Mutations

A mutation is an unusual error in DNA replication, involving incorrect base pairing, which leads to a change in the DNA base sequence.

Mutagens

Environmental agents that alter DNA and cause mutations are termed mutagens. The process of inducing a mutation is termed mutagenesis and the resulting mutations are termed induced mutations.

Many mutagens are carcinogenic (cancer-causing). This is because some mutations occur in genes that regulate the cell cycle or promote or suppress cell division. These mutations cause changes in the cell cycle that may result in increased cell division with no differentiation, resulting in masses of cells known as tumours (balls of undifferentiated cells).

Chemical mutagens

Chemical mutagens are chemicals that cause mutations if cells are exposed to them are high frequencies or for prolonged periods of time.

Examples:
- Ingested chemicals like alcohol, tar in tobacco smoke, some medications and chemicals in food - charred and fatty foods, preservatives such as nitrates
- Environmental irritants and poisons such as organic solvents, cleaning products, asbestos, coal tars, pesticides, and some hair dyes

Chemicals that are mutagenic are usually structurally similar to normal bases in DNA (purines and pyrimidines) and so they may mistakenly become incorporated into DNA during replication. This results in the insertion of incorrect nucleotides opposite them during replication termed mispairing.

Common examples of chemical mutagens that are molecules include
- Alkylating agents
- Deaminating agents
- Intercalating agents (chemicals that interact directly with DNA and change its structure)

Naturally occurring mutagens
Spontaneous mutations, such as DNA replication errors, arise during DNA replication and are retained because the normal mechanism of DNA repair does not correct them.

Naturally occurring mutagens are mutagenic agents that are present at normal levels within natural environments, and may cause mutations.

They can be divided into two groups:
- Biological naturally occurring - include viruses, bacteria, fungi and their products
- Non-biological naturally occurring mutagens - include metals, such as mercury and cadmium, that occur naturally in the environment
- Transposons - sections of DNA that spontaneously fragment and replicate or multiple within the genome. When these transposable elements into chromosomal DNA, they disrupt DNA functioning.
- Microbes are naturally occurring biological mutagens. These include viruses and bacteria. Mutagenic microbes may also directly alter the genetic material in cells.

Effects of biological mutagens
- Many are able to insert own base sequences into DNA and thus change functioning of genes and trigger cancers
- Some bacteria/their products cause inflammation, during which free radicals are produced, causing DNA damage, increasing mutation. Free radical release may also lead to oxidative stress, where the immune response is altered and the immune system does not fight off viral infections.

Physical mutagens
- Include heat and ionising radiation
- Radiation is any transfer of energy through space from a source, ionising radiation is the harmful type can break chemical bonds in molecules like DNA
- Ionising radiation includes shorter wavelengths of UV radiation as well as X-rays and gamma rays. Shorter wavelength and high energy of ionising radiation make it dangerous, causing cellular damage.

Because the integrity of DNA replication is so important, DNA repair mechanisms operate in cells, whereby enzymes that are involved in replication also play a role in removing damaged parts of DNA and repairing DNA. These include:
- Base excision repair - a damaged or incorrectly paired base is removed by a nuclease enzyme from its sugar linkage and replaced e.g. removal of pyrimidine dimer
- Mismatch repair - once DNA has replicated, the enzyme DNA polymerase carries out a ‘spell check’ for accuracy of replication.
Types of Mutations

Mutations can be distinguished according to five criteria:

1. The origin/cause of the mutation: spontaneous mutations arise randomly as a result of an error in a natural process such as DNA replication in cells, whereas induced mutations arise as a result of an environmental agent such as a chemical or radiation, which increases the chance of nucleotide sequences being changed.

2. The amount of genetic material changed: point mutations are changes to a single base pair of DNA and affect only a single gene (gene mutations). In contrast, chromosomal mutations move whole blocks of genes to different parts of a chromosome or to another chromosome entirely. Frameshift mutations may affect a single gene or a sequence of genes and arise as a result of a point mutation of a chromosomal mutation.

3. The effect of the mutation on the DNA: a nucleotide base may be substituted, inserted or deleted. This in turn may lead to a change in one amino acid (or no change if the new base forms a triplet that codes for the same amino acid as the original codon).

4. The effect of the mutation on the phenotype: there may be no change in the phenotype (silent mutation), or a small or large (or variation) in the phenotype depending on the type of amino acid substituted. This type of mutation is most often harmful, sometimes neutral, and very rarely, beneficial.

5. Heritability of mutations: the possibility of a mutation passing down through generations depends on whether the mutation occurs in a non-reproductive (somatic) cell or a reproductive (germline) cell.

**Point mutation**

Is a single nucleotide variation, which can have a significant change in phenotype even though these are small. Most point mutations result in a base substitution, though some result in a frameshift mutation.

- A specific example of a point mutation is the sickle cell gene point mutation. The triplet CTC is changed to CAC. This alters the shape of haemoglobin, and results in the disease sickle cell anaemia.

**Frameshift mutation**

A frameshift mutation is where the insertion or deletion of one base shifts the entire ‘reading frame’ of RNA, leading to the creation of a whole sequence of incorrect amino acids and the production of non-functional proteins.

- E.g. A base insert into the codons IWA NTO DIE would become IVW ANT ODI E
Changes in proteins (phenotype) due to point mutations

- **Nonsense mutations** change an amino acid to a stop codon, cutting proteins short. The resulting protein is typically non-functional, leading to a major phenotypic effect.
- **Missense mutations** are point mutations that result in an amino acid change.
- **Silent mutations** are changes in the DNA sequence that do not cause a change in amino acid. E.g. codons GCC and GCA on mRNA both code for the amino acid valine, so changing GCC to GCA will have no effect on the amino acid sequence of a protein, and thus the phenotype.
- **Neutral mutations** are changes in DNA sequence that are neither beneficial nor detrimental to the ability of an organism to survive and reproduce. E.g. eye colour

Chromosomal mutations

Chromosomal mutations (chromosomal aberrations) are large scale changes where either the overall structure of a chromosome is changed or the entire number of chromosomes in a cell is altered. Gene mutation, by contrast, are any changes to the DNA sequence within one gene. There are four main types of chromosomal mutation:

- **Chromosomal Deletion**
  - Occurs when a section of DNA is removed and not replaced, leading to a reduction in the number of genes in a chromosome. Often the result to exposure to high heat, viruses or radiation.

- **Chromosomal insertion (duplication)**
  - Occurs when a portion of DNA is duplicated (or doubled) and inserted, increasing the number of genes on the chromosome.
  - The position of the duplication, as well as the number of repeats of the sequence determine the phenotypic effect. Size also matters.
  - Huntington's chorea and fragile X syndrome seem to be linked to the number of duplications in a chromosome.

- **Chromosomal inversion**
  - Occurs when a section of DNA is removed, turned around 180 degrees (sequence turned back to front), and then reinserted into the chromosome so that the bases are in reverse order.
  - Haemophilia A is caused by an inversion mutation in the factor VII gene on the X chromosome.

- **Chromosomal translocation**
  - Occurs when a section of DNA is moved from one chromosome to a nonhomologous chromosome. This may lead to gene fusion, when the translocated region joins two normally separate genes.
Aneuploidy: changes in chromosome number
Aneuploidy occurs when one or more extra copies of an entire chromosome are made or go missing, leading to an abnormal number of chromosomes in a cell. Down syndrome is an example of a disorder, with the individual having an extra copy of chromosome 21.

Mutations and how they affect organisms
- At the cellular level, the type of cell affected by a mutation determines the extent of its influence. Germline cells will pass mutations to every cell in the offspring of the gamete, while somatic mutations may lead to localised effect.
- At the individual level, mutations differ their phenotypic effect, translating into physical, behavioural, physiological and biochemical changes. Some mutations can lead to significant phenotypic change, whereas others have little or no effect.
- At the population level, mutations are the direct source of all new alleles and introduce gamete variation into the population. If such new alleles are expressed as differences in phenotype, natural selection can take course, so undesirable traits are removed and desirable ones flourish.

Somatic mutations
Somatic mutations occur in somatic cells (non-reproductive body cells), often due to replications errors prior to mitosis.
- Spontaneous mutations may occur in the S phase of the cell cycle (where DNA is vulnerable during replication).
- If not repaired in the ‘proofreading’ G2 phase, it will be passed onto daughter cells. The mutated cell will continue to divide by mitosis, with the error amplified by the constant replication.
- Cancer is a common result of mutation in somatic cells - e.g. skin cancer, liver cancer and brain tumours.
- Somatic mutations aren’t always visible phenotypic changes, they can occur as physiological changes such as mutations for cystic fibrosis.

**Germline mutations**
Germline mutations (gametic mutations) occur in the sexual reproductive cells that give rise to gametes, and such mutations are passed to offspring. If the mutated gamete is successful during fertilisation, the mutation is replicated in every cell as the embryo divides and grows, affecting all cells in the resulting offspring.

**Coding and non-coding DNA**
Mutations in coding DNA and their significance
- **In Eukaryotes**
  - Mutations may also affect gene splicing and in this way modify the function or levels of the protein product
    - E.g. whether a mouse’s coat is white or grey depends on the presence of proteins and enzymes that make the pigment
  - Mutations directly affects the phenotypes of individuals
  - Errors in the gene of eukaryotes whose products are involved in DNA repair result in a general increase in mutations arising from errors in replication.
- E.g. The disease Xeroderma pigmentosum is caused by a mutation in a gene for DNA repair. Sufferers are extremely susceptible to cell damage from UV light, and are 1000x more susceptible to skin cancer than people without the mutation.

- **In prokaryotes**
  - The percentage of coding DNA is higher compared with eukaryotes.
  - Studies on simple organisms such as bacteria and yeast reveal that the coding DNA is largely made of genes for DNA repair enzymes.

**Mutations in non-coding DNA**
- Non-coding DNA can code for end products other than DNA, such as rRNA and small nuclear RNA.
  - Small nuclear RNA plays a role in determining which introns are spliced out of DNA before it leaves the nucleus.
  - rRNA is the machinery used by the cell for translation.
  - Mutations in these non-coding regions have been shown to affect gene expression and cell-functioning.
- There is growing evidence that mutations in non-coding genes are linked to developmental and congenital abnormalities, supporting the idea that non-coding DNA is important during embryonic development.
  - E.g. congenital heart defects result from a mutation of the TBX5 enhancer gene in a non-coding area of DNA.
- Mutations in regulatory part of DNA, such as enhancer sequences, have been shown to predispose adults to non-infectious diseases such as heart disease, diabetes, cancer and obesity.

**Junk DNA**
- Junk DNA are parts of non-coding DNA that seem to have neither a protein coding nor a regulatory function.
  - It does not include regulating sequences (promoters, silencers and enhancers) or non-coding DNA where specific functions have been identified.
- Only DNA that is highly repetitive is accepted by some molecular biologists as being of unknown function, and termed ‘junk DNA’.
- The portion of non-coding DNA contain hundreds and thousands of repeats of DNA sequences. They are believed to be viruses inserted, and may be transposons (transposed DNA) or retrotransposons (inserted viral RNA reverse transcribed to DNA). They are considered mutations if they occur near genes or in their promoter regions, where they change gene expression or functioning.
Causes of genetic variation
Mechanisms of sexual reproduction such as gamete formation (meiosis) and gamete fusion (fertilisation) increase gene recombination and therefore variation in individuals (new gene combinations) and variability in population (amount by which individuals in a population vary genetically).

Meiosis
- When gametes form, crossing over and random segregation in meiosis result in genetic recombination of paternal and maternal genes within each gamete.

Mutations
- Mutation plays a part in increasing the number of alleles for a trait, whereas meiosis and fertilisation play a significant role in recombining genetic material.
- Mutations occur either during replication of DNA (leading to replication errors) or during the separation (disjunction) of chromosomes

Chromosomal errors
- When crossing over goes wrong, chromosomal aberrations may be introduced. E.g. the DNA to be exchanged may be inverted before it is inserted into the arm of a corresponding chromatid

Changes in chromosomal numbers (non-disjunction)
- When one or more pairs of homologous chromosomes or sister chromatids do not separate as they should during nuclear division, an abnormal distribution of daughter chromosomes occur, which may lead to change in chromosome number
  - E.g. down syndrome, extra chromosome 21

Remember, the effect of environment on organisms are phenotypic, NOT GENETIC, in nature.
Population genetics

Gene flow
- when new individuals enter a population, or existing individuals leave, which may result in a change in allele frequency

Genetic drift
- A change in allele frequency due to random chance goddamn
- E.g. a natural disaster wipes out some organisms, while the lucky few escape. The alleles of frequencies of the survivors will increase as they reproduce.

<table>
<thead>
<tr>
<th>Factor</th>
<th>What is it?</th>
<th>Allele changes are due to:</th>
<th>Effect on the Next Generation</th>
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<tbody>
<tr>
<td><strong>Selective Pressure</strong></td>
<td>Mainly natural selection</td>
<td>Variation that are passed on because they make the individuals more likely to survive</td>
<td>Alleles that make individuals ‘fitter’ - more likely to survive and live to reproductive age- become most frequent</td>
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<tr>
<td><strong>Sexual selection</strong></td>
<td>Certain individuals are more attractive to mates and therefore more likely to breed.</td>
<td>Non-random mating (some individuals more than others)</td>
<td>Alleles of individuals who are most successful at mating are more common in the gene pool</td>
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<tr>
<td><strong>Mutation</strong></td>
<td>New genes arise due to ‘errors’ in DNA replication during meiosis (gametogenesis); they may be beneficial, neutral or harmful</td>
<td>New alleles arising during gametogenesis being introduced into a population</td>
<td>New alleles that are beneficial become more frequent in the population</td>
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<td><strong>Genetic drift</strong> (more obvious in smaller populations)</td>
<td>Random events (e.g. a tornado) lead to a change in gene frequency because some individuals are wiped out</td>
<td>Random chance (non-selective; does not depend on genetic make-up)</td>
<td>Causes individuals within a population to be different (not necessarily more successful) due to random choice</td>
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<tr>
<td><strong>Gene flow</strong> (more obvious in smaller populations)</td>
<td>Individuals with different genes come into a population and spread their alleles</td>
<td>Mixing with new genetically different individuals (e.g. immigration, emigration)</td>
<td>Allele frequency in the population change</td>
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