

9.2 Mechanism of inheritance/ disease transmission

There are several different types of inheritance patterns with different underlying mechanisms. These may involve single nuclear genes (autosomal dominant, autosomal recessive, X-linked recessive, X-linked dominant), single mitochondrial genes (section 9.3), chromosomal rearrangements, imprinting (section 9.4) and multifactorial inheritance (see figure).

Autosomal Dominant

- Vertical transmission, from one generation to the next.
- Female and males equally affected.
- Male to male transmission possible.
- Heterozygotes are phenotypically affected.
- Each child has a 50% chance of inheriting the gene mutation.
- Variable penetrance (frequency of developing the phenotype) and variable expression (severity of disease) due to modifiers (genetic and environmental).
- Anticipation is a worsening of disease severity in successive generations.
- Examples, dominant polycystic kidney disease, myotonic dystrophy, marfan syndrome, Huntington's disease, neurofibromatosis type 1, familial adenomatous polyposis, familial breast cancer.

Autosomal Recessive

- Usually affected siblings in one generation only, unless consanguineous family or high population carrier frequency.
- Female and males equally affected.
- Heterozygotes usually unaffected, i.e. healthy carriers.
- Heterozygotes may have a survival advantage, e.g. sickle cell trait and malaria protection.
- When both parents are carriers, each child has a 1 in 4 chance of developing phenotype, unaffected offspring have 2 in 3 carrier risk.
- All offspring of affected individuals will be obligate carriers.
- Examples, cystic fibrosis, thalassaemia, most inborn errors of metabolism, alpha1-antitrypsin deficiency.

X-linked Recessive

- Males more severely affected than females.
- Females may be affected if skewed X inactivation or has Turner syndrome (45,X0).
- No male to male transmission.
- For carrier female, each son and each daughter has 50% chance of inheriting the gene mutation.
- For affected males, all sons will be unaffected and all daughters will be carriers.
- Examples, duchenne muscular dystrophy, haemophilia, red-green colour blindness, fragile X syndrome, Alport syndrome.

X-linked Dominant

- Often lethal in males.
- Heterozygote females affected and more severe if skewed X inactivation or has Turner syndrome (45,X0).
- No male to male transmission.
- For carrier female, each son and each daughter has 50% chance of inheriting the gene mutation.
- For surviving affected male, all sons will be unaffected and all daughters will be affected.
- Males born with features of severe X-linked dominant condition that is normally lethal may have klinefelter syndrome (47,XXY).

- Examples, X-linked hypophosphatasia, incontinentia pigmenti, Rett syndrome.

Mitochondrial Disease

(See section 9.3)

Chromosomal Rearrangements

(see section 9.1)

Imprinting

(see section 9.4)

Multifactorial

- Development of disease depends on genetic and environmental factors.
- Risk greatest amongst close relatives and decreases with increasing distance of relationship.
- Risks to relatives greater if proband severely affected.
- If 2 or more affected relatives, increased risk to relatives.
- Examples, ischaemic heart disease, type 1 diabetes, schizophrenia.

Types of DNA mutation

Some mutations are clearly pathogenic, e.g. deltaF508 (a deletion of phenylalanine at codon position 508 of the CFTR gene) in cystic fibrosis. However, many mutations are now described which may represent normal variation within the general population (polymorphisms). If there is any doubt, mutation results should be discussed with a clinical or molecular geneticist.

Missense mutations

- A mutation that results in an altered amino acid sequence in the encoded protein. The protein is of normal length.
- Not all missense mutations are pathogenic.

Protein truncating mutations

- Mutations that result in a shortened protein are nearly always pathogenic.

Nonsense mutations

- Single nucleotide substitutions that encode 'stop' codons.

Frameshift mutations

- Base pair deletions or insertions that alter the reading frame, producing a premature 'stop' codon.

Splice site mutation

- A base pair change(s) that alters the position of splicing between exons and introns.

Large deletions or duplications

- May involve more than one gene

Trinucleotide expansion

- See section 9.4

Pictures: Examples of different inheritance patterns
Deletions/ Dups PMP22, 5pb deletion at codon 1061 in APC
gene
Splice site
Large deletions
Expansion