Section One

General principles of medical genetics

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Introduction

This section summarises the basic principles of normal inheritance and genetic disease and outlines the approaches for identification of people with or without risk factors for a genetic disorder.

Normal human inheritance

Medical genetics is concerned with human biological variation as it relates to health and disease. This variation may be attributable to inherited genetic information (nature) or to environmental factors (nurture). It can also result from combinations of these two influences. The genetic information is coded in DNA, which is packaged into chromosomes. Each chromosome contains a single DNA molecule consisting of two strands woven together as a double helix. Each nucleus has 46 chromosomes; these can be arranged into a karyotype of matching pairs, starting with the largest (numbered 1) down to the smallest (numbered 22) (Figure 1.1). This leaves the sex chromosomes, which are two X chromosomes in a female (Figure 1.1) and an X and a Y in a male (Figure 1.2). When an individual reproduces, only one of each pair will be transmitted to the egg or the sperm. Thus, each egg has only 23 chromosomes (1–22 and an X). Each sperm similarly has 23 chromosomes with one of each pair, 1–22 and either the X or the Y chromosome. Fusion of the egg and sperm restores the full complement of 46 chromosomes and establishes the sex of the embryo.

DNA is composed of four types of bases: adenine (A), cytosine (C), guanine (G) and thymine (T). These bases show specific pairing between the DNA strands of the double helix. A pairs with T and G pairs with C. The unit of length of DNA is a base pair (bp) of AT or CG. One thousand bps is a kilobase (kb) and one million bps is a megabase (Mb). The chromosomes vary in size and contain different amounts of DNA, from 249 Mb in each copy of chromosome 1, to 28 Mb in each copy of chromosome 21.

Information is stored in DNA using the sequence of bases (A, T, C or G) along a DNA strand. These bases are read three at a time as a

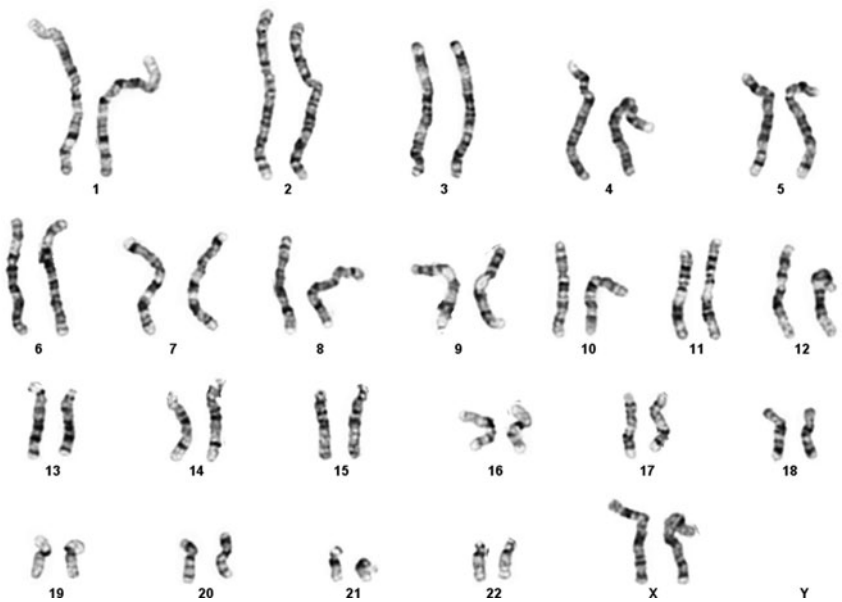

Figure 1.1 Normal female karyotype

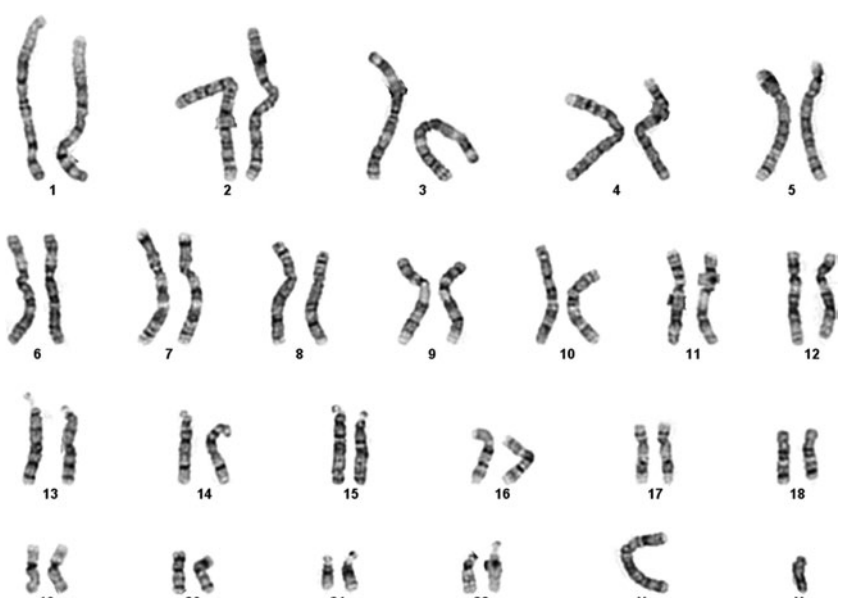

Figure 1.2 Normal male karyotype

codon and this provides 64 (i.e. 4^3) combinations. This is more than enough to code for the 20 amino acids that are used to make all proteins and to code for stop and start signals for protein synthesis. The region of the DNA that codes for a particular protein, together with its closely associated regulatory sequences (promoters) and intervening linking sequences (introns), is defined as its gene. Genes vary greatly in size; small genes may be under 1 kb in size, while enormous genes may be over 1 Mb in size. Some areas of the DNA between genes ('enhancers' and 'silencers') have roles in long-range regulation of gene function, but large areas of human DNA have no known function.

In total, approximately 30 000 genes are encoded in human DNA. Most of these have now been identified and their DNA sequence determined, at least in part. Some genes are unique (with a single copy in each chromosome) whereas others are repeated, with multiple copies that may be adjacent or scattered. The genes are not evenly distributed throughout the chromosomes. The dark banded areas of the chromosomes in Figures 1.1 and 1.2 are relatively 'gene poor' compared with the lighter banded areas. More genes are found towards the ends of the chromosomes (telomeres) than around the central constrictions (centromeres).

Not all of the genes encode proteins. In fact, in addition to over 21 500 protein-encoding genes, there are at least 8475 genes that encode RNA molecules. The latter include ribosomal and transfer RNA molecules as well as over 1000 of the more recently recognised regulatory 'micro RNA' molecules that can regulate the function of protein-encoding genes. In contrast to early assumptions, it is now also clear that a single gene can encode more than one protein molecule. This can result from 'alternative splicing' in which the actual protein-encoding segments ('exons') within a gene can be joined together in different arrangements during the process of 'splicing'. During this process, the intervening, non-protein encoding, segments ('introns') are removed from the messenger RNA, prior to the protein synthesis.

Types of genetic disease

With the exception of identical twins, individuals vary. This variation reflects inherited genetic factors, environmental influences and their interaction. In medical genetics, there are often difficulties in defining the boundary between 'normal' genetic variation and 'mild' genetic disease. It can also be hard to disentangle the influences of one gene on another and of environmental factors on genes. The subdivision into various types of genetic disease is therefore somewhat artificial and the

frequency of each group of genetic diseases depends on where the boundaries between normality and disease are placed. Traditionally, genetic diseases are subdivided into:

- chromosomal disorders
- single-gene disorders
- multifactorial disorders
- somatic cell genetic disorders.

Chromosomal disorders

By definition, a chromosomal disorder is present if there is a visible alteration in the number or structure of the chromosomes. These changes may affect either the sex chromosomes (X or Y) or the autosomes (numbers 1–22). Using routine light microscopy, multiple newborn cytogenetic surveys have revealed a frequency of six chromosomal disorders per 1000 births. Of these, approximately two-thirds result in either mental or physical disability. The liveborn infants with chromosomal abnormalities represent only a small proportion of all chromosomally abnormal conceptions. It is estimated that the rate of chromosomal abnormality in embryonic and fetal deaths is within the range 32–42%; the proportion of all recognised conceptuses that are chromosomally abnormal is 5–7%.

Normally, each sperm and egg has 23 chromosomes, with one of each pair of autosomes (1–22) and one sex chromosome. Malsegregation is common and can result in an egg or a sperm with either an extra copy of a chromosome (24 in total) or a missing chromosome (22 in total). In general, loss of chromosomal material is more serious than possession of additional material and autosomal imbalances are more serious than sex chromosome imbalances. In consequence, the types of chromosomal abnormality that predominate in miscarriages and in liveborn infants are different.

Additional copies of any autosome in the egg or sperm will result in 47 chromosomes in the fetus and these will generally result in miscarriage. For example, an extra copy of chromosome 16 (trisomy 16) is the most common autosomal trisomy in miscarriages, whereas trisomies for chromosome 21 (Down syndrome, Figure 1.3), 18 (Edwards syndrome, Figure 1.4) and 13 (Patau syndrome, Figure 1.5) are the most common trisomies in liveborn infants.

A missing autosome usually results in a very early pregnancy failure and is undetected. However, monosomy X with a single copy of the X chromosome and 45 chromosomes in total (45,X, Figure 1.6) occurs

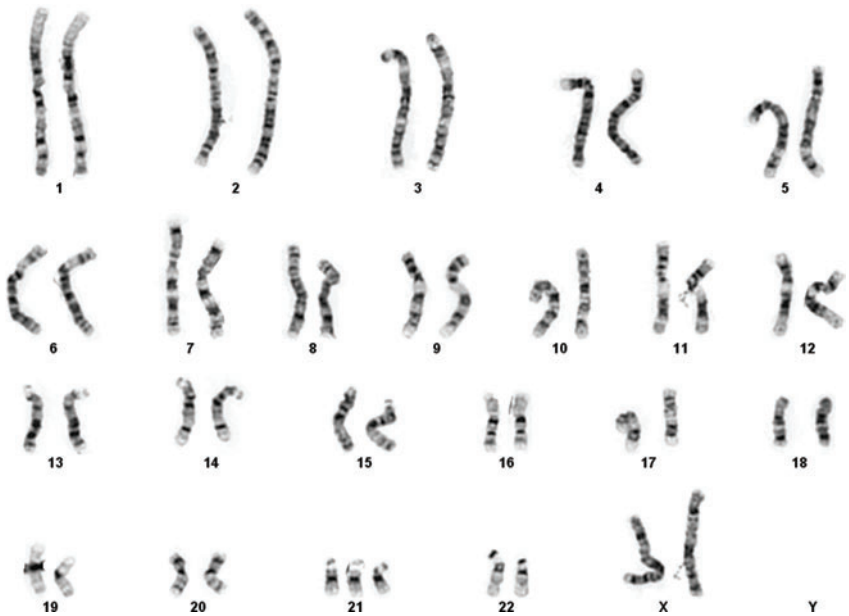

Figure 1.3 Trisomy 21 female

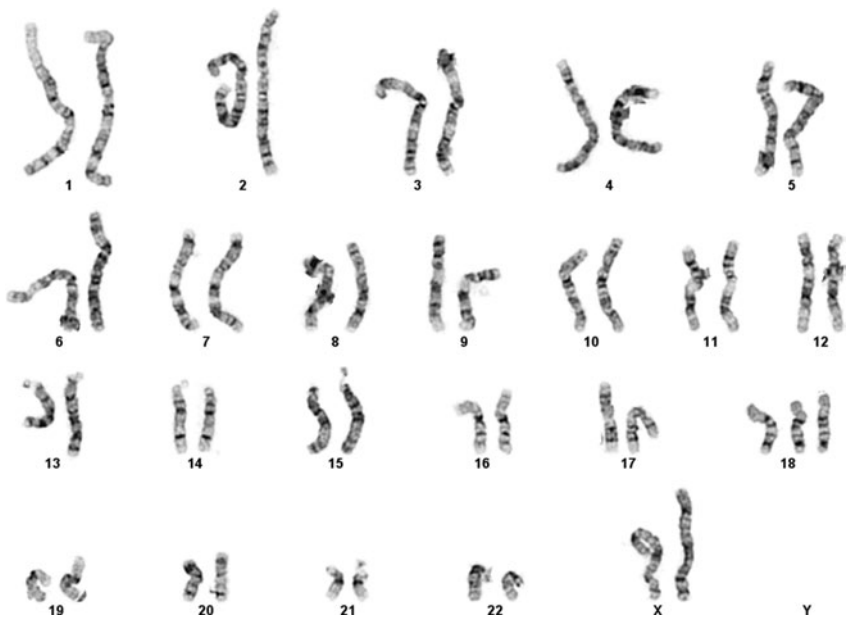

Figure 1.4 Trisomy 18 female

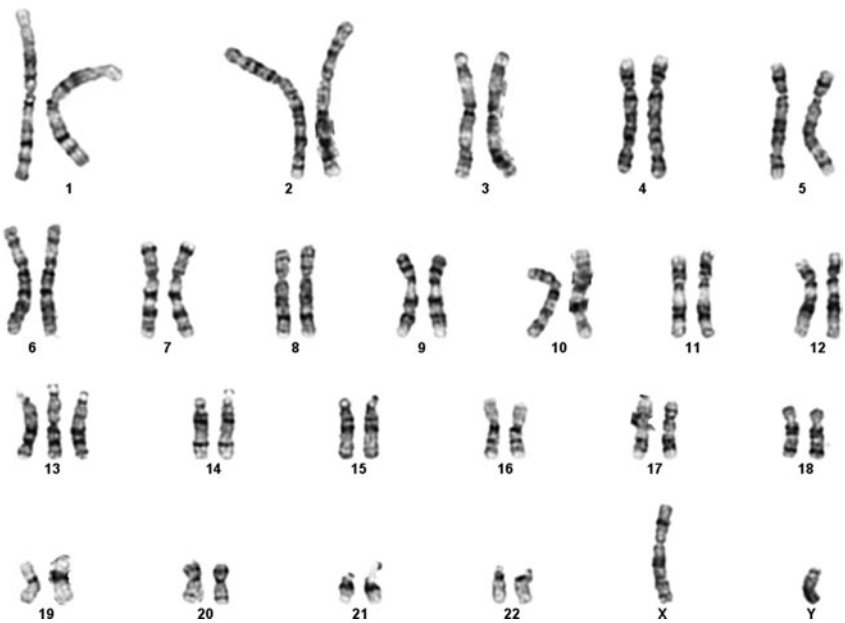

Figure 1.5 Trisomy 13 male

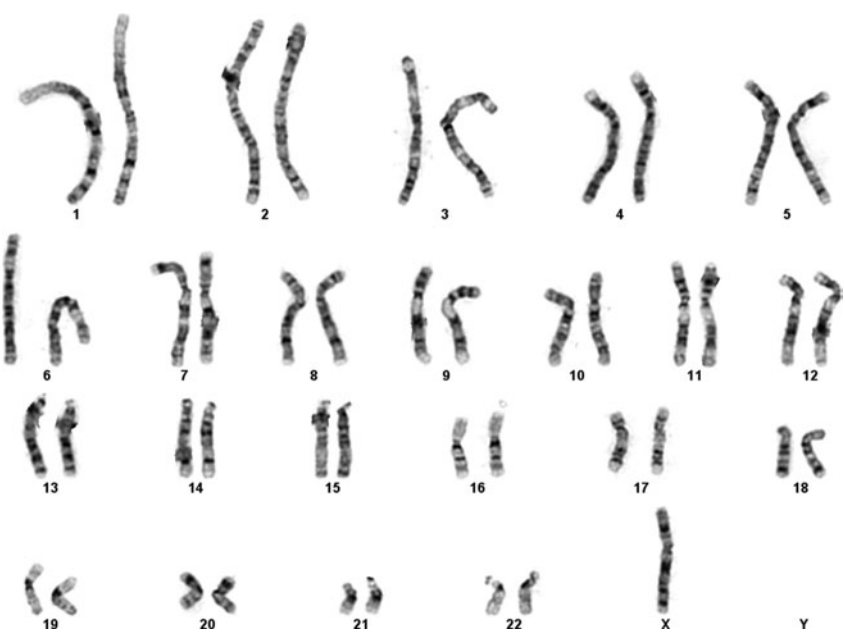

Figure 1.6 Turner syndrome: 45,X

Figure 1.7 Triploidy: 69,XXY

in approximately 1% of all conceptions although it is believed that over 98% of these pregnancies are spontaneously miscarried. This high lethality in the womb contrasts with the relatively mild postnatal features of children with 45,X (Turner syndrome).

An extra half set of chromosomes results from fertilisation of an egg by two sperm and leads to 69 chromosomes in total (triploidy, Figure 1.7). Triploidy usually results in a miscarriage but, exceptionally, infants may be liveborn.

Structural aberrations result from chromosomal breakage. When a chromosome breaks, two unstable sticky ends are produced. Generally, repair mechanisms rejoin these two ends. However, if more than one break has occurred, there is the possibility of joining the wrong ends as the repair mechanisms cannot distinguish one sticky end from another. The most common types of structural aberrations are translocations and deletions.

Translocations involve the transfer of chromosomal material between chromosomes. The process requires simultaneous breakage of two chromosomes, which then repair in an abnormal arrangement (Figure 1.8). This exchange can involve any two chromosomes and usually results in no loss of vital DNA. In this case, the individual is usually clinically normal

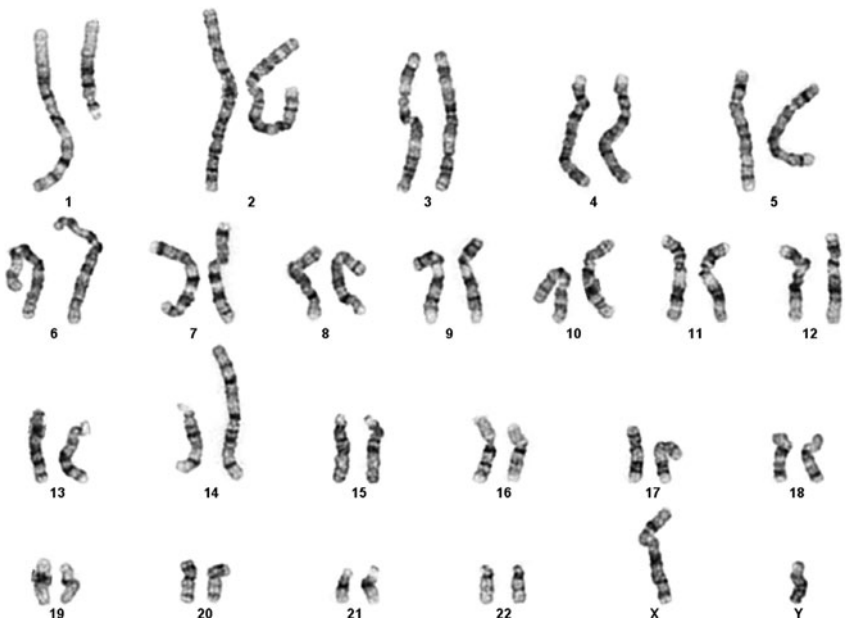

Figure 1.8 Male with a translocation between chromosomes 1 and 14

and is said to have a balanced translocation. The medical significance is, then, its relevance for future generations, because the carrier of a balanced translocation is at risk of producing chromosomally unbalanced offspring. The overall frequency of translocations in the general population is two per 1000.

Deletions arise from loss of chromosomal material between two breakpoints on the same chromosome. They can also result from a parent with a balanced translocation. Deletions of parts of the autosomes almost always produce clinical effects if they are visible by light microscopy. These clinical effects commonly include learning disabilities, congenital malformations and unusual facial features. Submicroscopic deletions (i.e. those that are too small to be detected by light microscopy) are also clinically important. The smallest visible change to a chromosome using the light microscope approximates to the loss of 4 Mb of DNA. Smaller losses (submicroscopic deletions or 'microdeletions') can easily include multiple genes and a large number of microdeletion syndromes have now been identified using DNA probes for the deleted area (Table 1.1). Geneticists may organise tests for such microdeletions (or microduplications)