River Valley High School
2025 JC1 H2 Biology

Lecture Topic 11: DNA Mutations

Name: _____ ( ) Class: 25J____ Date: _____

References

Textbook	Author
Biology (9th Edition)	Campbell and Reece
Molecular Biology of The Cell (5th Edition)	Alberts Johnson Lewis Raff Roberts Walter
Genomes (2nd Edition)	Brown
Longman A-Level Course in Biology: Core Syllabus Volume 1	Hoh
Biology: An Australian Focus (3rd Edition)	Knox, Ladiges, Evans and Saint

H2 Biology Syllabus 9477 (2025)

Candidates should be able to use the knowledge gained in the following section(s) in new situations or to solve related problems.

Related Topics	Content
Genetics and Inheritance	Gene Expression
Biological Evolution	Natural Selection, Evolution and Biodiversity

Learning Outcomes

2D. DNA Mutations

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

b. Explain how gene mutations can result in diseases (including sickle cell anaemia).

c. Discuss the bioethics of genetic maternal screening for mutations, including trisomy–21.

Lecture Outline

I. Introduction – DNA Mutations

II. Point Mutations

- A. Types of Point Mutations
- B. Effects of Point Mutations
- C. Sickle Cell Anaemia

III. Chromosomal Aberration

- A. Structural Alteration to Chromosomes
- B. Changes in Chromosome Number
- C. Diseases

IV. Bioethical Issues of Genetic Maternal Screening

- A. Genetic Screening and Genetic Testing
- B. Maternal Genetic Screening
- C. Bioethical issues

V. Mutagenesis

Websites

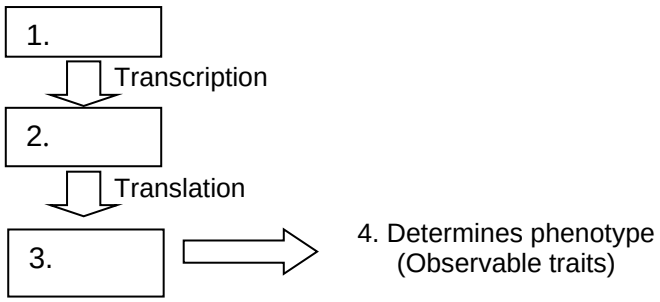
URL	Description
https://learn.concord.org/resources/779/mutations	Interactive animation to explore how changing the DNA sequence can change the amino acid sequence of a protein.
http://www.dnalc.org/resources/3d/17-sickle-cell.html	A detailed 3D animation of how a single gene mutation can affect haemoglobin and result in sickle cell disease.
https://learn.genetics.utah.edu/content/genetics/hemoglobin	Informative website detailing the sickle cell disease.
https://www.nature.com/articles/s41431-021-00970-2	Article on ethical landscapes of non-invasive prenatal testing

I. Introduction – DNA Mutations

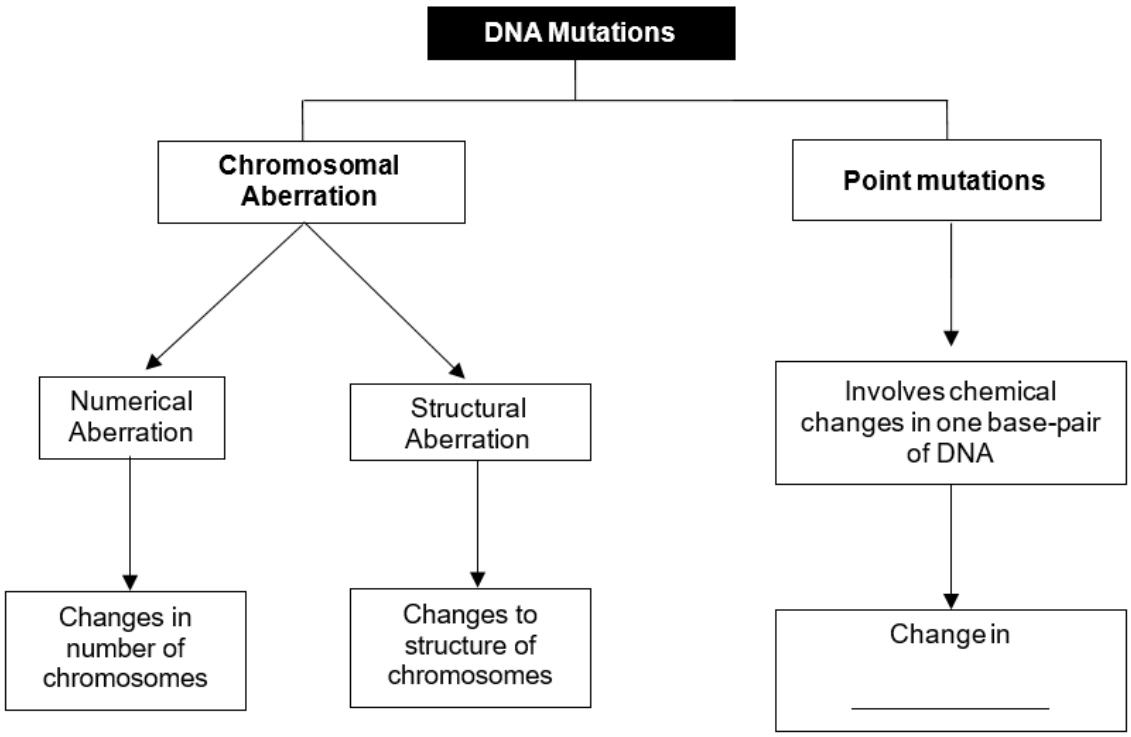
- Genetic information is stored in <u>linear sequences of base-pairs</u> in DNA. Transcription and translation convert this genetic information into polypeptides, which become functional proteins.
- These function as key intermediaries in the genetic control of **phenotype**.

Recall: Central Dogma of Molecular Biology

What is the significance of a change in DNA structure and sequence?



- A **mutation** is an inheritable change in the nucleotide base sequence of the DNA. This may result in an alteration to the organism's phenotype (i.e. characteristic).
- We can broadly classify DNA mutations into 2 categories:



- DNA mutations can have numerous biological implications:
    - Mutations to proto-oncogenes and tumour suppressor genes can contribute to the onset of cancer (*KIV: Cancer*).
    - Mutations can also create new gene variants, or novel genes, contributing to the diversity of genes observed in a population. Genetic and phenotypic diversity allow for natural selection and evolution to take place (*KIV: Biological Evolution)*

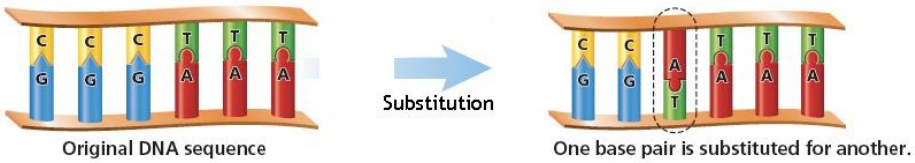
II. Point Mutations

- When a DNA mutation results in only a single base-pair of a given gene being permanently changed, it is called a **point mutation.**
- An alteration in the nucleotide sequence of a DNA will change the corresponding codon on the transcribed mRNA.
    - This may result in a change in the amino acid sequence of a polypeptide chain.
    - Which may change the 3-D conformation of a protein, resulting in a change in its structure, properties, and function.
    - As a result, the **phenotype** of the organism may be altered.

A. Types of Point Mutations

- **Base-pair Substitution**

  This involves the replacement of one base pair with other nucleotides.



- **Base-pair Addition**

  This involves the insertion of one base pair to a sequence of nucleotides. Such mutations can also be termed as base-pair insertions.

- **Base-pair Deletion**

  This involves the removal of one base pair from a sequence of nucleotides.

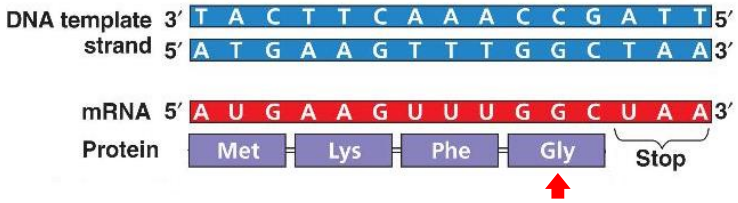
B. Effects of Point Mutations

- The effect of a point mutation on the amino acid sequence depends on the type of gene mutation, and the number of affected nucleotide sequences.
- When base-pair substitution of nucleotides is involved, it can result in the following effects:
    - **Silent Mutations**
    - **Missense Mutations**
    - **Nonsense Mutations**
- Where base-pair addition or base-pair deletion of nucleotides is involved, it can result in a **frameshift mutation.**
- Let us examine how different types of gene mutations to a given sequence of DNA can result in different effects of mutations.

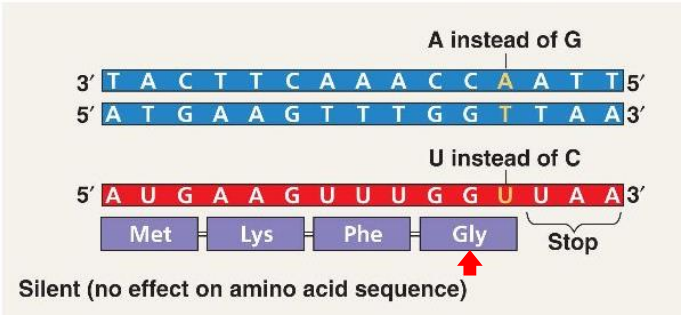
1. Silent Mutations

- A silent mutation occurs when the base-pair substitution of the nucleotide has no effect on the amino acid sequence.

Original DNA sequence



After base-pair substitution



- In the above base-pair substitution, the codon “GGC” on the original mRNA molecule becomes “GGU”. However, both codons code for glycine.
- This is due to the degenerate nature of the genetic code, where one single amino acid can be coded for by more than one codon.
- As such, there is no change to the amino acid sequence, and no change to the properties of the R groups.
- The interactions between R groups of the amino acid residue are the same, and the polypeptide chain bends and folds to produce the same, specific three-dimensional conformation.
- This results in the formation of the same protein with the same properties and function.
- The mutation is not observed at the phenotype level and therefore is described as silent.

2. Missense Mutations

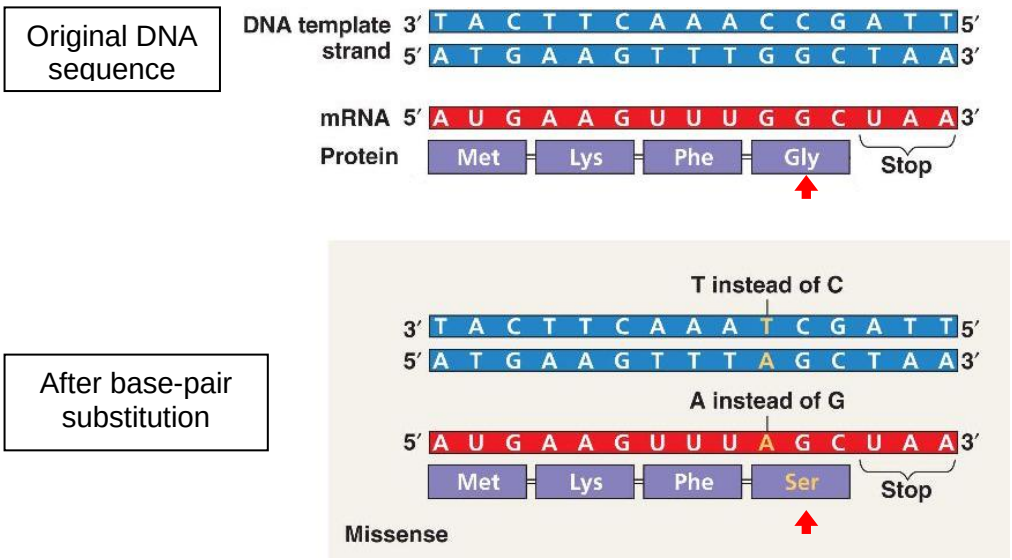
- Missense mutations occur when the **base-pair substitution** of nucleotides results in another amino acid being coded for.
- Missense mutations can result in two different outcomes.
  A. Have little effect on the final protein
  B. Cause a major change to, the final protein.

A. Little Effect on Protein

- Missense mutations can have little effect on the final protein if the new amino acid:
  - has same or similar properties to those of the amino acid it replaces,
    - E.g. Glycine to Alanine (Both are small and non-polar)
  - is in a region where the exact sequence of amino acids is not essential to the protein's function.
- The amino acid sequence is different, but the properties of the R groups are the same / similar.
  - E.g. mRNA codon is changed from "GAU" to "GAA"
  - Aspartic acid (GAU) is replaced by glutamic acid (GAA)
  - Both have negatively charged R groups, and can still form ionic bonds with another amino acid residue that has a positively charged (basic) R group.
- The interactions between R groups of the amino acid residue are the same, and the polypeptide chain bends and folds to produce a protein with the same three-dimensional conformation as the original.
- This results in the formation of a protein with the same properties and function.

B. Major Change to Protein

- Missense mutations can also cause a major change to a protein.



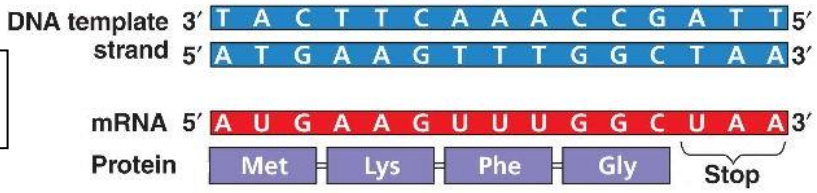
- The above base-pair substitution causes the codon "GGC" to become "AGC", which codes for serine instead of glycine.
- The new amino acid has different properties from the one it replaced.
  - Serine is polar, but glycine is non-polar.

- The interactions between R groups of amino acid residues change, and the polypeptide chain bends and folds to produce a protein with a different three-dimensional conformation from the original.
- This results in the formation of a protein with different properties and function.
- If the base-pair substitution occurs in the active site of an enzyme, it can affect the shape of the active site.
    - The enzyme active site no longer has a complementary shape to the substrate, and they cannot bind to form an enzyme-substrate complex.
- Missense mutations can thus produce a protein that is either less active or completely non-functional.

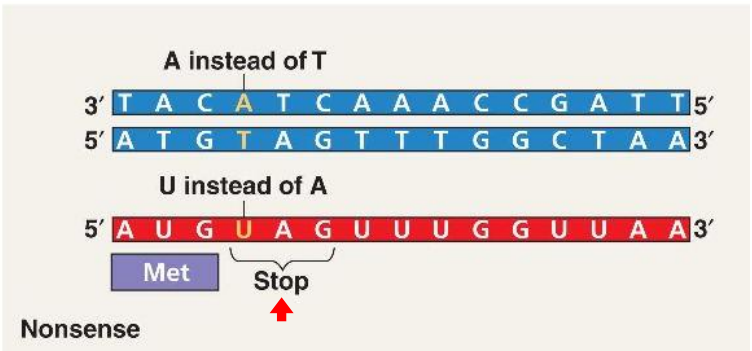
3. Nonsense Mutations

- Nonsense mutations occur when the **base-pair substitution** of nucleotides results in the production of a stop codon.

Original DNA sequence



After base-pair substitution

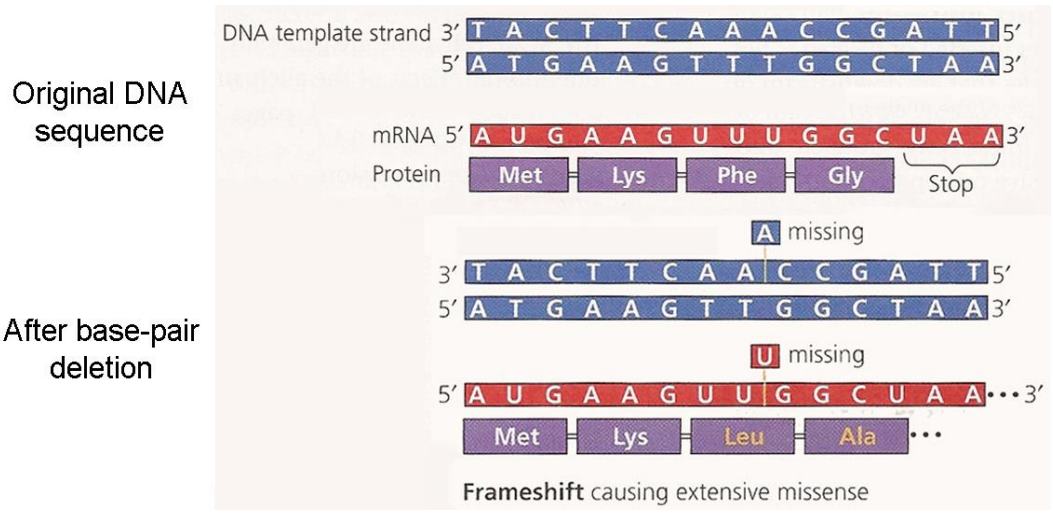


- In the example above, the base-pair substitution causes the codon “AAG” to become “UAG”, which is a stop codon.
- This causes premature termination of translation, leading to the production of a truncated polypeptide.
- The polypeptide chain cannot form the specific three-dimensional conformation of the original protein.
- This leads to the production of a non-functional protein, or no protein produced at all.

4. Frameshift Mutations

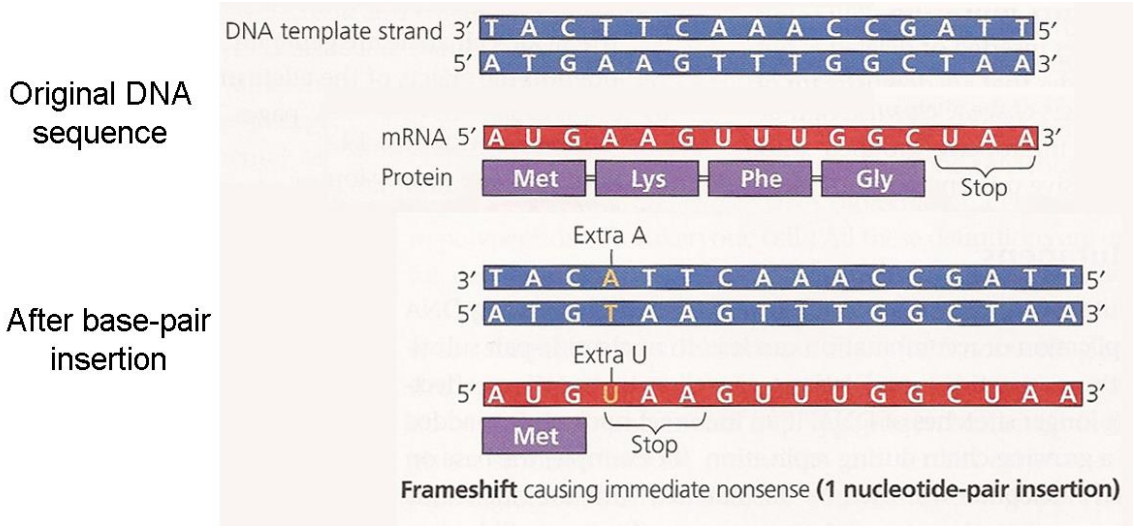
- If the **base-pair addition** or **base-pair deletion** does not occur in multiples of three nucleotides, a **frameshift mutation** can occur.
- Frameshift mutations can have severe consequences, leading to:
    - Missense mutation – Different amino acid sequence in encoded polypeptide from point of mutation resulting in a non-functional protein.
    - Nonsense mutation – Generation of stop codon leading to production of a truncated polypeptide.

Missense



- The above base-pair deletion causes the codon “UUU” to become “UUG”, coding for leucine instead of phenylalanine.
- The codons downstream of the deletion are also differently grouped, resulting in a shift in reading frame of the genetic message.
- There sequence of codons is altered, and the primary structure of the translated polypeptide will be significantly different.
- The types of interactions between R groups of amino acid residues will change drastically, resulting in differential bending and folding to form a protein that has a different three-dimensional conformation from the original.
- The protein is non-functional due to the presence of extensive missense.

Nonsense



- Frameshift mutations can also result in the generation of stop codons ("UAA", "UAG", "UGA") that lead to nonsense mutations (premature termination of the polypeptide chain), as seen above.
- The truncated polypeptide chain cannot form the specific three-dimensional conformation of the original protein. The result is a protein that is non-functional, or no protein produced at all.

Summary on Outcomes of Mutation Events

<table>
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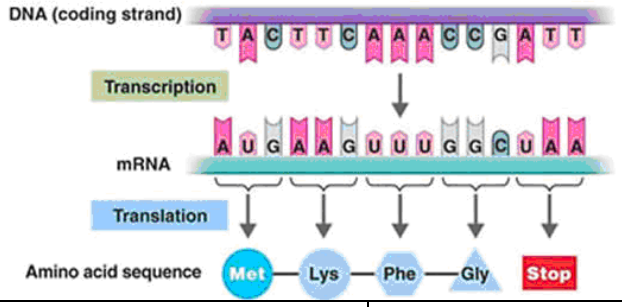
<tr><td colspan="2"> 
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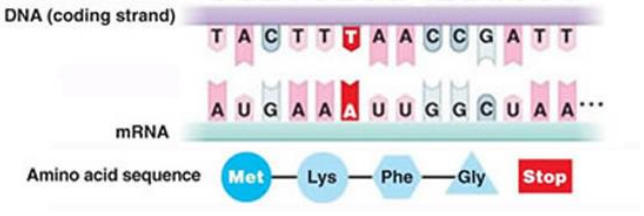
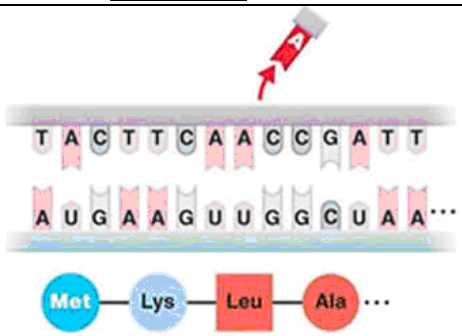
<tr><td>Silent mutation</td><td>Frameshift mutation</td></tr>
<tr><td> 
</td><td> 
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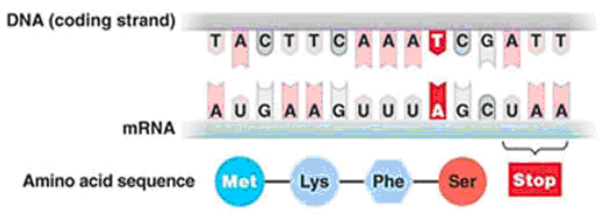
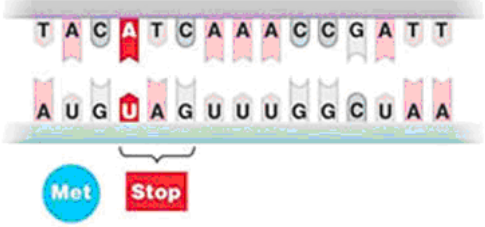
<tr><td>Missense mutation</td><td>Nonsense mutation</td></tr>
<tr><td> 
</td><td> 
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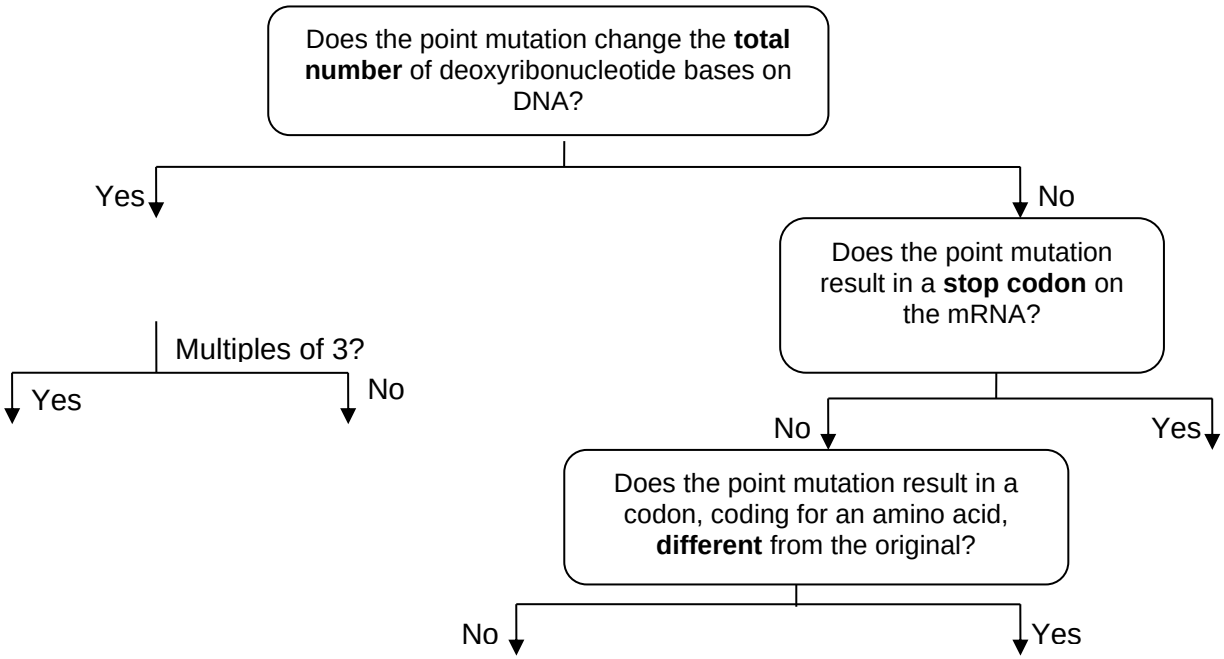
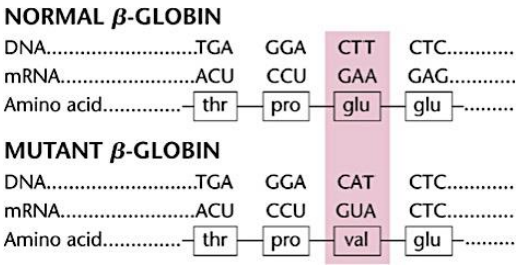
Lecture Practice

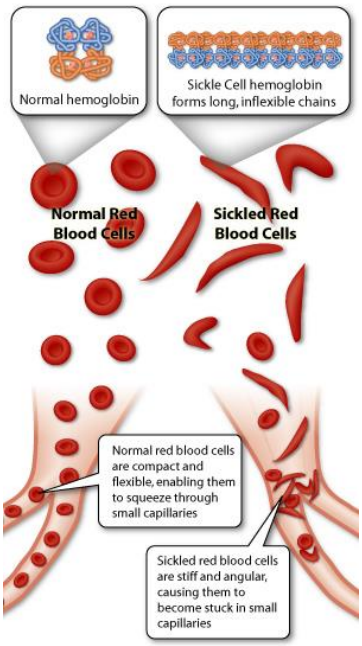


C. Sickle Cell Anaemia

- Gene mutations can result in proteins with improved functions, or novel capabilities.
- But more often than not, gene mutations are detrimental, leading to a less active, or non-functional protein that can severely impair cellular processes.
- In a normal adult, the normal **haemoglobin A** (HbA) has a quaternary structure consisting of two α-globin and two β-globin chains (*Recall: Proteins)*.
- In individuals with sickle-cell anaemia, **haemoglobin S** (HbS) is produced instead.
- Sickle-cell anaemia is caused by a single base-pair substitution on a gene on chromosome 11 that codes for the β-globin chain of the haemoglobin molecule.
- The mutation results in thymine being replaced by adenine at the 17th nucleotide of the original gene sequence.
- In the mRNA produced, the 6th codon is changed from "GAA" to "GUA".
- As a result, a neutral valine residue replaces the negatively charged glutamic acid residue.
    - Valine is hydrophobic while glutamic acid is hydrophilic.
    - This decreases the solubility of deoxygenated HbS in the red blood cell.
- Since HbS is less soluble than HbA, it is less efficient at binding to and transporting oxygen.



- The effects of HbS occur at low oxygen concentrations,
    - A sticky patch (hydrophobic regions) on the haemoglobin molecule is exposed.
    - Adjacent HbS molecules associate with each other via the sticky patches.
    - The HbS molecules polymerise, and precipitate out of the solution to form crystalline structures.
    - This causes the red blood cells to change from a circular, biconcave shape to a sickle shape.



- The sickle-shaped red blood cells result in a number of complications and symptoms, that can lead to the death of individuals who suffer from the disease:
    - Sickled red blood cells form clumps and obstruct blood vessels, and interfere with blood circulation.
        - Organs, especially the bones and kidneys, are deprived of oxygen, resulting in organ damage.
    - Sickled red blood cells are more fragile than normal red blood cells.
        - The sickled red blood cells haemolyse readily, resulting in anaemia.
    - Sickled red blood cells accumulate in the spleen for destruction.
        - This causes the abnormal enlargement of the spleen.

Overview of Sickle Cell Anaemia

Features	Normal condition	Sickle-cell anaemia
Gene coding for β-globin gene	… T …	… A …
Resultant codon on mRNA	… GAA …	… GUA …
Resultant amino acid residue	Glutamic acid	Valine
Resultant haemoglobin	Haemoglobin A	Haemoblogin S
Solubility of haemoglobin (normal O_2 concentration)	Soluble	Less soluble
Solubility of haemoglobin in Red Blood Cell (RBC) (low O_2 concentration)	Remains soluble in RBC	Forms crystalline structures due to interaction via hydrophobic regions, precipitates out in RBC
Appearance of red blood cell	Circular biconcave shape	Sickle shape

III. Chromosomal Aberration

A. Structural Alteration to Chromosomes

- During meiosis, a chromosome may break into one or more segments, causing changes to the structure of chromosome.

(a) Deletion - loss of gene

- ♦ A chromosome breaks at two points, and the middle portion of the chromosome is displaced with the two ends joining together. A shorter chromosome containing fewer genes will form.

(b) Duplication - addition of genes

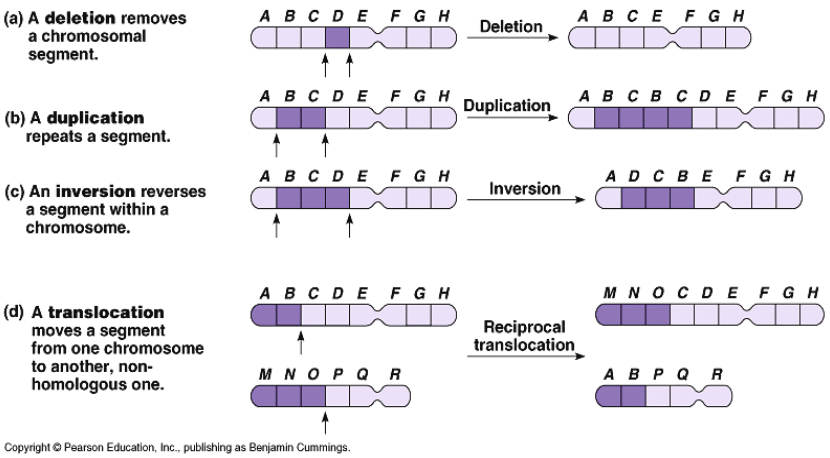
- ♦ A section of a chromosome replicates so that a set of gene loci is repeated.

(c) Inversion

- ♦ A chromosome breaks at two locations, and the middle portion inverts 180^o before re-joining.

(d) Translocation

- ♦ A section of chromosome breaks off and become attached to another chromosome, leading to a new combination of alleles.



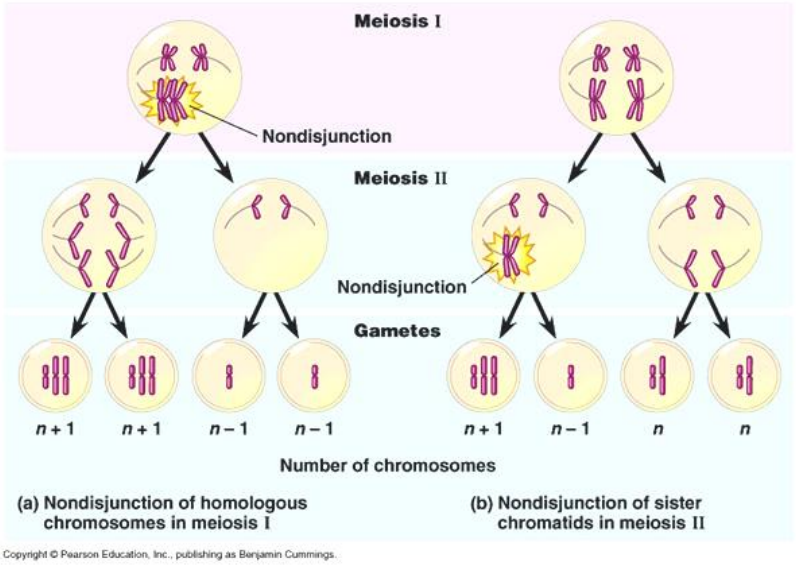
Alterations of chromosome structure.

Vertical arrows indicate breakage points. Shaded region highlights the chromosomal parts affected by the rearrangements. *Source: Biology (8th Edition) pp. 29*

B. Changes in Chromosome Number

- Involves the addition or loss of one or more chromosomes.

- Sometimes during cell division, chromosomes do not separate normally. For example, during meiosis, homologous chromosomes that should have moved away from each other to opposite poles of the spindle move as a non-separated pair to the same pole to be incorporated into the same daughter nucleus. This phenomenon is called **non-disjunction**.



Meiotic nondisjunction

Gametes with an abnormal chromosome number can arise by nondisjunction in either meiosis I or meiosis II.

Source: Biology (8th Edition) pp. 297

- The consequence of non-disjunction leads to the formation of two types of gamete in unequal proportion - one has 2 copies of the same chromosomes while the other has none.

- Chromosomal mutations can result in

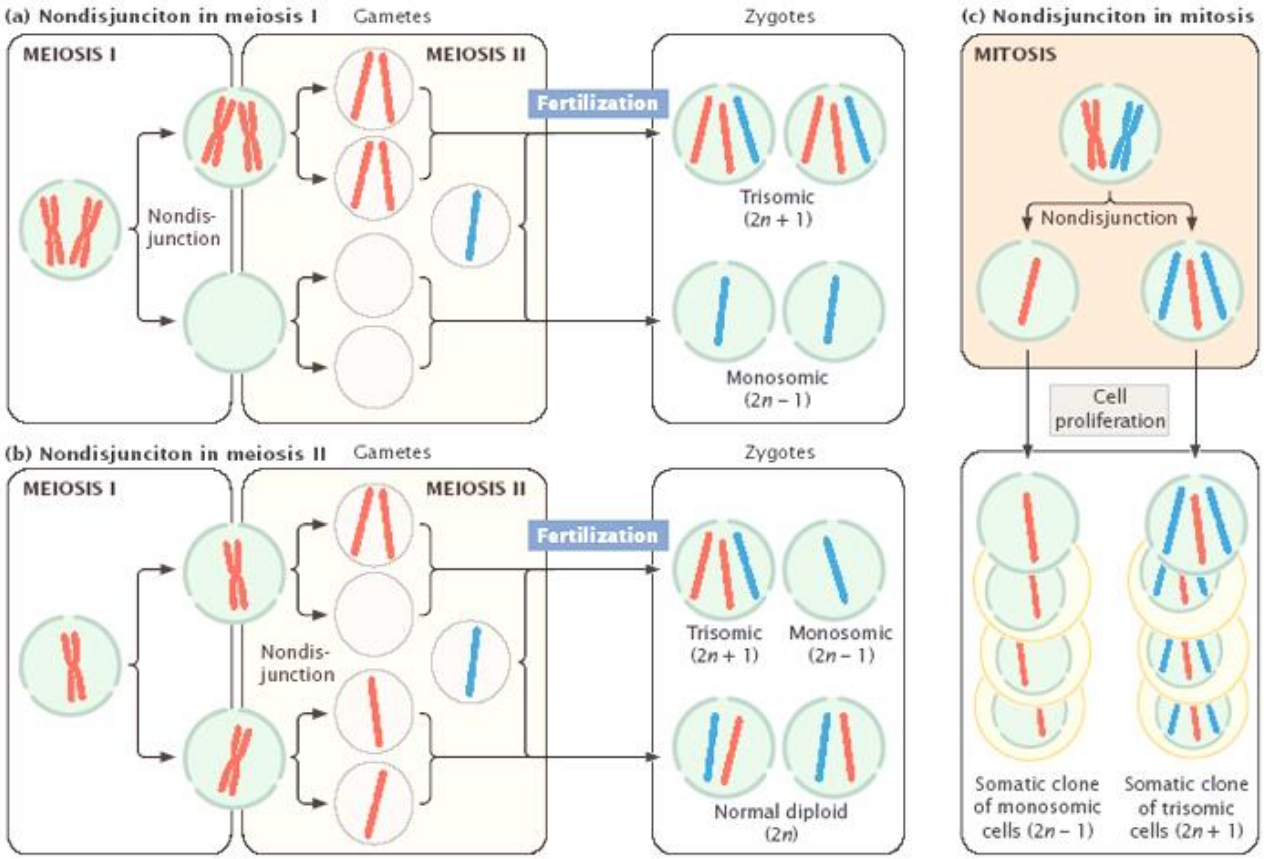
  (a) aneuploidy and

  (b) polyploidy

(a) Aneuploidy

- A condition of the nucleus where there are one or several chromosomes more than or less than the diploid number of chromosomes, e.g. 2n-2, 2n-1, 2n+1 and 2n+2.

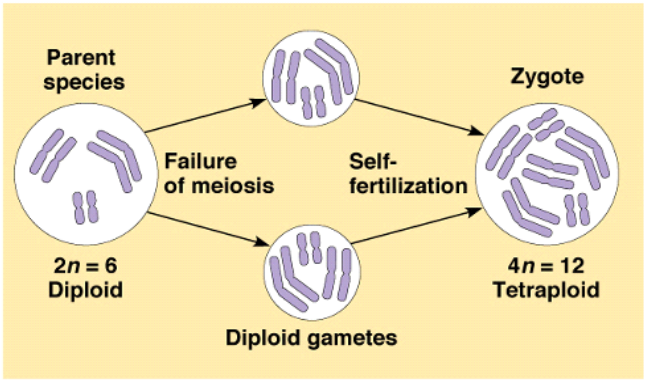
- It can result from **nondisjunction** during meiosis**,** where chromosome(s) fail to separate during anaphase. The gamete produced contains extra/lesser chromosome(s). The fusion of this gamete (e.g. carrying n-2, n-1, n+1 or n+2 chromosomes) with a normal haploid gamete (n) results in the offspring with extra or lesser chromosome(s).



***Aneuploids can be produced through nondisjunction in (a) meiosis I, (b) meiosis II, and (c) mitosis*.**
Source: http://www.nature.com/scitable/topicpage/Mitosis-Meiosis-and-Inheritance-476

(b) Polyploidy

- A condition of the nucleus where there are three or more times the haploid number of chromosomes, e.g. 3n, 4n and 5n.
- It can result from non-disjunction, the fusion of a diploid gamete with a normal haploid gamete giving a triploid nucleus.



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Polyploidy zygote produced due to non-disjunction

Source:
http://departments.oxy.edu
/biology/bbraker/courses/bio105/
class_notes/notes_3_1_00.htm

C. Diseases

1. Down Syndrome

- An aneuploid condition, where an **extra copy of chromosome 21** is found within an individual's cells.
- This can result from **nondisjunction** when homologous chromosomes 21 fail to separate to opposite poles of the cell during anaphase I **or** sister chromatids of chromosome 21 fail to separate during anaphase II of meiosis. This results in a gamete carrying two copies of chromosome 21.
- Subsequent fusion of this gamete with a normal gamete result in a zygote with three copies of chromosome 21.
- Sufferers are mentally retarded and display a variety of characteristic physical features such as broad head, rounded face, almond-shaped eyes, a flattened bridge of the nose, small irregular teeth and short stature.

2. Klinefelter's Syndrome

- A result of fusion of a Y sperm with an XX egg or the fusion of an XY sperm with an X egg.
- Although **XXY individuals** are phenotypically man, they have very small genitals and are infertile. They may also develop breasts.
- Testosterone therapy at puberty is often used to alleviate the symptoms.

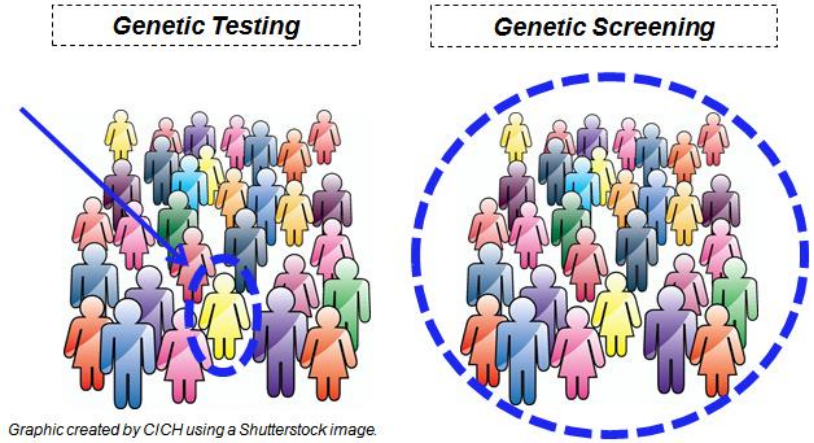
3. Turner Syndrome

- Sufferers have 22 normal pairs of autosomal chromosomes and a **single X chromosome**.
- They are infertile females and the phenotypic effects are relatively minor.
- Oestrogen replacement therapy together with hormone application can help allow normal pubertal development.

IV. Bioethical Issues of Genetic Maternal Screening

A. GENETIC SCREENING AND TESTING

- Genetic screening is conducted for a particular condition in **individuals, groups, or populations without family history** of the condition. It is typically used for preventive purposes, aiming to detect potential risks early and reduce disease impact through early intervention.
- Genetic testing is performed on **individuals** who is suspected of being at increased risk due to their **family history** or the result of a genetic screening test.
- Both genetic testing and genetic screening involve the same testing processes to examine an individual's chromosomes, DNA, RNA or the analysis of human proteins or certain metabolites with the primary purpose of detecting a heritable genotype, mutation, phenotype or karyotype.



Source: https://cichprofile.ca/module/2/section/4/page/introduction-to-genetic-testing-and-screening/

B. GENETIC MATERNAL SCREENING

- Many pregnant women are screened prenatally (period of time before birth of child) to to allow for the early detection of genetic abnormalities, such as mutations and chromosomal aneuploidies (e.g. trisomy 21, causing Down syndrome) in foetuses.
- Prenatal screening procedures include:

  (a) Non-invasive prenatal tests (NIPT) are commonly offered to pregnant women at 10th week of pregnancy onwards, and involve a simple blood test to analyse small fragments of free foetal DNA (cell-free DNA) circulating in the mother's blood. This can detect Down Syndrome (trisomy-21), and other genetic conditions such as Edward syndrome (trisomy-18) and Patau Syndrome (trisomy-13) with an accuracy of 99.5%.

  (b) The One-stop Clinic for Assessment of Risk test (OSCAR test), is usually offered to pregnant women between 11-14 weeks of pregnancy. It involves an ultrasound scan to assess the thickness of the skin in the neck of the foetus, and blood test from the mother to measure levels of proteins produced by the foetus and placenta. The test allows for a calculation of the risk for genetic conditions such as Down syndrome (trisomy-21) in the foetus.

- Generally, a woman aged 35 years or older is at higher risk of having a baby with a chromosomal abnormality and the risk increases with age. E.g. the risk of having a Down syndrome baby rises from 1 in 350 by age 35, to 1 in 100 by age 40, and 1 in 25 at the age of 45. This is because errors in meiosis may be more likely to happen as a result of the aging process and women are born with all of their eggs already in their ovaries.

C. BIOETHICAL ISSUES

- Genetic maternal screening informs parents early of the possibility of their children having genetic diseases to facilitate their decision-making. However, it also raises complex bioethical issues.
- Bioethics involve the **ethical**, **legal** and **social** issues arising from genetic maternal screening.

1. Autonomy and Informed Consent

- **Informed Consent**: It is crucial to ensure that pregnant women are fully informed about the purpose, process, and implications of genetic screening with pre-test counselling. This includes understanding what conditions are being screened for, such as trisomy-21, and the possible outcomes and decisions that might follow.
- **Autonomy**: Respecting the autonomy of the pregnant woman to make an informed decision about whether to undergo genetic screening is fundamental. She must have the right to accept or decline the screening without coercion.

2. Privacy and Confidentiality

- **Genetic Information Privacy**: The results of genetic screenings are highly sensitive. Protecting the confidentiality of this information to only parents and medical personnel is essential to prevent misuse and discrimination. Breaches could have severe consequences for individuals and families.
- **Potential for Discrimination**: There is a risk that genetic information could be used to discriminate against individuals in areas such as insurance and employment. Laws and policies must be in place to prevent such outcomes.

3. Non-Maleficence and Beneficence

- **Non-Maleficence**: The principle of "do no harm" must be considered, including the **psychological impact** on parents receiving news of a potential genetic disorder. It can cause significant stress and anxiety for parents, particularly if the condition has no cure or effective treatment. Parents may also be distressed knowing the physical risks associated with invasive diagnostic procedures like amniocentesis that are usually carried out after their foetuses were assessed as high
- **Beneficence (promote and protect well-being)**: The potential benefits of genetic screening include early intervention and informed decision-making. For instance, knowing about a trisomy-21 diagnosis in advance can help parents prepare for the specific needs of their child and access early intervention programmes, potentially improving the child's outcome. In some cases, genetic information can guide the development of personalised medicine and targeted therapies for the foetus or child.

4. Justice and Equity

- **Access to Screening**: Ethical considerations must address whether genetic screening is accessible to all pregnant women, regardless of socioeconomic status. Inequities in access could worsen existing health disparities.

5. Social and Ethical Implications

- **Potential for Stigmatisation**: Identifying foetuses with genetic mutations can lead to stigmatisation and marginalisation of individuals with these conditions. Society must address and mitigate such risks.
- **Implications for Disability Rights**: Screening for conditions like trisomy-21 raises significant ethical questions about societal attitudes toward disability. Disability rights advocates argue that such practices can contribute to a devaluation of lives with disabilities.

6. Informed Reproductive Choices

- **Prenatal Decision-Making**: Screening for genetic mutations can inform couples regarding their reproductive decisions, including whether to continue or terminate a pregnancy. This raises ethical issues related to the moral status of the foetus and the rights of parents.
- **Impact on Families**: The knowledge gained from genetic screening can have profound effects on families, influencing decisions about family planning and creating potential psychological burdens.

7. Clinical issues

- **Accuracy of genetic screening**: As most screening methods are not 100% sensitive and specific, a screening result is possibly inaccurate (i.e. false positive or false negative). False positives can generate psychological distress and often result in further investigations to determine if the genetic condition is present. With false negatives, parents might feel reassured when in fact their child has a genetic condition.

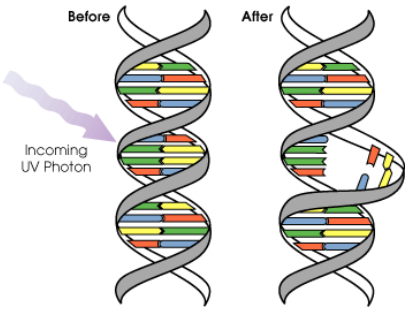
THE CASE OF TRISOMY-21 (DOWN SYNDROME)

- Trisomy-21 screening presents a specific set of bioethical considerations:
- **Spectrum of severity:** Down syndrome can vary greatly in severity. Screening doesn't necessarily predict the specific challenges a child might face.
- **Termination of pregnancy:** Some parents may choose to terminate a pregnancy upon learning of a trisomy-21 diagnosis. This raises ethical questions about the value of a life with Down syndrome.
- **Evolving societal views:** There's growing recognition of the rights and contributions of people with Down syndrome. Increased screening could lead to a decrease in the Down syndrome population, raising concerns about eugenics (selective breeding for desired traits).

V. Mutagenesis

- **Mutagenesis** is the process of forming mutations. It can occur by:
  - **Spontaneous mutations** – These are due to errors during DNA replication, DNA repair or recombination and can lead to both gene and chromosomal mutations.
  - **Induced mutations** – These are due to interactions of **mutagens** with DNA. Mutagens are physical and chemical agents that cause DNA mutations.
- Mutagens include UV light, high energy radiation and ethidium bromide.

- UV Light
  - UV light causes thymine dimers to form.
  - The presence of the dimers interferes with the structure of the DNA molecule, as seen in the above diagram.
  - During DNA replication, the presence of the dimers interferes with the DNA replication enzymes, which skip over the dimer.
  - This results in the deletion of base pairs in the newly synthesised strand.



- High Energy Radiation
  - High energy radiation such as X-rays and gamma rays can be mutagenic.
  - They result in the formation of ions that react with nucleotides and the sugar-phosphate backbone of the DNA molecule.
  - **Double-stranded breaks** can occur in the DNA molecule, and large sequences of nucleotides can be lost in the process.
  - As such, high energy radiation often results in base-pair deletions that can result in frameshift mutations.

- Ethidium bromide
  - Ethidium bromide is an intercalating agent that fluoresces under UV light. It is often used to stain and visualise DNA bands during gel electrophoresis.
  - Ethidium bromide intercalates with DNA, distorting the structure of the DNA helix by increasing the distance between adjacent base pairs.
  - The increased space between adjacent base pairs can result in addition or deletion of nucleotides during the process of DNA replication, leading to frameshift mutations.