Chapter 3 —> Genetics

3.1 Genes

Genes and loci:

- DNA is the genetic blueprint which codes for, and determines, the characteristics of an organism
- Influences physical, behavioural and physiological features of the organism
- Chromosomes —> structures in which DNA is packaged and organised
- Gene —> a sequence of DNA that encodes for a specific trait
- Locus —> the position of a gene on a particular chromosome

Alleles:

- Are alternative form of a gene that code for the different variations of a specific trait
- Differ from each other by one or a few bases

Mutations:

- A change in the nucleotide sequence of a section of DNA coding for a specific trait
- Beneficial mutations —> (missense mutations) —> create new variations of a trait
- Detrimental mutations —> (nonsense mutations) —> truncate the gene sequence (stop)
- Neutral mutations —> (silent mutations) —> have no effect on the functioning of the feature
- Frameshift mutations —> addition or removal of a base alters the reading frame of the gene
  —> affect every codon beyond the point of mutation

Sickle cell Anaemia:

- Results from a change to the 6th codon in the beta chain of haemoglobin
- DNA —> changes from GAG to GTG (glutamic acid to valine produce)
- mRNA —> changes from GAG to GUG on the 6th codon position
- Insoluble fibrous strands form —> insoluble haemoglobin cannot carry oxygen as effectively
  —> individual constantly tired
  —> sickle shape forms —> creates clots within the capillaries
  —> sickle cells destroy more rapidly, so low red blood (anaemia)

Genome:

- The totality of genetic information of a cell, organism or organelle
- Human genome —> 46 chromosomes, 21000 genes, 3 billion base pairs
- Human Genome Project —> an international cooperative to sequence the human genome
  —> mapping —> number, location, size and sequence of human genes
  —> screening —> allowed to detect sufferers and carriers of diseases
  —> medicine —> new protein discovery lead to improved treatments
  —> ancestry —> lead to insight into origins, evolution a patterns of man

Gene comparisons:

Species	*Escherichia coli*	*Gallus gallus*	*Homo sapiens*	*Daphnia pulex*	*Oryza sativa*
Number of Genes	~4,200	~17,000	~21,000	~31,000	~38,000
Common Name	 Bacteria	 Chicken	 Human	 Water flea	 Rice

-Number of genes is not a valid indicator of biological complexity

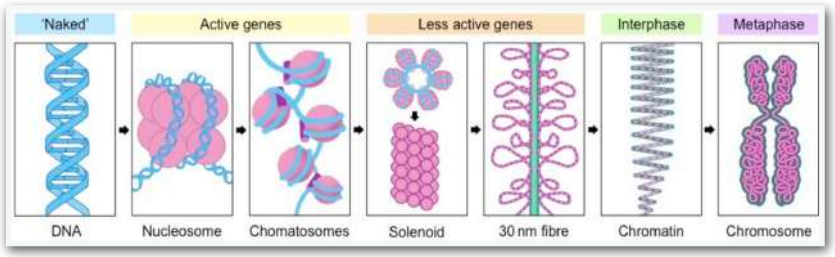
3.2 Chromosomes

Prokaryotic genetics:

- Prokaryotes do not possess a nucleus
- DNA is instead naked and in the cytoplasm (nucleoid)
- Plasmids —> small, circular DNA molecules that contain a few genes and can self-replicate
  —> bacterial cells may exchange plasmids via their sex pili
- Genophore —> naked strand of DNA

Eukaryote Genetics:

- The packaging of DNA with histone proteins results in a greatly compacted structure



Identifying Genes (ex. 7q31) :

- p arm —> longer section
- q arm —> shorter section
- First number —> chromosome number
- Third letter —> position of the arm

Homologous pairs:

- Sexually reproducing organisms inherit their genetic sequences from both parents (2 x chrom.)
- Homologous chromosomes —> maternal and paternal chromosome pairs
  —> share the same structural features
  —> share the same genes at the same loci position, alleles may differ

Diploid vs Haploid:

- Diploid (2n) —> two sets of chromosomes
  —> will possess two gene copies (alleles) for each trait
  —> all somatic body cells are diploid, new ones created via mitosis
- Haploid (n) —> sex cells (gametes) with half the number of chromosomes
  —> will possess a single gene copy (allele) for each trait
  —> all sex cells are derived from diploid cells via meiosis

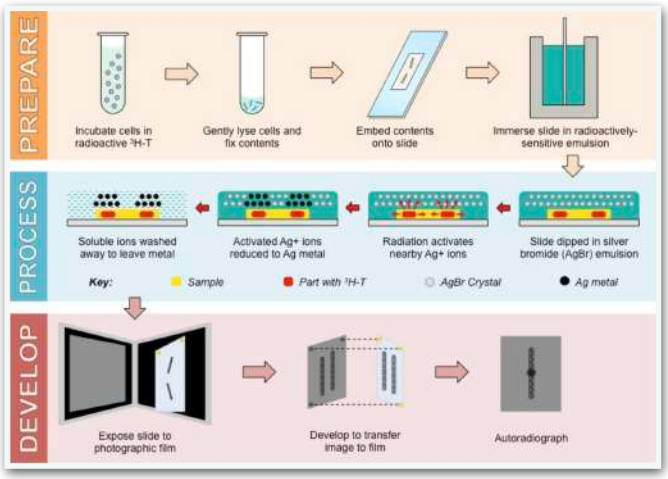
Autosome vs Heterosome:

- Sex chromosomes —> determine the sex of individual (xx female) (xy male non-homologous)
- The Y chromosome contains the genes for developing male sex characteristics
- The Y chromosome is contained in the male sperm
- Autosomes —> the remaining chromosome in the organism

Karyograms:

- Karyotypes —> the number and types of chromosomes in a eukaryotic cell —> harvesting cells and chemically inducing cell division and arresting mitosis while chromosomes are condensed
- Karyograms —> the visual profile generated

Autoradiography:



Chromosome length:

-John Cairns —> invented a technique for measuring the length of DNA molecules
-Previously chromosomes only measured while condensed
-DNA replication involves formation of a replication bubble
-DNA replication is bi-directional

3.3 Meiosis

Meiotic division:

- Meiosis —> the process by which sex cells are made in the reproductive organs
- Reduction division of a diploid germline cell into four genetically distinct haploid nuclei
- Consists of two cellular divisions —> first meiotic division separates pairs of homologous chromosomes to halve the chromosome number (diploid —> haploid)
  —> second meiotic division separates sister chromatids
- Sister chromatids —> separated during meiosis II

Stages of meiosis:

- Interphase —> DNA is replicated to produce chromosomes consisting of two sis chromatids
- Interkinesis —> may occur between meiosis I and II, but no DNA replication occurs

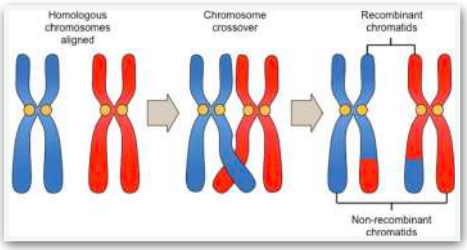
Meiosis I:

- P I —> chromosomes condense, nuclear membrane dissolves, hom. chromosomes form bivalents and crossing over occurs
- M I —> spindle fibres from opposing centrosomes connect to bivalents and align at the equator
- A I —> spindle fibres contract and split the bivalent, hom. Chromosomes move to opposites
- T I —> chromosomes decondense, nuclear membrane reform, cytokinesis (two haploid cells)

Meiosis II:

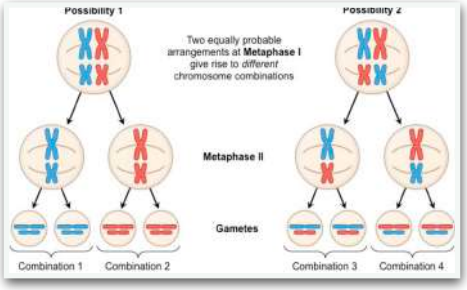
- P II —> chromosomes condense, nuclear membrane dissolves, centrosomes move to opposites
- M II —> spindle fibres from opposing centrosomes attach to chrom. and align at the equator
- A II —> spindle fibres contract and separate the sis chromatids bringing them to opposites
- T II —> chromosomes decondense, nuclear membrane reforms, cytokinesis (four haploid cells)

Crossing over:



- May occur in prophase I —> hom. chromosomes undergo synapsis, in which they pair up in bivalents
- Chiasmata —> were hom. chromosomes are held together
- Recombination —> new gene combinations are formed on chromatids
- If crossing over occurs the haploid cells will be genetically distinct (sister chromatids are no longer identical)

Random/independent Assortment:



- During metaphase I —> hom. chromosomes line up at the equator as bivalents in 2 possibilities
- Random —> the orientation of pairs of hom. chromosomes is random
- Gamete combinations —> 2^n (23 haploid number for humans)

Sexual life cycle:

- In order to reproduce, organisms need to make gametes that are haploid
- Fertilisation of two haploid gametes (egg + sperm) results in the formation of a diploid zygote
- If chromosome number was not halved in gametes, chromosomes would double each generation

Genetic variation:

- Meiotic division and sexual reproduction promote genetic variation in offsprings

- Crossing over —> Offspring with recombinant chromosomes will have unique gene combinations which are not present in either parent
- Random orientation —> if crossing over also occurs, the number of different gamete combinations becomes immeasurable
- Random fertilisation —> will always generate different zygotes

Non-disjunction:

- Refers to the chromosomes failing to separate correctly, resulting in gametes with one extra or missing chromosome (aneuploidy)
- May occur via —> failure of homologues to separate in anaphase I
  —> failure of sister chromatids to separate in anaphase II
- Chromosomal abnormalities —> if a zygote is formed from a gamete that has experience non-disjunction, the resulting offspring will have extra or missing chromosomes in every body cell
- Monosomy —> one chromosome less ; Trisomy —> one chromosome more

Down syndrome:

- Have three copies of chromosome 21 (trisomy 21) as a result of non-disjunction
- Studies show that the chances of non-disjunction increase as the age of parents increase

Karyotyping:

- Typically used to determine the gender of an unborn child and see chromosomal abnormalities

Chorionic Villi sampling:

- The removal of a sample of the chorionic villus (placental tissue) via a tube inserted via cervix
- It can be done at around 11 weeks of pregnancy with a slight risk of inducing miscarriage +-1%

Amniocentesis:

- Involves the extraction of a small amount of amniotic fluid (contains fetal cells) with a needle
- Usually done around 16 weeks of pregnancy with a low risk of miscarriage +- 0.5%

Nuclear translucency scan:

- Non-invasive test —> done in the 11 / 13 week of pregnancy with an ultra-sound scan
- Large amount of nuchal fluid is strongly correlated with down syndrome

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3.4 Inheritance

Mendel's law:

- An Austrian monk who developed the principles of inheritance from experiments on pea plants
- Organisms have discrete factors that determine its features
- Organisms possess two versions of each factor and each gamete has one version of each factor
- Parents contribute equally to the inheritance of offspring
- For each factor, one version is dominant over another and will be expressed

1) Law of segregation —> when gametes form, alleles separate so that each gamete carries only one allele for each gene
2) Law of independent assortment —> the segregation of alleles for one gene occurs independently to that of any other gene
3) Principle of dominance —> recessive alleles will be masked by dominant alleles

Haploid gametes and zygosity:

- Gametes —> haploid sex cells formed by meiosis (males produce sperm; women produce ova)
- As gametes contain only one copy of each chromosome, they can only carry one allele per gene
- During fertilisation, two alleles are present for each gene apart for the male sex chromosome Y

- Homozygous —> the maternal and paternal alleles are the same
- Heterozygous —> the maternal and paternal alleles are different
- Hemizygous —> only one allele present (XY combination)

Modes of Inheritance:

- Genotype —> the gene composition for a specific trait
- Phenotype —> the observable characteristic of a specific trait (determined by genotype and env.)

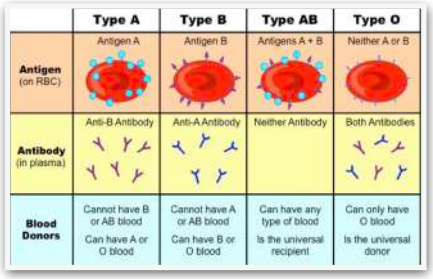
Complete dominance:
- The dominant (A) allele will mask the recessive (a) allele when in a heterozygous state
- Homozygous dominant and heterozygous forms will be phenotypically indistinguishable
- The recessive allele will only be expressed in the phenotype when in a homozygous state

Co-dominance:

- Occurs when pairs of alleles are both expressed equally in the phenotype of a heterozygous
- Have an altered phenotype as the alleles are having a joint effect

ABO human red blood:

- A and B alleles are co-dominant and each modify the structure of the antigen to produce variants
- O allele is recessive and does not modify the basic antigenic structure
- I^A I^B i^O
- Blood transfusions are not compatible between certain blood groups



Punnet grids:

- A monohybrid cross determines the allele combinations for potential offspring for one gene only
- The genotypic and phenotypic ratios calculated via Punnet grids are probabilities

Genetic diseases:

- Are caused when mutations to a gene abrogate normal cellular function, leading to the development of a disease phenotype
- Can be caused by recessive, dominant or co-dominant alleles
- Autosomal recessive genetic diseases need both alleles to be faulty (remain carriers)
- Autosomal dominant genetic diseases only require one copy of a faulty allele to occur
- Co-dominant genetic diseases require one copy of a faulty allele to occur (milder symptoms)

Cystic fibrosis:

- An autosomal recessive disorder caused by a mutation in the CFTR gene on chromosome 7
- Individuals produce mucus which is unusually thick and sticky
- The mucus clogs the airways and secretory ducts of the digestive system —> respiratory failure and pancreatic cysts
- Malaria cannot infect sickle cell as red blood cells are too small Hb^A Hb^S s = sickle / a= normal

Huntington's disease:

- An autosomal dominant disorder caused by a mutation to the HTT gene on chromosome 4
- HTT gene —> possesses a repeating CAG that is usually present in low amounts (10-25 repeats)
- More than 28 CAG repeats are unstable and cause the sequence to amplify
- When repeats exceed 40, the protein will misfiled and cause neurodegeneration
- Usually occurs in late adulthood around 40 years
- Symptoms —> uncontrollable spasmodic movements and dementia

Sex linked genes:

- When a gene controlling a characteristic is located on a sex chromosome
- Y chromosome —> much shorter than the X chromosome and contains only a few genes
- X chromosome —> longer and contains many genes not present in the Y chromosome
- Sex-linked conditions are usually X-linked as very few genes exist on the Y chromosome
- X-linked dominant traits are more common in females
- X-linked recessive traits are more common in males as disease cannot be masked by other allele

Haemophilia:
- A recessive genetic disorder in which the body's ability to control blood clotting is impaired
- Coagulation factors are located on the X chromosome
- Fibrin formation is prevented (responsible to stop blood)
- Different forms can occur depending on which coagulation factor is mutated
- Can be treated by using injections of clotting factors produced industrially via gene transfer

Red-Green colour blindness:
- A recessive genetic disorder in which an individual fails to discriminate between red and green
- Caused by a mutation to the red or green retinal photoreceptors (located on the X chromosome)
- Can be diagnosed using the Ishihara colour test

Gene mutation rates:

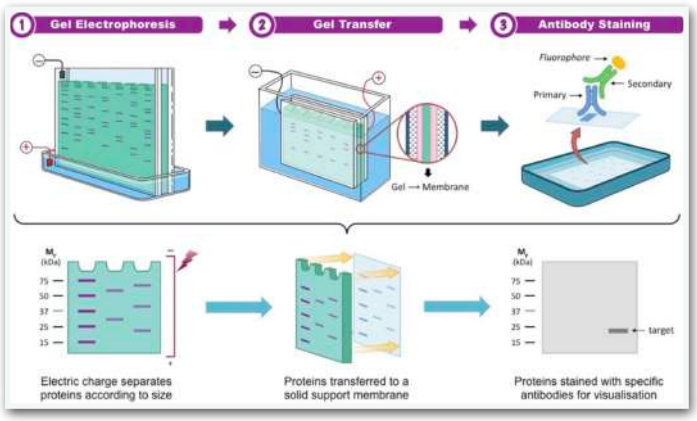
- A change to the base sequence of a gene that can affect the structure and function of the protein
- Mutations can be spontaneous or induced by exposure to external elements
- Radiation, chemical and biological elements can cause mutations
- Mutagens —> agents which increase the rate of genetic mutations and can lead to mutations

- Hiroshima —> elevated rate of leukemia
  —> elevated rates of other cancers
- Chernobyl —> at least 6000 thyroid cancers
  —> horses and cattle died
  —> contained meat banned for year

3.5 Genetic modification and biotechnology

Gel electrophoresis and DNA profiling:

- Laboratory technique used to separate and isolate proteins or DNA fragments based on size
- DNA profiling —> a technique by which individuals can be identified and compared via their respective profiles
- Short tandem repeats —> DNA made up of repeating elements
- Commonly used in criminal investigations and to settle paternity disputes —> the more DNA fragments combine higher the match

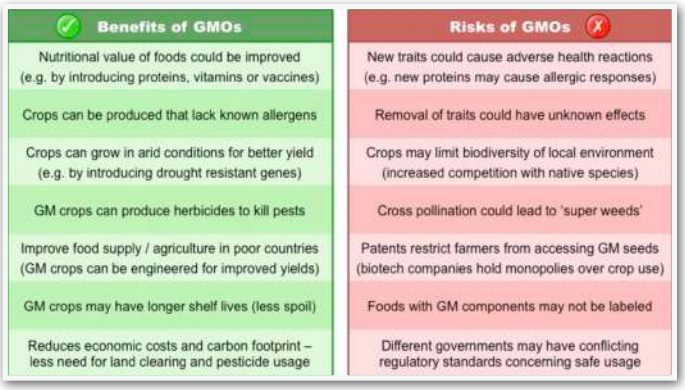


Gene transfer:

1) isolation of gene and vector by PCR
   —> bacterial plasmids are commonly used as vectors as they can self-replicate and express
2) Digestion of gene and vector by restriction endonuclease
   —> restriction enzymes cleave the sugar-phosphate generating sticky ends
3) Ligation of gene and vector by DNA ligase

—> the gene of interest is inserted into the plasmid vector, and this is possible only because the sticky ends of the gene and vector overlap via complementary base pairing

4) Selection and expression of transgenic construct
the recombinant construct is introduced into an appropriate host cell or organism



Benefits of GMOs	Risks of GMOs
Nutritional value of foods could be improved (e.g. by introducing proteins, vitamins or vaccines)	New traits could cause adverse health reactions (e.g. new proteins may cause allergic responses)
Crops can be produced that lack known allergens	Removal of traits could have unknown effects
Crops can grow in arid conditions for better yield (e.g. by introducing drought resistant genes)	Crops may limit biodiversity of local environment (increased competition with native species)
GM crops can produce herbicides to kill pests	Cross pollination could lead to 'super weeds'
Improve food supply / agriculture in poor countries (GM crops can be engineered for improved yields)	Patents restrict farmers from accessing GM seeds (biotech companies hold monopolies over crop use)
GM crops may have longer shelf lives (less spoil)	Foods with GM components may not be labeled
Reduces economic costs and carbon footprint – less need for land clearing and pesticide usage	Different governments may have conflicting regulatory standards concerning safe usage

GMO debate:

-GMO organisms are used in agriculture to improve crop yields and reduce farming costs
-GM crops can be used to improve human nutritional standards

Bt corn:
- A genetically modified maize lethal to certain types of larvae
- The caterpillar stage of the monarch feeds on milkweed which commonly grows on the edge of corn fields
- Studies show that monarchs fed with milkweed leaves covered with Bt corn pollen tend to have a high rate of mortality

Clones:

- A group of genetically identical organisms or cells derived form a single original parent cell
- Mechanisms exist whereby sexually reproducing organisms can produce clones
- Stem cells can be artificially generated from adult tissue using SCNT

Somatic Cell Nuclear Transfer:
- A method by which cloned embryos can be produced using differentiated adult cells
- The advantage is that it is known what traits the clones will develop
- Reproductive (offspring) or therapeutic cloning (new tissues or organs)

1) Somatic cells are removed form the adult donor and are culture
2) An unfertilised egg is removed from a female adult and its haploid nucleus is removed
3) The enucleated egg cell fuses with the nucleus from the adult donor to make a diploid egg cell
4) An electric current is used to stimulate the egg to divide and develop into an embryo
5) The embryo is the implanted into the uterus of a surrogate and will develop into a genetic clone

Natural cloning:
- Binary fission —> the parent organism divides equally in two to produce two genetically identical daughter organisms
- Budding —> cells split off the parent organism generating a smaller daughter organism which eventually separates from the parent
- Fragmentation —> new organisms grow from a separated fragment of the parent organism
- Parthenogenesis —> embryos are formed from unfertilised ova
- Vegetative propagation —> small pieces can be induced to grow independently thanks to the totipotent meristematic tissue possessed by the adult plants
- Monozygotic twins —> created when a fertilised egg splits into two identical cells, two embryos
- Dizygotic twins —> an unfertilised egg splits into two cells, then fertilised by two diff. sperms

Embryonic cells:

- Are pluripotent and can be separated artificially in the laboratory or naturally
- The separation of embryonic cells has to happen early in the development cycle (8th stage)
- The separated groups of cells are then implanted into the uterus of a surrogate
- The embryo used is formed randomly via sexual reproduction, so the genetic features can vary

Stem cutting:

- A separated portion of plant stem that can regrow into an independent clone via vegetative prop.
- Nodes —> points from which a leaf, branch or aerial root may grow
- Internode —> points between nodes
- Stem cutting is a common method employed to rapidly propagate plant species
- Variables are —> cutting position and length, growth medium, concentration of growth hormones, temperature conditions, availability of water and other environmental conditions

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Extra:

Sickle cell versus malaria:

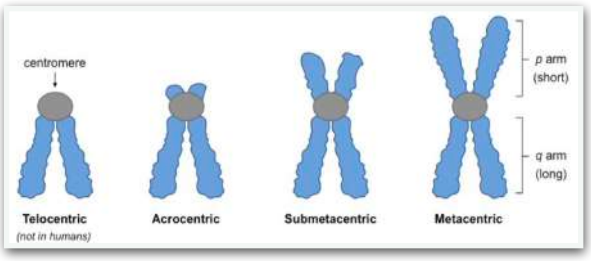
- Sickle cell anaemia is controlled by a single gene mutation
- Individuals who only possess the sickle cell allele will have abnormally shaped red blood cells that are destroyed by the spleen —> reduction in red blood cells
- Individuals who only possess the normal blood cell allele do not suffer from sickle cell anaemia but are more susceptible to malaria
- Incidence of malaria —> in areas where malaria is common there is a higher incidence who carry both alleles —> produce enough normal blood to avoid severe effects, but also produce enough sickle cells to give an increased resistance to the malarial parasite (heterozygous advantage)

Genome structure:

- Comprises of roughly 3.2 billion base pairs across 46 chromosomes —> only a small fraction of 1.5 % of these, sequences code for functional genes
- The remainder is made up of repeating elements, pseudogenes, microsatellites and transposons
- Transposons —> a segment of DNA that inserts itself into another section within the genome
- Pseudogenes —> a non functional sequence of DNA that is homologous to an active gene
  —> Processed pseudogenes —> portion of DNA raised from reversed transcription
  —> Non-processed pseu. —> arise from gene duplication and inactivation mutation

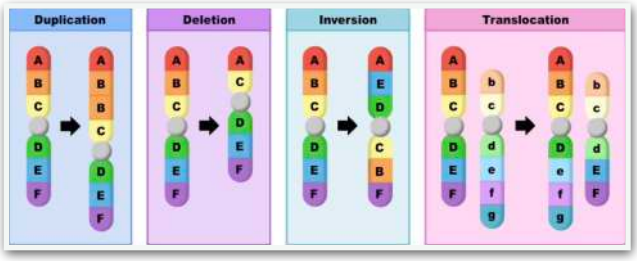
Chromosome types:

- Metacentric —> centromere in the middle
- Submetacentric —> centromere off-centre vs top
- Acrocentric —> centromere off-set severely
- Telocentric —> centromere at end of chromosome



Block mutations:

- Are caused by transposons, which by changing positions within the genome alter the sequence



Mitosis versus Meiosis:

	Mitosis	Meiosis
Divisions	One	Two
Independent Assortment	No	Yes (metaphase I)
Synapsis	No	Yes – form bivalents
Crossing Over	No	Yes (prophase I)
Outcome	Two cells	Four cells
Ploidy	Diploid	Haploid
Use	Body cells	Sex cells (gametes)
Genetics	Identical cells	Variation

Somatic vs Germline mutations:

-Somatic mutations —> occur in a single body cell and cannot be inherited
-Germline mutations —> occur in gametes and can be passed onto offspring

Polyploidy:

- A condition whereby an organism has more than two complete sets of chromosomes in all cells
- Far more common in plant species which lack separate sexes and are capable of self-pollination
- Very rare in animal species due to the consequences of having extra allele copies of every gene

Lethal alleles:

- Alleles that cause an organism to die only when present in a homozygous condition —> the gene involved is considered an essential gene and the lethal allele may be either dominant or recessive
- Achondroplasia —> a genetic condition which causes dwarfism —> when dominant and present in the homozygous state it causes death, heterozygous will be dwarf, and homozygous recessive people will be in normal size

Epistasis:

- Describes a condition whereby one gene controls the expression of another gene
- Example —> Black fur is dominant to brown fur, but in absence of hair pigment mice will appear albino

Pleiotropy:

- Occurs when a single gene affects multiple traits —> mutations will tend to be severe and affect multiple systems
- Sickle cell anaemia —> the rapid breakdown of red blood cells causes anaemia —> leads to increased lethargy and higher risks of infection
  —> clotting of sickle cells in vessels can cause heart attacks + brain damage
  —> accumulation of blood cells in specific organs can lead to loss function

Mosaicism:

- Describes presence of two populations of cells with distinct genotypes within a single organism
- More pronounced when errors occur in early embryo development (affects more cells)

Vector delivery:

- A vehicle that is used to deliver genetic material to a target cell via horizontal gene transfer
- Non-viral delivery —> commonly via plasmids which can be introduced in cells by:
  —> electroporation —> electric current applied (makes holes in membrane)
  —> heat shocking —> heat destabilises the cell membrane
  —> particle bombardment —> DNA-coated particles are shot into the cells
  —> microinjection —> a glass micropipette injects vector directly in the cell
  —> lipofection —> vector is transferred within a liposome in the cell
- Viral delivery —> transduction —> insertion of a viral vector into a cell
  —> viruses integrate their DNA into the host genome (beneficial or detrimental)
  —> advantage —> protein synthesis will be driven by endogenous expressions
  —> disadvantage —>random insertion into the genome may abrogate key host genes
- Viruses can have either a DNA genome (adenovirus) or an RNA genome (retrovirus)

Examples of GMOs:

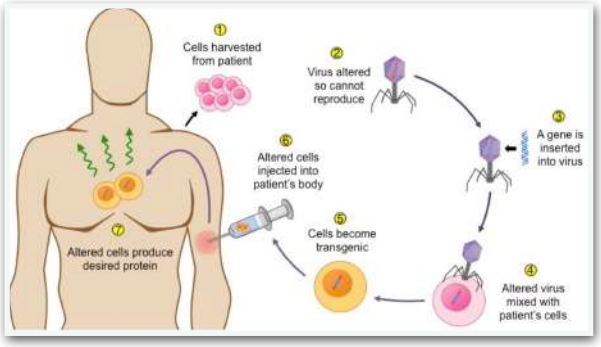
GMO	Description	Picture
Golden Rice	Rice modified with daffodil genes to have more beta-carotene, which the body converts to Vitamin A	
Flavr Savr Tomatoes	Tomatoes modified by the removal of genes responsible for the softening of fruit, meaning the tomatoes spoil more slowly	
Bt Corn	Corn modified with a bacterial insecticide gene so that it produces insect toxins within its cells, protecting it from pest species	
Aqua Advantage Salmon	Salmon modified with growth hormone regulating genes in order to grow to market sizes in significantly less time	
Glow in the Dark Animals	Animals modified with genes for fluorescent proteins will glow in the dark – this novel feature serves no practical purpose	

cDNA and Microarrays:

-Individuals can be screened for genetic diseases and cancers by using cDNA and microarrays
-cDNA —> a molecule synthesised from an mRNA template via reverse transcription —> represent gene sequences that are actively transcribed by cells
-Microarray —> a collection of microscopic DNA sequences attached to a solid surface —> represent fractions of a large library of genes present in a cell
—> If a gene is active within a cell, then the cDNA (produced from the mRNA transcript) will bind to its complementary oligo

Gene therapy:

- Inserting genes into an individual's cells to treat hereditary diseases (replaces defective alleles)
- Example —> in humans, in the treatment of adenosine deaminase (ADA) deficiency (autosomal recessive disease causing severe combined immunodeficiency (SCID) in sufferers) —> Individuals who have done gene therapy show an increase in the levels of ADA



Gene silencing:

- The ability of a cell to prevent the expression of a particular gene
- Gene knockout —> genetic technique in which a specific gene is made inoperative in a organism
- The Cre-LoxP system uses the enzyme Cre recombinase to remove genetic sequences located between two Lox sites —> Using recombinant DNA technology, LoxP sequences are inserted on either side of a gene of interest in a test animal —> The Cre gene is inserted next to a tissue-specific promoter in another test animal —> When the two animals are bred, the resulting offspring will possess LoxP sequences and a tissue-specific Cre recombinase —> The Cre recombinase removes the gene located between the Lox sites (creates a conditional knockout)