Pathology - Topic 11 - Genetic and pediatric diseases

Genetic Mechanisms of Disease

- Genetic disease results when an alteration in genetic material disturbs development, cellular function or regulation.

Genes, Chromosomes and Variation

- The alteration may affect a single gene, a chromosome segment, chromosome number or interactions between several genes and the environment.
- A genetic disorder is not necessarily inherited from a parent because a new alteration can arise in an egg, sperm or early embryo.
    - A hereditary disorder is transmitted through the germline, while a somatic alteration is restricted to affected body-cell lineages.
- **Genotype** describes the genetic constitution, while **phenotype** describes the observed features.
    - The same genotype may produce variable severity because of other genes, environment and chance developmental events.

Important Types of Gene Alteration

1. Sequence Variants

- A **missense** change replaces one amino acid with another, which may alter protein structure or function.
    - A **nonsense** change creates a premature stop signal and may reduce or eliminate a functional protein.
- An insertion or deletion can cause a **frameshift** when it changes the reading frame.
    - A splice-site change can alter the way RNA segments are joined and produce an abnormal transcript.
- Some variants are harmless, while others cause loss of function, gain of function or a harmful interaction with a normal protein.

Examples That Link Mutation to Disease

- The sickle haemoglobin substitution changes the beta-globin protein and permits deoxygenated haemoglobin polymerisation.
- Loss-of-function variants in CFTR impair epithelial chloride transport in cystic fibrosis, with effects on airway and ductal secretions.
- A dominant-negative variant produces an abnormal protein that interferes with the normal protein product, as in selected structural-protein disorders.
- A gain-of-function variant increases or alters protein activity, so one abnormal allele may cause disease even when another functional allele remains.

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2. Copy-Number and Repeat Changes

- Deletion or duplication of a DNA segment can reduce or increase the dosage of one or more genes.
    - The effect depends on the size, location and biological roles of the affected genes.
- Expansion of repeated DNA sequences can impair gene function or create a harmful product.
    - Some repeat disorders show **anticipation**, with earlier or more severe disease in successive generations as the repeat expands.
- Fragile X syndrome commonly involves expansion of a CGG repeat with methylation-associated silencing of FMR1.
- Repeat expansion may require a dedicated assay because standard sequencing does not detect every repeat size reliably.

Inheritance Patterns

1. Autosomal Dominant and Recessive Patterns

A. Autosomal Dominant Inheritance

- In an autosomal dominant disorder, one pathogenic allele may be sufficient to produce disease.
- An affected person may have an affected parent, but a new variant or reduced penetrance can obscure the family pattern.

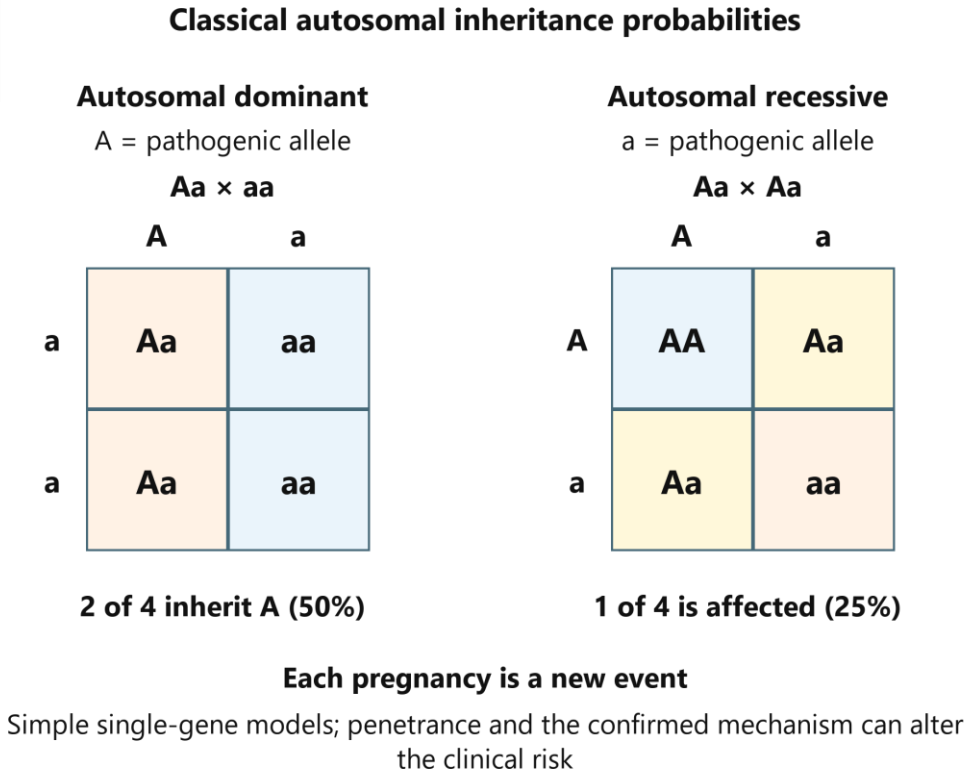
B. Autosomal Recessive Inheritance

- In an autosomal recessive disorder, disease usually results when both copies of a relevant gene carry pathogenic alterations.
- Parents are often clinically unaffected carriers, and consanguinity can increase the chance of sharing a rare allele.

C. Classical Pedigree Probabilities

- In a simple autosomal dominant model, a heterozygous affected parent and an unaffected parent have a one-in-two chance of transmitting the variant in each pregnancy.
- Two carriers of the same autosomal recessive disorder have a one-in-four chance of an affected child in each pregnancy.
- These are model probabilities, and recurrence counselling also depends on the confirmed mechanism, penetrance and parental testing.

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Classical autosomal inheritance probabilities

2. X-Linked and Mitochondrial Patterns

A. X-Linked Inheritance

- X-linked disorders can affect males more severely because they usually have only one X chromosome.
- Females may also be affected, depending on the disorder and X-chromosome inactivation.

B. Mitochondrial Inheritance

- Pathogenic mitochondrial DNA variants are usually transmitted through the mother.
- Variable mixtures of normal and altered mitochondrial DNA, called heteroplasmy, help explain differences in severity.

Penetrance and Variable Expressivity

- **Penetrance** is the proportion of people with a genotype who show its associated phenotype.
  - **Variable expressivity** means that affected people show different degrees or combinations of features.

Genomic Imprinting

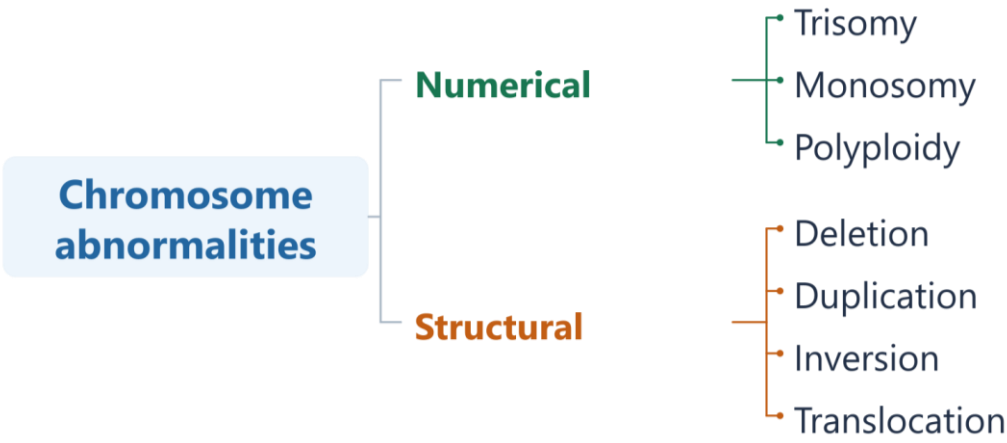
- Genomic imprinting makes the expression of some genes depend on the parent from whom the allele was inherited.
  - An alteration affecting an imprinted region can therefore have different consequences according to parental origin.

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Cytogenetic Abnormalities

- Cytogenetic abnormalities are changes in chromosome number or structure that may disturb development or cellular function.

Numerical and Structural Changes



1. Numerical Changes

- **Aneuploidy** is an abnormal number of individual chromosomes, such as a trisomy or monosomy.
  - Meiotic nondisjunction can produce an egg or sperm with an extra or missing chromosome.
- **Polyploidy** means an additional complete set of chromosomes, as in triploidy.
  - It usually causes severe developmental abnormalities and differs from an extra copy of one chromosome.
- A post-zygotic error can produce **mosaicism**, in which different cell populations have different chromosome complements.
  - The clinical effects depend partly on the distribution of those populations among tissues.

2. Structural Changes

- Structural abnormalities include deletions, duplications, inversions and translocations.
  - A balanced rearrangement may preserve the total amount of genetic material but can still disrupt a gene or affect reproductive risk.
- An unbalanced rearrangement changes the dosage of genetic material and can cause developmental abnormalities.

Down Syndrome

- Down syndrome results from extra genetic material from chromosome 21, most often a full trisomy.

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Chromosome 21 and Clinical Features

- Less commonly, a translocation or mosaicism produces the relevant dosage imbalance.
- Features may include characteristic facial appearance, hypotonia, developmental differences and congenital heart disease.
    - Atrioventricular septal defects are an important cardiac association.
- There is increased susceptibility to selected haematological disorders and later Alzheimer-type pathology.
    - The exact clinical pattern varies, and a karyotype helps define the mechanism relevant to family counselling.

Chromosome Mechanism and Morphological Associations

- Most cases result from meiotic nondisjunction, with a maternal-age association; a smaller proportion involves Robertsonian translocation or mosaicism.
- A single transverse palmar crease, epicanthic folds and a flattened facial profile are supportive physical features rather than individually diagnostic findings.
- Duodenal atresia and Hirschsprung disease are important gastrointestinal associations.

Trisomy 18 and Trisomy 13

- Trisomy 18 and trisomy 13 are chromosomal disorders caused by an extra copy of chromosome 18 or chromosome 13, respectively.

Pathogenesis and Pathological Features

- Trisomy 18 can produce severe developmental impairment, growth restriction, clenched hands with overlapping fingers, rocker-bottom feet and organ malformations.
    - Trisomy 13 can produce holoprosencephaly, microphthalmia, cleft lip or palate, polydactyly and congenital heart defects.
- Both disorders have variable presentations influenced by the chromosome abnormality and associated malformations.
    - A phenotype suggests the diagnosis, but chromosome testing confirms it and identifies mosaic or structural forms.

Turner Syndrome

- Turner syndrome results from complete or partial loss of one sex chromosome in a person with a female developmental phenotype.

Chromosomal Basis

- The chromosome pattern may be 45,X or a mosaic or structural variant.

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