

# Genetics

## Basic concepts

### Karyotyping

- used to view the arrangement of the chromosomal make-up of somatic cells
- the procedure is as follows:
  1. arrest cell division at an appropriate stage
  2. disperse the chromosomes
  3. fix the chromosomes
  4. stain the chromosomes
  5. photograph the chromosomes
  6. identify the chromosomes
  7. arrange the chromosomes

### Chromosomes

- centromere = the constricted region of each chromosome that is particularly evident during mitosis and meiosis
- metacentric chromosomes = centrally or almost centrally positioned centromere
- acrocentric chromosomes = centromere is near one end
- chromosomal map: agreed at the International Paris Conference in 1971:
  - 1<sup>st</sup> position: a number (1-22) or letter (X or Y) which identifies the chromosome
  - 2<sup>nd</sup> position: p (short arm) or q (long arm) of chromosome
  - 3<sup>rd</sup> position: a digit corresponding to a stretch of the chromosome lying between two relatively distinct morphological landmarks
  - 4<sup>th</sup> position: a digit corresponding to a band derived from the staining properties of the chromosome

### Mitosis

1. interphase
2. prophase
3. metaphase
4. anaphase
5. telophase

### Meiosis

- occurs during gametogenesis and involves two stages of cell division

  1. interphase
  2. prophase I – recombination takes place
  3. metaphase I
  4. anaphase I
  5. telophase I
  6. prophase II
  7. metaphase II
  8. anaphase II
  9. telophase II

## Gene structure

- consist of codons, which are grouped into:
  - introns: intervening nucleotide sequences
  - exons: code for amino acids
- a typical eukaryotic cell, starting from the 5' end (upstream) contains:
  - upstream site regulating transcription
  - promotor (TATA)
  - transcription initiation site
  - 5' noncoding region
  - exons
  - introns
  - 3' noncoding region, containing a poly A addition site

## Patterns of inheritance

### Law of uniformity

- consider two homozygous parents with genotypes RR and rr; mating results in the first generation (F1) as follows:
  - Parents: RR x rr
  - F1: Rr

### Mendel's first law (the law of segregation)

- Parents: Rr x rr
- F1: RR: Rr: rr = 1:2:1

### Mendel's second law (the law of independent assortment)

- Parents: RRSS x rrss
- F1: RrSs
- F2: independent assortment of different alleles → RRSS, RRSs, ..., rrss

## Autosomal Dominant

1. the phenotypic trait is present in all individuals carrying the dominant allele
  2. the phenotypic trait does not skip generations – vertical transmission takes place
  3. males and females are affected
  4. male to male transmission can take place
  5. transmission is not solely dependent on parental consanguineous matings
  6. if one parent is homozygous for the abnormal dominant allele, all the members of F1 will manifest the abnormal phenotypic trait
  7. half the offspring of an affected heterozygote will exhibit the abnormal trait
- variable expressivity can cause clinical features of autosomal dominant disorders to vary between individuals
  - together with reduced penetrance, this can give the appearance that the disorder has skipped a generation

### Autosomal recessive

1. heterozygous individuals are generally carriers who do not manifest the abnormal phenotypic trait
2. the rarer the disorder, the more likely it is that the parents are consanguineous
3. the disorder tends to miss generations but the affected individuals in a family tend to be found among siblings – horizontal transmission takes place

### X-linked recessive

1. all male offspring manifest the abnormal phenotypic trait
2. male-to-male transmission does not take place – all of the daughters of an affected male will be carriers
3. female heterozygotes are carriers; affected females are rare

### X-linked dominant

1. if an affected male mates with an unaffected female, all the daughters and none of the sons are affected
2. if an unaffected male mates with an affected heterozygous female, half the daughters and half the sons are affected
3. male-to-male transmission does not take place

### Some terms

- **anticipation** – refers to the occurrence of an autosomal dominant disorder at earlier ages of onset or with greater severity in the succeeding generations
- **mosaicism** – abnormalities in mitosis can give rise to an abnormal cell line
- **uniparental disomy** – refers to the phenomenon in which an individual inherits both homologues of a chromosome pair from the same parent
- **genomic imprinting** – an allele is differentially expressed depending on whether it is maternally or parentally derived
- **mitochondrial inheritance** – may explain some cases of disorders that affect both male and females but are transmitted through females only and not through males

### Family studies

- an individual's first-degree relatives (parents, siblings, and children) share on average 50% of his genes, while his second-degree relatives share on average 25% of his genes
- shared environment can also be a powerful source of resemblance between relatives, especially for behavioural traits
- tuberculosis, or going to medical school run in families

### Twin studies

- resemblance between twins for continuous variables such as IQ is expressed in terms of an *intraclass correlation coefficient*
- for discrete traits resemblance is expressed in terms of *concordance* rates
- it is the ratio of the MZ:DZ concordance rates that indicates the extent of the genetic contribution, not the MZ concordance by itself
- haphazardly collected twin samples result in:
  - bias in the direction of concordance

- increase in the number of MZ pairs
- in most white European populations the MZ:DZ ratio is about 1:2
- a special type of twin study is to examine MZ twins reared apart (MZA)

### **Adoption studies**

- one of the main flaws is that the placement of adoptees is almost never a random procedure – most agencies will ‘match’ adoptees and adopting parents, so the usual assumption of no correlation between the environments of biological and adopting parents is not completely assured
- parents who put their children up for adoption tend to be more deviant than ordinary parents, and more likely to appear on criminal and alcohol abuse registers

### **Techniques in molecular genetics**

#### Restriction enzymes

- cleave DNA only at locations containing specific nucleotide sequences

#### Gene library

- is a set of cloned DNA fragments representing all the genes of an organism or a particular chromosome

#### Molecular cloning

- can be used to create a gene library
- first, the DNA is cleaved using a restriction enzyme
- the DNA is then spliced into a bacterial plasmid having at least one antibiotic resistant gene
- after the reintroduction of the resulting recombinant plasmid into bacteria, antibiotic selective pressure causes these bacteria to reproduce

#### Gene probes

- lengths of DNA that are constructed so that they have a nucleotide sequence complementary, or almost complementary, to that of a given part of the genome

#### Oligonucleotide probes

- are small gene probes which can detect single-base mutations

#### Southern blotting

- allows the transfer of DNA fragments from gel, where electrophoresis and DNA denaturation have taken place, to a nylon or nitrocellular filter
- autoradiography can then be used to identify the fragments of interest on the filter

#### Restriction fragment length polymorphisms (RFLPs)

- polymorphisms at restriction enzyme cleavage sites that give rise to fragments of different lengths
- they can be used as DNA markers and are usually inherited in a simple Mendelian fashion

## Recombination

- there is alignment and contact of homologous chromosome pairs during prophase I, allowing genetic information to cross over between adjacent chromatids

## Linkage analysis

### Linkage

- is the phenomenon whereby two genes close to each other on the same chromosome are likely to be inherited together

### Linkage phases

- for two alleles occurring at two linked loci in a double heterozygote, the following linkage phases can occur:
  - coupling = the two alleles are on the same chromosome
  - repulsion = the two alleles are on opposite chromosomes of a pair

### Recombination fraction

- this is a measure of how often the alleles at two loci are separated during meiotic recombination
- it can vary between zero and 0.5

### Lod scores

- the lod score for a given recombinant fraction is the logarithm to base 10 of the odds  $P_1:P_2$
- $P_1$  = probability of there being linkage
- $P_2$  = probability of there being no measurable linkage
- gives a measure of the probability of two loci being linked