OCR (B) Biology A-level

5.1 Genetics in the 21st century

Notes

5.1.1 Patterns of inheritance

Key terms:

Allele – alternative form of a gene

Locus – the specific position of a gene on a chromosome; the two alleles of a gene are found at the same loci on the chromosome pairs

Phenotype – observable characteristics of an organism which are as a result of genotype and environment

Genotype – the alleles present within cells of an organism, for a particular trait or characteristic

Dominant – only a single allele is required for the characteristic to be expressed, that is the allele is always expressed in the phenotype

Recessive – the characteristic is only expressed if there is no dominant allele present

Homozygous – two identical alleles

Heterozygous – two different alleles

Codominance – when both alleles are expressed in a heterozygote, that is, both alleles contribute towards the phenotype. Examples include blood type.

Linkage is the phenomenon where genes for different characteristics, located at different loci on the same chromosome are linked.

Monogenic inheritance – when a phenotype or trait is controlled by a single gene. For instance, cystic fibrosis where the individuals with doubly recessive phenotype are affected.

Dihybrid cross – inheritance of two genes

Sex linkage – expression of an allele dependent on the gender of the individual as the gene is located on a sex chromosome. For instance, males are more likely to inherit an X-chromosome linked condition because they only have a single copy of the X chromosome. An example of sex linkage is haemophilia which is a recessive condition. Other examples include Duchenne muscular dystrophy.

Autosomal linkage – genes which are located on the same chromosome and tend to be expressed together in the offspring

Epistasis – the interaction of different loci on the gene, one gene locus affects the other gene locus. One gene loci can either mask or suppress the expression of another gene locus.

Recessive epistasis occurs when the presence of a recessive allele prevents the expression of another allele at a second locus. Recessive epistasis gives the ratio of **9:3:4.**

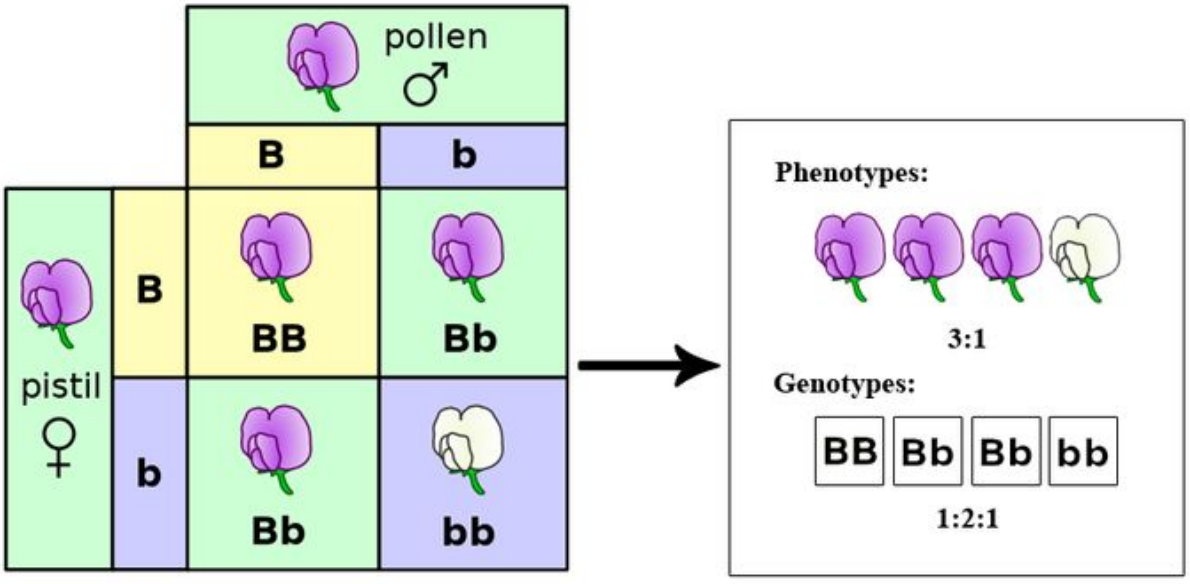
Dominant epistasis is when a dominant allele at one locus completely masks the alleles at a second locus. Dominant epistasis gives a ratio of **12:3:1.**

Basics

Homozygous: [Aa] ; [AA] – same alleles present
Heterozygous: [Aa] – different alleles present

Examples:

This grid format of demonstrating alleles is known as a **Punnett Square:**



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Chi-squared test

$$X^2 = \sum \frac{(\text{observed} - \text{expected})^2}{\text{expected}}$$

The **chi squared test** is **a statistical** test which can be used to establish whether the difference between **observed and expected results** is small enough to occur purely due to chance.

- It can be used if the **sample size** is sufficiently large, i.e. over 20. It can only be used for **discontinuous variation** data in the form of raw counts.
- The chi squared test can be used to determine whether the **null hypothesis** is correct or not. The null hypothesis is the assumption that there is no difference between observed and expected results.
- The value obtained is compared to the **critical value**, and in a case where the value obtained is less than the critical value, the null hypothesis is accepted as the difference due to chance is not significant
- Whereas in a case where the x^2 value is greater than the critical value, the null hypothesis is rejected meaning that the difference between observed and expected results is not due to chance, and is significant.

Mutations

Mutations are changes in the sequence of nucleotides in DNA molecules.

Types of mutations include:

- **Insertion/deletion mutations** where one or more nucleotide pairs are inserted or deleted from the sequence. This type of mutation alters the sequence of nucleotides after the insertion/deletion point known as a frameshift.
- **Point mutation/substitution** occurs where one base pair is replaced by another.
- **A nonsense mutation** is one where a translation is stopped early thus giving rise to a truncated polypeptide due to premature introduction of a stop codon.
- **A missense mutation** is a codon change which results in the production of a different amino acid, thus resulting in altered tertiary structure of the protein
- **A silent mutation** is a codon change which does not affect the amino acid sequence produced.

Mutations can either have **neutral effects** where the mutation causes no change to the organism, for example in a case where the mutation occurs in a non-coding region of DNA or is a silent mutation, as described above. A mutation can also be neutral when a **change in tertiary structure of the protein has no effect on** the organism.

Some mutations are beneficial, for instance, humans developed trichromatic vision through a mutation. Harmful mutations include a mutation in the CFTR protein which causes **cystic fibrosis.**

An example of chromosomal mutation is Down's syndrome where a third copy of chromosome 21 is present.

Other examples:

1. Deletion where a nucleotide base is deleted. AGTCA becomes AGCA.

2. Substitution where a nucleotide base is replaced by another. AGTCA becomes AGTCG.

3. Insertion where a nucleotide base is added as extra. AGTCA becomes ATGTCA.

Summary:

ABO Blood group [CODOMINANCE]:

- Demonstrates co-dominant inheritance
- Consists of three alleles: I^A, I^B and i
- I^A and I^B are co-dominant; both are dominant to i
  - i.e. in the heterozygote I^AI^B, both are expressed
- The presence of I^iI^i, yields the O blood group.

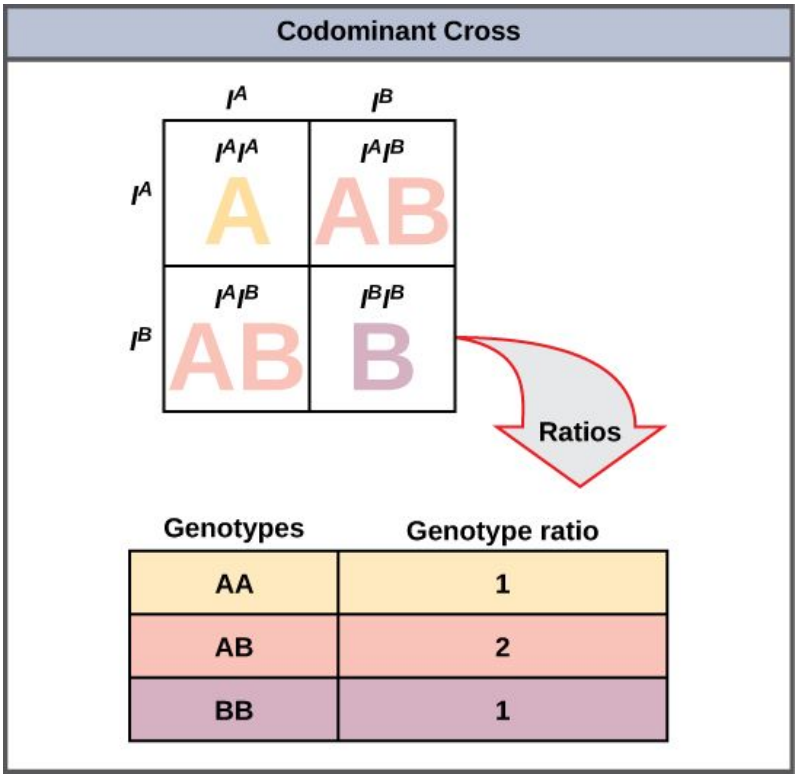


Image source: opentextbc.ca

Haemophilia

- Clotting disorder; there are different types such as Haemophilia A and B depending on the clotting protein affected.
- X-linked condition

X chromosome affected - XX child [female] has another unaffected X chromosome to fall back on and be able to produce the essential protein. The carrier XY child [male] only has the affected X chromosome and cannot make the protein – hence developing the condition.

Cystic fibrosis [AUTOSOMAL RECESSIVE]

- Monogenic mutation [affects one gene] – CFTR [cystic fibrosis transmembrane conductance regulator] gene on chromosome 7 mutates.
- Results in dysfunction of the movement of chloride ions out of cells – accumulation of thick mucus, cough, sputum, affects other glands such as the pancreas resulting in diarrhoea and difficulty gaining weight.
- These individuals are more prone to infections and require regular monitoring by a range of healthcare professionals including dieticians, physiotherapists, nurses and doctors.

Huntington's disease [AUTOSOMAL DOMINANT]

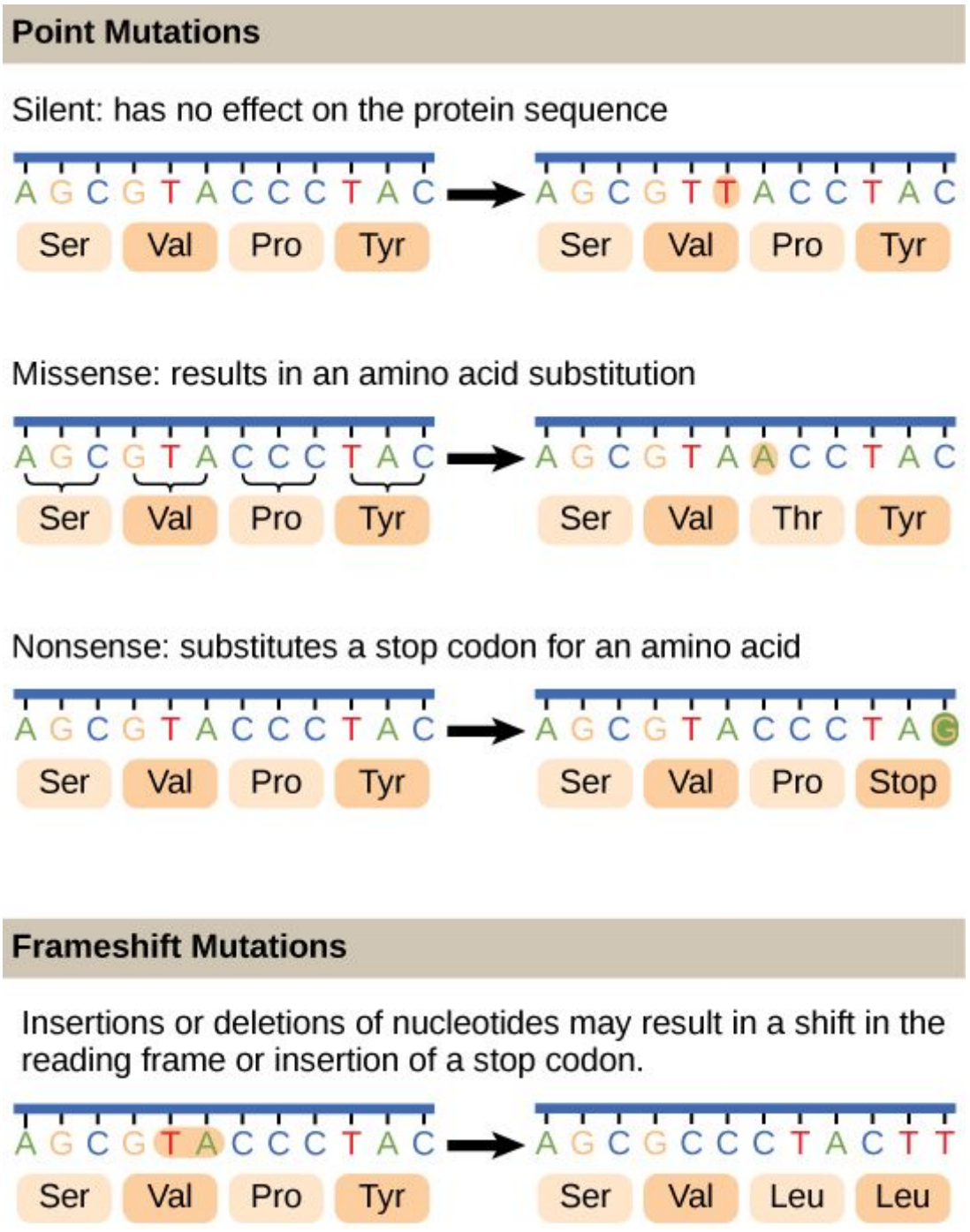
- Autosomal dominant condition
- Mutated gene coding for huntingtin
- Increased insertion of CAG beyond the number of repeats. CAG codes for important amino acid – glutamine – forming part of a protein structure
- Damage of brain cells with symptoms arising in middle age (~40-50 y/o).
- Jerky movements, cognitive decline and memory loss that results in dementia.

Down's syndrome involves an extra chromosome 21, and expresses itself in terms of many different features, some of which are detrimental to health. Common outcomes include unique facial features, slower overall development, higher incidence of congenital heart abnormalities, decreased or absent fertility and overall lower life expectancy.

Turner's syndrome is in a way the "reverse" of Down's syndrome as it presents one fewer chromosome rather than one extra. Specifically, it is a diminished or absent X chromosome. Since XY embryos missing their only X chromosome would not be viable, this syndrome only presents itself in births of would-be XX babies who end up having just one X chromosome or one X and a partial X.

Klinefelter's syndrome is a relatively common chromosomal variation (up to 1 in 500 male assigned births) where an XY individual has an extra X chromosome, hence being an XXY individual. Life expectancy is comparable to XY individuals. Symptoms of the condition include reduced fertility or infertility, lower levels of testosterone, increased height, reduced muscle strength and coordination, breast growth and learning and speech difficulties.

Chromosomal mutations



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Screening and diagnostic tests are available for genetic conditions. However, there are many ethical considerations that must be discussed with the family. Genetic counselling is a method of informing individuals on the risk of future children developing certain conditions.

5.1.3 Gene technologies

DNA sequencing begins with the process of **mapping** where the existing information about the genome is used to **identify the locus of a particular gene within the genome**. The gene is **fragmented** with the use of **restriction enzymes** and the fragments produced are inserted into **bacterial artificial chromosomes**. This step results in the formation of a **genomic DNA library.** The fragments obtained from the **bacterial cultures** are again broken down into smaller fragments with **restriction enzymes and sequenced** with the use of the **chain-termination**. This technique was developed by Sanger and is based on **selective incorporation of chain terminating nucleotides** into a growing chain by **DNA polymerase during replication.**

It occurs as following:

- The DNA sample is divided into **four separate sequencing reactions** which contain all **four standard** nucleotides, DNA polymerase, primers required for replication and **modified nucleotides** [which have been **fluorescently labelled** for ease of identification].
- When a modified nucleotide is incorporated into a growing chain, replication is **terminated**
- DNA fragments of **different lengths** are formed across the **reaction vessels**
- **High resolution electrophoresis** is used to **separate the fragments by size** – single base differences can be seen
- The fragments are **visualised under UV light**, thus enabling the **base sequence** to be **read from the bottom of the gel upwards**

The **rapid advancement** of techniques used in sequencing increased the speed of sequencing and allowed **whole genome sequencing**, that is. **high-throughput sequencing.**

Gene sequencing allows for **genome-wide comparisons** between **individuals and between species**. Comparing genomes between species is significant as it allows **evolutionary relationship**s between species to be determined, and it is also beneficial to **medical research.** Comparing genomes of individuals enables differences to be identified which can then be used for **development of personalised medicine** tailored to a particular genome, as well as in studies of **human diseases.**

Apart from allowing genome-wide comparisons to be made, gene sequencing has allowed for the **sequences of amino acids in polypeptides to be predicted** and has allowed for the **development of synthetic biology.**

The **Human Genome Project** is an international scientific project which has successful determined the sequence of bases of a human genome.

Potential applications include: screening for mutated sequences, carriers and pre-implantation screening as well as screening for disorders such as Huntington's disease before the symptoms appear. However, there are many ethical concerns regarding the Human Genome Project, such as people being discriminated against as well as regarding the misuse and ownership of the genetic information.

DNA profiling

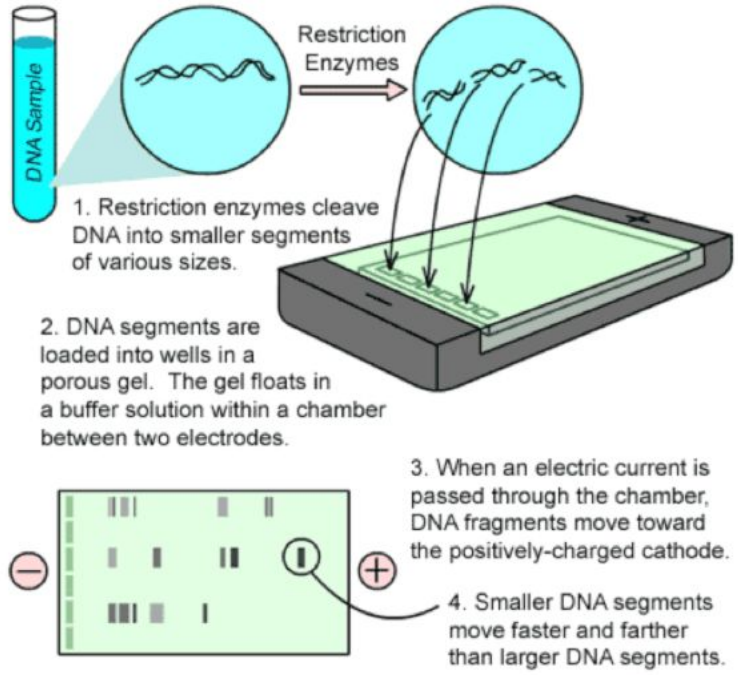
DNA profiling is a forensic technique used to **identify individuals by characteristics of their DNA**. It can also be used to **determine genetic relationships** between organisms. Main techniques used in DNA profiling are:

- **Polymerase chain reaction known as PCR** which is used to amplify the DNA by making millions of copies of a given DNA sample. It occurs as following:

  1) A reaction mixture is set up by mixing the **DNA sample, primers, free nucleotides and DNA polymerase** which is the enzyme involved in creating new DNA strands
  2) The mixture is then **heated to 95 degrees** to break the hydrogen bonds and to separate the two strands
  3) The mixture is then **cooled to a temperature between 50-65 degrees** depending on the type of primers used, so that they can bind to the strands
  4) Temperature is increased to about **70 degrees** as this is the temperature DNA polymerase works at
  5) **DNA polymerase** creates a copy of the sample by **complementary base pairing using the free nucleotides**
  6) **This cycle is repeated around 30 times** and gives rise to an amount of DNA sufficient to create a DNA profile.

- **Gel electrophoresis** is a process used to **separate the DNA fragments and proteins according to their size using an electric current**. The diagram below demonstrates how the process is carried out

Figure S-2: Gel Electrophoresis



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Genetic engineering

Isolated DNA fragments can be placed in plasmids in a following way:

- Plasmid and gene are cut with the same restriction enzyme to create **complementary ends.** If sticky ends are missing, they can be added
- The fragments are **incubated with the plasmids.** If a plasmid takes up the insert, base pairing takes place between the complementary ends which are then **sealed with the use of DNA ligase which forms phosphodiester linkages**
- A **recombinant DNA** molecule is created

In the formation of **transgenic microorganisms**, **electroporation** is used to stimulate bacterial cells to take up plasmids. Electroporation facilitates the process by **increasing the permeability of bacterial membranes thus increasing the chance of success**. This is achieved via the use of **calcium salts and rapid temperature change from 0 to 40 degrees**. Bacteria which have successfully taken up a plasmid with the help of **marker genes**. For instance, if a plasmid contains an **antibiotic resistance gene**, the bacteria will be resistant to the antibiotic, and if grown on the media, **only the bacteria which have been successfully transformed will survive.**

Other types of vectors include **bacteriophages, liposomes and yeast artificial chromosome**s.

Cystic fibrosis

Cystic fibrosis is a genetic disorder caused by a mutation of a single gene which is the gene coding for the **CTFR protein**. CTFR is a channel protein **which transports chloride ions out and into the mucus**, this channel protein makes the mucus watery as it causes water to move into mucus by osmosis. Therefore, a **mutation in this gene makes the mucus very thick** as a mutant CTFR protein is less efficient at transporting chloride ions. Sticky and thick mucus causes many problems in **gas exchange, reproduction and digestion.**

Respiratory system:

- Build-up of mucus in the **lungs traps bacteria thus increasing the risk of infection**
- Build-up of mucus in the airways decreases the number of **alveoli** exposed to fresh air therefore **reducing the surface area for gas exchange**

Reproductive system:

- Cervical mucus **prevents the sperm from reaching the egg**
- In men, the **sperm duct is blocked** with mucus meaning that **sperm produced cannot leave the testes**

Digestive system:

- The **pancreatic duct** which connects the pancreas to the small intestine can become blocked with mucus, therefore the **digestive enzymes do not reach the small intestine**, as a result of that food is not properly digested hence **fewer nutrients are absorbed**
- The **mucus lining in the duodenum is very thick** thus reducing the absorption of nutrients
- Mucus can cause **cysts** to form in the pancreas and damage the insulin producing cells thus leading to **diabetes**

Gene therapy

Gene therapy is the insertion of a normal allele into target cells to **replace a faulty allele**, such as the allele which causes cystic fibrosis. There are two types of gene therapy: **somatic gene therapy** where the allele is introduced to the **target cells only** and **germ line gene therapy** where the allele is introduced to **embryonic cells**, thus meaning **every cell contains the normal allele**. **Somatic** gene therapy is a **short-term solution only** and needs to be repeated, whereas **germ-line** therapy is a **permanent solution which will be passed down to the offspring.**

There are many **ethical considerations** regarding genetic engineering. Benefits of genetic engineering include insect resistance in crops such as soya and genetically used animals used to produce pharmaceuticals. Some people object to genetic engineering due to the potential effect it might have on the environment, or because of the idea that genetically modified seeds would not be as easily available to poorer farmers.

Cystic fibrosis can be treated via somatic cell therapy with the use of liposomes which serve as a means of delivering the gene for a normal CTFR gene into the epithelial cells in the lungs.

Genetic technology applied to medicine

Bioinformatics is the science of collecting and analysing biological data using computer software. For instance, in can be used to build a database of gene sequences as well as complete genomes. This can be used to determine the extent of relatedness of organisms, as well as for identification of human gene counterparts in other organisms. Studying the genome of parasites such as Plasmodium can be used to develop new means of controlling them.

Genetic technology enables screening for genetic conditions such as breast cancer caused by faulty alleles of BRCA1 and BRCA2 genes. In a case where a positive carrier is identified, they can undergo vasectomy to reduce their risk of breast cancer. Genetic screening can also be used **for preimplantation genetic diagnosis and prenatal testing** such as **chorionic villus sampling and amniocentesis.**

Pre-implantation genetic diagnosis – embryos created through IVF are tested for genetic disorders before they are implanted into the woman's uterus.

Chorionic villus sampling – this test is carried out at **8 to 12 weeks** of pregnancy and a sample of **embryonic tissue** is taken from the placenta and the DNA is then analysed, this form of testing is quicker than amniocentesis

Amniocentesis is carried out at **14-16 weeks** and a sample of **amniotic fluid** is obtained using a needle which contains **fetal cells**, the DNA is then analysed. Results are available after 2-3 weeks as fetal cells need to be grown in culture first.

There are many social and ethical issues surrounding genetic testing. Some of the viewpoints are:

- There's a **risk of harm to foetus** of miscarriage
- The outcome of testing might lead to an **abortion**
- **Right to life**
- **The cost** of bringing up a baby with a genetic disorder
- **Emotional and psychosocial issues** surrounding the birth a baby with a disorder

Genetically modified organisms (GMOs) in agriculture

The production of crops such as **soya beans,** which is the source of vegetable oil and biodiesel fuel, may be increased by using varieties that are genetically modified for **herbicide resistance**.

Crop yield increases when the fields are sprayed with herbicide, as weeds which **compete** with the plant for resources are killed, thus making it easier for the plant to grow.

However, there is a chance that the **pollen** transfers the gene for herbicide and insect resistance to wild relatives, thus producing **hybrid offspring** which are herbicide resistant weeds.

Insect-resistant crops can also be created to increase yield, for instance genetically modified **Bt maize** is able to produce own insecticide in the form of **Bt toxin**. This makes Bt maize resistant to **corn borers.**

The increasing demand for food in the world can be solved with the use of genetic engineering. Examples include, **golden rice** containing **beta-carotene** producing genes taken from daffodils and ***Pantoea ananatis*** which can be used to treat **vitamin A deficiency.** This is useful as beta-carotene produced by the plants can be converted to vitamin A in **human cells**.

However, genetically modified seeds need to be purchased each season and are expensive, therefore they are not available to all farmers.

Other examples of GMOs used in food production is the **FlavrSavr tomato** which has an additional gene for an enzyme involved in pectin breakdown in tomatoes. Tomatoes with the additional gene have a longer shelf life and a better flavour.

Stem cells

Stem cells are undifferentiated cells which can keep dividing to give rise to other cell types. Types of stem cells include:

- **Pluripotent cells** - able to **give rise to many types of specialised cells** apart from embryonic cells
- **Totipotent cells –** able to **give rise to all types of specialised cells** including embryonic cells.

Sources of stem cells include **embryonic stem cells, adult stem cells and fused cells**.

Stem cells can be used to **treat a variety of diseases** such as diabetes, multiple sclerosis and Parkinson's disease. They can also be used to **replace damaged tissues** such as nerve tissue in spinal cord injuries. However, there are many **ethical issues** related to the use of stem cells. Stem cells **could save many lives and improve the quality of life** of many people, however many people believe it's unethical as **embryos are killed in the process** of stem cell extraction. Moreover, there's a **risk of infection when cells are transplanted, and they may become cancerous**.