Mutations

Gene Mutation = Change in sequence of nucleotide bases in DNA (gene) → Change in sequence of amino acids in polypeptide chain (primary structure) → Change in R groups affecting type and location of bonds formed ⟶ Change in secondary and tertiary structure → Change in unique 3D conformation → Change in function (binding/active site no longer complementary in shape and hence cannot bind to DNA sequences/other proteins/substrate) → Change in phenotype

Types:

1. Substitution = One nucleotide replaced by another
2. Insertion/Deletion mutation = one or several nucleotides inserted into/removed from a sequence
    - Frame shift mutation if not in multiples of 3 in coding region
        - All codons downstream of the point of mutation read incorrectly ⇒ Different R groups which cannot fold to form a functional protein
    - If multiples of 3 consecutive nucleotides
        - Restoration of the reading frame
        - Addition/deletion of a single amino acid
        - Deletion of essential amino acids (e.g. contact/catalytic residues in enzymes)
3. Inversion = Segment of nucleotide sequences separates from allele and rejoins at the original psoition but is inverted

Location of Mutations:

1. Mutation in Promoter
    - Promoter sequence no longer complementary in shape and charge to DNA binding site of general transcription factors
    - General transcription factors unable to bind to promoter and hence unable to recruit RNA polymerase to form transcription initiation complex
    - Unable to transcribe coding region of gene to mRNA
    - Unable to translate and synthesise protein from mRNA
2. Mutations leading to premature stop codon
    - Resulting in truncated polypeptide
3. Silent
    - Mutation occurs in non-coding regions such as introns ⇒ Does not result in change in sequence of codons in mature mRNA ⇒ No change in sequence of amino acids in polypeptide chain ⇒ No change in specific conformation of protein ⇒ Hence, functional protein still produced
    - Point substitution mutation may result in codon that codes for the same amino acid due to the degeneracy of the triplet code/amino acid that has R group with similar properties ⇒ No change in sequence of amino acids ⇒ No change in

specific 3D conformation of protein ⇒ Functional protein still produced

Chromosomal Mutation =

Sickle-Cell Anaemia
Type of mutation: Point substitution mutation (single base)

Protein affected: β-globin chain of haemoglobin (HbA → HbS)

Mutation:

- Point substitution mutation
- CTC → CAC in the template DNA strand of gene coding for the **β-globin chain** ⇒ GAG → GUG in the 6th triplet codon in mRNA
- Amino acid glutamate → valine
- Valine is a non-polar, hydrophobic amino acid whereas glutamate is a charged, hydrophilic amino acid

Effect of mutation:

- Normal haemoglobin (HbA) → Sickle cell haemoglobin (HbS)
- Low [O_2] ⇒ Hydrophobic areas on different HbS stick together causing HbS to polymerise into abnormal rigid rod-like fibres that distort the circular biconcave shape of red blood cells ⇒ Sickle shape of RBC

Type of disease: Autosomal recessive disease → Requires 2 copies of HbS for symptoms to occur

Effect of disease

- Sickle RBC more fragile ⇒ More susceptible to lysis and active destruction by the spleen ⇒ Shortage of RBC + Poor oxygen transport ⇒ Anaemia + Lack of energy + Heart failure
- Sickle-shaped RBC may get lodged in small blood vessels ⇒ Interfere with blood circulation ⇒ Organ damage

Prevalence in malaria stricken areas of Africa

- HbAHbA ⇒ Individuals have normal haemoglobin ⇒ Susceptible to malaria
- HbSHbS ⇒ Individuals have sickle cell anaemia ⇒ Early death
- HbAHbS ⇒ Individuals do not develop sickle cell anaemia + Less chance of

contracting malaria
    - Maintains both HbA and HbS recessive allele in the population
    - Sickle shape of RBC ⇒ Lower oxygen carrying capacity ⇒ Malaria parasite cannot survive
    - Heterozygotes have selective advantage in regions of endemic malaria over both homozygotes

Cystic Fibrosis
Type of mutation: Deletion of 3 nucleotides

Protein affected: Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) → Controls movement of Cl^- into or out of the cells

Mutation:

- Deletion of 3 nucleotides on exon 10 of chromosome 7 ⇒ Loss of phenylalanine from the CFTR polypeptide

Effect of mutation

- Defective/missing CFTR protein
    - Cl^- not transported out of epithelial cells into lumen of air cavity ⇒ Na^+ not transported out ⇒ More negative water potential in cell ⇒ Water retained in the cell ⇒ Mucus in lumen becomes thick and undiluted ⇒ Reduced gaseous exchange ⇒ Remains too long in the respiratory tract ⇒ Lung infection + severe breathing difficulty

Effect of disease:

- Lung infection due to bacteria growth in respiratory tract ⇒ Severe breathing difficulty
- Pancreatic duct choked by thick mucus preventing release of enzymes ⇒ Indigestion
- Thick mucus layer in intestines ⇒ Reduced absorption of digested food
- Very salty and copius sweat production
- Death usually occurs by age 30