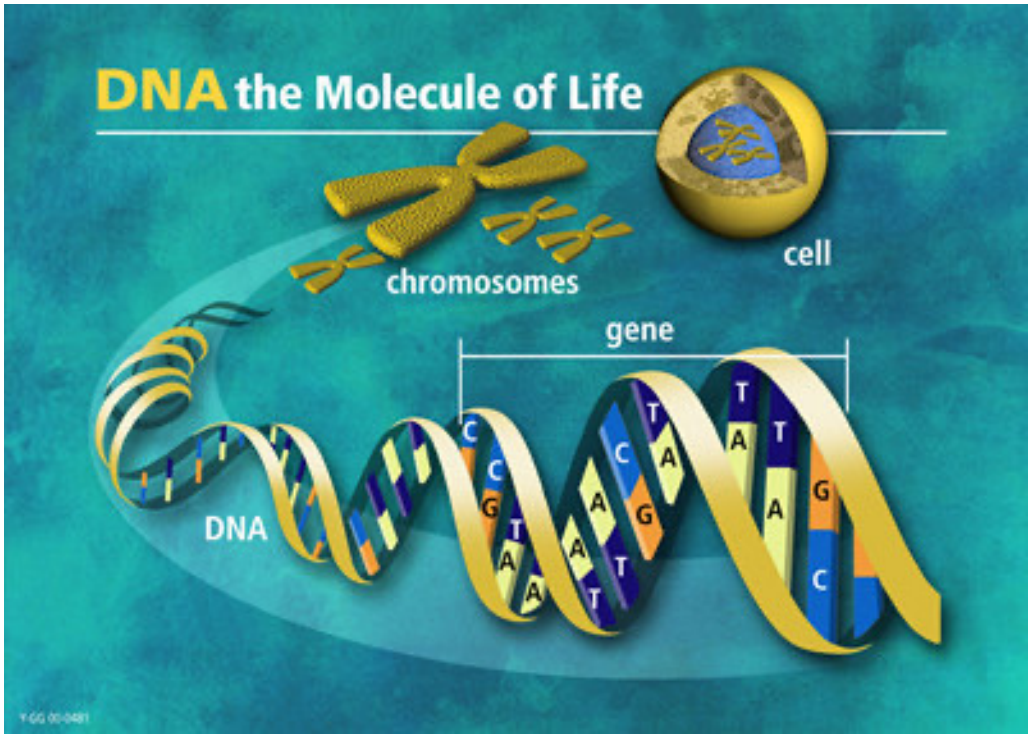
THE MOLECULAR BASIS OF GENE

MUTATION

Zoo 551	Advanced Genetics 3 (2+1)
Objective	This course is intended to develop the general understanding of the student with regards to recent advances in genetics. Also to improve the student's ability in performing experimental techniques in genetics.
Contents	Mutations, recombination in bacteria, transposable genetic elements, genetic control of the immune response and cell division (oncogenes and proto oncogenes). Some important studies in genetics, like the experiments of Lederberg and Tatum, Hershey and Chase, Meselson and Stahl, Chargaff's rules and Griffith experiments. The contributions of Watsom and Crick in the studing of DNA structure.

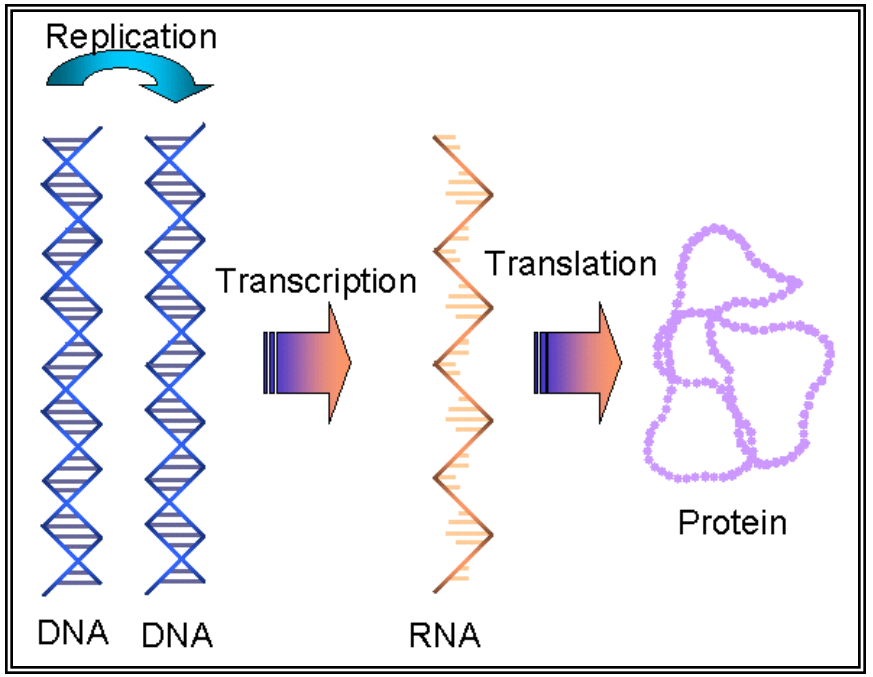
INTRODUCTION

- Genetic material is located in nucleus
- The genetic information is stored in Deoxyribonucleic acid, DNA
- DNA contains the information needed to build an individual
- The basic function of DNA is to store the information for the synthesis of cellular proteins.



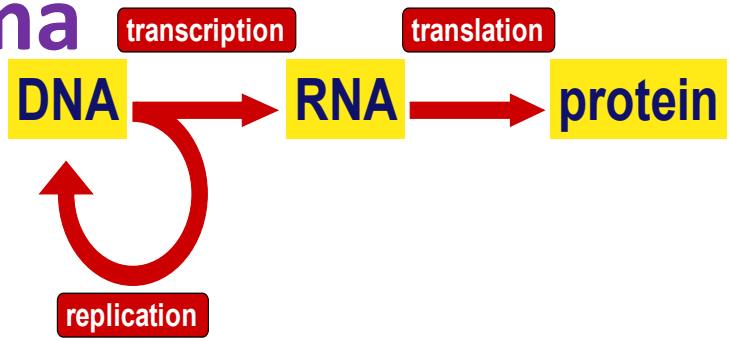
What is DNA needed for?

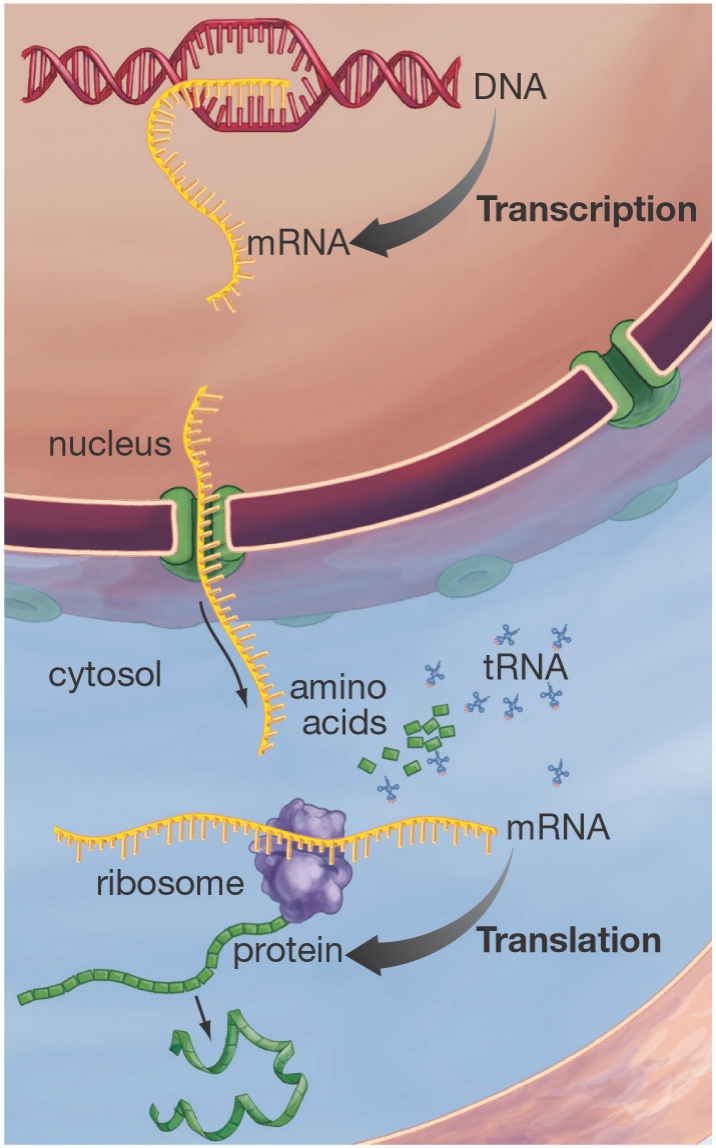
- Genetic information is
- transferred from DNA and converted to protein
- RNA molecules work as messengers
- Proteins are the biological workers
- Information of the DNA is copied to a RNA molecule in **transcription**
- RNA directs the protein synthesis in a **translation**
- Protein's 3D structure determines it's function
- Information transfer only in one direction



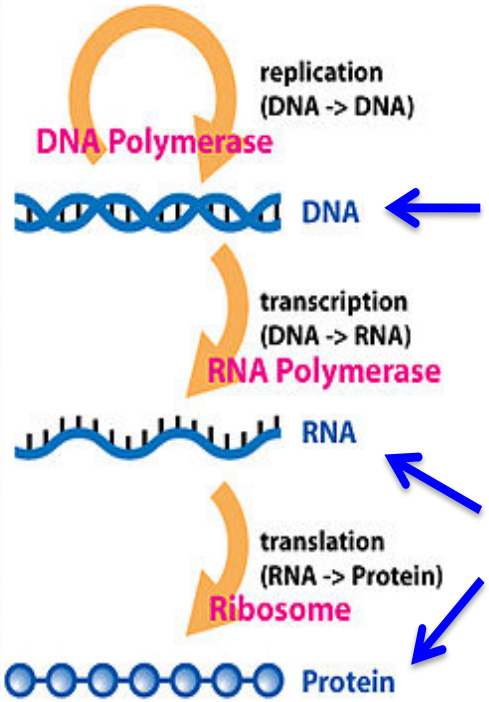
The "Central Dogma"

- Flow of genetic information in a cell





Attention: If any error takes place in DNA replication



Mutations happen here

Effects play out here

What Are Mutations ?

- Changes in the nucleotide sequence of DNA
- May occur in somatic cells
- May occur in gametes (eggs & sperm) and be passed to offspring
- The subject of mutation is an important topic for all branches of genetics, including molecular genetics and Mendelian heredity and evolution.
- Because the mutations are responsible for allelic variation that determines the phenotypic differences between the various members of the same species.

- In terms of phenotypic effects of mutations, mutations are either neutral or beneficial or harmful:

- Advantage: mutations are necessary to sustain life, which helps the species change and adapt to their environments. And mutations are the basis of evolutionary change of species
- The disadvantage: the new mutations are likely to be harmful to individuals. For example, many genetic diseases in humans arise from mutant genes. This is in addition to diseases such as skin cancer and lung cancer that could be arise from environmental factors known to cause mutations in DNA.
- For these reasons, understanding the molecular nature of mutations is one of the important topics in modern genetics.

Types of Mutations

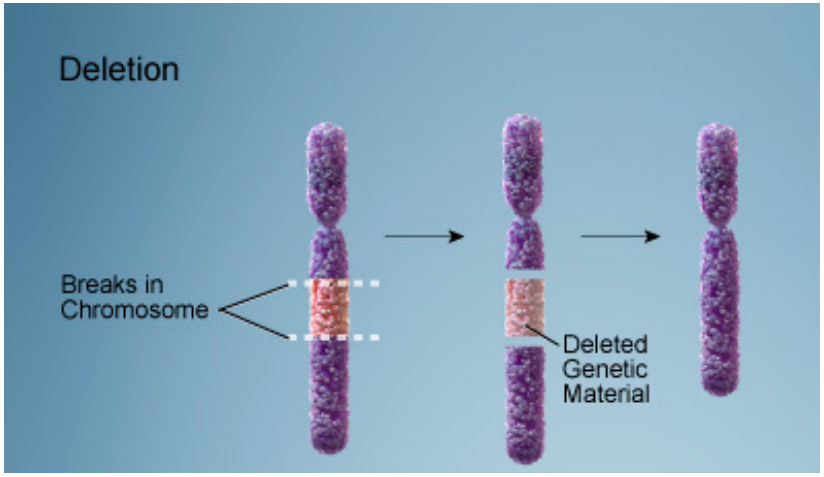
Chromosome Mutations

- May Involve:
  - Changing the structure of a chromosome
  - The loss or gain of part of a chromosome

- Five types exist:
  - **Deletion**
  - **Inversion**
  - **Translocation**
  - **Nondisjunction**
  - **Duplication**

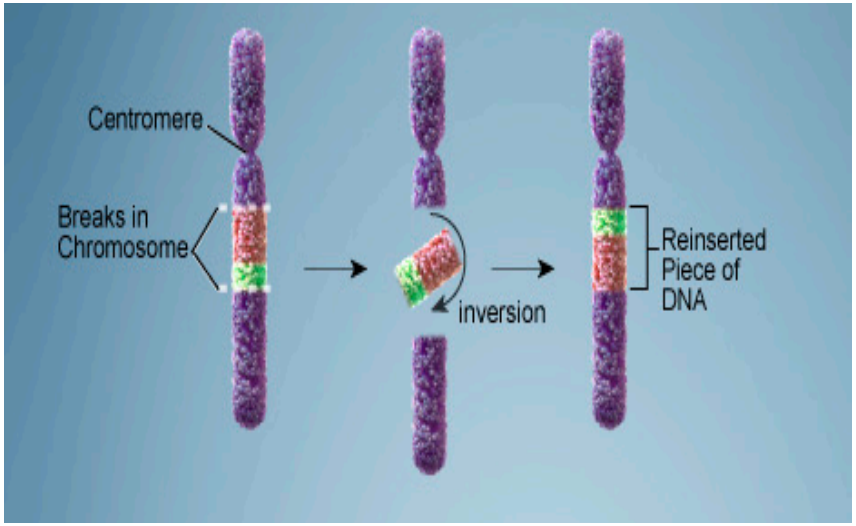
Deletion

- Due to **breakage**
- A **piece** of a chromosome is **lost**



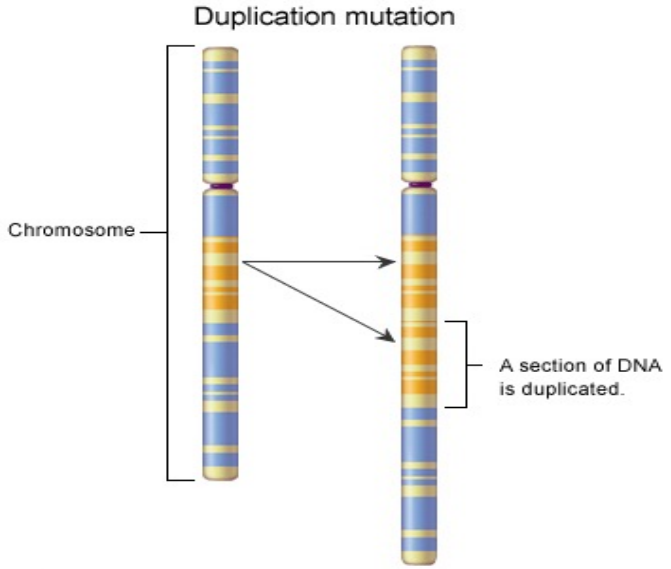
Inversion

- Chromosome segment **breaks off**
- Segment flips around **backwards**
- Segment **reattaches**



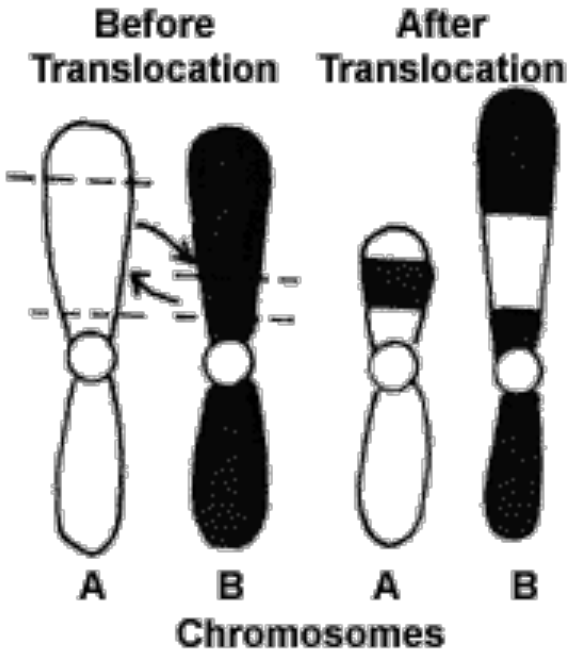
Duplication

- Occurs when a gene **sequence is repeated**



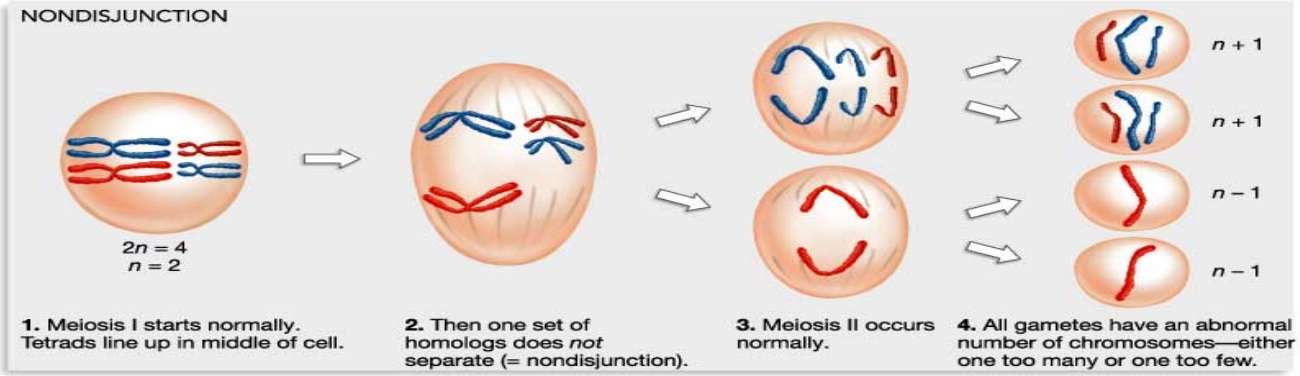
Translocation

- Involves **two chromosomes** that aren't homologous
- **Part** of one chromosome is **transferred to another** chromosomes

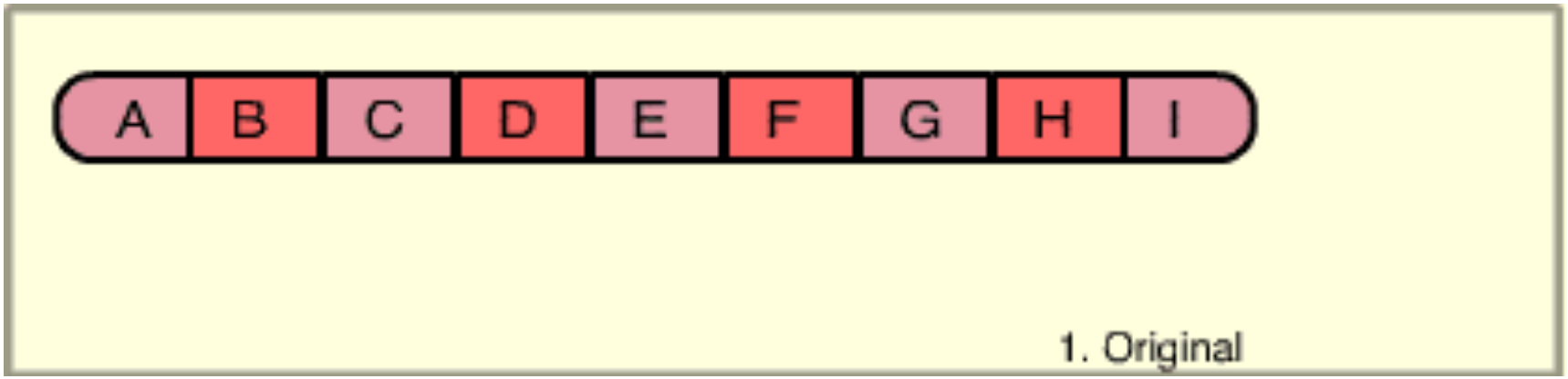


Nondisjunction

- Failure of chromosomes to separate during meiosis
- Causes gamete to have too many or too few chromosomes
- Disorders:
  - Down Syndrome – three 21st chromosomes
  - Turner Syndrome – single X chromosome
  - Klinefelter's Syndrome – XXY chromosomes



Chromosome Mutation Animation



Gene Mutations

- Change in the nucleotide sequence of a gene
- A heritable change in the genetic material
- May only involve a single nucleotide
- May be due to copying errors, chemicals, viruses, etc.

- Include:
  - Point Mutations
  - Substitutions
  - Insertions
  - Deletions
  - Frameshift

Mutations are quantified in two ways:

1. Mutation rate = probability of a particular type of mutation per unit time (or generation).

2. Mutation frequency = number of times a particular mutation occurs in a population of cells or individuals

Gene Mutations:
They affect protein structure and function

- **Mutations** are changes in the genetic material of a cell (or virus).
- These include large-scale mutations in which long segments of DNA are affected (e.g., translocations, duplications, and inversions).

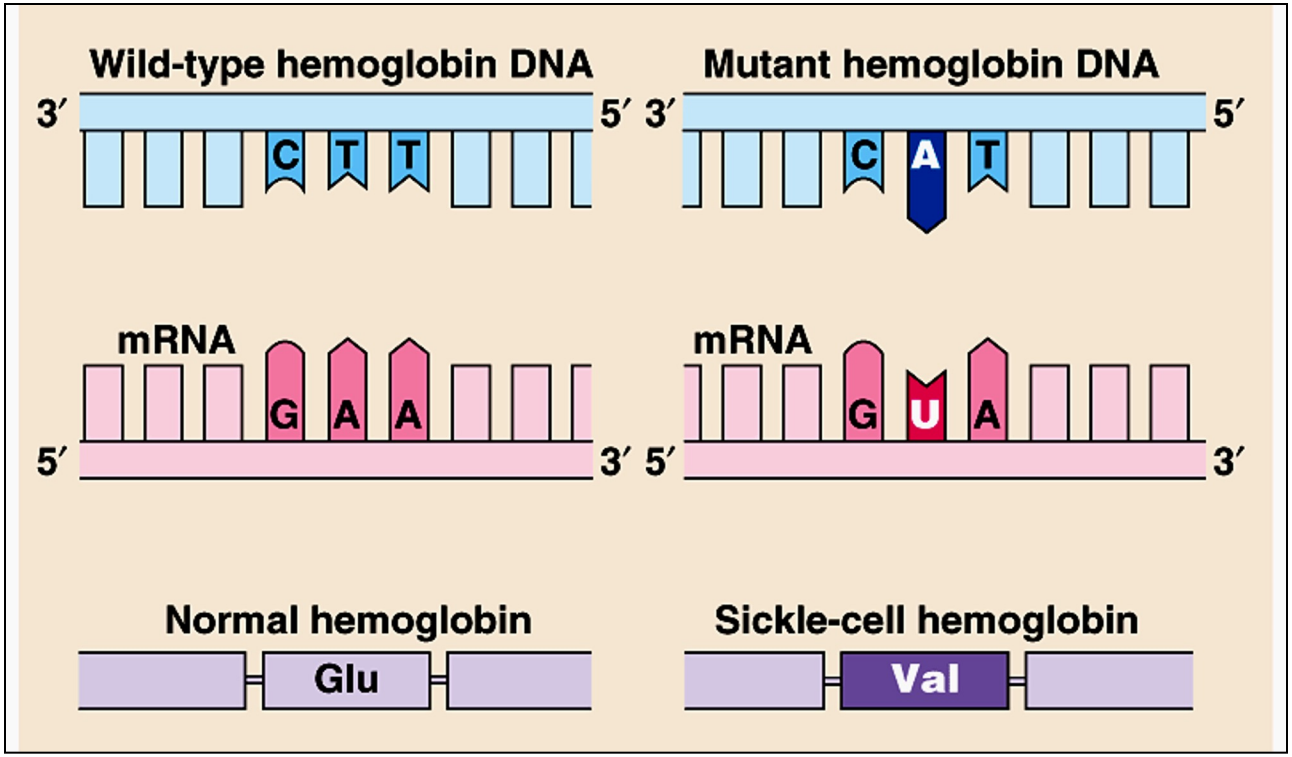
I. Point mutation :

is a chemical change in just one base pair of a gene.

- If these occur in cells producing gametes, they may be transmitted to future generations (offspring).

For e.g., sickle-cell disease is caused by a mutation of a single base pair in the gene that codes for one of the polypeptides of hemoglobin.

A change in a single nucleotide from T to A in the DNA template leads to an abnormal protein.



A)- Base-pair substitution

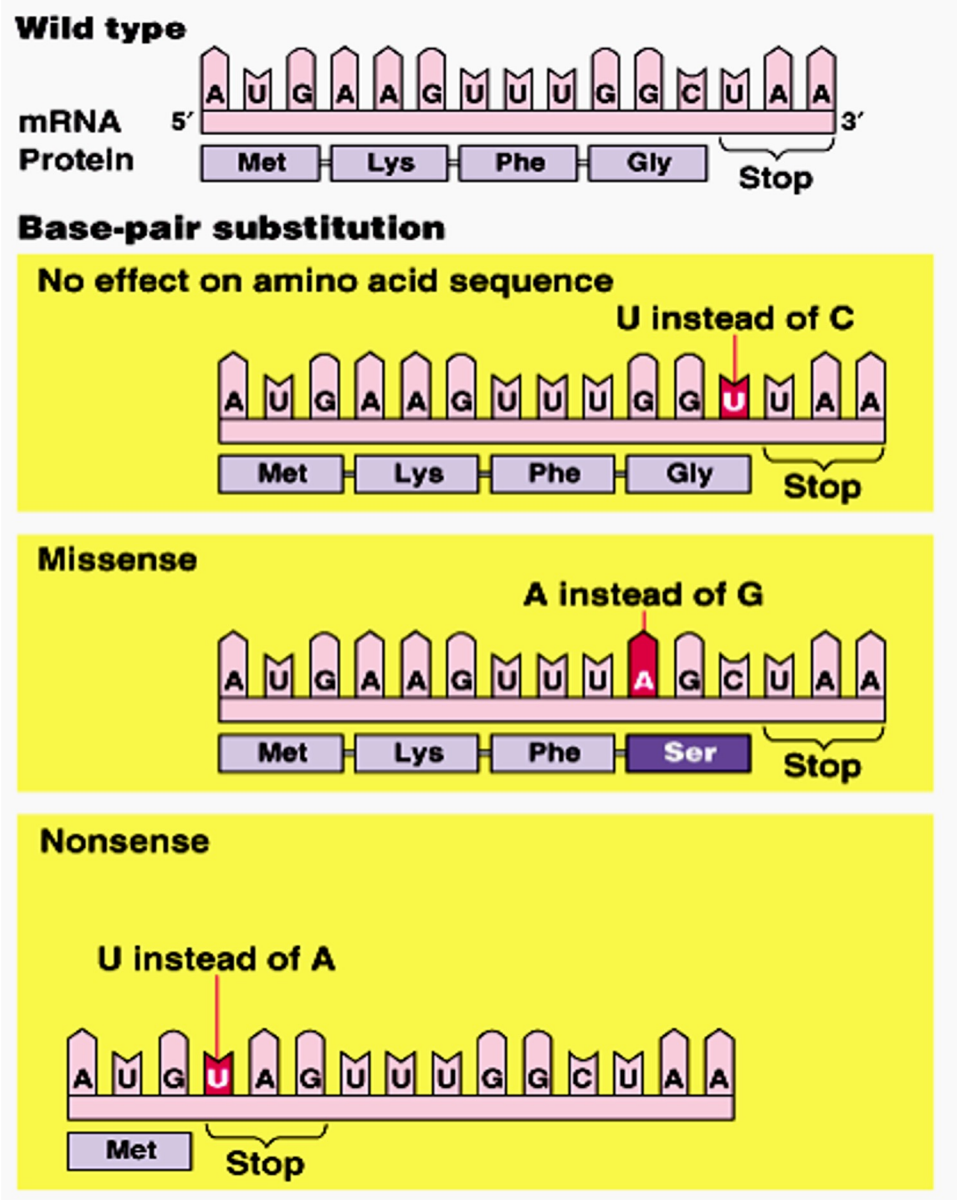
- It is a point mutation that results in replacement of a pair of complimentary nucleotides with another nucleotide pair.

a) **Silent mutation:** some base-pair substitutions (point mutation) have little or no impact on protein function which lead to switches from one amino acid to another with similar properties.

Other base-pair substitutions cause a detectable change in a protein which impact function.

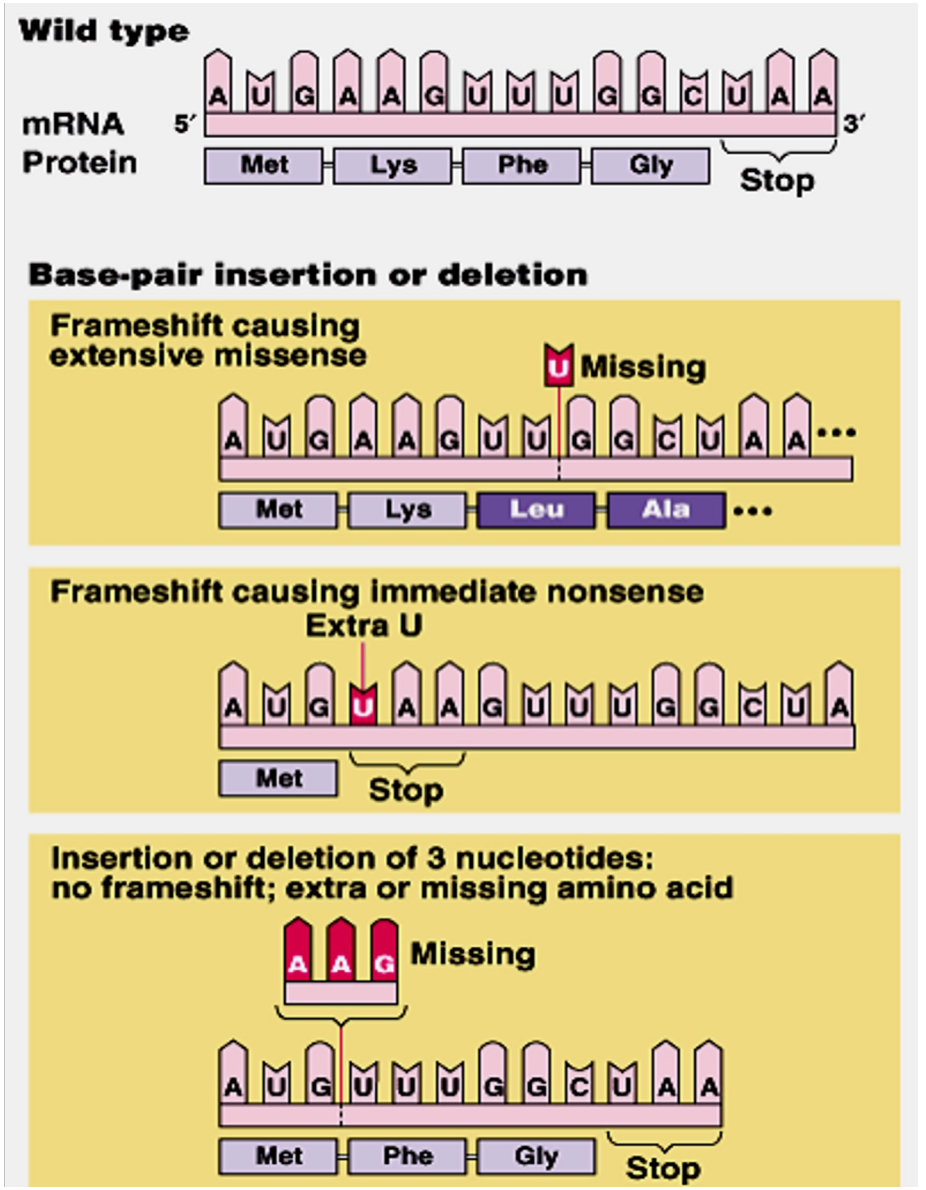
b) **Missense mutations:** a point mutation that still code for an amino acid but change the resulting protein.

c) **Nonsense mutations:** change an amino acid codon into a stop codon, nearly always leading to a nonfunctional protein.



B)- Insertions and deletions

- It is a mutation in which additions or losses of nucleotide pairs occurs and causes Frame-shift mutation.
  - These have a disastrous effect on the resulting protein
- When frame-shift occurs, all the nucleotides downstream of the deletion or insertion will be improperly grouped into new codons.
  - The result will be extensive missense, ending sooner or later in nonsense - premature termination.



- **Mutations can occur in a number of ways.**
  - Errors can occur during DNA replication, DNA repair, or DNA recombination.
  - These can lead to base-pair substitutions, insertions, or deletions, as well as mutations affecting longer stretches of DNA.
  - These are called *spontaneous mutations.*

- **Mutagens** : are chemical or physical agents that interact with DNA to cause mutations.

1. Physical agents include high-energy radiation like X-rays and ultraviolet light.

2. Chemical agents may operate in several ways.
   - Some chemicals are base analogues that may be substituted into DNA, but that pair incorrectly during DNA replication.
   - Other mutagens interfere with DNA replication by inserting into DNA and distorting the double helix.
   - Still others cause chemical changes in bases that change their pairing properties.

The molecular basis of mutations

Mutations are classified as mentioned above to:

Spontaneous mutations:
Changes occur in DNA synthesis caused by deviations in the biological processes that occur within the body of the organism/arises from within the cells.
Induced mutation:
Changes occur in DNA synthesis caused by environmental factors / causes arise from outside the cells

Spontaneous mutations:
Spontaneous mutations are random events (Random events). There were two hypotheses about the emergence of mutations:

A. Physiological adaptation hypothesis
Mutations occur as a result of the imposition of the behavior of the organism or exposure to certain environmental conditions. Mutation rate is supposed to be relatively constant and depends on the exposure of the organism to those circumstances. Physiological adaptation hypothesis predicts that the rate of mutation will be relatively constant between the different Population.
B The hypothesis that mutations are random events:
The presence of genetic variation within the tribe and the contrast of natural selection in the chances of survival and the success of reproduction of living organisms.
Useful mutations = random events to adapt the best chances of survival and reproductive success

Human Phenotype Variations

- **Genetic** and **environmental factors** are the two main reasons that cause human phenotype variations.

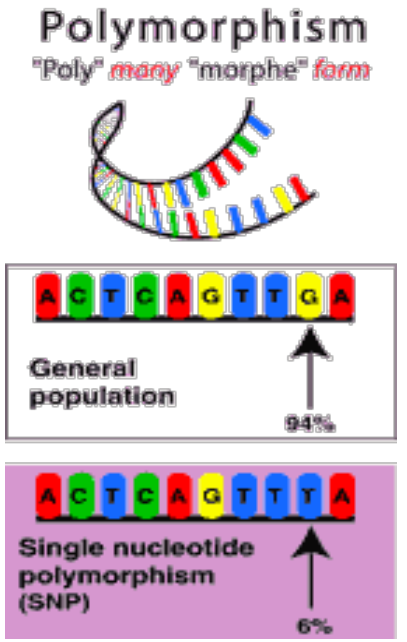
How different is one human genome from another?

- The DNA sequence of exactly the **same region** on a chromosome of **different persons** is very similar.
- Corresponding sequences from the **same genes** in two people differ by an average of less than one nucleotide in 1,000.
- Consequently, the DNA of most people is **99.9% the same**. Although we are look quiet different from one another.

What kind of genome variations are there?

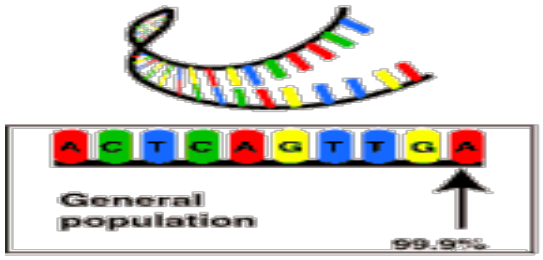
Polymorphism

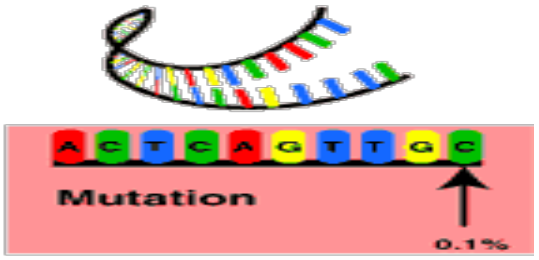
- is a DNA variation in which each possible sequence is present in at **least 1%** of people.
- **Genetic polymorphism** promotes diversity within a population.



Mutation

- If one of the possible sequences is present in **less than 1 %** of people
  - Figure below showing 99.9 % of people have a G and 0.1 % have a C





http://www.genomenewsnetwork.org/resources/whats_a_genome/Chp4_1.shtml

Genetic Polymorphism: Is It the Same as a Mutation?

Mutations by themselves do not classify as polymorphisms.

- A polymorphism is a DNA sequence variation that is common in the population.
- A mutation, on the other hand, is any change in a DNA sequence away from normal (implying that there is a normal allele running through the population and that the mutation changes this normal allele to a rare and abnormal variant.).
- In polymorphisms, there are two or more equally acceptable alternatives and to be classified as a polymorphism, the least common allele must have a frequency of 1% or more in the population. If the frequency is lower that this, the allele is regarded as a mutation.

The diagram shows the base substitutions that are possible in DNA. These include four transitions purine for purine or pyrimidine for pyrimidine (Black arrows) and eight transversions, purine for pyrimidine and pyrimidine for purine (Blue arrow)

Type of mutation	Result and example(s)
Forward mutations	
Single-nucleotide-pair (base-pair) substitutions	
At DNA level	
Transition	Purine replaced by a different purine, or pyrimidine replaced by a different pyrimidine: A·T ⟶ C·G C·G ⟶ A·T C·G ⟶ T·A T·A ⟶ C·G
Transversion	Purine replaced by a pyrimidine, or pyrimidine replaced by a purine: A·T ⟶ C·G A·T ⟶ T·A G·C ⟶ T·A G·C ⟶ C·G T·A ⟶ G·C T·A ⟶ A·T C·G ⟶ A·T C·G ⟶ G·C
At protein level	
Silent mutation	Triplet codes for same amino acid: AGG ⟶ CGG both code for Arg
Missense mutation	Codon specifies a different amino acid.
Synonymous missense mutation	Codon specifies chemically similar amino acid: AAA ⟶ AGA changing basic Lys to basic Arg (does not alter protein function in many cases)
Nonsynonymous missense mutation	Codon specifies chemically dissimilar amino acid: UUU ⟶ UCU Hydrophobic Phenylalanine — Polar Serine
Nonsense mutation	Codon signals chain termination: CAG ⟶ UAG changing from a codon for Gln to an amber termination codon
Single-nucleotide-pair addition or deletion: frameshift mutation Addition or deletion of several to many nucleotide pairs	Any addition or deletion of base pairs that is not a multiple of 3 changes the reading frame in DNA segments that code for proteins, resulting in different amino acids from that point on and frequently chain termination.
Reverse mutations	
Exact reversion	AAA (Lys) Wild-type —forward→ GAA (Glu) Mutant —reverse→ AAA (Lys) Wild-type

Summary of Mutation Types