STUDY UNIT 2: ORIGINS OF HUMAN GENETIC VARIABILITY AND ITS CONSEQUENCES

TEXTBOOK CHAPTERS 4, 5, 6 AND 7

LECTURE 1 – (CHAPTER 4)

- Genetic variation describes differences between the DNA sequences of individual genomes.
- Each person has 2 nuclear genomes (a paternal and a maternal genome) and due to this genetic variation occurs within and between individuals.
- In addition to the inherited genetic variation that is present in the cells , DNA changes occur in the DNA of cells throughout life (post-zygotic or somatic genetic variation)
- Programmed, cell- specific DNA changes occur in maturing B and T cells that allow each of us to make a wide range of different antibodies and T-cell receptors.
- Genetic variation is not the only explanation for differences in phenotype
  - A fertilized egg cell can split in 2 in early development and give rise to genetically identical twins that grow up to be different.
  - During development, additional effects on the phenotype occur by a combination of stochastic (random) factors, differential gene– environment interactions and epigenetic variation that is not attributable to changes in base sequence.
- DNA repair mechanisms seek to minimize the effects of DNA sequence variation.
- Genetic variation is most highly developed in genes that work in recognizing foreign , potentially harmful molecules which have been introduced into the body.
  - Sometimes under independent genetic control because they originate from another organism (microbial pathogens and plant toxins)
  - 2 types of Darwinian Natural Selection may oppose each other (Natural selection working on the organism and Natural selection working on the human) ➔ Natural selection is the process whereby some allele or combination of alleles determines a phenotype that may confer increased or decreaed chance of survival and reproductive success (Increase frequency of favourable alleles and decrease frequency of disadvantageous alleles)
- In human beings 99.9% of bases are the same , the remaining 0.1% makes a person unique (Different attributes and characteristics such as how the person looks and diseases they may develop)

- Variations can be :

1. Harmless(Change in phenotype)
2. Harmful (diabetes , cancer , heart disease , Huntington's disease and haemophilia)
3. Latent (various mutations in coding and regulatory regions that are not harmful on their own – changes in genes only become apparent under certain conditions eg susceptibility to lung cancer)

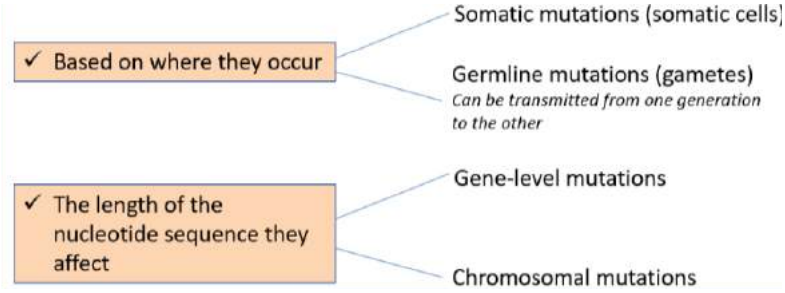
- Variation occurs in germ cells (inherited) and somatic cells
- Major sources of variation are :
- Mutations – permanent alterations to a DNA sequence
- Recombination – mixture of genetic material from both parents

1) ORIGINS OF DNA SEQUENCE VARIATION

- **Mutation** describes both a process that produces altered DNA sequences (either a change in the base sequence or in the number of copies of a specific DNA sequence) and

the outcome of that change (the altered DNA sequence

- Mutations originate as a result of changes in our DNA that are not corrected by cellular DNA repair systems ➔From environment(radiation and chemicals) and endogenous sources (Spontaneous erors in chromosome segregation and recombination , DNA replication and DNA repair ; also includes spontaneous DNA chemical damage)
  - ➢ Mutations are permanent and transmissible changes in DNA sequence.
  - ➢ During replication , DNA undergoes frequent chemical changes that usually undergo repair BUT those that are not repaired result in mutations



Gene level mutations	Chromosomal mutations
• **Point mutations** ➢ **Silent:** changes that do not alter encoded amino acid ➢ **Missense:** changes to a codon for another amino acid (harmful or neutral) ➢ **Nonsene:** change from an amino acid to a stop codon = shortened protein • **Frameshift mutation:** Insertion or deletion of base pairs producing a stop codon downstream and shortened protein	Alter long stretches of DNA (ranging from multiple genes up to entire chromosomes)

1.1.1) GENETIC VARIATION ARISING FROM ENDOGENOUS ERRORS IN CHROMOSOME AND DNA FUNCTION

DNA Replication errors

- ➢ Errors made are quickly corrected by DNA polymerase
- ➢ The DNA polymerase has intrinsic 3'→5' exonuclease activity with a *proofreading function*. If, by error, the wrong base is inserted, the 3'→5' exonuclease is activated and degrades the newly synthesized DNA strand from its 3' end, removing the wrongly inserted nucleotide and a short stretch before it. Then the DNA polymerase resumes synthesis again.
- ➢ If mispaired bases are not eliminated by the DNA polymerase, a DNA mismatch repair system is activated

- ➢ Another type of DNA replication error commonly occurs within regions of DNA where there are short tandem oligonucleotide repeats = Replication slippage
- ➢ The DNA polymerase encounters a 30-nucleotide sequence with 15 sequential repeats of AT dinucleotide or 10 sequential repeats of the CAA trinucleotide, there will be an increased chance that during DNA replication a mistake is made in aligning the growing DNA strand with its template strand
- ➢ Although we have many effective DNA repair pathways, DNA repair is not 100% effective