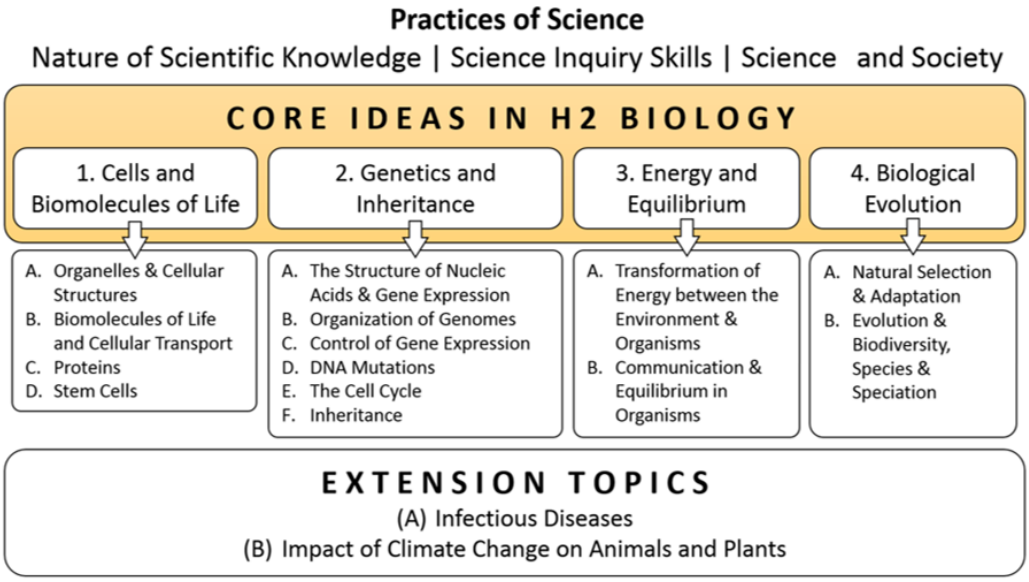
Core Idea 2D | 2E

6. Genetics & Inheritance (III) – DNA Mutations & Their Consequences



SYLLABUS OVERVIEW		
No.	**Overarching Idea**	**Topics**
1	**Core Idea 1** The Cell and Biomolecules of Life	Cell – The Basic Unit of Life
2		Biomolecules of Life and Cellular Transport
3	**Core Idea 3** Energy and Equilibrium	Transformation of Energy – Photosynthesis and Cellular Respiration
4	**Core Idea 2** Genetics and Inheritance	Genetics and Inheritance (I) – The Cell Cycle
5		Genetics and Inheritance (II) – DNA Replication and Gene Expression
6		Genetics and Inheritance (III) – DNA Mutations and their Consequences
7		Genetics and Inheritance (IV) – Molecular Techniques in DNA Analysis
8		Genetics and Inheritance (V) – Organization of Genome & Control of Gene Expression in Eukaryotes *[Includes Core Idea 1D: Stem Cells]*
9		Genetics and Inheritance (VI) – Organization and Inheritance of Viral Genomes
10		Genetics and Inheritance (VII) – Organization of Genome & Control of Gene Expression in Prokaryotes
11		Genetics and Inheritance (VIII) - Inheritance
12	**Core Idea 3** Energy and Equilibrium	Communication and Equilibrium in Multicellular Organisms
13	**Core Idea 4** Biological Evolution	Biological Evolution
14	**Extension Topic A** Infectious Diseases	Immunity and Infectious Diseases
15	**Extension Topic B** Impact of Climate Change on Animals & Plants	Climate Change – Causes and Impacts on Animals and Plants

TOPIC SYNOPSIS

An understanding of *Genetics and Inheritance* that would help make sense of the transition from molecular to organismal level. *Genetics and Inheritance* provides the molecular basis to the understanding of how variations in populations arise and this is important in the study of biological evolution. At the cellular level, expression of genes involves cellular structures such as the nucleus, endoplasmic reticulum and ribosome. Many essential products of gene expression are enzymes involved in biochemical pathways which control physiological functions. As such, mutation of genes may give rise to dysfunctional proteins which in turn could result in diseases. Sickle cell anemia and cancer are raised as examples of a monogenic and a multi-genic disease respectively.

The following questions should help you frame your learning:

- How does the genetic make-up of an organism influence its appearance, behavior and survival?
- How can we ensure continuity of human as a species?

Mutation arises from imperfect replication of genetic information. Together with other biological processes, such mutations increase genetic variation.

Based on the central dogma, a change in the sequence of DNA nucleotide, i.e. gene mutation, may affect the amino acid sequence in the polypeptide and hence the phenotype of the organism. Many mutations are detrimental to the individual since they affect the normal functioning of the gene product, e.g. genetic diseases such as sickle cell anemia and cancer. Others are neutral, often because they have no effect on the phenotype, e.g. a change in a DNA triplet which still codes for the same amino acid. Occasionally, mutations may be beneficial. For example, individuals who are heterozygous for a mutated hemoglobin gene that causes sickle cell anemia have selective advantage in areas where malaria is common. Besides mutation of genes, chromosomal mutation and change in chromosome number may also occur. Down's syndrome arises due to the presence of an additional copy of chromosome 21.

The development of cancer is a multi-step process that comprises gene mutations caused by environmental factors, biological agents or hereditary predispositions. These mutations might cause cells to bypass cell cycle checkpoints. Normally, two groups of genes are involves in regulating cell division: tumor-suppressor genes and proto-oncogenes. Mutations in either or both of these groups of genes may lead to the development of cancer. Cancer has a much higher incidence in Singapore compared to other diseases and accounts for as much as 30% of the death in this country. The recorded incidence of cancer is on the rise and this could be due to the accumulation of mutations from one generation to the next, although other reasons have also been proposed: increased exposure to carcinogens and increased detection rates as a result of effective cancer screening programmes. As such, an understanding of how cancer develops is important as this would set the platform for discussion of developing anti-cancer drugs.

LEARNING OUTCOMES

Core Idea 2D: DNA Mutations
Changes to the DNA sequence or amount of could have huge physiological impact on organisms. This concept illustrates how DNA mutations could result in sickle cell anemia and Down syndrome in humans.

l) Explain what is meant by the terms *gene mutation* and *chromosome aberration*. For gene mutation, knowledge of how substitution, addition, deletion could change the amino acid sequence (e.g. frameshift) is required. For chromosomal aberration, knowledge of numerical (e.g. aneuploidy, as in the case of trisomy 21, i.e. Down syndrome) and structural (e.g. translocation, duplication, inversion, deletion) aberration is required.

m) Explain how gene mutations can result in diseases (including sickle-cell anemia).

Core Idea 2E: The Cell Cycle

p) Identify the causative factors, including genetic, chemical carcinogens, ionizing radiation and loss of immunity, which may increase the chances of cancerous growth.

q) Explain how the loss of function mutation of tumor suppressor genes, including *p53*, and gain in function mutation of proto-oncogenes, including *ras*, results in uncontrolled cell division.

r) Describe the development of cancer as a multi-step process that includes accumulation of mutations, angiogenesis and metastasis.

LECTURE OUTLINE

1. Overview of Mutation

2. Gene Mutations
- 2.1 Types of Gene Mutations
  - 2.1.1 Base Pair Substitution
  - 2.1.2 Base Pair Insertion and Deletions
- 2.2 Non-cancerous Genetic Disorders caused by Gene Mutations
  - 2.2.1 Sickle Cell Anemia
  - 2.2.2 Cystic Fibrosis (FYI only)
- 2.3 DNA Repair

3 Chromosomal Aberrations
- 3.1 Chromosomal Aberrations (Numerical)
  - 3.1.1 Aneuploidy
  - 3.1.2 Polyploidy
- 3.2 Chromosomal Aberrations (Structural)
  - 3.2.1 Deletion
  - 3.2.2 Duplication
  - 3.2.3 Inversion
  - 3.2.4 Translocation
  - 3.2.5 Summary of Chromosomal Aberrations (Structural)

4. The Development of Cancer as a Result of Mutations
- 4.1 Introduction to Cancer
- 4.2 Control of the Eukaryotic Cell Cycle
- 4.3 The Role of Mutations in the Development of Cancer
- 4.4. Gain of Function Mutations in Proto-oncogenes
- 4.5 Loss of Function Mutations in Tumour-Suppressor Genes
- 4.6 The Development of Cancer as a Multi-step Process
- 4.7 Factors that Increase the Chances of Cancerous Growth

1. Overview of Mutations

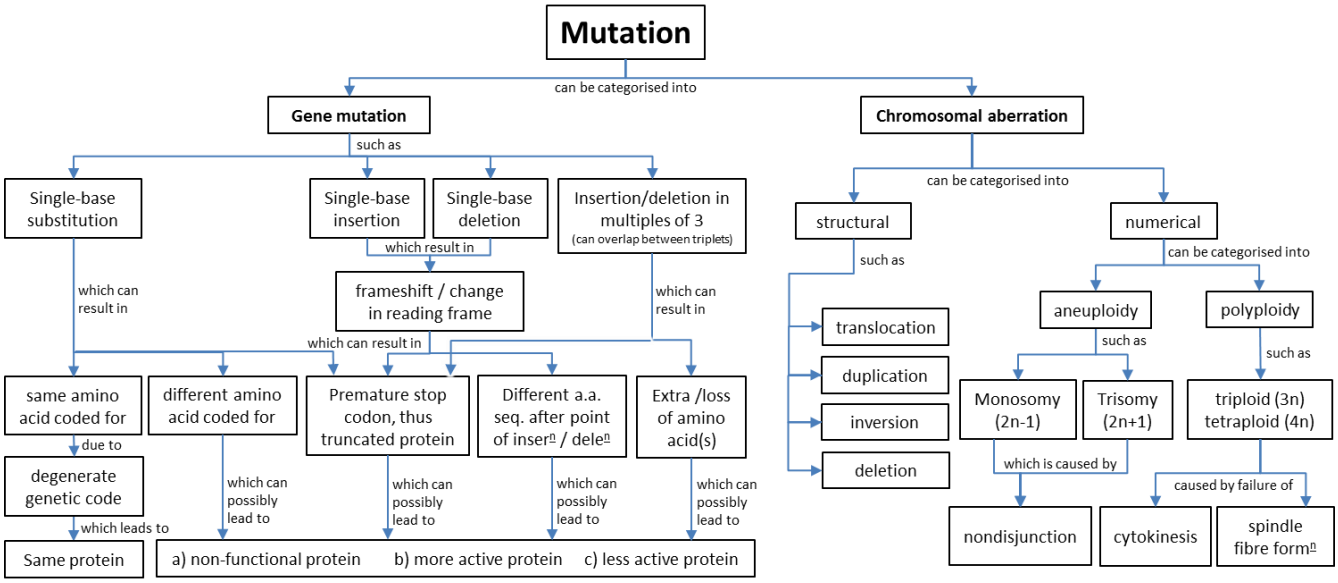


Fig. 1.1: A summary of genetic mutations.

a) Mutations

- Mutation is the **change in the amount, arrangement or structure of the DNA** in an organism.
- Mutations occur mostly during **flawed DNA replication** or **nuclear division**.
- Mutations occurring in **germ cells** that produce gametes (sperms/eggs) can be inherited by the offspring during fertilization. This is known as **germline mutation**.
- Mutations occurring in **somatic cells** (e.g. skin cells, breast cells) will not be passed down to the offspring. This is known as **somatic mutation**.
- Mutations resulting from **a change in nucleotide sequence of the DNA at a single locus** are known as **gene mutation**.
- Large scale mutations resulting from a **change in the number or structure of chromosomes** is known as **chromosomal mutation** or **chromosomal aberration**.

2. Gene Mutations

2.1 Types of Gene Mutations

- Gene mutations can be divided into two main categories: (a) **base pair substitution** and (b) **base pair insertion/addition and deletion**.

- A **change in just one base pair** of a gene is known as **point mutation**. **Single base pair** substitution, addition and deletion are **point** mutations.

- Gene mutations can **change the structure** of a protein the same way a change in a single letter will change the structure of a sentence or how it is read in the analogy below.

Analogy:

Think of the sentence:	the fat cat ate the big rat
Substitution:	the far cat ate the big rat
Insertion:	the afa tca tat eth ebi gra t
Deletion:	thf atc ata tet heb igr at

- Gene mutations give rise to **new alleles** which code for **potential new traits**. Gene mutations can also result in **inheritable diseases**.

- The following examples of gene mutations can be compared to the wild-type (Fig. 2.1) or normal allele.

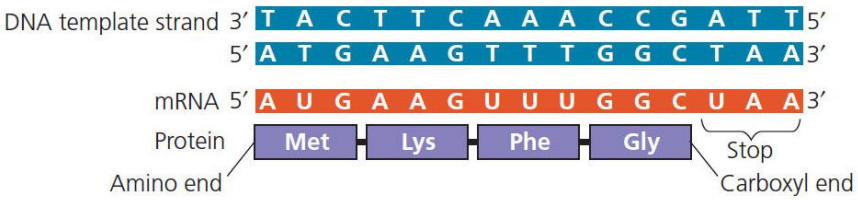


Fig. 2.1: Wild-type allele coding for a normal protein.

2.1.1 Base Pair Substitution

- Base pair substitution is the **replacement** of one nucleotide pair with another pair of nucleotides.
- Possible outcomes of a single base pair substitution in exons :

(1) The same amino acid is coded for:

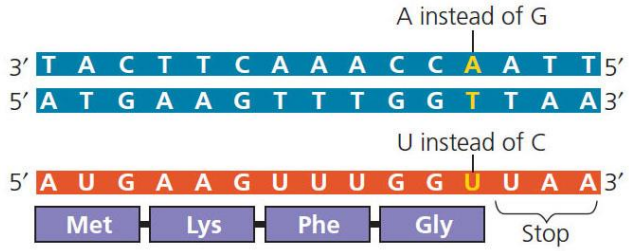


Fig. 2.2: Single base substitution resulting in a silent mutation.

- Substitution may result in a **silent mutation** (Fig. 2.2).
- As the **genetic code** is **degenerate**, mutations in DNA triplets lead to changes in mRNA **codon** with a different **3rd base**, the altered codon may still code for the **same amino acid**.
- Hence, primary structure of protein remains unchanged (still the same protein).

(2) Different type of amino acid is coded for:

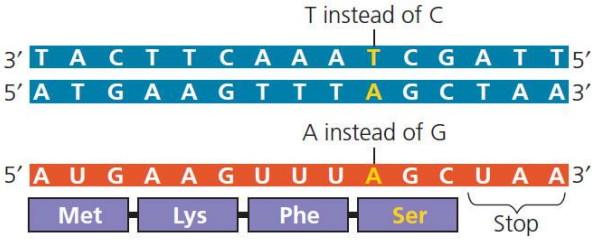


Fig. 2.3: Single base substitution resulting in a different amino acid coded for.

- Substitution may result in a **different amino acid** in the primary structure (Fig. 2.3).
- The different amino acid may have **different properties** from the original amino acid.
- **Tertiary structure** of a protein is **altered** leading to altered activity.
- The protein may become **more active** or **less active** or **non-functional**.
- In the case of an enzyme, the active site might be altered and unable to bind substrate effectively.

(3) A truncated protein is produced (Fig. 2.4):

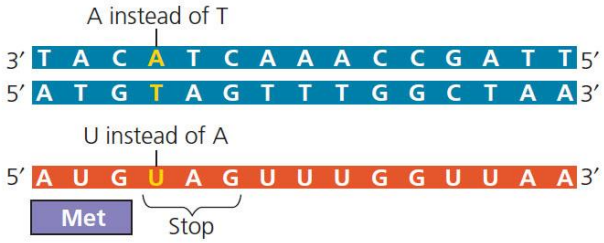


Fig. 2.4: Single base substitution resulting in a stop codon and a truncated protein.

- Substitution may result in a **premature STOP codon** (UGA, UAG, UAA).
- Translation terminates prematurely and the polypeptide will be shorter than normal (a **truncated protein** results).

2.1.2 Base Pair Insertion and Deletion

- It is the **addition or loss** of one or more nucleotide pair(s) in a gene.
- Insertions and deletions usually lead to more disastrous outcomes than substitution mutation.
- Possible outcomes of a **single** insertion/deletion in exons:

(1) Truncated protein (Fig. 2.5):

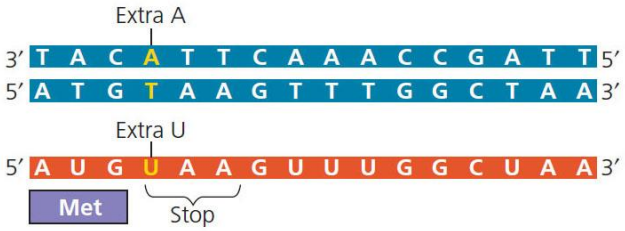


Fig. 2.5: Single base insertion resulting in a stop codon and a truncated protein.

- May result in a **premature STOP codon**.
- Translation terminates prematurely and the polypeptide will be shorter than normal (**truncated protein**).
- This results in a **non-functional** protein.

(2) Different amino acids after point of insertion or deletion (Fig. 2.6):

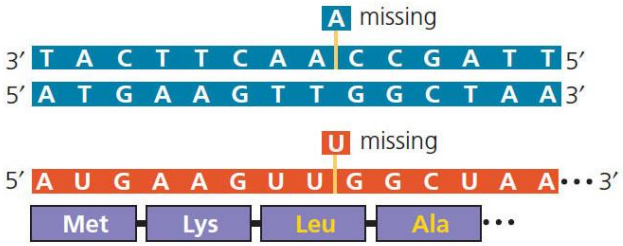


Fig. 2.6: Single base insertion resulting in a stop codon and a truncated protein.

- The **reading frame** (triplets of bases) of the genetic message is altered from the point of insertion or deletion.
- The sequence of amino acids is **completely different** from the original protein from the point of insertion or deletion.
- This normally leads to a **non-functional protein**
- The resulting mutation is known as a **frameshift mutation**.

- Possible outcomes of insertion/deletion in multiples of three nucleotide pairs in exons:

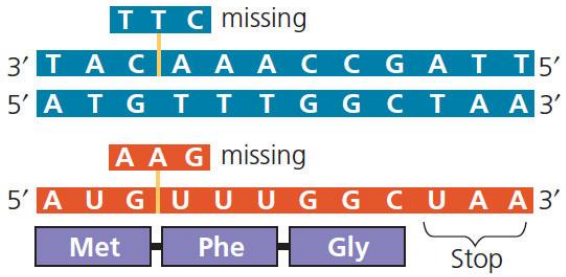
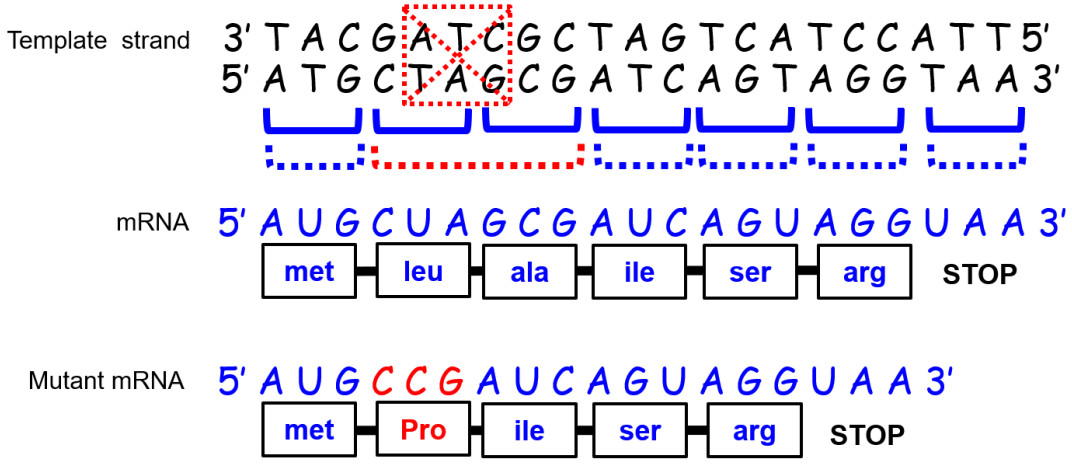


Fig. 2.7: Deletion of a triplet of bases resulting in a protein with one missing amino acid.

  - There is **no frameshift mutation**.
  - The resulting protein would have one or more **extra** amino acid(s) (for insertion) or one or more **missing** amino acid(s) (for deletion).
  - This could lead to the polypeptide **folding** in a different way to give a **different three-dimensional configuration**.
  - The protein may become **more active** or **less active** or **non-functional** as a result.

Possible outcome of insertion or deletion in multiples of 3

- The 3 nucleotides deleted/inserted need not be the actual triplet.
- It can overlap between two triplets.



OUTCOME: One missing amino acid + (a change in one amino acid)

2.2 Non-cancerous Genetic Disorders caused by Gene Mutations

2.2.1 Sickle Cell Anemia

- The mutated version of the allele is produced by a **single-base substitution** mutation in the **β-globin gene** (located on chromosome 11) which codes for the beta chain of haemoglobin. The 17th nucleotide of the gene is changed from **'A' to 'T'** on the **non-template DNA strand** resulting in a change from a 5' GAG 3' to a 5' GTG 3'.

  NOTE:
  1) State the direction that transcription proceeds in: **5' to 3'**
  2) The **DNA template strand** is read from → **3' to 5' direction** (so that a 5' to 3' complementary mRNA can be synthesised).
  3) Therefore, a change from 5' GAG 3' to 5' GTG 3' on the non-template DNA strand means → **change from 3' CTC 5' to 3' CAC 5' on the DNA template strand** (Fig 2.8).

- This changes the **mRNA codon** from **5' GAG 3' to 5'GUG 3',** resulting in the 6th amino acid of the chain being changed from **glutamic acid** (charged, hence hydrophilic) **to valine** (hydrophobic) (Fig 2.8). The mutant haemoglobin produced is known as **Haemoglobin S** (HbS).

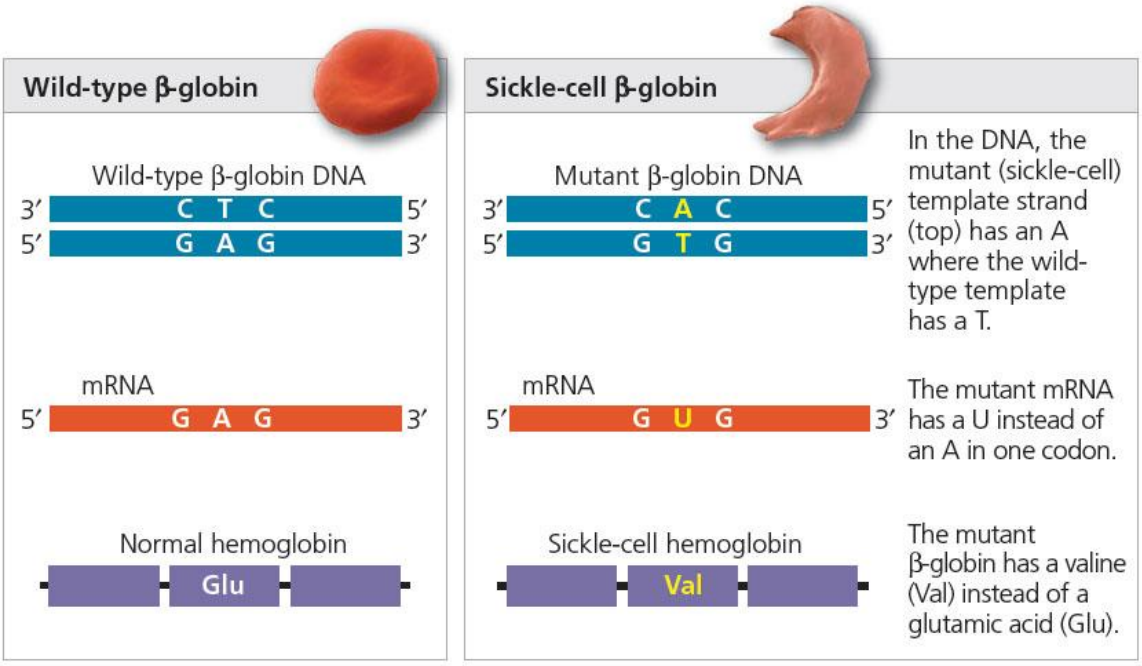


Fig. 2.8: A single base substitution results in a mutant allele for sickle-cell β-globin.

- This substitution of one single base in the beta globin gene alters the tertiary and quaternary structure of haemoglobin, which has a profound influence on the physiology and wellbeing of the individual.

Normal red blood cells

- Normal red blood cells are bi-concave in shape (Fig. 2.10A). They move easily through the blood vessels.

Abnormal Sickle cells

- The hydrophobic R group of valine inserts into the hydrophobic pocket of another β-globin, causing the **HbS** to **crystallise** to form **long fibres** at low oxygen concentration (Fig. 2.9).
- The fibrous HbS protein cause the RBC to assume a sickle or crescent shape (Fig. 2.10B).

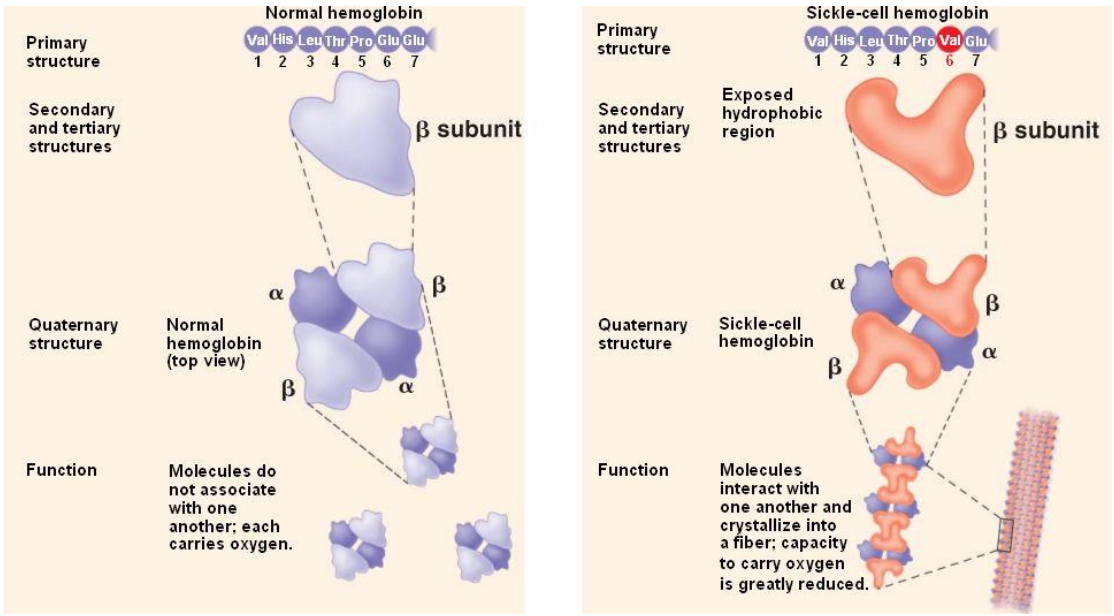


Fig. 2.9: The different in protein folding between normal haemoglobin and HbS.

- Sickle-shaped cells do not move easily through the blood vessels. They are stiff and sticky and tend to **form clumps** and get stuck in the blood vessels (Fig. 2.10B).

- The clumps of sickle cells **obstruct blood flow** in the blood vessels that lead to the limbs and organs. Blocked blood vessels can cause pain, serious infections, and organ damage.

- In addition, the sickle cells rupture easily, resulting in severe anemia. Victims usually suffer an early death.

- Note that the sickle-cell β-globin allele is usually passed down from parent to offspring.

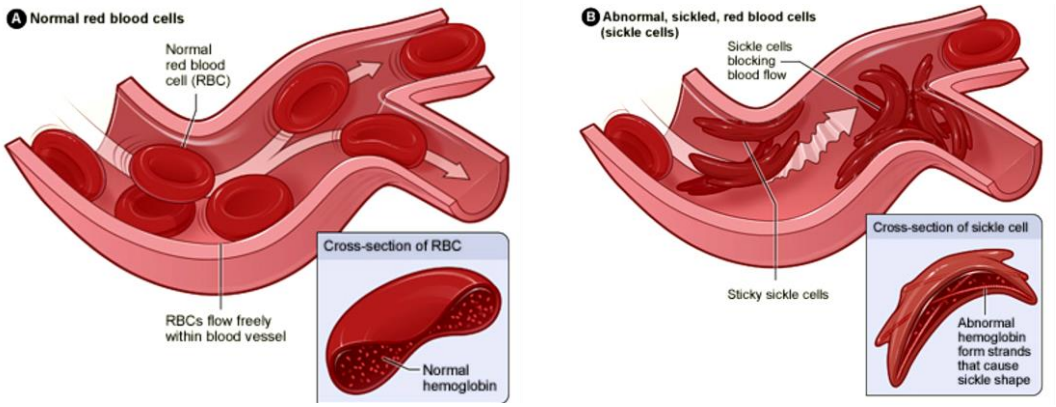


Fig. 2.10: Red blood cells in both (A) healthy and (B) sickle cell anemic patients.

2.2.2 Cystic Fibrosis (FYI only)

- Cystic fibrosis is a severe **inherited** genetic disease that involves both the lungs and the gastrointestinal tract. It occurs in about one in every two thousand births among white children and at a far lower rate in Asian and Black children.

- There are now **more than 500 different mutations** known to cause the disease (*Fig. 2.11*). These mutations occur in a huge gene (>6000 nucleotides) on **chromosome 7** that encodes a protein of 1480 amino acids called the **cystic fibrosis transmembrane conductance regulator (CFTR)**. This protein **transports chloride ions <u>out</u>** of cells (Fig. 2.12).

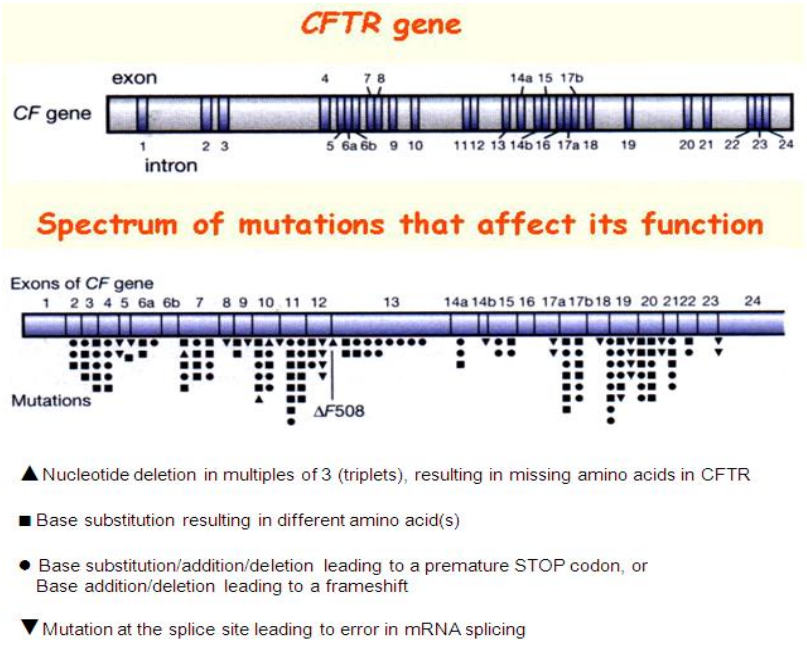


Fig. 2.11 : Mutations that occur anywhere along the CFTR gene can result in a non-functional CFTR protein, which ultimately causes cystic fibrosis.

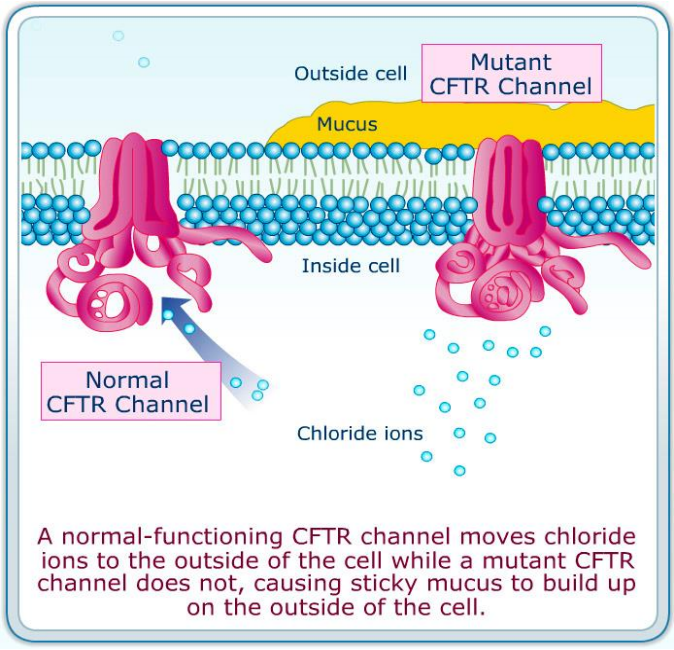


Fig. 2.12 : Diagram showing the difference between normal and mutated CFTR.

- This disease results from a number of different mutations in the CFTR gene. Some of the more common mutations include:

  (1) **Deletion of a DNA triplet** resulting in the **deletion of the amino acid phenylalanine at position 508**.

  (2) A **substitution mutation at position 551** resulting in an **aspartic acid being substituted for a glutamic acid**.

  (3) A **mutation at position 542** resulting in a **stop codon instead of one that codes for glycine** and hence a truncated protein.

  (4) Other mutations at the splice sites of introns (non-coding regions of a gene).

- Cystic fibrosis exerts its effects in several ways:

  (1) **Lungs**
  - The thick mucus **blocks the airways**.
  - The build-up of mucus makes it **easy for bacteria to grow**. This leads to repeated, serious lung **infections**. Over time, these infections can severely damage the lungs.

  (2) **Pancreas and the digestive system**
  - The thick, sticky mucus also **block tubes, or ducts,** in the **pancreas**.
  - The **digestive enzymes that the pancreas makes cannot reach the intestine**
  - These enzymes help break down the food. Without them, digestion of **fats and proteins is ineffective**. This can **cause vitamin deficiency and malnutrition** because nutrients leave the body unused.
  - It also can cause bulky stools, intestinal gas, a swollen belly from severe constipation, and pain or discomfort

  (3) **Water balance**
  - Sweat becomes very salty. As a result, the body **loses large amounts of salt** during perspiration. This can upset the balance of minerals in the blood and cause a number of health problems.
  - Examples include **dehydration** increased heart rate, tiredness, weakness, decreased blood pressure and heat stroke.

  (4) **Infertility**
  - Infertility in men.
  - Blocked fallopian tubes in women.

2.3 DNA repair

- Damages or changes to DNA may occur as a result of exposure to physical and chemical agents, e.g. reactive chemicals, carcinogenic substances, radioactive emissions, X-rays or UV light.
- DNA polymerase proofreads and repairs DNA by excising damaged DNA (Fig. 2.13).
- **Excision repair** includes cutting out the damaged segment, fill in resulting gap with properly paired nucleotides using the intact strand as a template.
- Xeroderma pigmentosum, a rare hereditary defect of an enzyme that repairs UV-induced DNA damage, results in extreme sensitivity to sunlight and a tendency to develop skin cancer.
- A failure to correct mutations may lead to the creation of new alleles that can be passed onto offspring if the mutations occur in the germ-line cells.

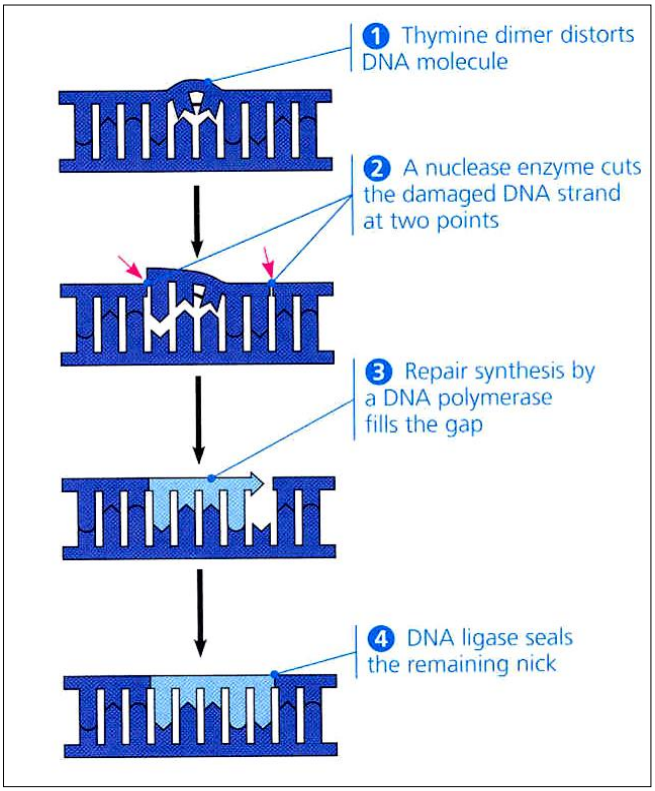


Fig. 2.13: Mechanism of DNA repair

3. Chromosomal Aberrations

- There are two main categories of chromosomal aberrations (mutations): **changes in chromosome numbers** and **changes in chromosome structure**.

3.1 Chromosome Aberrations (Numerical)

- Chromosomal aberrations can result in **aneuploid** or **polyploid** organisms.

- Changes in the number of chromosomes usually occur as the result of errors **during meiosis** but they can also occur **during mitosis** after fertilisation.

3.1.1 Aneuploidy

- As a result of **nondisjunction** (failure of chromosome to separate) (*Fig. 3.1*) during meiosis, the gametes produced could have either an extra chromosome (n + 1) or a missing chromosome (n – 1).

- During fertilization, fusion of an aberrant gamete with a normal haploid gamete produces a zygote with an odd number of chromosomes.

- The resultant offspring is an aneuploid. The offspring could be **trisomic** [having 3 copies of chromosome (2n+1)] or **monosomic** [having only a single copy of chromosome (2n-1)].

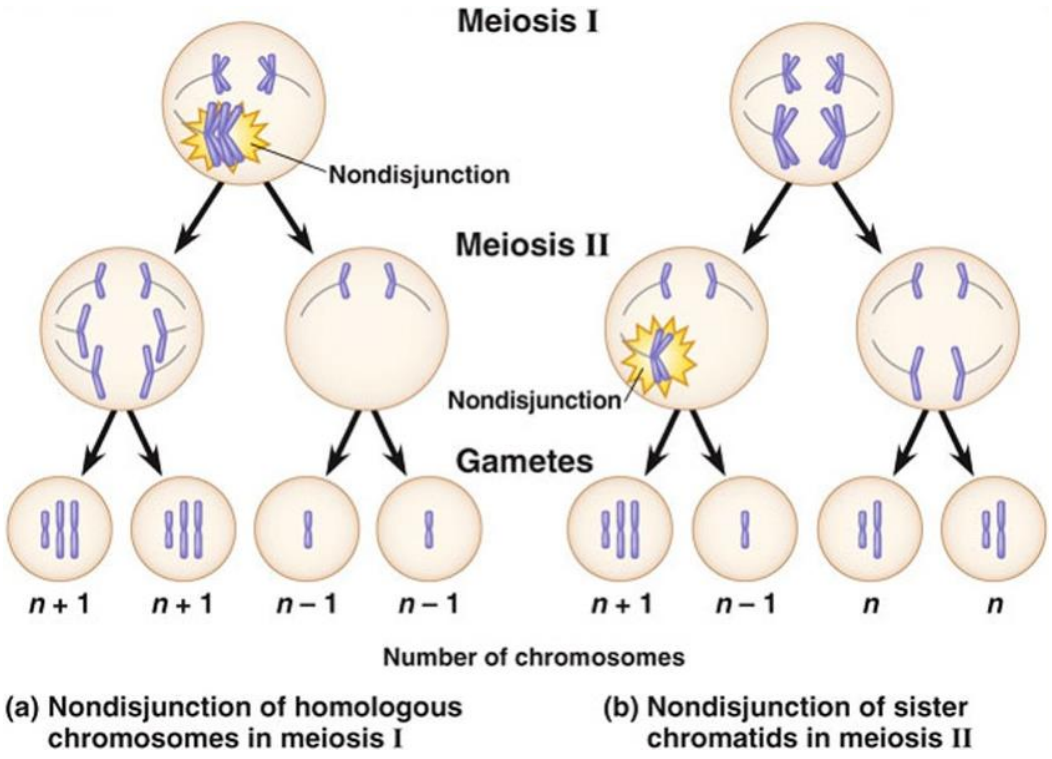


Fig. 3.1: Nondisjunction can occur in **(a)** meiosis I or **(b)** meiosis II.

How Nondisjunction Occurs

- Sometimes, mistakes occur during the process of mitosis or meiosis.
- Non-disjunction is a type of **chromosomal mutation** that take place during **meiosis or mitosis** in which members of a **pair of homologous chromosomes** or a **pair of sister chromatids fail** to **separate** properly from each other.
- There are three ways in which nondisjunction can occur:

1. During **meiosis I, nondisjunction of homologous chromosomes (**Fig 3.1a).

- At metaphase I, bivalents align at the equator.
- Under normal circumstances, every pair of homologous chromosomes would separate to opposite poles during anaphase I.
- However, when **one bivalent fails to separate**, nondisjunction is said to have occurred.
- This results in one pole with **an extra chromosome** and the other pole with **one less chromosome**.
- When meiosis II takes place normally, **two of the daughter cells** will have **(n+1)** chromosomes while **the other two** will have **(n–1)** chromosomes.

2. During **meiosis II, nondisjunction of sister chromatids** (Fig. 3.1b).

- At metaphase II, chromosomes align at the equator in single row.
- Under normal circumstances, every pair of sister chromatids separate to opposite poles during anaphase II.
- However, when **the sister chromatids of one chromosome fail to separate**, nondisjunction is said to have occurred.
- This results in one pole with **an extra chromosome** and the other pole with **one less chromosome**.
- If meiosis I takes place normally, **two of the four daughter cells** will have **n** number of chromosomes while **one of the other** will have **(n–1)** chromosomes and **one** will have **(n+1)** chromosomes.

3. During **anaphase of mitosis: nondisjunction of sister chromatids** (Fig. 3.1c).

- At metaphase, chromosomes align at the equator in single row.
- Under normal circumstances, every pair of sister chromatids separate to opposite poles during anaphase.
- However, **the sister chromatids of one chromosome fail to separate**, nondisjunction is said to have occurred.
- This results in one pole with **an extra chromosome** and the other pole with **one less chromosome**.
- After mitosis, **one of the daughter cells** will have **(2n–1)** chromosomes and **the other** will have **(2n+1)** chromosomes.

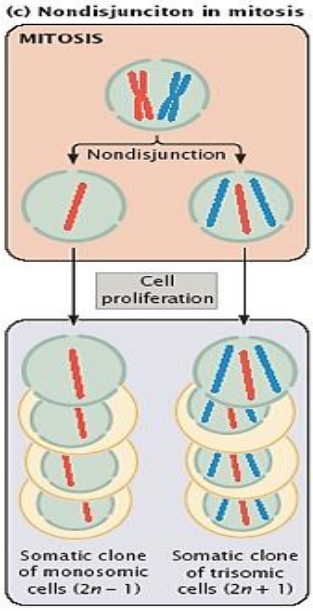


Fig. 3.1c: Nondisjunction in mitosis.

Case study 1: Down's Syndrome (47, +21), Trisomy 21

- A person with Down's Syndrome has an **extra chromosome 21** (Fig. 3.1).
- Features: **slow cognition**, **webbed neck**, **upward slanting eyes**, **flattened nose and face**, amongst many others. Their **life expectancy is shortened**, although some are known to survive into their 50s.

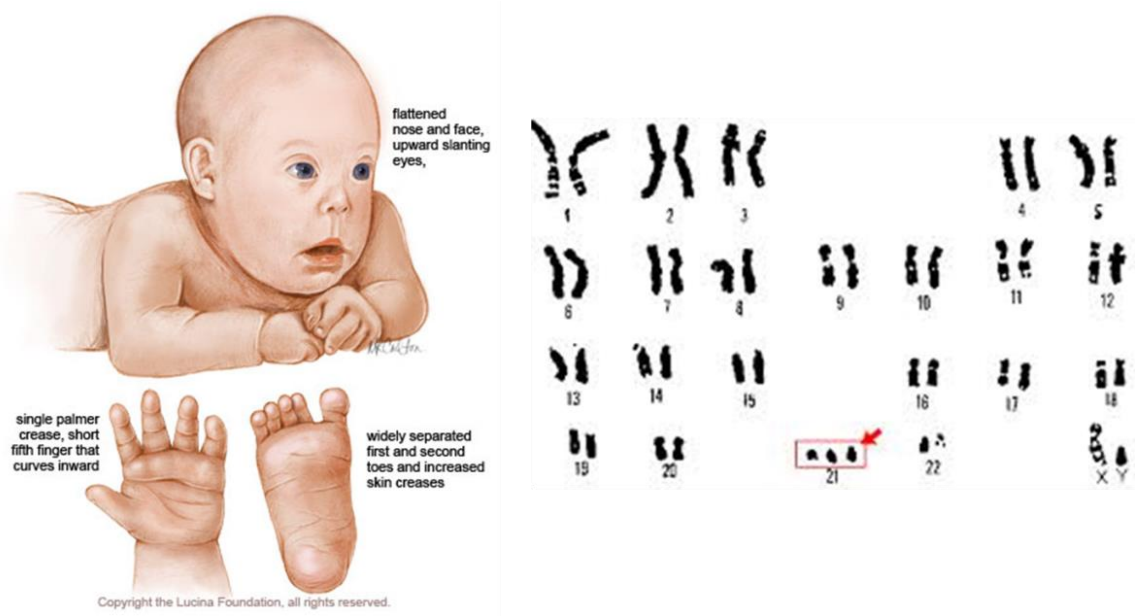


Fig. 3.2: The karyotype and traits of a Down's Syndrome individual.

Case study 2: Turner's Syndrome (45, X), Monosomy X **(FYI only)**

- An individual with Turner's Syndrome has only one X chromosome (Fig. 3.3) in each cell.
- Turner's Syndrome affects growth and sexual development.
- Females with this disorder are shorter than normal, and may fail to start puberty when they should. This is because the ovaries (which produce eggs, as well as the sex hormones estrogen and progesterone) fail to develop properly.

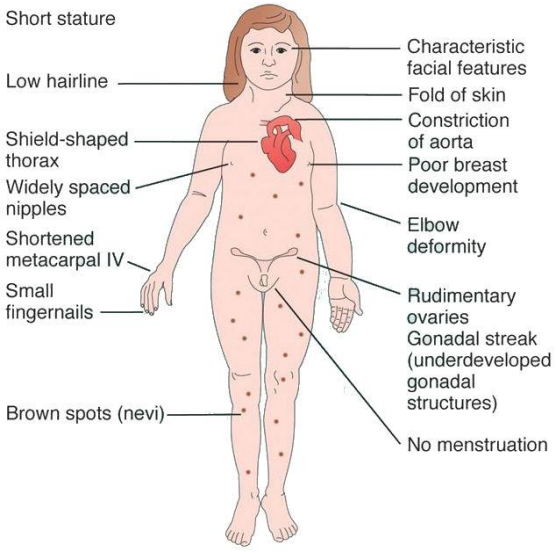


Fig. 3.3: A female with Turner's Syndrome has only one X chromosome.

Case study 3: Klinefelter Syndrome (47, XXY), Trisomy **(FYI only)**

- A male with Klinefelter Syndrome has one extra X chromosome (Fig. 3.4).
- Many males with this disorder have no idea they have it until they hit puberty or try to have children.
- At puberty, men with this syndrome often develop more breast tissue than normal, have a less muscular body, and grow very little facial or body hair.
- When men with Klinefelter syndrome try to have children, most discover that they are sterile because they cannot produce sperm. Learning disabilities (not categorised as mental retardation) are also a common problem for them.

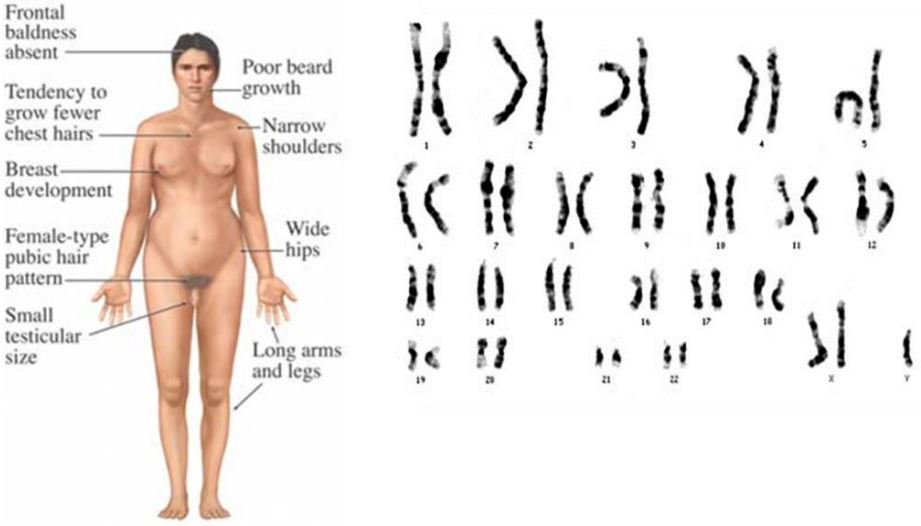


Fig. 3.4: A male with Klinefelter Syndrome has one extra X chromosome.

Case study 4: Patau Syndrome (47, +13), Trisomy 13 **(FYI only)**

- An infant with Patau Syndrome has one extra chromosome 13 (Fig. 3.5).
- Affected infants are not mentally alert, are thought to be deaf, and characteristically having a harelip and cleft palate. Most organs malfunction, and the average survival of these infants is about 3 months.

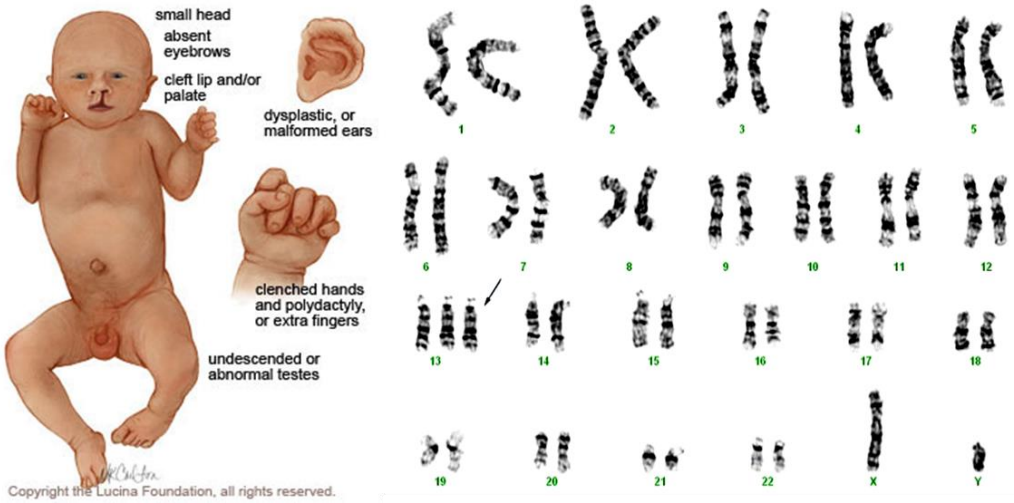


Fig. 3.5: A male infant with Patau Syndrome.

3.1.2 Polyploidy

- **Polyploidy** is the condition whereby an organism has **more than two complete chromosome sets**, i.e. 3n, 4n, 5n, etc.

- Polyploidy is due to:

  (1) The **failure of cytokinesis** to occur.

  (2) The **failure of spindle fibre formation** and the nuclear membrane reforms around the unseparated chromatids (in mitosis or meiosis II) or the unseparated chromosomes (in meiosis I).

  (3) Rarely, but possible, disjunction, where all chromosomes are pulled towards one pole.

- Gametes and somatic cells containing multiples of haploid number of chromosomes are called **polyploid** cells.

- Some organisms may have **3 sets of chromosomes (triploidy)** or **4 sets of chromosomes (tetraploidy)**. This situation is common in the plant kingdom (Fig. 3.6a) but is extremely rare in animals (triploid carps and the tetraploid Plains Viscacha rat).

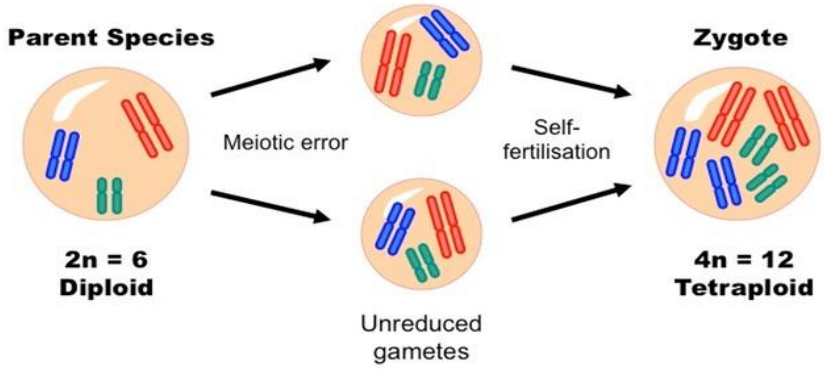


Fig. 3.6a: In plants, tetraploid individuals may arise when unreduced gametes fuse with each other.

- **Allopolyploidy** occurs when a polyploidy individual has sets of chromosomes derived from **different species** (Fig. 3.6b). E.g. A horse and a donkey can mate to produce a mule, which exhibits allopolyploidy.

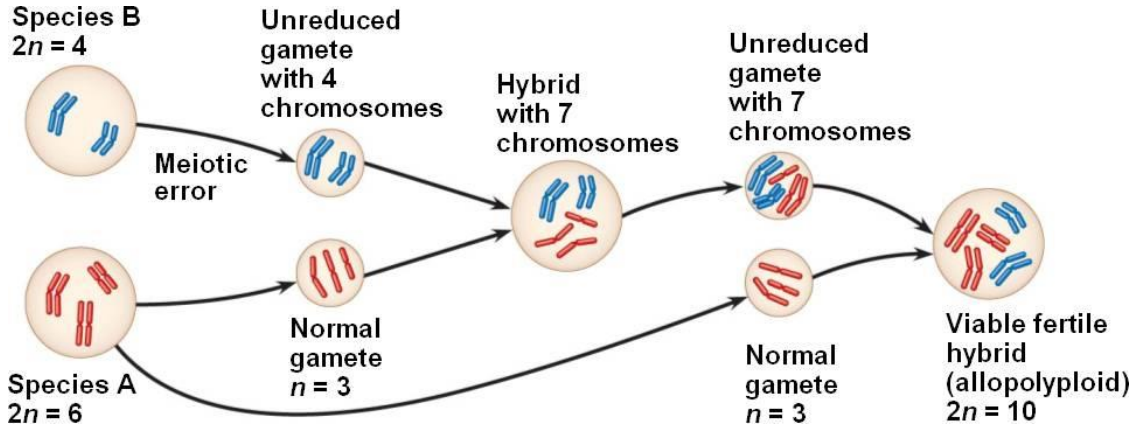


Fig. 3.6b: How allopolyploidy arises.

3.2 Chromosomal Aberrations (Structural)

- Alterations to chromosomal structure are caused by **breakage of a chromosome** and can lead to one of the four types of aberrations: **deletion**, **duplication**, **inversion** and **translocation**.

- Such mutations may result in genetic disorders.

3.2.1 Deletion

- Involves the **loss of a region of a chromosome**, either from the ends or internally. This may result in the loss of certain genes (Fig. 3.7).

- Deletion can affect one of the homologous pair of chromosomes, and in such cases, the allele present on the non-deficient chromosome will be expressed even if recessive.

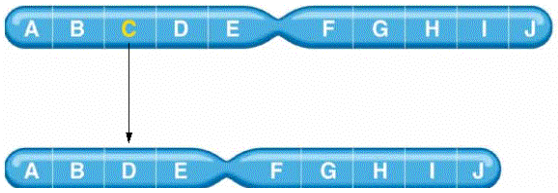


Fig. 3.7: Chromosomal deletion leads to a loss of genes.

Case study: Cri-du-chat Syndrome – deletion at Chromosome 5 (FYI only)

- An individual with Cri-du-chat syndrome has part of the genes from the p-arm of chromosome 5 deleted (Fig. 3.8).

- "Cri-du-chat" is a French word for "cry of the cat". The affected infant's cry sounds like that of a cat due to defects of the larynx and the nervous system.

Fig. 3.8: The karyotype of an individual with Cri-du-chat Syndrome. The arrow indicates the chromosome where a region was deleted.

3.2.2 Duplication

- Duplication occurs when additional set(s) of genes **replicate** (Fig. 3.9).
- The additional region of genes may be incorporated within the chromosome or at one end of the chromosome, or become attached to another chromosome.
- Duplication may affect phenotype by altering gene dosage. For example, the amount of proteins synthesised is often proportional to the number of gene copies present, hence extra genes can lead to excess proteins. As most embryonic developmental processes are heavily dependent on carefully balanced levels of proteins, duplications resulting in extra gene copies can lead to developmental defects.

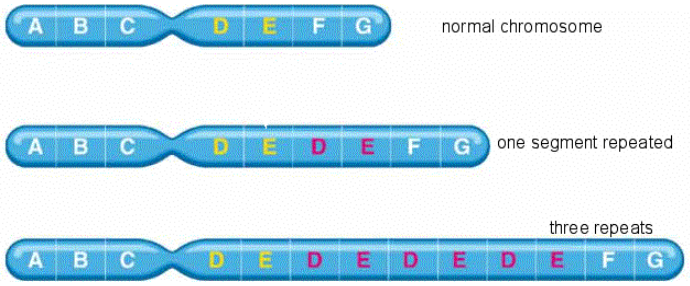


Fig. 3.9: Chromosomal duplication can occur a few times, resulting in multiple copies of the gene(s).

Case study: *Drosophila* Bar eye mutation (FYI only)

- The Bar phenotype in *Drosophila melanogaster* results from an X-linked duplication (Fig. 3.10).
- In (a) Wild-type fruit flies have normal-size eyes. In (b) Flies heterozygous and (c) homozygous for the Bar mutation have smaller, bar-shaped eyes.
- In (d) Flies with three copies of the duplication have much smaller bar-shaped eyes.

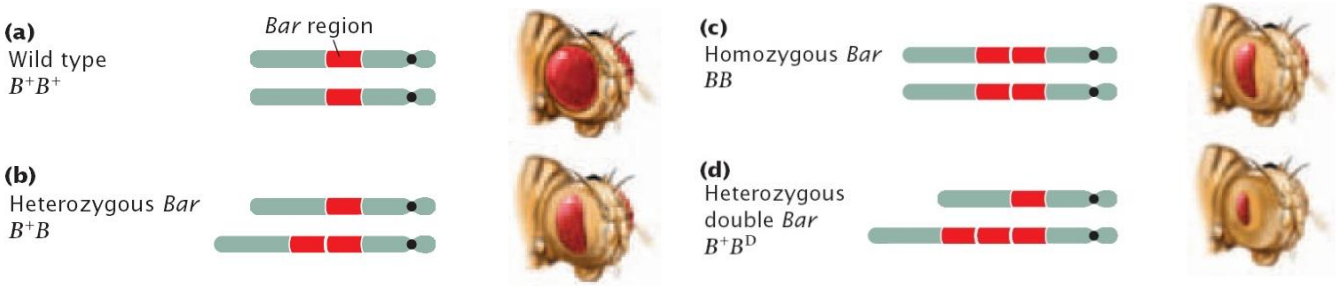


Fig. 3.10: The Bar phenotype in *Drosophila melanogaster* is the result of X-linked duplication.

3.2.3 Inversion

- Occurs when a region of the chromosome **breaks off** and **rotates through 180°** before **rejoining** back the chromosome (Fig. 3.11).
- Does not involve a loss of genetic information, but simply rearranges the linear gene sequence.
- If the expression of the gene is altered as a result of its relocation, a change in phenotype may result.

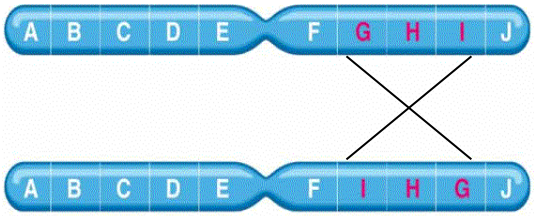


Fig. 3.11: Chromosomal inversion changes the sequence of genes.

Case Study: Eye colour in *Drosophila* (FYI only)

- Wild-type flies with a normal *white* gene have red eyes. If the *white* gene is inactivated by a mutation, the eyes become white (hence the name of the gene).
- In flies with a chromosomal inversion that moves the *white* gene near a heterochromatic (transcriptionally inactive) region (Fig. 3.12), the eyes are mottled, with red and white patches. The white patches represent cells where the *white* gene is silenced and red patches represent cells that express the *white* gene.
- The difference is thought to arise from variations in how far along the chromosome the heterochromatin spreads early in eye development. Once established, the state of *white* expression is heritable, producing patches of many cells that express *white* as well as patches of cells where *white* is silenced.

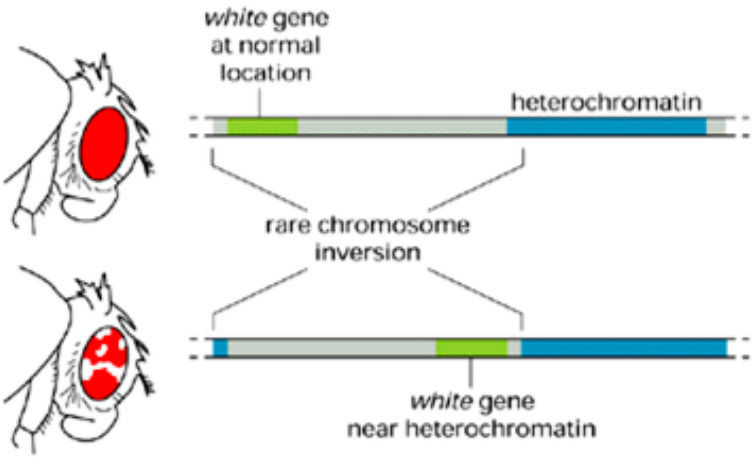


Fig. 3.12: Example of chromosomal mutation in *Drosophila*.

3.2.4 Translocation

- **Non-reciprocal translocation** occurs when a segment of chromosome **breaks** and **rejoins** either to the other end of the **same chromosome** (Fig. 3.13a) or **another non-homologous chromosome** (Fig. 3.13b).

- **Reciprocal translocation** occurs when **two non-homologous chromosomes break** and **exchange fragments** (Fig. 3.13c).

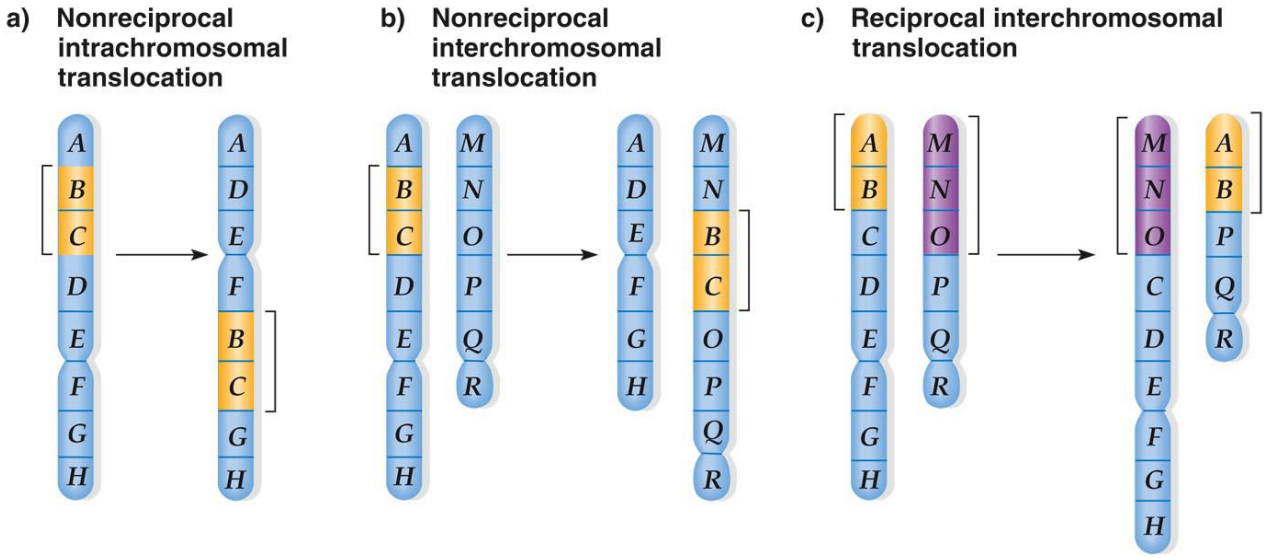


Fig. 3.13: (a) Non-reciprocal translocation within the same chromosome. (b) Non-reciprocal translocation to another chromosome. (c) Reciprocal translocation.

- This is similar to inversion in that it does not involve a loss of genetic information, but there is a rearrangement of existing genes.

- If the expression of the gene is altered as a result of its relocation, a change in phenotype may result.

Case study: Chronic Myelogenous Leukemia (FYI only)

- In CML, there is an exchange of gene segments between chromosome 9 and 22 (Fig. 3.14). CML patients are characterised by unregulated growth of white blood cells, leading to unusually high number of such cells in the bone marrow and blood.

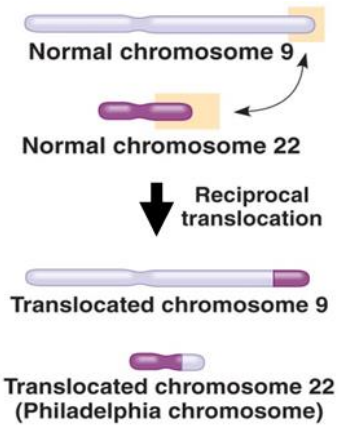


Fig. 3.14: Example of chromosomal translocation (CML).

3.2.5 Summary of Chromosomal Aberrations (Structure)

- Deletion and translocation are especially likely to occur together during meiosis, resulting in one chromosome with a deleted segment and the other gaining the segment.

- Possible consequences of the above four types of chromosomal aberrations include:

  (1) A diploid embryo that has a large deletion in its chromosome structure would have lost a number of essential genes; this condition is normally lethal.

  (2) In animals/humans, inversion, duplication and translocation tend to have harmful effects, which may lead to tumour growth (*refer to section 4*).

- Previously distant genes (i.e. Gene A and Gene B located at different locus on the same chromosome or located at different chromosomes) may now fuse with each other to produce a new gene (Fusion Gene A-B), which will alter the phenotype by either producing a new protein or a change in gene expression.

4. The Development of Cancer as a Result of Mutations

4.1 Introduction to Cancer

- Cancer is a set of diseases in which **cells *escape* from normal regulation of cell division**, resulting in **uncontrolled cell division**.

- Characteristics of Cancer Cells

  1) They exhibit excessive, **uncontrolled cell division**

  2) They do not undergo **apoptosis** (programmed cell death when damages occur to its DNA)

  3) They **remain undifferentiated**

  4) They stimulate growth of blood vessels towards themselves (**angiogenesis**)

  5) They **do not exhibit contact inhibition**

  6) They spread to other parts of the body via circulatory system to form secondary tumours (**metastasis**)

Normal Cell	Cancer cell
Require external growth factors to divide. Behave as part of a tissue.	**Divide independently** of growth factors. Does not behave as part of a tissue
Show contact inhibition, stop dividing when in contact with other cells (e.g. gap of wound is filled)	**Lost this ability**, hence form large mass of cells called tumour
Ages and die. Replaced by new cells in an orderly way. Divide limited times due to lack of telomerase. Apoptosis occur	**Immortal**. Cancerous cells may divide indefinitely as telomerase is activated No apoptosis

Table 1: Differences between a normal cell and cancer cell.

4.2 Control of Eukaryotic Cell Cycle

- In **normal** eukaryotic cell cycle, cells divide when required for growth and for replacement in a **controlled way**.

- The cell cycle is regulated by a molecular control system involving a set of **signalling molecules** in cell that **coordinates the cell cycle**.

- These molecules (e.g. proteins) regulate the cell cycle at various **checkpoints** to ensure normal cell cycle (Fig. 4.1).

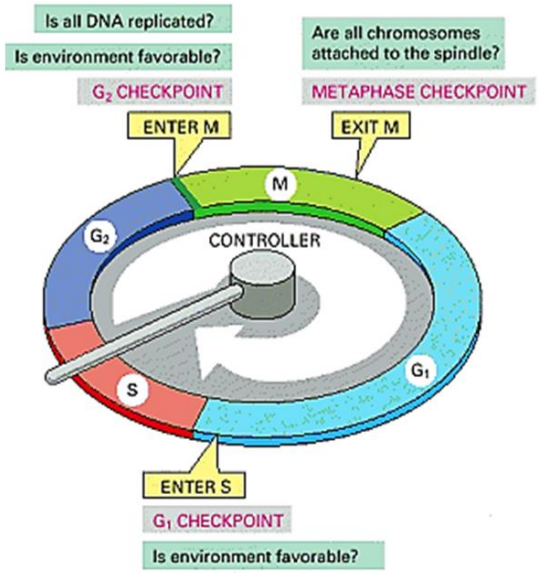


Fig. 4.1: Checkpoints in the regulation of cell cycle

- To minimise mistakes in cell cycle events, the cell cycle progress is monitored at 3 key checkpoints:
  - G_1 checkpoint
  - G_2 checkpoint
  - M phase checkpoint

- Control mechanisms that operate at these checkpoints ensure that damaged DNA is repaired before proceeding to next stage and that each stage of the cell cycle is completed before the following stage is initiated.

- There are two types of genes are involved in the **normal regulation of cell division** at the various checkpoints:

  (1) **Proto-oncogenes** are **normal genes** that code for **proteins** that **stimulate normal cell growth** and **division** (likened to the accelerator of a car).

  (2) **Tumour suppressor genes** play a critical role in regulating when cells are allowed to divide and increase in number. They are **normal genes** that code for **proteins** that **prevent uncontrolled cell division** (likened to be the brakes of a car). E.g. the p53 protein, a tumour suppressor protein, halts the cell cycle by arresting cells with damaged DNA at the G_1 phase.

4.3 The Role of Mutations in the Development of Cancer

- Cancer cells can arise from:
    - **Mutations** in **proto-oncogenes** and **tumour-suppressor genes**;
    - **Activation** of the **telomerase gene** (*details in Topic 8*). This removes a natural limit on the number of times the cell can divide.

- Mutations in proto-oncogenes and tumour-suppressor genes can cause cell to bypass cell cycle checkpoints. This will cause **dysregulation of cell cycle checkpoints**, resulting in cells dividing uncontrollably. Further **accumulation of mutations in this cell** results in formation of cancer cell.

- A cell is **most susceptible to mutations** when it is **replicating its DNA** during the **S phase** of the cell cycle. High rate of mitosis increases the number of times cells replicate, hence increasing the likelihood of mutation.

4.4 Gain-of-Function Mutations in Proto-oncogenes

- **Gain-of-function mutations** lead to the production of
  (1) **Excessive amount** of proteins due to **increased transcription** that eventually leads to increase in translation (protein synthesis).
  (2) **Hyperactive** proteins due to changes to the 3D conformation of the protein that confer abnormally high activity.

- When a proto-oncogene undergoes a genetic change that leads to an **increase** either in the **amount** of the proto-oncogene's protein product or in the **activity** of each protein molecule, there is **over-stimulation of the cell cycle** / **uncontrolled cell division** that leads to **cancer.**

- The **proto-oncogene** is said to have **mutated to become an oncogene.**

- This type of mutation is known as **gain-of-function mutation** as the mutated allele is more active than the normal allele. (Fig. 4.2).

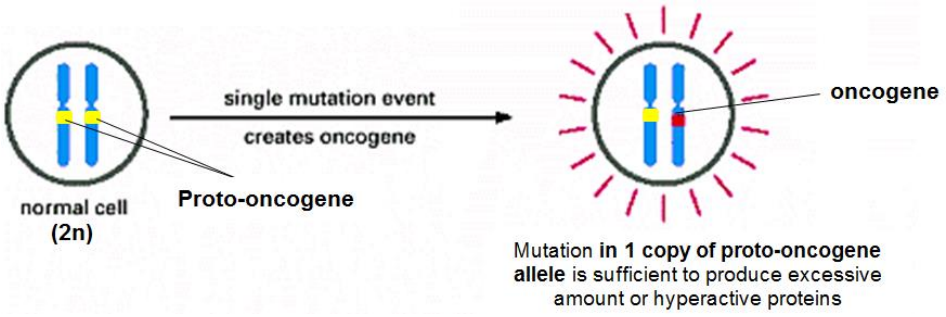


Fig. 4.2: Gain-of-function mutation in proto-oncogene produces oncogene which stimulates the cell to undergo excessive cell division.

- Most oncogenes are **dominant alleles.**

- Mutation in just **one of the two** proto-oncogene alleles would be sufficient in producing excess proteins or hyperactive protein to induce cancer.

- The genetic changes that convert a proto-oncogene to an oncogene falls into three main categories:

1. **Point mutations in the proto-oncogene itself OR a control element** (Fig. 4.3).

    - A point mutation in the proto-oncogene results in a **hyperactive protein** than the normal protein (Fig. 4.3a) due to changes in its 3D conformation. Example: point mutation of *Ras* gene in colorectal cancer.

    - A point mutation occurs in the **promoter** or **enhancer** (details in Topic 8) that controls a proto-oncogene. This makes the altered promoter or enhancer **binds to transcription factors more strongly**, leading to an increase in expression of the proto-oncogene (Fig. 4.3b).

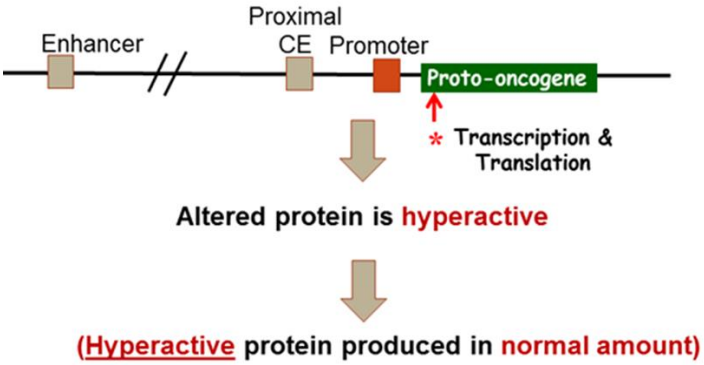


Fig. 4.3a: A point mutation in a proto-oncogene results in the production of a hyperactive protein.

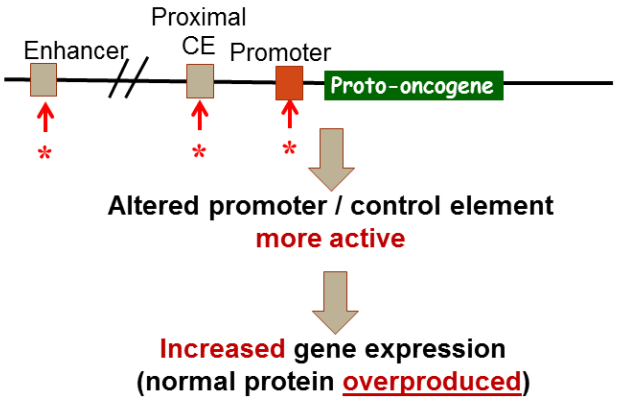


Fig. 4.3b: A point mutation in the promoter of a proto-oncogene results in the production of more proteins.

2. **Amplification of a proto-oncogene**

   - **Increase the number of copies of the proto-oncogene** in the cell through **repeated gene duplication** leads to **excessive amount of the encoded protein** in the cell (Fig. 4.4).

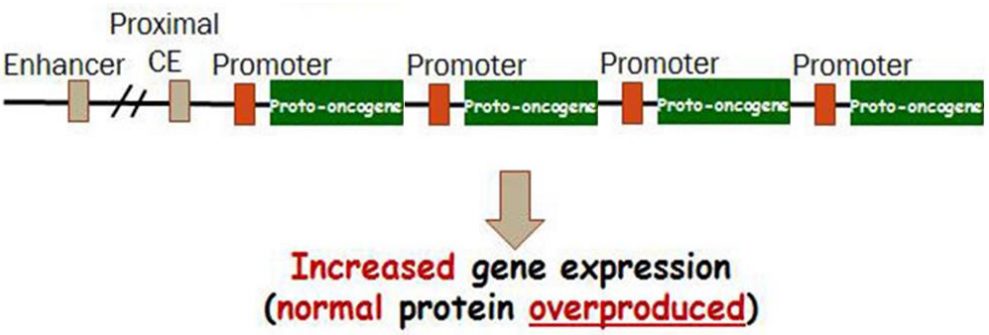


Fig. 4.4: Amplification of a proto-oncogene results in the production of more proteins.

3. **Chromosomal translocation within the genome**

   - Translocation involves a region of a chromosome breaking off and re-joining either to the same chromosome or another non-homologous chromosome (Fig. 4.5).

   - A proto-oncogene may be **translocated** downstream of an **active promoter** or other **control elements,** resulting in **increased rate of transcription and translation of the protein that stimulates cell division**.

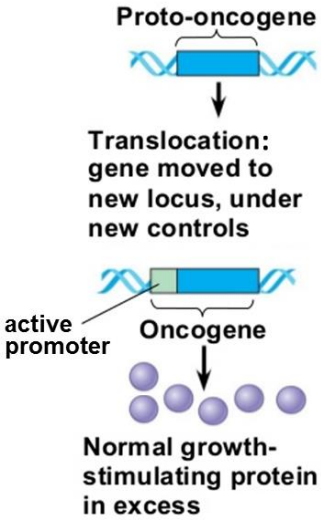


Fig. 4.5: Chromosomal translocation of an active promoter results in an increased rate of protein synthesis.

- Note that for amplification of proto-oncogene and chromosomal translocation of proto-oncogene downstream of an active promoter, the resulted oncogene protein structure is identical to the normal proto-oncogene protein (i.e. the protein is not hyperactive). The oncogenic effect is due to the **excessive amount of protein produced**.

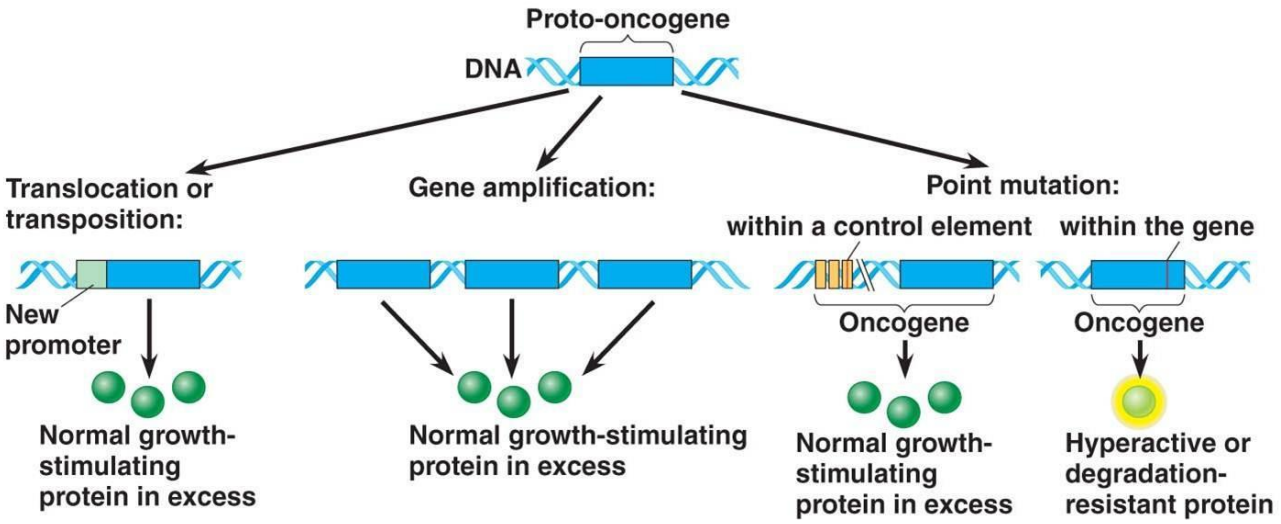


Fig. 4.6: Summary of mutations to proto-oncogene.

Example of proto-oncogene: *Ras* gene

- The **Ras protein** is a component of a signal-transduction pathway (*details in Topic 12: Communication and Equilibrium in Multicellular Organisms*) which eventually activates a protein that stimulates cell cycle to promote growth in the organism.

  Signal Transduction Pathway: A series of chemical reactions in the cell that convey signals from the external environment of the cell to the DNA in the nucleus.

- Ras protein is a G-protein that relays a growth signal from a growth factor receptor to a cascade of protein kinases.

- At the end of the pathway is the synthesis of a protein that **stimulates the cell cycle** (Fig. 4.7).

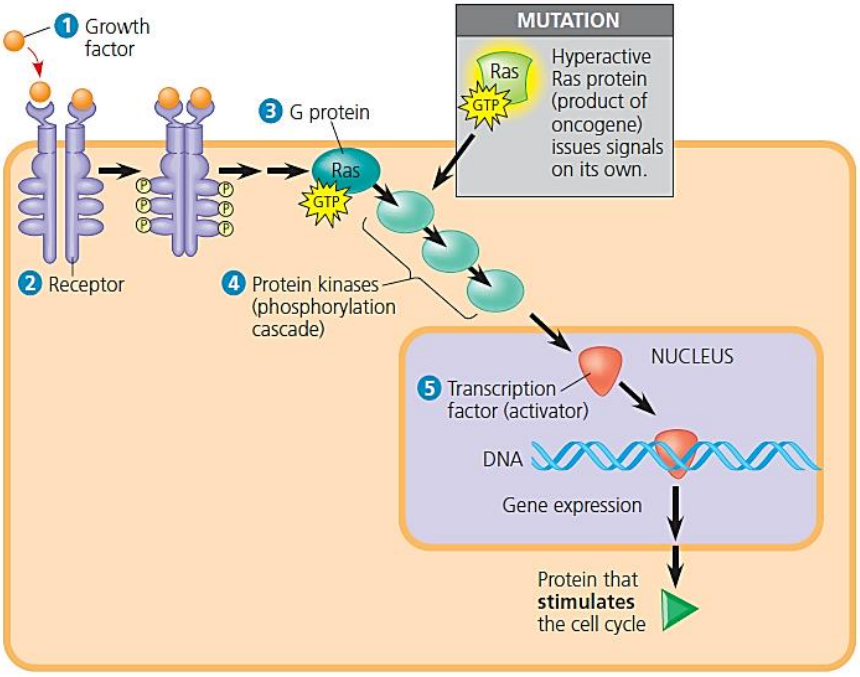


Fig. 4.7: Cell cycle-stimulating pathway – The signal transduction pathway relays the signal from the growth factor from outside the cell to the DNA in the nucleus to start transcription.

- **Cell cycle-stimulating pathway** (Fig. 4.7):

  1, 2 A growth factor (a type of hormone) binds to its receptor (tyrosine-kinase receptor) and activates the receptor.
  3 The signal is relayed to the *Ras* protein, which is then activated by the binding of GTP.
  4 The activated *Ras* protein passes the signal to a series of protein kinases.
  5 The last protein kinase activates a transcription factor (an activator) that initiates transcription of one or more genes that code for proteins that stimulate the cell cycle.

  Outcomes: Increased rate of mitosis and cell division occurs at the faster rate.

- However, if the *ras* gene is mutated, the oncogene produces a **hyperactive** *Ras* protein.

- The hyperactive *Ras* protein is able to activate protein kinase **even in the absence** of the **growth factor**. Hence, **genes that stimulate the cell cycle** are **transcribed continuously**, leading to uncontrolled cell division.

- Note: the activation of proteins occurs via **phosphorylation**. Kinases are enzymes that add phosphate groups to other proteins.

An example of mutation in the Ras proto-oncogene (details are not required):

- A common mutation to *Ras* proto-oncogene causes **substitution of glycine at position 12** to another amino acid. This **alters the three-dimensional structure** of the *Ras* protein (Fig. 4.8).

- This **point mutation** leads to a **hyperactive Ras protein** which can send signals on its own (i.e. constitutively active), resulting in **excessive cell division** (Fig. 4.7).

- This effect is **dominant** – The **gain-of-function mutation** in just **one of the two alleles** at the locus of the *Ras* gene is sufficient in producing a hyperactive *Ras* protein which resulted in uncontrolled cell division.

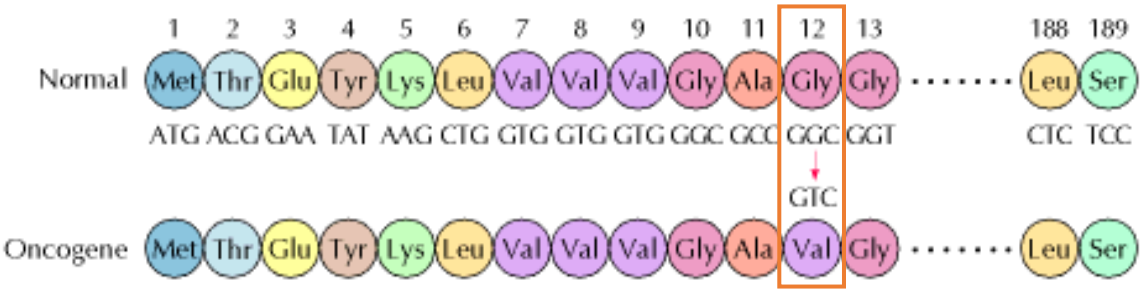


Fig. 4.8: Point mutation of *Ras* proto-oncogene converts it into an oncogene.

Case study: Burkitt's Lymphoma (FYI only)

- Burkitt's lymphoma is cancer of B lymphocytes in the lymphatic system.
- Normal B lymphocytes make antibodies (proteins).
- The genes for producing the antibodies are located on chromosome 14.
- In Burkitt's lymphoma, the **proto-oncogene *c-myc*** on chromosome 8 is translocated to a location to chromosome 14 (Fig. 4.9), near an enhancer that normally drives the expression of antibodies in B cells.
- This resulted in **overproduction of c-Myc protein**.
- c-Myc protein is a transcription factor (activator) that stimulates the expression of genes required for mitosis in mammalian cells.
- As a result, there is excessive cell division of the mutated B cells, resulting in a clone of cancer cells, Burkitt's lymphoma.

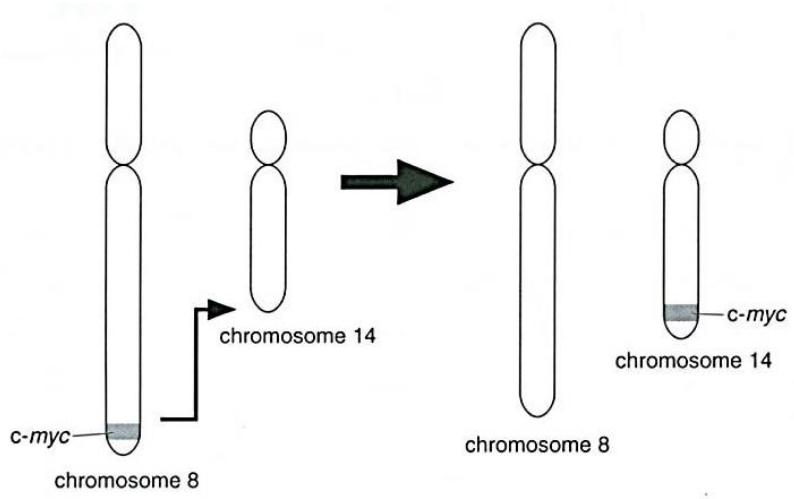


Fig. 4.9: Chromosomal translocation in Burkitt's lymphoma *(adapted from A Level Paper 2011)*

4.5 Loss of Function Mutations in the Tumour Suppressor Genes

- **Loss-of-function mutations** lead to the production of
  (1) **Reduced amount** of proteins due to **decreased transcription** that eventually leads to decrease in translation (protein synthesis).
  (2) Proteins with **reduced activity or non-functional** due to changes to the 3D conformation of the protein that abolish function.

- Tumour suppressor genes function to **inhibit uncontrolled cell division**. Hence a loss-of-function mutation of a tumour suppressor gene results in **loss in ability to inhibit uncontrolled cell division.** This leads to **uncontrolled cell division.**

- Tumour suppressor proteins include those that

  1. **detect DNA damage at the checkpoints and halt the cell cycle** to allow time for DNA repair.
  2. **repair damaged DNA** and prevent the cell from accumulating cancer-causing mutations.
  3. **control the adhesion of cells to each other or the extracellular matrix**. (adhesion of cells is present in normal cells but not cancerous cells)
  4. are **receptors for hormones** (e.g. tumour-derived growth factor) that function to **inhibit cell proliferation.**
  5. **activate apoptosis**, that is, stimulate cell to undergo programme cell death when damaged DNA cannot be repaired. This will prevent cells with DNA damage to continue to divide and **pass on the defects** to daughter cells. Hence, prevent **accumulation of additional mutations** that will lead to the formation of a tumour.

- **Normal** tumour suppressor genes are **dominant alleles** while **mutated** tumour suppressor genes are **recessive alleles.** In a heterozygote,

  - **the single normal copy** of the tumour suppressor gene is sufficient to synthesise **enough proteins** to inhibit cell proliferation.
  - the dominant normal tumour suppressor allele **masks the effect** of the **recessive mutated tumour suppressor allele**.

- Hence**,** for a cancerous cell to develop**, both alleles** of a tumour suppressor gene must be **mutated** and unable to produce the protein required to inhibit cell division (Fig. 4.10).

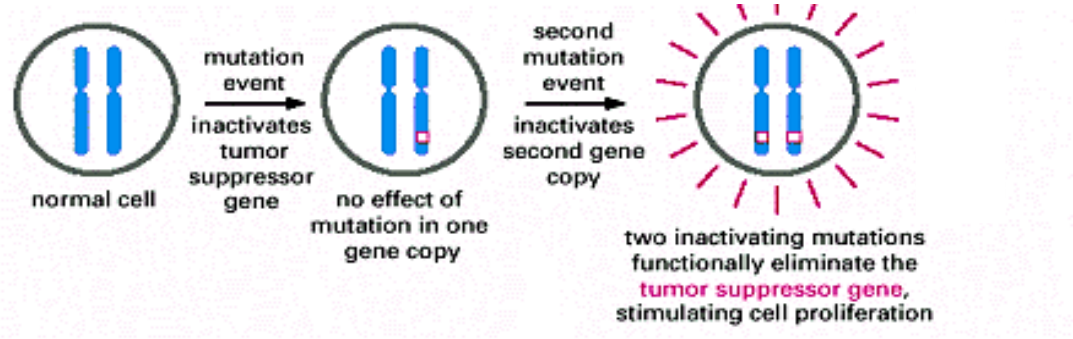


Fig. 4.10: Loss-of-function mutation in *both* copies of tumour suppressor gene on the homologous chromosomes stimulates the cell to undergo excessive cell division.

- Loss-of-function mutations in tumour suppressor genes can occur in various ways:

  1. Mutations in **promoters or control elements** lead to down-regulation (decreased expression) of tumour suppressor gene expression.

  2. Mutations within tumour suppressor gene may have one of the three following consequences:
     - **No protein produced**.
     - Production of protein that binds to its substrate with **decreased affinity**.
     - Production of a **non-functional protein** due to loss of protein structure.

  3. **Chromatin modifications** *(details in Topic 8)* can inactivate tumour suppressor genes

     - Many tumour cells expressed high level of histone deacetylase (HDAC) that **deacetylates histones** and increases the positive charge on the histone protein. This results in **DNA coiling tightly around histones**, such that the **tumour suppressor genes** are **silenced**.

     - Excessive **histone methylation** or packaging of genes as **heterochromatin** will also effectively shut down gene expression of tumour suppressor genes.

Example of tumour suppressor gene: *p53* gene

- The *p53* gene codes for the **p53 protein**. The normal p53 protein functions at crucial **cell-cycle checkpoints** (mainly **checkpoint G_1**), to stop the cell cycle when damage to DNA is detected.

- The normal p53 protein is an **activator** which initiates transcription of the following 3 types of genes:

  1. ***p21* gene**, whose protein product, **p21 protein** (a cyclin-kinase inhibitor), binds to cyclin-dependent kinases protein, and hence, **halts the cell cycle**. This allows time for the cell to repair the DNA (Fig. 4.11).

  2. **DNA repair genes**: e.g. *p53R2* gene, whose protein repairs damaged DNA.

  3. "**Suicide genes**" whose protein products cause cell death by **apoptosis** (programmed cell death) when DNA damage is irreparable.

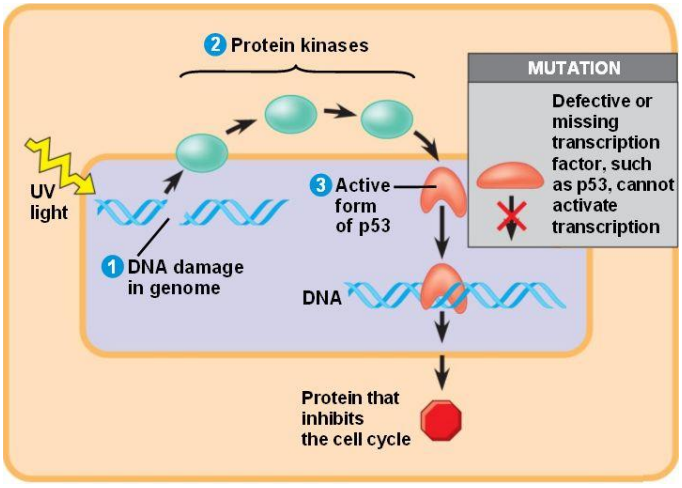


Fig. 4.11: Cell cycle inhibiting pathway: The signal transduction pathway that activates p53 protein to initiates transcription of a protein that inhibits the cell cycle

- The p53 protein itself **is also directly involved in DNA repair** by interacting with DNA polymerase in base excision repair.

- **Cell cycle inhibiting pathway** (Fig. 4.11):
  1) **DNA damage** acts as a signal that is passed via
  2) **protein kinases**.
  3) This leads to **activation of p53 protein**. Activated *p53* promotes **transcription of the gene** which codes for a **protein** eg p21 protein that **inhibits the cell cycle.** The resulting suppression of cell division ensures that the **damaged DNA is not replicated**. If the DNA damage is irreparable, the p53 signal leads to programmed cell death (apoptosis).

Case study: Retinoblastoma (FYI only)

- Retinoblastoma is a cancerous tumour of the retina that developed in early childhood.
- Caused by the **loss-of-function mutation** of the *Rb* gene (a **tumour suppressor gene**).
- Condition is marked by a deletion of a segment of DNA sequence on chromosome 13.
- A mutation on both alleles of the gene results in a cell that produces non-functional *Rb* protein.
- *Rb* protein prevents mitosis by blocking cells from entering S phase of the cell cycle.

- There are two forms of retinoblastoma (Fig. 4.12):

1. Hereditary Retinoblastoma
   - Occurs when fetus inherits one of the parents' chromosome 13 that has its *Rb* locus deleted.
   - Hence, all cells in the body lack one of the two functional copies of the *Rb* tumour suppressor gene.
   - Loss or inactivation of the remaining copy by a somatic mutation in any retinal cell removes the inhibition provided by the Rb protein and the affected cell grows into a tumour.

2. Non-hereditary Retinoblastoma
   - Both inherited *Rb* genes are normal
   - A single retinal cell must have both copies of the gene lost or inactivated by a somatic mutation (often deletion) in order to develop into a tumour.
   - Occurrence of such tumour is rare. (1 in 30,000).

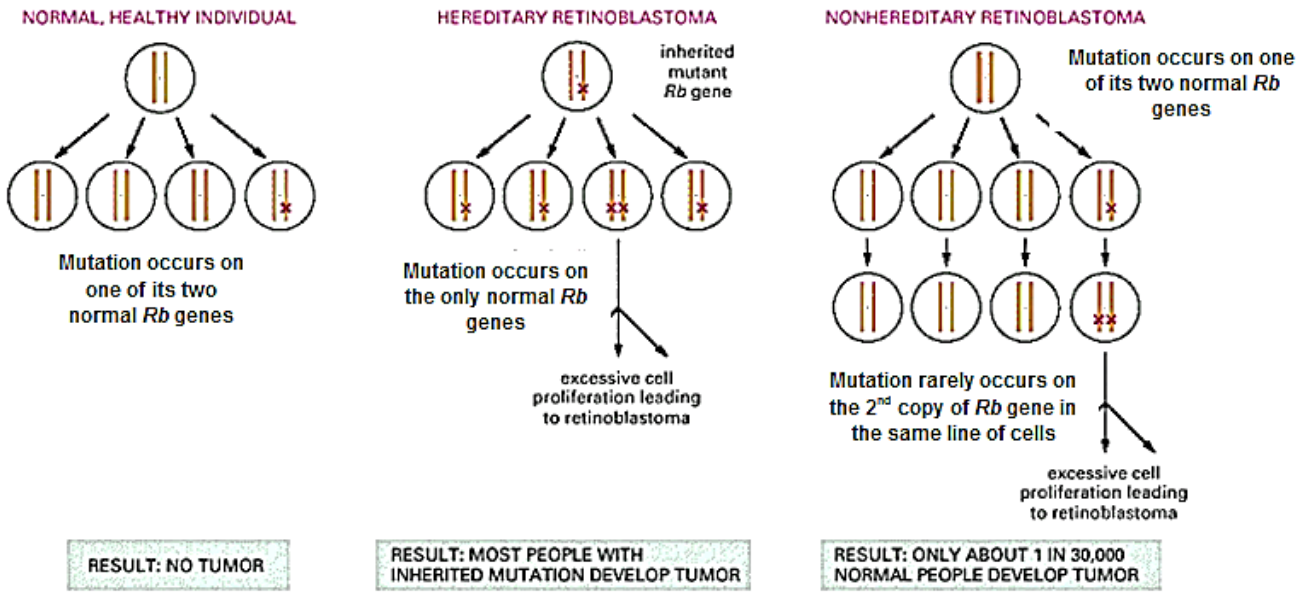


Fig. 4.12: Genetic mechanisms underlying retinoblastoma.

4.6 The Development of Cancer as a Multi-step Process

- The eventual development of cancer in an individual does not result from a single mutation in a cell. A **single cell** needs to **accumulate mutations** (Fig. 4.13) in both tumour suppressor genes and proto-oncogenes to become a cancer cell.

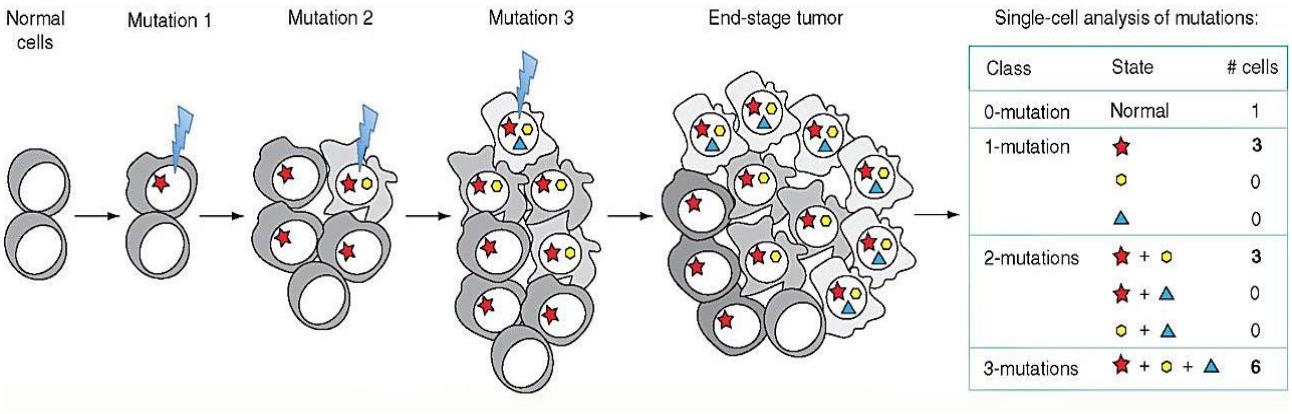


Fig. 4.13: Accumulation of mutations

- As mutation can occur throughout one's lifetime, the **chances of cancer development increases with increasing age** (Fig. 4.14).

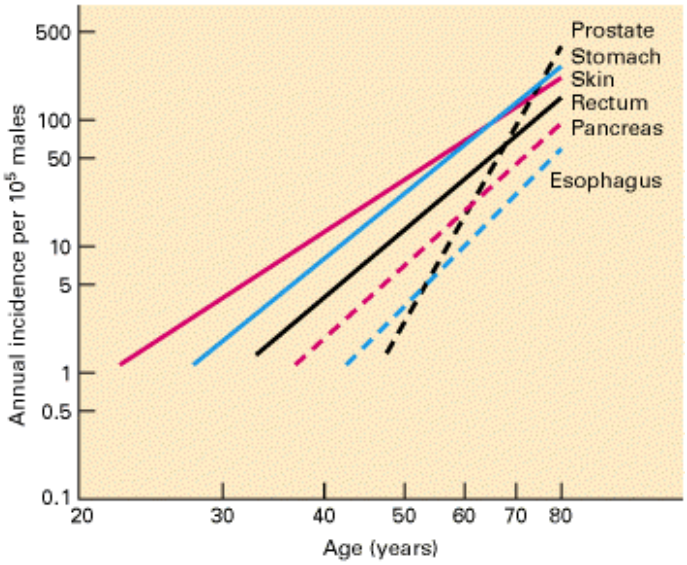


Fig. 4.14: Incidences of Cancer increase with Age

- An individual that **inherits** an oncogene or a mutant allele of a tumour-suppressor gene from their parents will be one step closer to accumulating the necessary mutations for cancer development. He is said to be **predisposed to cancer**.

Case Study: Colorectal Cancer (FYI only)

- Colorectal cancer illustrates a multi-step process of cancer development (Fig. 4.15, 4.16 and 4.17).

- The first sign is often **formation of polyps**, small benign growths in the colon lining with fast dividing cells***.***

- Through gradual **accumulation of mutations** that **activates oncogenes** (e.g. **mutant *Ras* gene**) and **knock-out tumour-suppressor genes** (e.g. ***p53* gene**), the **polyp can develop into a malignant tumour**.

- These usually include the **appearance of at least one active oncogene** and the **mutation or loss of several tumour-suppressor genes**.

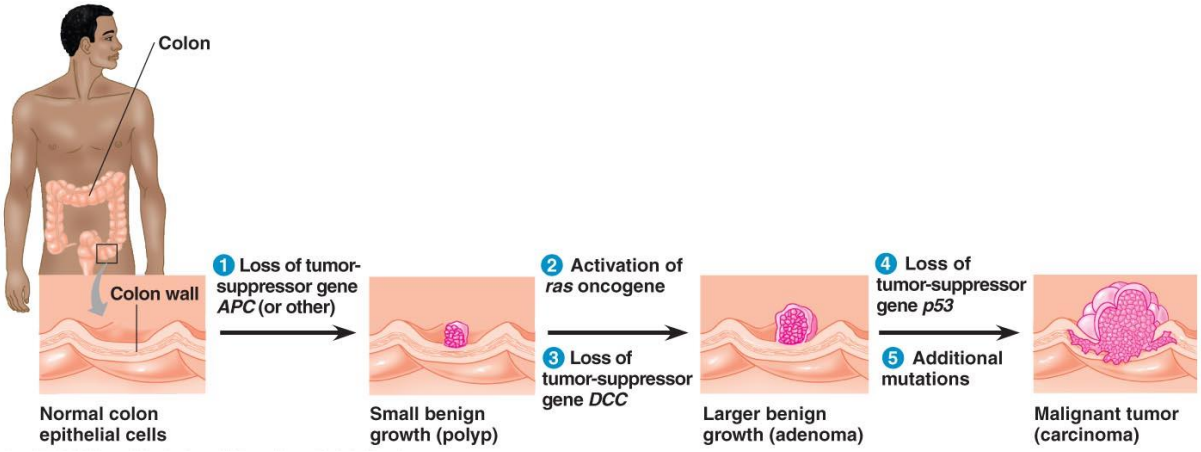


Fig 4.15: Multi-step developmental path of colorectal cancer showing an accumulation of mutations in critical genes involved in cancer development (i.e. tumour suppressor genes & oncogenes).

- Since mutant **tumour-suppressor alleles** are usually **recessive**, **mutations must occur in *both* alleles**.

- As tumour suppressor genes (e.g. *p53* gene) usually code for proteins that control the cell cycle and DNA repair, mutations in the tumour suppressor alleles would result in the cell being unable to repair damaged DNA. This will lead to **accumulation** of mutations over time.

- Most oncogenes behave as **dominant alleles**, hence the **mutation of one of two copies** of the gene would **contribute** to the development of cancer.

- As oncogenes generally result in the production of **hyperactive proteins**, such mutations would cause an increase in the rate of cell division.

- In the early phases of multi-step tumour progression, cancer cells multiply and form a **primary tumour** mass.

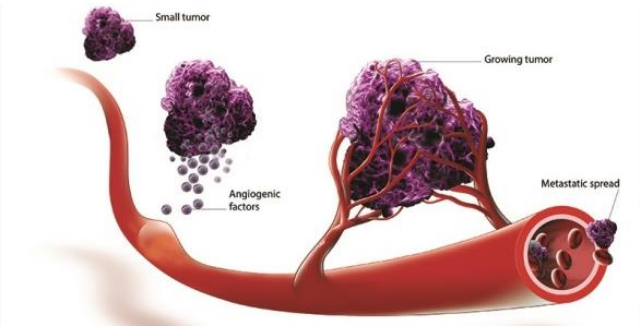


Fig 4.16: Tumours produce angiogenic factors that cause blood vessels to grow towards the tumours.

- The cancerous cells produce angiogenic factors or **growth factors** (Fig. 4.16) that cause **blood vessels** to grow towards and into the tumour. This process is known as **angiogensis**.

- Angiogensis is required before the primary tumour (a small ball of cells) can grow into a larger tumour (a large mass of cells). Angiogenesis is a pre-requisite for metastasis (Fig. 4.17).

- **Metastasis** occurs when some cancer cells dislodge from the primary tumour, penetrate the wall of the blood vessels and spread via the circulatory system to locations distant from their original site, thus forming new tumours (secondary tumours) at other body parts.

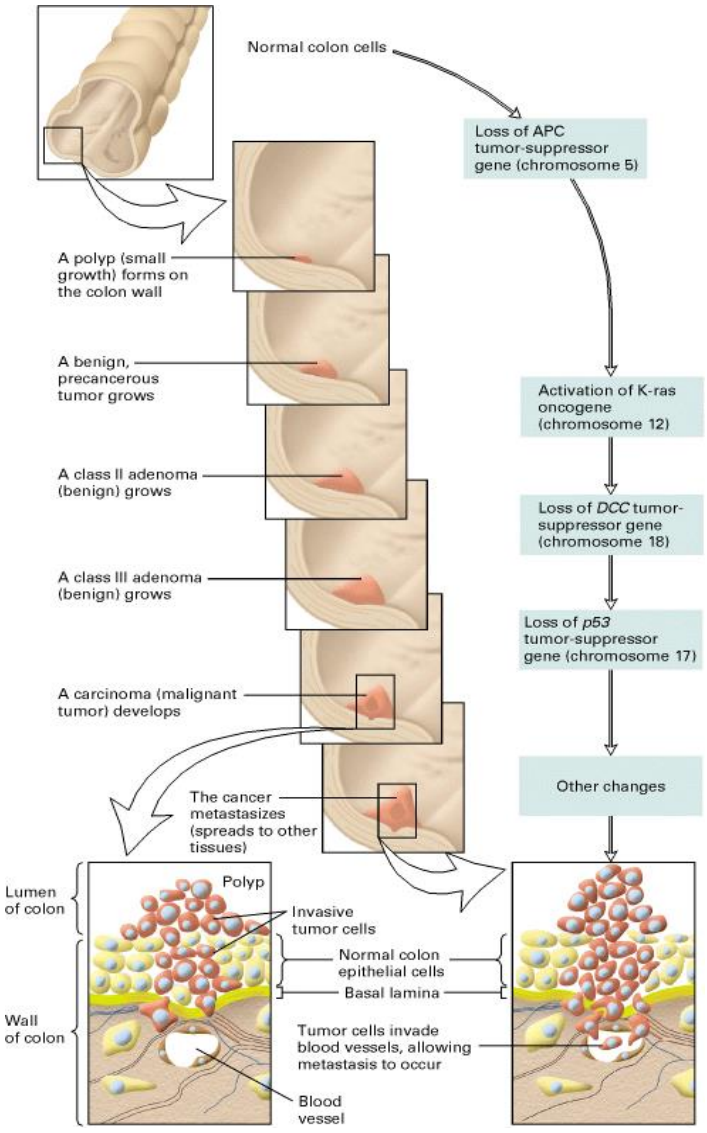


Fig. 4.17: Colorectal Cancer: A Model of the Multi-step Process.

4.7 Factors that Increase the Chances of Cancer

- Causative factors that could increase the **chances of mutations** leading to cancer include:

1. Exposure to chemical **carcinogens** (chemicals that cause cancer) e.g. ethidium bromide, benzo(a)pyrene in cigarette smoke, sodium nitrite in preserved food, etc.

2. Exposure to excessive **ionizing radiation and UV radiation.**
   - Ionizing radiation includes cosmic radiation (from outer space), radioactive fallout, radon gas, x-rays, gamma-rays, etc.
   - UV radiation from the sun.

3. Agents that cause **inflammation,** which generates **DNA-damaging oxidizing agents** in the cell.

4. Infection by certain **viruses and bacteria**
   - Hepatitis B and C are closely associated with liver cancer,
   - Human papillomavirus is associated with cervical cancer,
   - Human Immunodeficiency virus (HIV), the virus that causes AIDS. People who have HIV infection are at greater risk of cancer such as lymphoma and a rare cancer called Kaposi sarcoma.
   - Epstein barr virus is associated with Burkitt's lymphoma and nasopharyngeal carcinoma.
   - *Helicobacter pyloris*, a bacterium that causes stomach ulcers. It also can cause stomach cancer and lymphoma in the stomach lining
   - Viruses promote cancer development by
     - integrating viral DNA or viral oncogene into the DNA of infected cells ,
     - insertion of viral DNA may disrupt a tumour-suppressor gene or convert a proto-oncogene to an oncogene.

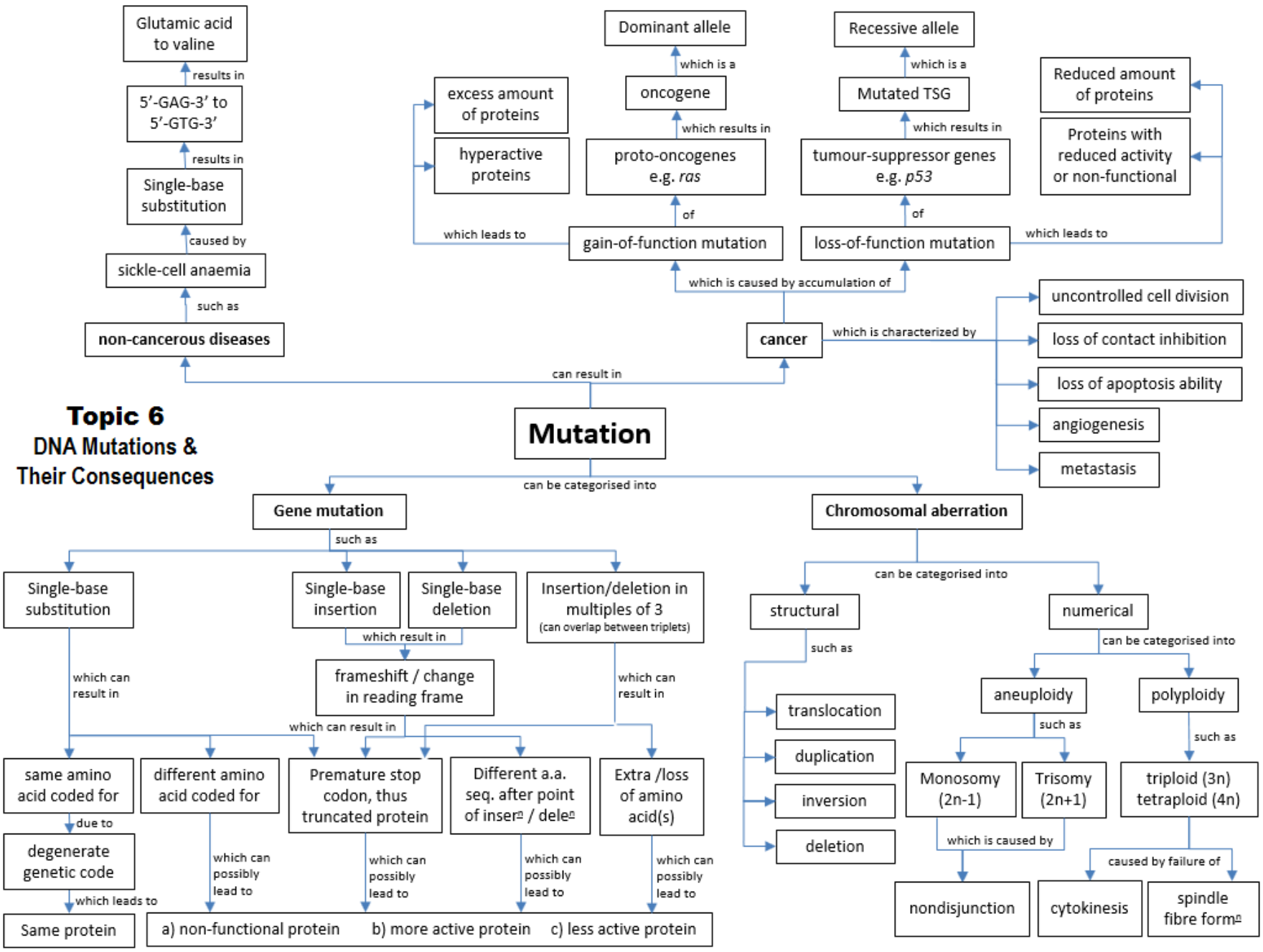
- Other factors contributing to cancer include

5. **Age**
   - **A cell** usually **needs to accumulate mutations** in both tumour suppressor genes and proto-oncogenes **to become a cancer cell**. More than one somatic mutation is generally required to produce all the changes characteristic of a full-fledged cancer cell. As cancer results from an accumulation of mutations, and if mutations occur throughout one's life, then the longer we live, the more likely we are to develop cancer.

6. **Inherited predisposition**
   - If an oncogene or a mutated tumour suppressor gene is already present in the sperm of the father or egg of the mother, this genetic damage can be passed on to their children.
   - An individual inheriting an oncogene or a mutant allele of a tumour suppressor gene is one step closer to accumulating the necessary mutations for cancer to develop than is an individual without any such mutations.

7. **Loss of immunity**
   - As immunity decreases, the likelihood of cancerous growths and metastasis increases. An experiment discovered that mice with T cell deficiency died sooner than control mice that were not immunocompromised after tumours were introduced.

☺ End of Topic 6 ☺


Topic 6
DNA Mutations & Their Consequences
Mutation
can result in
non-cancerous diseases
such as
sickle-cell anaemia
caused by
Single-base substitution
results in
5'-GAG-3' to 5'-GTG-3'
results in
Glutamic acid to valine
cancer
which is characterized by
uncontrolled cell division
loss of contact inhibition
loss of apoptosis ability
angiogenesis
metastasis
which is caused by accumulation of
gain-of-function mutation
which leads to
excess amount of proteins
hyperactive proteins
of
proto-oncogenes e.g. ras
which results in
oncogene
which is a
Dominant allele
loss-of-function mutation
which leads to
Reduced amount of proteins
Proteins with reduced activity or non-functional
of
tumour-suppressor genes e.g. p53
which results in
Mutated TSG
which is a
Recessive allele
can be categorised into
Gene mutation
such as
Single-base substitution
Single-base insertion
Single-base deletion
Insertion/deletion in multiples of 3
(can overlap between triplets)
which result in
frameshift / change in reading frame
which can result in
which can result in
same amino acid coded for
due to
degenerate genetic code
which leads to
Same protein
different amino acid coded for
Premature stop codon, thus truncated protein
Different a.a. seq. after point of inser / dele
Extra /loss of amino acid(s)
which can possibly lead to
which can possibly lead to
which can possibly lead to
which can possibly lead to
a) non-functional protein
b) more active protein
c) less active protein
Chromosomal aberration
can be categorised into
structural
such as
translocation
duplication
inversion
deletion
numerical
can be categorised into
aneuploidy
such as
Monosomy (2n-1)
Trisomy (2n+1)
which is caused by
nondisjunction
polyploidy
such as
triploid (3n) tetraploid (4n)
caused by failure of
cytokinesis
spindle fibre form