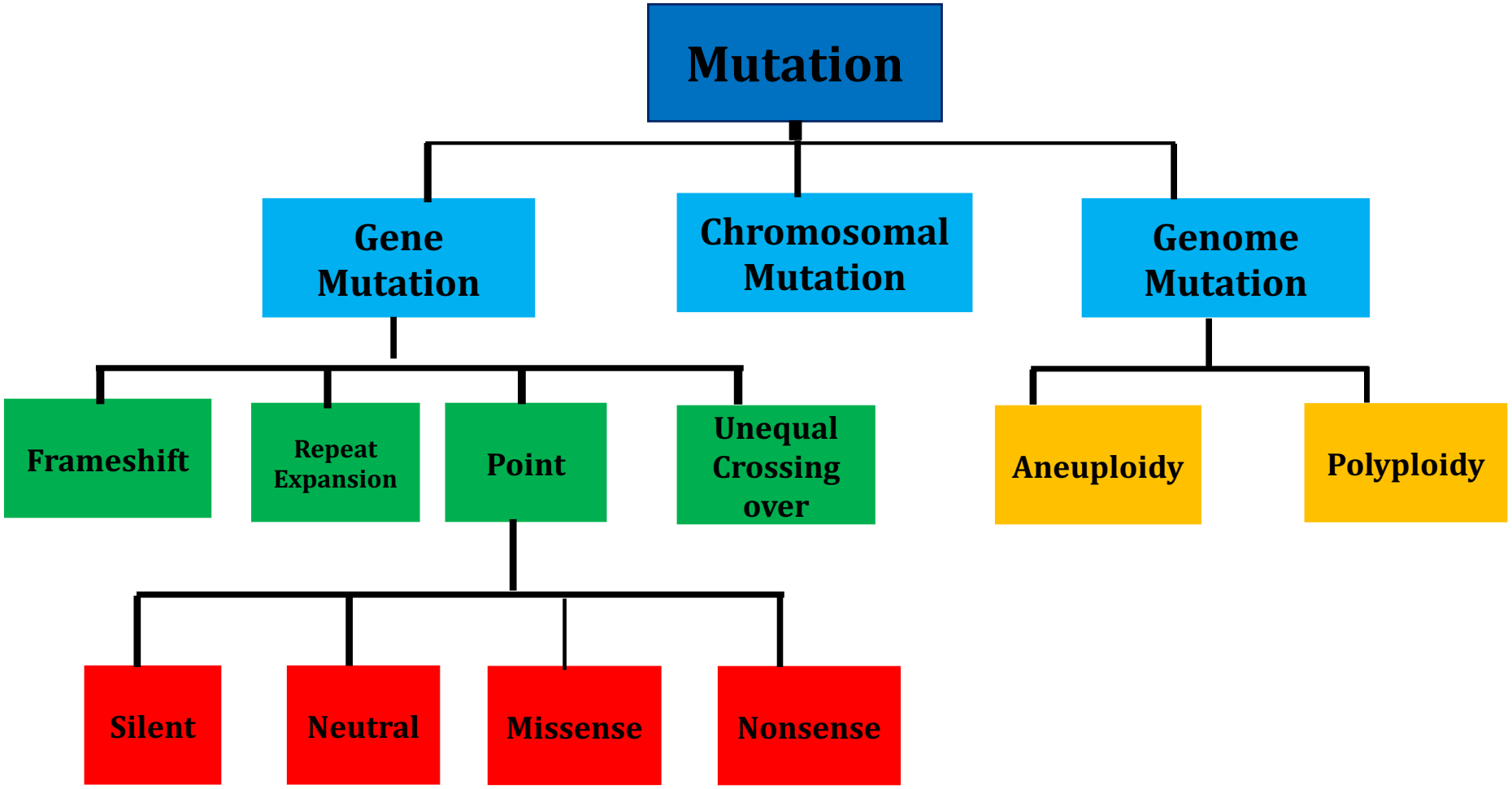
- Mutations can interfere with protein synthesis at various levels.
- Transcription may be suppressed with gene deletions and point mutations involving promoter sequences.
- Abnormal mRNA processing may result from mutations affecting introns or splice junctions or both.
- Translation is affected if a stop codon is created within an exon.
- Finally, some point mutations may lead to the formation of an abnormal protein without impairing any step in protein synthesis

Table 12.6 Types of Mutations

A sentence comprised of three-letter words can provide an analogy to the effect of mutations on a gene's DNA sequence:

Normal	THE ONE BIG FLY HAD ONE RED EYE
Missense	THQ ONE BIG FLY HAD ONE RED EYE
Nonsense	THE ONE BIG
Frameshift	THE ONE QBI GFL YHA DON ERE DEY
Deletion	THE ONE BIG HAD ONE RED EYE
Insertion	THE ONE BIG WET FLY HAD ONE RED EYE
Duplication	THE ONE BIG FLY FLY HAD ONE RED EYE
Expanding mutation	
generation 1	THE ONE BIG FLY HAD ONE RED EYE
generation 2	THE ONE BIG FLY FLY FLY HAD ONE RED EYE
generation 3	THE ONE BIG FLY FLY FLY FLY FLY HAD ONE RED EYE

Summary


Mutation
Gene Mutation
Chromosomal Mutation
Genome Mutation
Frameshift
Repeat Expansion
Point
Unequal Crossing over
Aneuploidy
Polyploidy
Silent
Neutral
Missense
Nonsense

References & Credits

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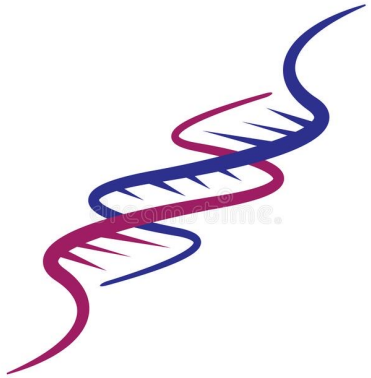
End of Lecture



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