Proteins

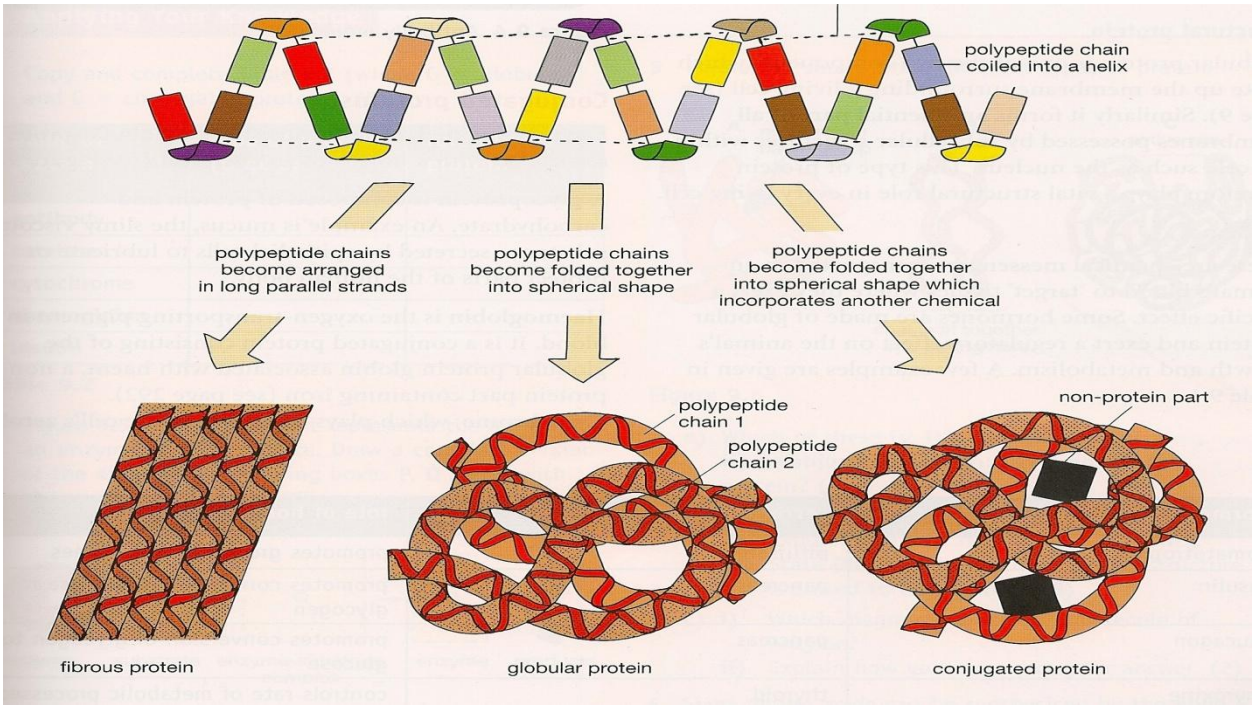
Protein – carbon, hydrogen, oxygen, nitrogen and often sulphur

Length of protein varies from thousands of amino acids to only a few – insulin only 51 amino acids

During protein synthesis, amino acids are joined in an order determined by the sequence of bases on a section of DNA,the sequence of amino acids determines the protein structure and function

Amino acids joined by peptide bonds become a polypeptide

The amino acids in the chain and the order in which they appear is the **primary structure** of a protein



Secondary Structure

Hydrogen bonds form between certain amino acids causing the chain to become coiled or folded, the way a protein coils up into a helix is the secondary structure

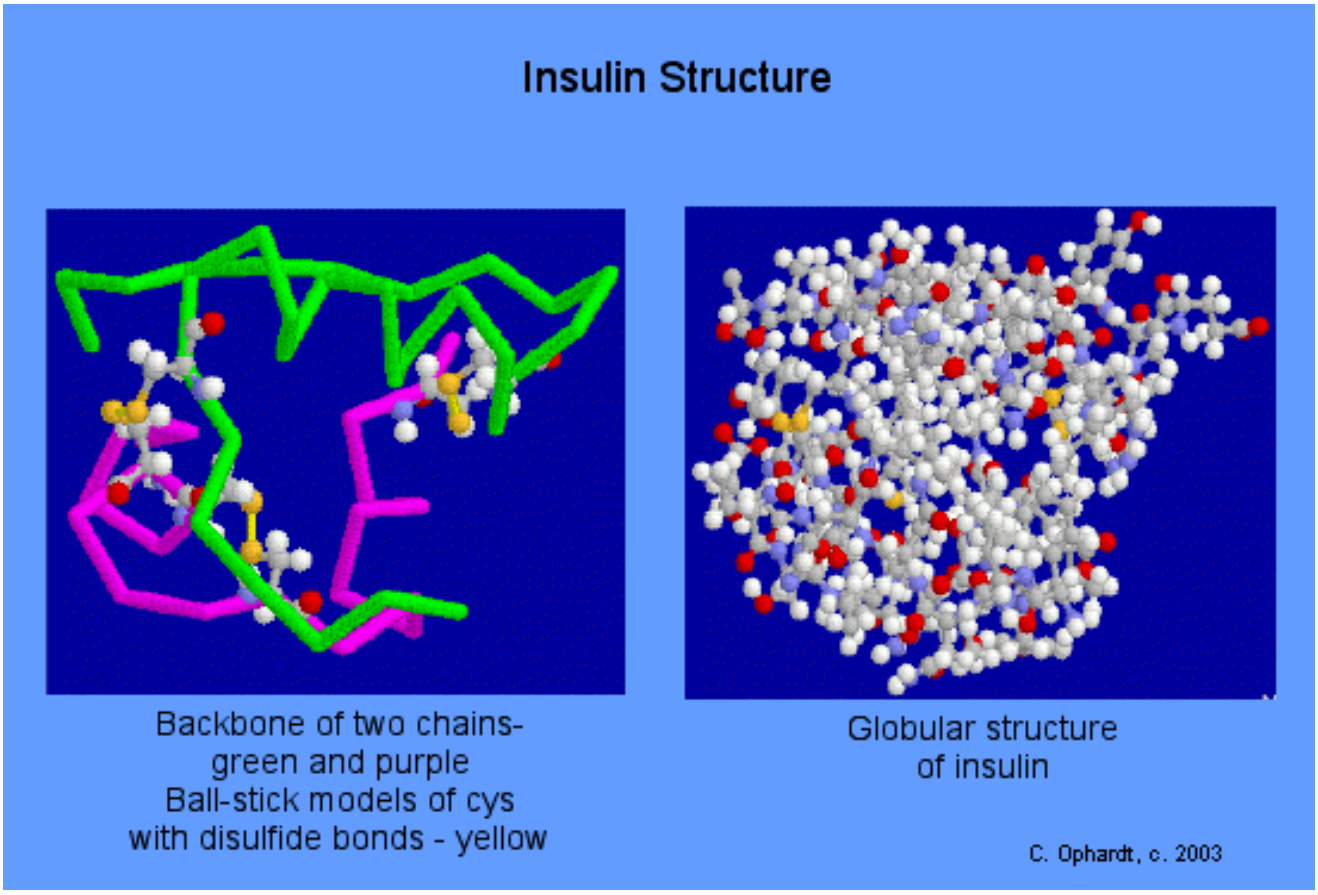
Proteins which have a secondary structure tend to be Fibrous protein arranged in long parallel strands e.g. tendons, collagen and muscle

Tertiary Structure

Proteins with a tertiary structure are Globular proteins with the final complex structure folded into a spherical shape e.g. enzymes and hormones.

Various types of other bonds are involved including ‘bridges’ between sulphur atoms

Cross connections cause the molecule to adopt its final 3D structure which it needs for its specific function



Important proteins with Globular Structure

- Enzymes
- Hormones
- Antibodies
- Structural Proteins of cell membrane

Conjugated protein

These are made up of a number of individual polypeptide sub-units folded together into a spherical shape and held together by a non-protein such as iron in haemoglobin

Summary of Types of proteins

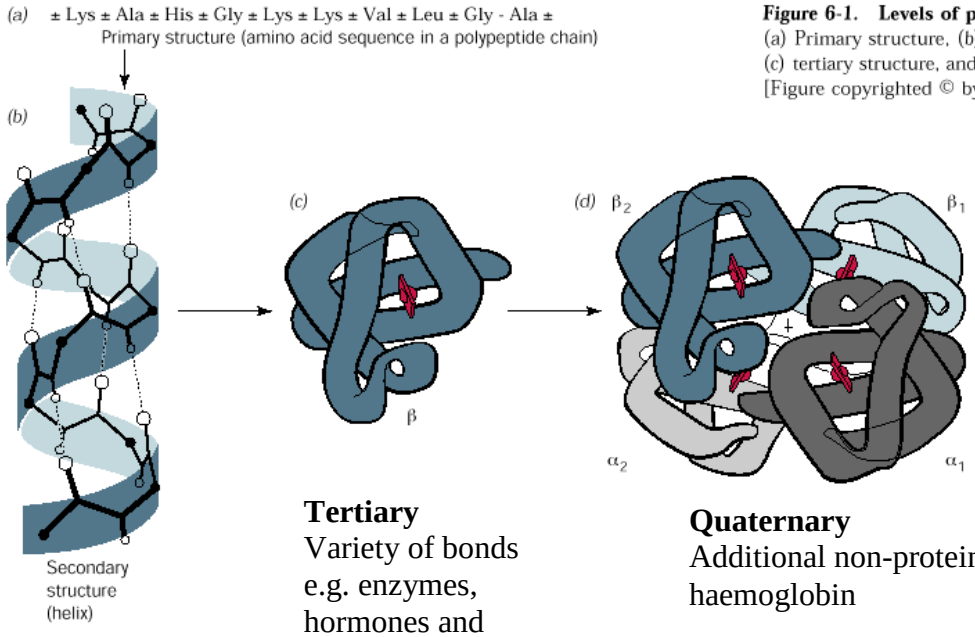


Figure 6-1. Levels of protein structure.
(a) Primary structure, (b) secondary structure, (c) tertiary structure, and (d) quaternary structure. [Figure copyrighted © by Irving Geis.]

Secondary
Hydrogen bonds
e.g. collagen

Tertiary
Variety of bonds
e.g. enzymes, hormones and antibodies

Quaternary
Additional non-protein e.g. haemoglobin

Function of Proteins

Enzymes

Are folded in a particular way to expose an active surface that readily combines with a specific substrate

Enzymes are necessary for respiration, protein synthesis etc.

Structural proteins

Structural proteins are one of the two main components that make up the cell membrane and the membranes of cell organelles

Hormones

- Some hormones are made of protein –
- Insulin, secreted by the pancreas regulates the concentration of glucose in the blood
- ADH, secreted by the pituitary regulates water balance
- Human growth hormone, secreted by the pituitary promotes the growth of long bones

Antibodies

- Antibodies, made of protein, have a characteristic Y shape
- They are produced by white blood cells to defend against antigens

Mutations

Mutation – change in structure/composition of genome

Genetic disorder – a condition/disease that is directly related to an individual's genotype

For a protein to function properly it must have the correct sequence of amino acids

Mutation results in a version of a protein with the wrong shape that does not function properly

Single gene mutation

Single gene mutation – alteration of a nucleotide sequence

Point mutation – change in one nucleotide

Types of point mutations –

- Substitution
- Insertion
- Deletion

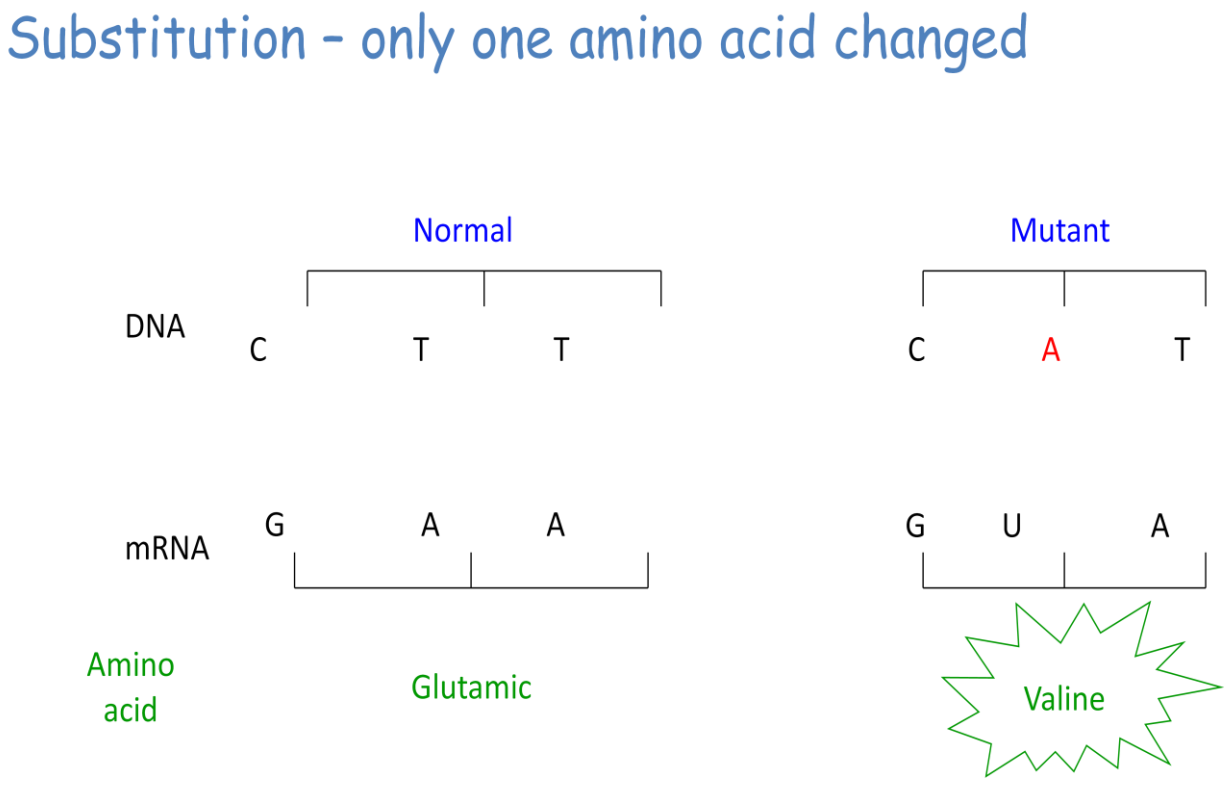
Substitution – These cause three types of substitution point mutations

- Missesnse
- Nonsense
- Splice site

Note - These are all substitution mutations affecting a single gene and therefore amino acid by changing it at one point in case you are getting confused

Missense Substitution mutation

Following substitution, an amino acid is coded for that makes sense but not the original sense i.e a different amino acid results



Examples of substitution missesnse conditions

Sickle-cell disease

- Mutation occurs on chromosome 11
- Mutation is a point mutation, a substitution
- Nucleotide with base 'A' has replaced nucleotide with base 'T'
- Instead of normal haemoglobin being assembled, an unusual form calledhaemoglobin S is made
- This is an example of a missense mutation
- Only one amino acid is different but there is a profound effect
- Sufferer has distorted sickle-shaped red blood cells
- These stick together and interfere with the blood circulation

Problems include –

- Severe oxygen shortage
- Damage to vital organs
- In many cases, death

Note

- People who are heterozygous suffer 'sickle-cell trait' – red blood cells have both types of haemoglobin
- Sickle-cell trait sufferers are resistant to Malaria
- The parasite cannot make use of red blood cells containing haemoglobin S

Phenylketonuria, PKU

- Mutation occurs on chromosome 12
- Phenylalanine and tyrosine are amino acids we obtain from protein in our diet
- Usually, phenylalanine is converted, by enzyme action, to tyrosine
- Tyrosine is converted to melanin (skin pigment)
- With PKU phenylalanine is not converted to tyrosine
- It accumulates and some of it is converted to toxins

Problems include –

- Brain fails to develop properly

Note

New born babies are screened and, if they have the condition, are placed on a diet containing minimum phenylalanine

Nonsense Substitution mutation

As a result of substitution, a codon that used to code for an amino acid is exchanged for one that acts as a stop codon

Protein synthesis halted prematurely and results in the formation of a polypeptide chain that is shorter than normal and unable to function.

Example of nonsense substitution condition

Duchene Muscular Dystrophy

- Caused by a mutation on the X chromosome such as a nonsense mutation
- Affected gene fails to code for dystrophin, necessary for normal functioning of muscles – strengthens skeletal and cardiac muscle
- Skeletal muscles become weak
- Progressive loss of co-ordination
- DMD is a muscle wasting disease

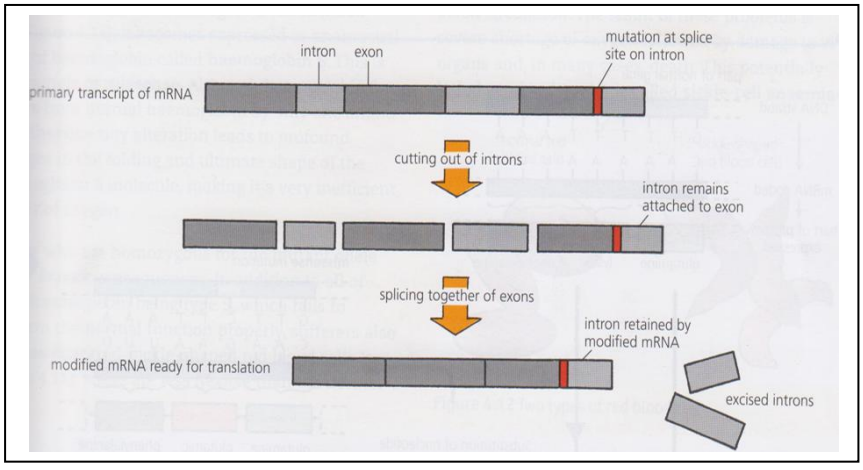
Splice-site substitution mutation

If one or more introns have been retained by modified mRNA this results in a protein that does not function properly

Example of s splice site substitutioncondition

B thalassemia

- Caused by a mutation on chromosome 11
- Sufferers have an excess of alpha globulin in their bloodstream
- This damages the red blood cells
- Many patients require blood transfusions

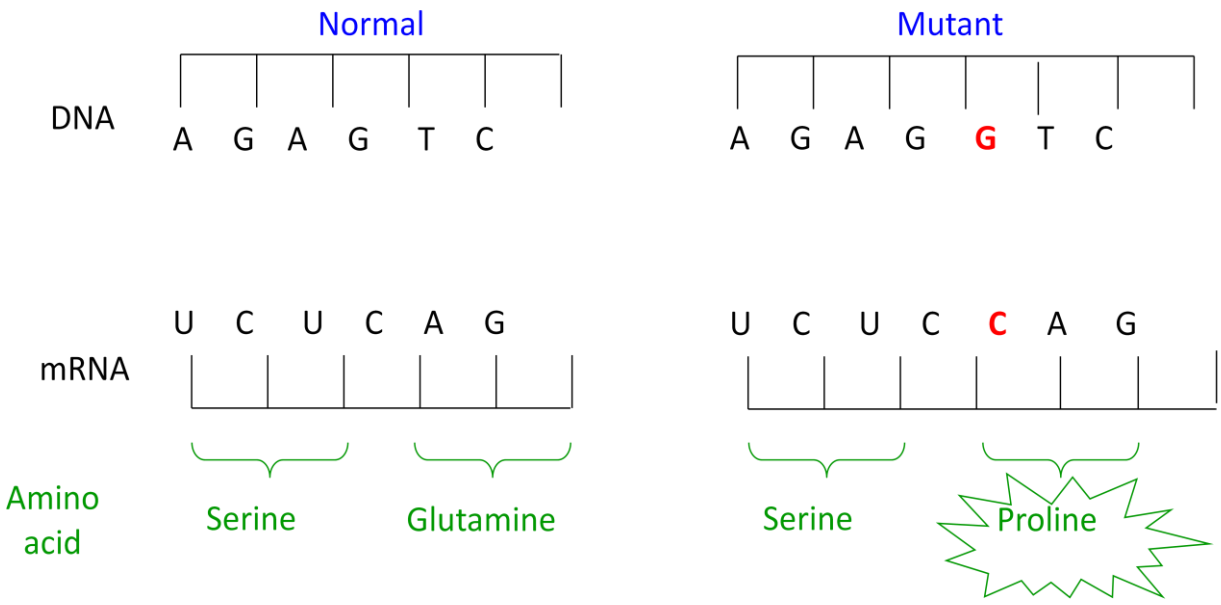


Insertion and deletion

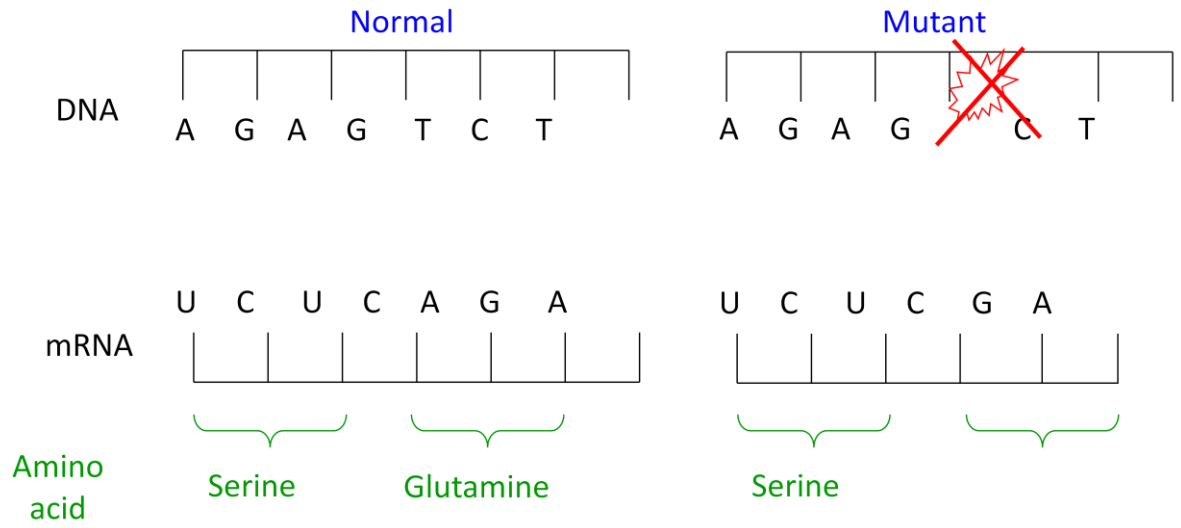
If a base is inserted or deleted this leads to a **frameshift mutation**

Every codon and amino acid coded for is altered from the point where the insertion or deletion has happened

Insertion – all amino acids altered (frameshift)



Deletion – all amino acids altered (frameshift)



Example of frame-shift conditions

Cystic fibrosis - three base-pair deletion on chromosome 7

- A non-functioning protein is produced
- Normally it is a membrane protein, that assists the transport of chlorine ions into and out of cells, that is coded for
- In the absence of this protein a high concentration of chloride gathers outside cells
- This causes mucus to become thicker and stickier

Outcome

Lungs, pancreas and alimentary canal becomes congested and blocked

Tay-sachs syndrome

- Mutation on chromosome 15
- Usually the gene codes for an enzyme that controls a biochemical reaction in nerve cells
- As a result of deletion or insertion a 'frameshift' is caused
- The protein expressed is non-functional
- The enzyme's unprocessed substrate accumulates in the brain

Outcome

This leads to neurological degeneration, paralysis and death by four years of age

Nucleotide sequence repeat expansion

Results in a defective protein with a string of extra copies of one particular amino acid

Sometimes the repeat occurs to such an extent that the gene is 'silenced' and fails to produce any protein

Examples of conditions caused by nucleotide repeat expansion

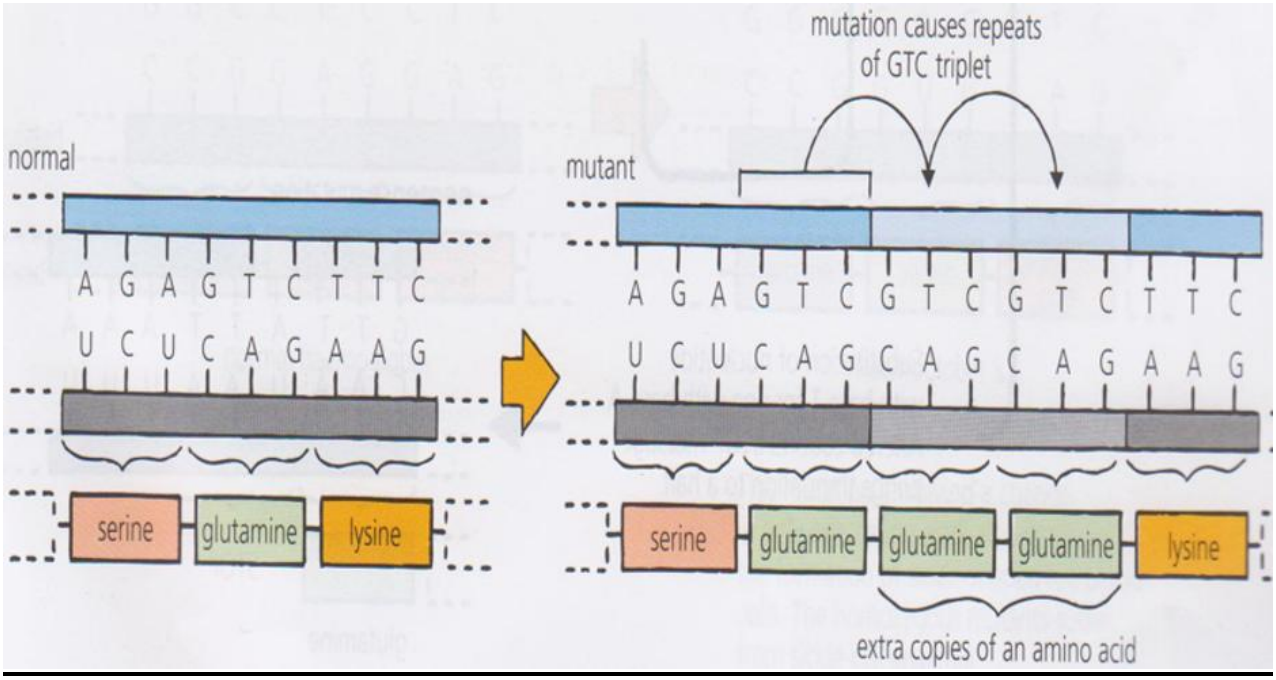
Huntington's

Causes –

- Codon CAG is repeated more than 35 times
- This results in a defective protein containing repeats of 'glutamine'

Outcomes

- Symptoms of this genetic disorder do not usually appear until middle age
- Death of neurons in the brain
- Decreased production of neurotransmitters
- Progressive degeneration of the CNS
- Rapid deterioration in patient and early death



Fragile X syndrome

Causes

- Is caused by a nucleotide sequence repeat expansion of CGG on the X chromosome
- Sufferer may have 4000 repeats of CGG
- Mutation results in failure to encode a protein involved in synapse plasticity

Outcomes

Lack of the essential protein results in retarded neural development, a wide spectrum of mental disability

Chromosome Structure Mutations

This type of mutation brings about a change in the number or sequence of genes in a chromosome

Often, the mutation is lethal due to the loss of several functional genes

This type of mutation involves the breakage of one or more chromosomes- the broken end is 'sticky' and can join to another broken end

Three types of chromosome structure mutations are –

- Deletion
- Duplication
- Translocation

Deletion

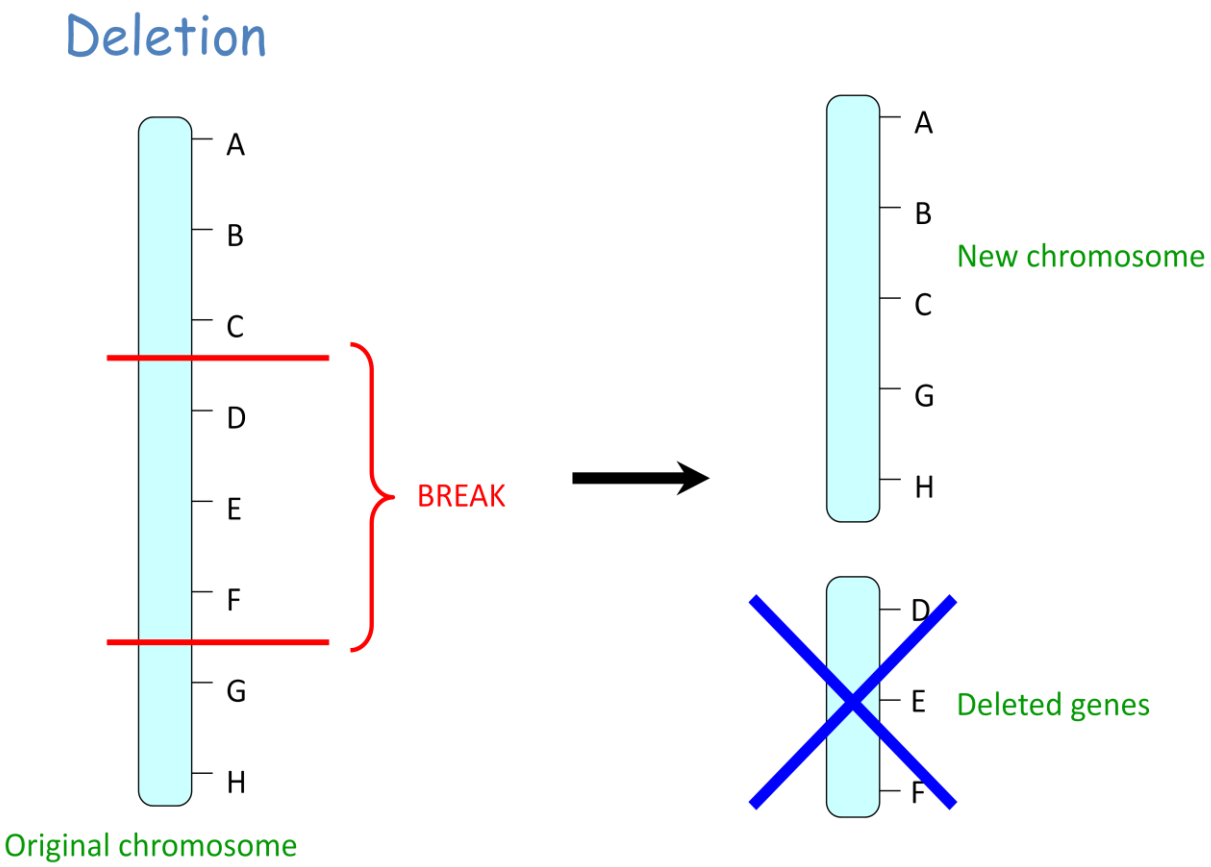
A chromosome breaks in two places and a segment becomes detached

Chromosome with genes ABCDEFGH

Breaks in two places ABC DEF GH

'short' chromosome ABCGH + deleted genes DEF

Deletion normally has a drastic effect as the 'shorter' chromosome lacks certain genes



Example of condition caused by chromosome structure deletion

<u>Cri-du-chat</u>

<u>Cause</u>

- Caused by a deletion on part of chromosome 5

<u>Outcomes</u>

- Children born with this have severe learning difficulties
- Have unusual facial features and small head
- Affected individuals usually die in early childhood

Duplication

From previous work, we know that chromosomes exist as homologous pairs

In duplication, a segment of genes deleted from its matching partner becomes attached to one end of the first chromosome or inserted somewhere along its length

The results is that a set of genes is repeated

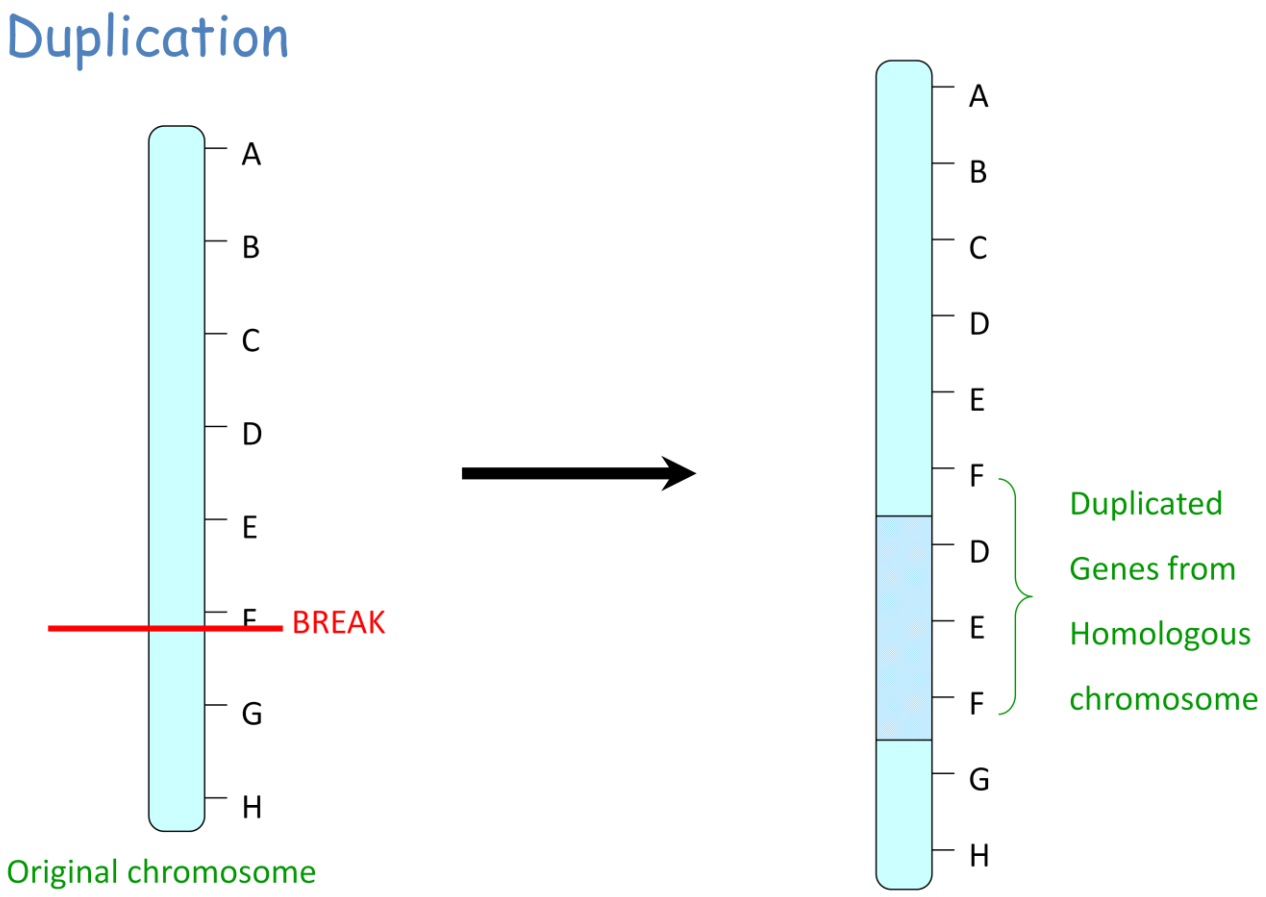
Duplication of certain genes is a common cause of cancer but some duplications are not harmful such as those giving rise to variety of blood group antigenic markers

Example

Chromosome ABCDEFGH breaks, becoming ABCDEF GH

Genes, DEF, that have been deleted from its homologous, matching chromosome, join

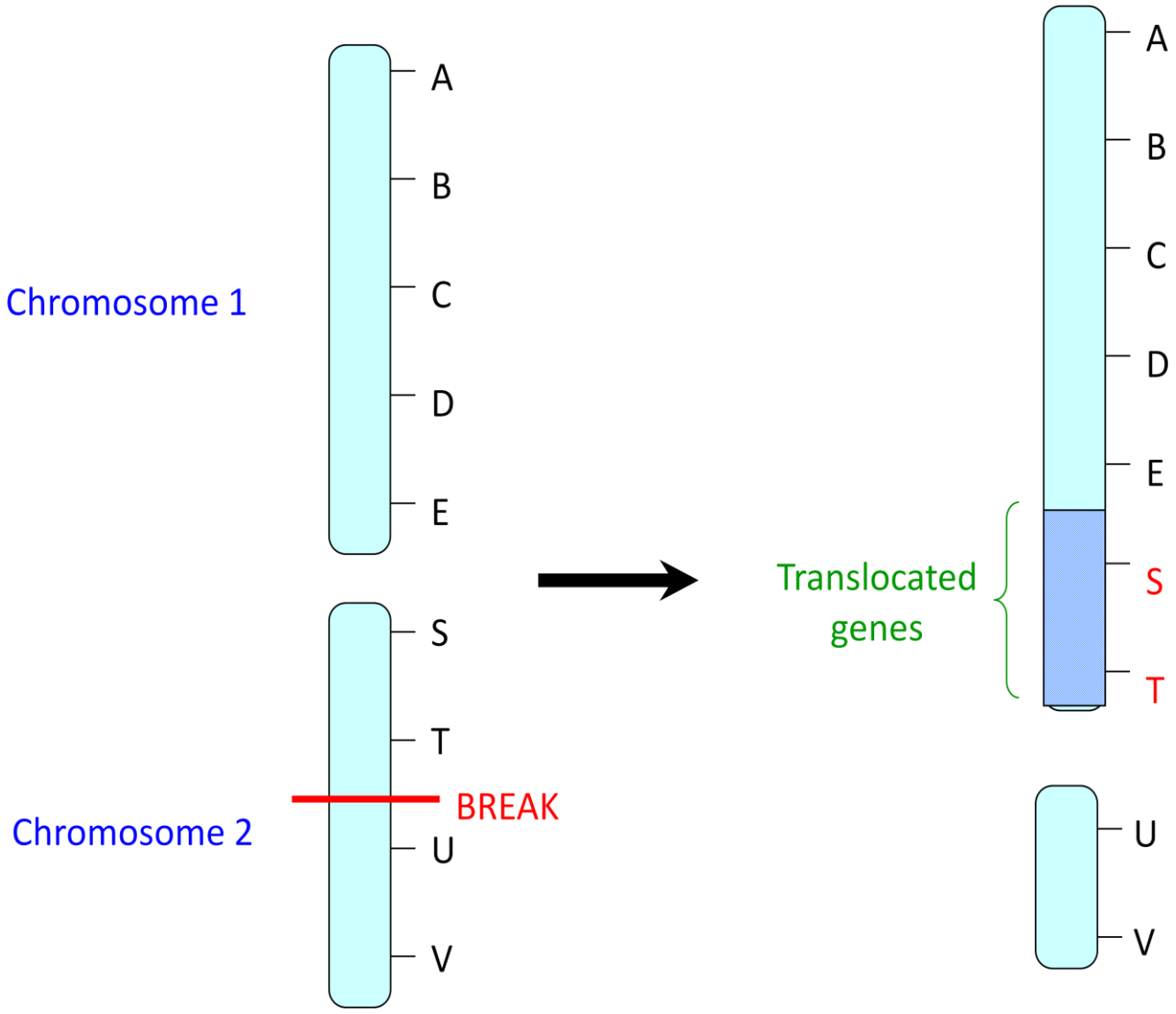
Now chromosome has ABCDEFDEFGH



Translocation

This involves a section of one chromosome breaking off and becoming attached to another chromosome that is not its matching partner

Chromosome 1 ABCDE
Chromosome 2 STUV
Chromosome 2 breaks becoming ST UV (ST joins chrom.1)
Chromosome 1 now becomes ABCDEST
Chromosome 2 is now UV



Conditions caused by translocation

Chronic Myeloid Leukaemia

- Form of cancer that affects stem cells that give rise to white blood cells
- These stem cells are affected by reciprocal translocation of chromosomes 9 and 22
- The translocation results in what is called a cancer causing oncogene
- An oncogene encodes for a protein that promotes uncontrolled cell growth, cancer

Familial Down's syndrome

Note – Most cases of Down's syndrome involve the person having an extra chromosome 21. This is not a translocation mutation but you may have noticed that some people with Down's are affected to a different degree. This is called familial Down's syndrome which is caused by translocation

5 % of Down's syndrome cases result from a reciprocal translocation between chromosomes 14 and 21 of one of the sufferer's parents

The parent of the Familial Down's syndrome individual is a 'carrier' of the mutated chromosome but is phenotypically unaffected

Gamete formation in familial Down's syndrome

At gamete formation, some of the 'carrier' parent's sex cells receive a copy of the mutated chromosome 14 + 21 and a copy of the 'normal' chromosome 21

If one of these 'abnormal' gametes meets a 'normal' gamete the resulting zygote develops into a sufferer of Familial Down's syndrome

Individuals have three copies of chromosome 21 but also have additional genetic material from the mutated chromosome