HUTCHISON'S
PAEDIATRICS

2nd Edition



Krishna M Goel
Devendra K Gupta

Foreword
Terence Stephenson

JAYPEE

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Margo L Whiteford

CHAPTER 4

Paediatric Genetics

INTRODUCTION

With the improvements in treatment of infectious diseases in the developed world, conditions, which are either wholly or partially genetic in their aetiology, have become more prominent as a cause of childhood morbidity and mortality. It is estimated that around one-third of admissions to paediatric wards are due to conditions with some genetic component and therefore an understanding of basic genetic principles is becoming increasingly important.

The field of medical genetics is an ever expanding one and, within the context of this text it is not possible to cover all areas of the speciality in detail. Instead, this chapter tries to provide enough basic genetic information to allow understanding of the aspects of medical genetics encountered during day-to-day paediatric practice.

In practice, clinical genetics does not differ from any other speciality, in that the clinician's ability to make a diagnosis relies on the same skills, i.e. the ability to take a detailed history, including pregnancy and family history, perform a physical examination, arrange appropriate investigations and interpret the results. However, the emphasis may be slightly different with more time being taken over the family history and the physical examination may extend to other members of the family as well as the child who is the patient.

HISTORY

A detailed history of a child's illness is always required when a child is seen as an outpatient or admitted to hospital. Obviously if a child is admitted acutely unwell then treating the current illness is paramount, but if a genetic cause for the illness is suspected it is important, once the child's condition is stable, to return to asking questions about the child's previous health, growth and development in much more detail.

In addition to trying to ascertain genetic factors which may have contributed to the child's illness it is equally important to look for nongenetic factors which may offer an explanation and allow a genetic cause to be excluded: for instance a history of significant perinatal asphyxia in a child with severe microcephaly and seizures or the ingestion of teratogens such as alcohol or antiepileptic medication during pregnancy if a child has multiple congenital anomalies.

Care has to be taken when drawing family trees in order to get the correct information without causing offence or distress to the family. For instance, many parents feel guilty if their child has been diagnosed with a genetically inherited condition and worry that it may have been inherited from their side of the family. In the developed world, it is not unusual for a woman to have had children by several different partners and sensitivity must be used while obtaining this information. Similarly, in other populations, asking questions about consanguineous (related) marriages may also cause concern.

Within the genetics clinic, family trees or 'pedigrees' are usually drawn to at least three generations. An example of various family trees is shown in Figure 4.1. The child, who brings the family to medical attention is usually known as the 'proband' with his parents being referred to as 'consultands'. By convention, males are represented by squares and are drawn to the left of a couple and females are represented by circles. 'Affected' individuals are shaded in, while carriers of recessive disorders and chromosome translocations are half shaded and female carriers of X-linked disorders are indicated by a central dot. Other commonly used family tree symbols are listed in Figure 4.1.

Well before people were interested in human genetics, patterns of inheritance had been recognised both in animal breeding and plant crossing experiments. In the 19th century, Gregor Mendel was the first person to propose the idea of 'recessive' genes to explain why some traits appeared to 'skip generations'. Nowadays many patterns of inheritance are recognised and often by drawing a family tree it is possible to predict the 'risk' to offspring of subsequent generations

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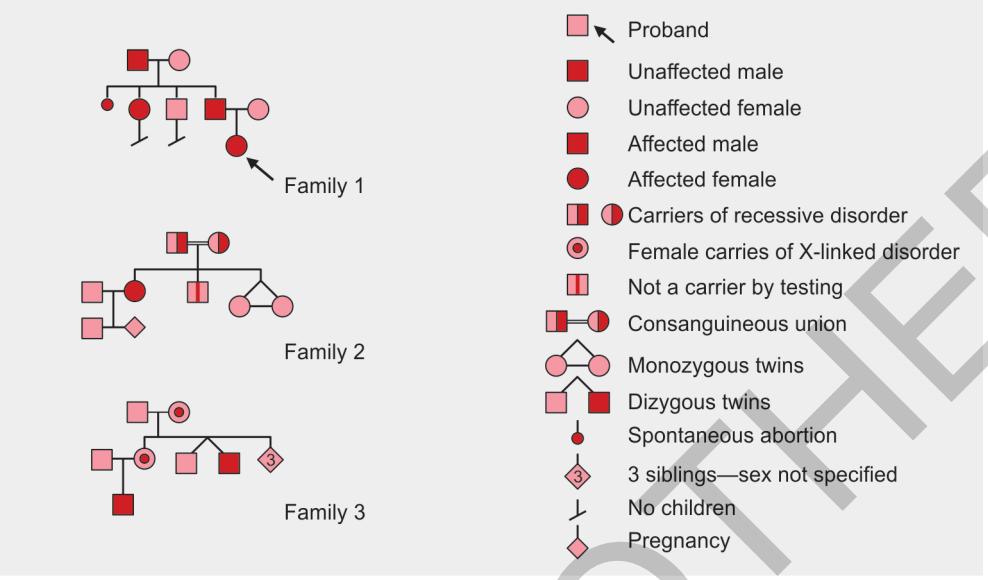

Fig. 4.1: Patterns of inheritance

even in situations where no specific genetic diagnosis has been made.

PATTERNS OF INHERITANCE

Autosomal Dominant Inheritance

With conditions which are autosomal dominantly inherited the condition typically appears to occur in all generations of a family and males and females are equally affected [Fig. 4.1 (Family 1)]. The important point to note with dominantly inherited conditions is that males can pass the condition to their sons and this can be a useful feature for distinguishing an autosomal dominant condition from an X-linked condition where females are sometimes 'affected'.

The clinical status of an individual is usually referred to as 'phenotype' whereas their genetic constitution is the 'genotype'. Some autosomal dominant conditions are not fully penetrant, which means that not all individuals, who inherit the mutant gene, will be clinically affected and others may be so mildly affected that the condition is not immediately noticed. For this reason an autosomal dominant condition may appear to 'skip' a generation and then return. Thus, when a condition is known to have variable penetrance it is important to exercise caution when determining the risk to the next generation, even when an individual has a normal phenotype.

Males and females affected by an autosomal dominant condition will transmit the condition to 50% of their sons and 50% of their daughters.

Autosomal Recessive Inheritance

Typically autosomal recessive conditions only affect individuals in one generation of a family [Fig. 4.1 (Family 2)] but exceptions to this will occur when the carrier frequency of the gene in a population is high, e.g. 1:10 people of Caucasian origin are carriers of a haemochromatosis gene mutation and therefore it is not uncommon for a person who is affected by haemochromatosis to have a partner who is a carrier of the condition, resulting in the possibility of their offspring also being affected. This phenomenon is known as 'pseudodominance'. Autosomal recessive conditions may also occur in more than one generation of a family if there are many consanguineous marriages within the family.

When both parents are carriers of an autosomal recessive condition they will transmit the condition to 25% of their children whether they are male or female and 50% of their children will be carriers. A person affected by an autosomal recessive condition will have a low-risk of having an affected child, provided that their partner is not a relative and that the carrier frequency of the condition in the population is low.

X-Linked Recessive Inheritance

X-linked recessive conditions generally only affect males and never pass from father to son [Fig. 4.1 (Family 3)]. However, occasionally a female may be affected by an X-linked recessive condition if she only has one X-chromosome (as a result of also having Turner's syndrome), if she has a skewed X-inactivation pattern (discussed later) or if she has inherited

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a mutant gene on both of her X-chromosomes, which may occur if (a) her father is affected by the condition and her mother is a carrier, (b) a new mutation arises in the gene on one X-chromosome and her other X-chromosome is inherited from a parent who is affected or a carrier.

Female carriers of an X-linked recessive condition will have a 25% chance of having an affected son and a 25% chance of having a carrier daughter. All of the daughters of a male affected by an X-linked recessive condition will be carriers and none of his sons will be affected.

X-Linked Dominant Inheritance

X-linked dominant conditions also affect both males and females and occur in several generations of a family but their distinguishing feature is that they never pass from father to son.

A female affected by an X-linked dominant condition will transmit the condition to 50% of her sons and 50% of her daughters. A male affected by an X-linked dominant condition will transmit the condition to all of his daughters and none of his sons.

Mitochondrial Inheritance

Although the majority of DNA inherited from parents occurs within the chromosomes in the nucleus of cells, a small amount of DNA also occurs within the mitochondria, which are the organelles responsible for cell energy production. As sperm do not contain any mitochondria, conditions, which occur as a result of mutations in mitochondrial DNA, are always maternally transmitted.

The proportion of mitochondria containing the mutant gene varies from cell-to-cell in all tissues of the body and therefore an individual's phenotype will also vary depending on the proportion of mutant mitochondria in relation to normal or 'wild-type' mitochondria. It can be extremely difficult to predict the chance of a woman having an affected child, if she is either affected by or a carrier of a mitochondrial condition. The various possibilities arising in this situation are illustrated in Figure 4.2.

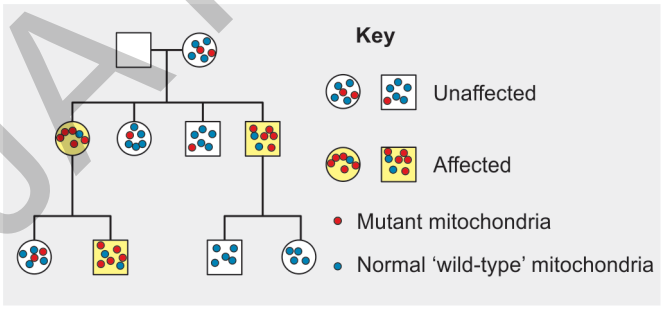

Fig. 4.2: Mitochondrial inheritance

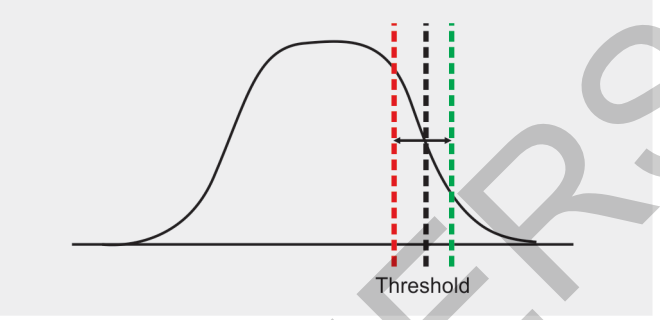

Fig. 4.3: Threshold effect

Polygenic Inheritance

Many congenital anomalies and later onset diseases, e.g. diabetes and hypertension occur more commonly in some families than would be predicted from the population incidence of the disorder, but do not follow the patterns of single gene inheritance, described above. Such conditions are referred to as 'polygenic' or 'multifactorial' and their aetiology involves both genetic and environmental factors. In this situation the disorder only occurs if an individual inherits a sufficient quantity of 'susceptibility' genes and is also exposed to specific environmental factors. Many of these multifactorial conditions exhibit a threshold effect (Fig. 4.3) and it is only when this threshold is exceeded that the condition occurs.

For the majority of multifactorial disorders neither the susceptibility genes nor the specific causative environmental factors are known. The exception to this is perhaps illustrated with neural tube defects where the result of the MRC multivitamin trial published in 1991, concluded that the risk of neural tube defects occurring could be reduced by 60–70% with periconceptual folic acid supplementation. This in effect moved the 'threshold' to the right of the curve. Conversely, it is well-recognised that taking folic acid antagonists, such as some antiepileptic drugs, during pregnancy increases the risk of neural tube defect and in this case the threshold is shifted to the left of the curve (Figs 4.4A and B).

In order to predict the recurrence risk for multifactorial conditions, geneticists rely on population studies which provide 'empiric' recurrence risks. For most of the congenital anomalies the risk figures lie between 2 and 5%. If a couple have a second affected child the risk increases, since it is more likely that for this particular family genetic factors are involved.

Clinical Examination and Dysmorphology

The clinical examination of a child within the genetics clinic does not differ in any way from that carried out elsewhere, but making a 'genetic diagnosis' often relies on the recognition

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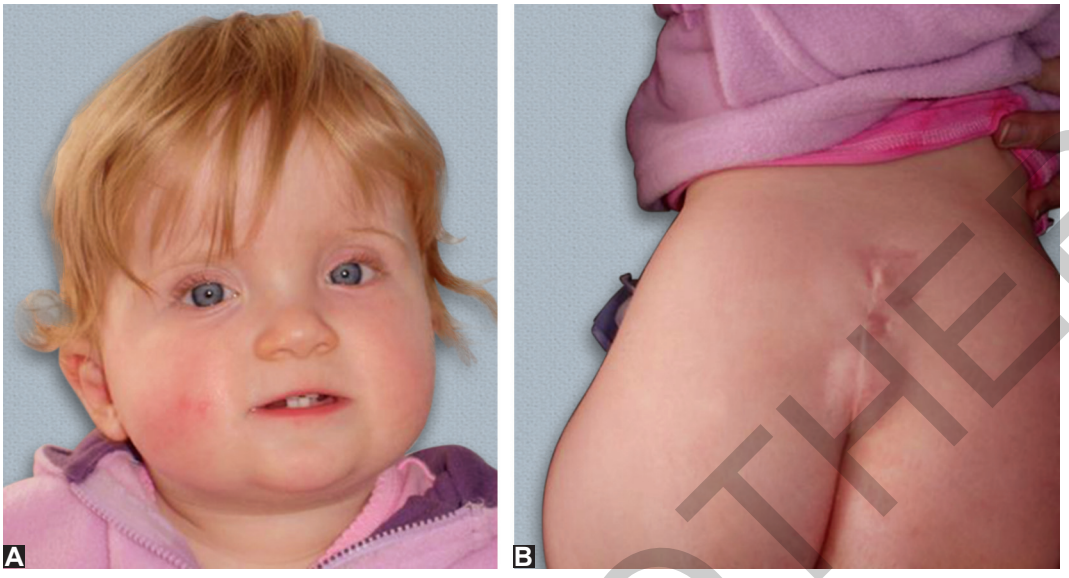

Figs 4.4A and B: Repaired neural tube defect in a girl who also has facial features of 'foetal valproate syndrome' (flat nasal bridge, hypertelorism, infraorbital crease, long smooth philtrum)

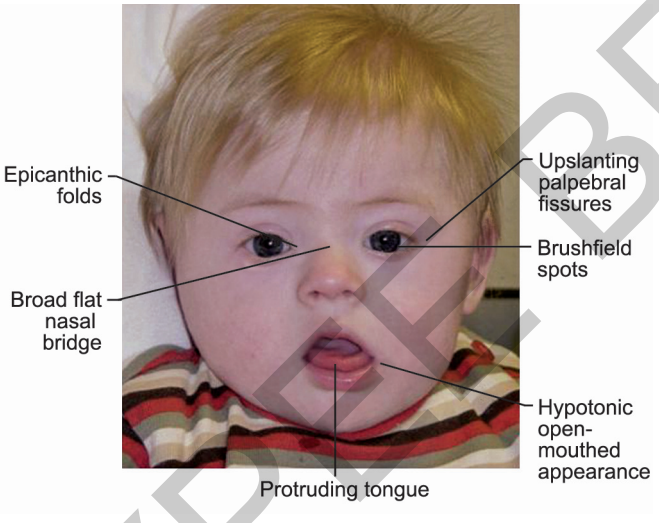

Fig. 4.5: Down's syndrome (trisomy 21) facial appearance



Fig. 4.6: Ectrodactyly (split-foot)

of patterns of clinical features and symptoms. It is only with experience that the more common 'syndromes' become easily recognised and often it is a facial 'gestalt', i.e. overall appearance, rather than individual features which suggests a likely diagnosis. For instance the child with Down's syndrome (Fig. 4.5) is easily identified by people who have no medical knowledge, because it is a relatively common condition. It is impractical to memorise the features of hundreds of genetic syndromes and modern day geneticists frequently use computerised dysmorphology databases to aid diagnosis. These databases contain information on the clinical features of syndromes compiled from the published literature and by searching on a patient's key clinical features it is possible to obtain a list of suggested diagnoses, which aids the direction of further investigations in order to confirm or exclude a particular diagnosis. Clinical features may be regarded as 'hard handles' if they only occur with a small number of conditions, e.g. ectrodactyly (Fig. 4.6), whereas features such as single palmar creases and hypoplastic nails (Figs 4.7A and B) are 'soft signs', which occur with many different genetic diagnoses. Features such as marked asymmetry of any part of the body (Fig. 4.8) or patchy abnormalities of skin pigmentation are suggestive of 'mosaicism' and a skin biopsy should be considered.

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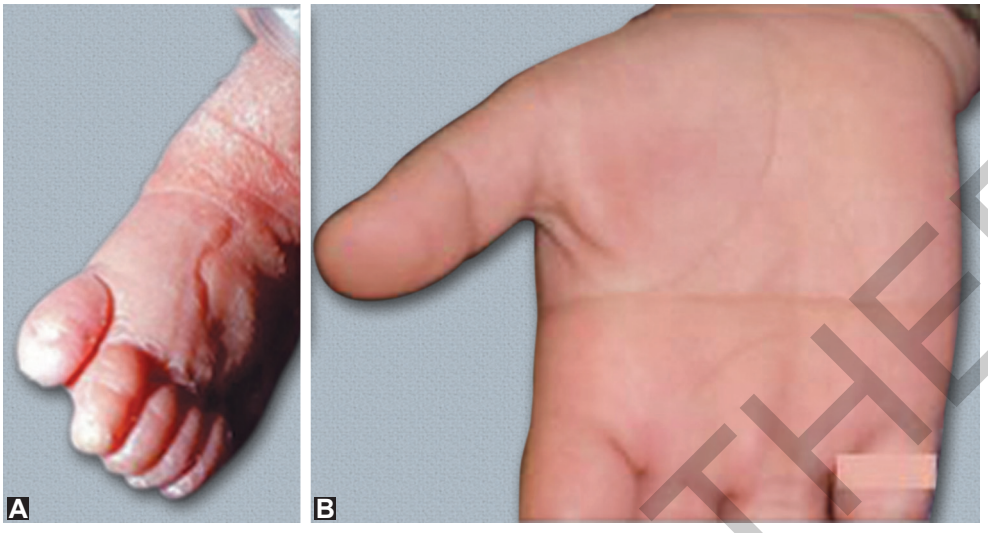

Figs 4.7A and B: (A) Hypoplastic nails; (B) Single palmar crease

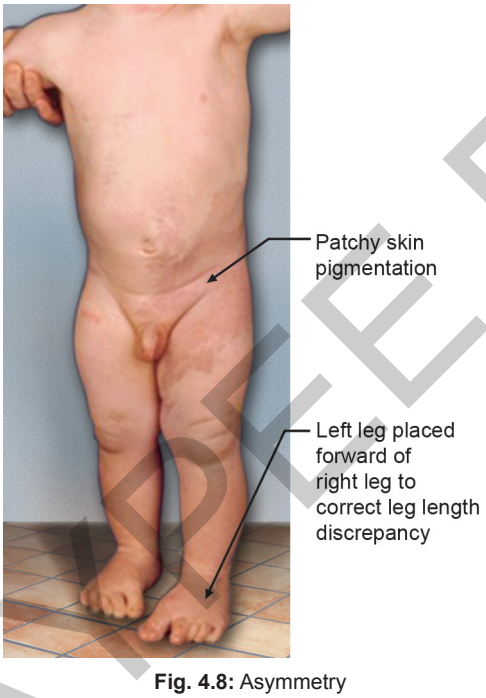

Fig. 4.8: Asymmetry

INVESTIGATIONS

The diagnosis of many genetic disorders can be made on the basis of biochemistry results, e.g. sweat electrolytes in the case of cystic fibrosis or urinary glycosaminoglycans in the case of the mucopolysaccharidoses. Similarily, radiographs are an essential tool for the diagnosis of inherited skeletal dysplasias (discussed in Chapter 32). However, the investigations specific to the field of genetics are chromosome tests (cytogenetics) and DNA analysis (molecular genetics), which are discussed in more detail below.

Cytogenetics

The study of chromosomes was perhaps the earliest branch of medical genetics to develop, with Hsu and Levan being the first to accurately observe human chromosomes in 1952 and the correct human chromosome number being recorded, in 1956, by Tjio and Levan.

Chromosomes are the structures in the nucleus of the cell into which DNA is packaged. In humans there are 46 chromosomes in all nucleated cells except the gametes. The 46 chromosomes occur as 23 pairs, with one copy of each pair being inherited from the mother and the other from the father. The first 22 pairs of chromosomes are the same whether an individual is male or female and are known as 'autosomes' and the remaining pair are the 'sex chromosomes'. Females have two X sex chromosomes while males have one X and one Y sex chromosome. The chromosome constitution of an individual is usually referred to as their karyotype and the normal karyotype for a female is denoted 46, XX and for a male 46, XY.

The chromosomes can only be examined in dividing cells and are best seen during the metaphase stage of mitosis. For this reason it usually takes around 1 week to get the result of a chromosome test. Various staining techniques can be used to examine chromosomes with the light microscope in order to show the 'banding pattern' along the length of each chromosome. The stain most commonly used is Giemsa which reveals dark and light regions of chromosomes rather like a bar-code (Fig. 4.9) and by searching for variations in

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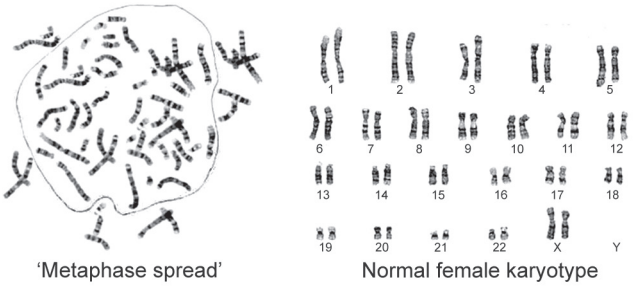

Fig. 4.9: Giemsa-banded chromosomes

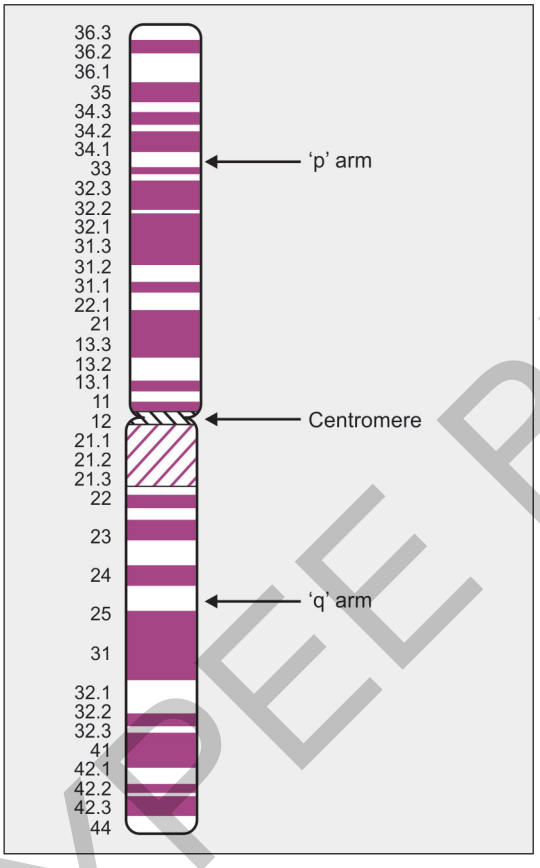

Fig. 4.10: Chromosome diagram

the pattern created by these bands, trained cytogeneticists are able to identify structural abnormalities along the length of any chromosome. The chromosomes are photographed and then arranged in their pairs starting with the largest autosome to the smallest and finally the sex chromosomes. The diagrammatic representation of a chromosome (Fig. 4.10) shows that the chromosome is divided into two arms—(1) the 'p' short arm and (2) the 'q' long arm—by the narrowed centromere region. With the larger chromosomes the 'short arms' are almost as long as the 'long arms'.

Numerical Chromosome Abnormalities

Soon after the correct number of human chromosomes was determined it was recognised that numerical abnormalities of chromosomes were associated with clinical disorders. Numerical abnormalities can arise with both the autosomes and sex chromosomes.

Numerical Abnormalities of Autosomes

Extra or missing copies of any of the autosomes can arise as a result of nondysjunction occurring during meiosis, which is the process by which the total chromosome number is halved during gamete formation. Numerical abnormalities of chromosomes are known as 'aneuploidy' and most autosome aneuploidies are incompatible with survival, leading to spontaneous abortions of affected pregnancies. The exceptions to this are trisomies of chromosomes 13, 18 and 21 and the clinical features of these conditions are summarised in Table 4.1.

Trisomy 13 (Fig. 4.11) and trisomy 18 (Fig. 4.12) are both associated with multiple congenital anomalies and the majority of babies born with these conditions die within the first year of life. These autosomal trisomies occur with increased frequency with increasing maternal age and tables are available for advising women of their age-related risk of having a live born baby with an autosomal trisomy. After a couple have had a child with an autosomal trisomy, the risk of recurrence for future pregnancies is around 1% and prenatal diagnosis could be offered in the form of chorionic villus sampling or amniocentesis.

The most frequent autosomal trisomies found in tissue from spontaneous abortions are trisomy 16 and trisomy 22, but these are generally only found in live born babies in the mosaic state, i.e. the situation where only a proportion of the patient's cells have the chromosome abnormality (Fig. 4.13). Such mosaic aneuploidies are often only identified by carrying out chromosome analysis of a fibroblast culture from a skin biopsy. Analysis of skin chromosomes should always be considered if a patient has marked asymmetry or if a diagnosis of Pallister-Killian is being considered. Pallister-Killian arises as a result of mosaic tetrasomy 12p, i.e. some cells have two additional copies of the short arms of chromosome 12 joined together to form an additional chromosome. The clinical features of Pallister-Killian syndrome are summarised in Table 4.2.

Numerical Abnormalities of Sex Chromosomes

It is unusual for abnormalities of the sex chromosome number to be detected in newborn babies as they are not usually associated with physical abnormalities. The exception to this may be girls affected by Turner's syndrome, who have only one X-chromosome (i.e. a 45, XO karyotype) and who

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Table 4.1: Autosomal trisomies

Trisomy	*Name*	*Approximate birth incidence*	*Main clinical features*
13	Patau's syndrome	1:5,000	Cleft lip and palate, microcephaly, holoprosencephaly, seizures, severe learning disability, scalp defects, colobomata, microphthalmia, cardiac defects, exomphalos, polydactyly
18	Edwards syndrome	1:3,000	Low birth weight, female preponderance, small facial features, prominent occiput, severe learning disability, low set malformed ears, cardiac defects, renal anomalies, flexion deformities of fingers, rocker-bottom feet
21	Down's syndrome	1:700	Hypotonia, flat occiput, up-slanting palpebral fissures, epicanthic folds, Brushfield spots, flat nasal bridge, protruding tongue, learning disability, cardiac defects, intestinal atresia, imperforate anus, Hirschsprung's disease

Table 4.2: Pallister-Killian syndrome—clinical features

Pallister-Killian syndrome	
Neurological features	Profound learning disability, seizures profound hypotonia
Dysmorphic facial features	General 'coarse' appearance, high forehead, sparseness of hair in frontal region in infancy, hypertelorism, epicanthic folds, flat nasal bridge, large mouth with down turned corners, macroglossia, abnormal ears
Other features	Pigmentary skin anomalies, short neck, diaphragmatic hernia, supernumerary nipples



Fig. 4.11: Trisomy 13—note exomphalos and polydactyly



Fig. 4.12: Trisomy 18—typical overlapping fingers



Fig. 4.13: Mosaic trisomy 22—note marked facial asymmetry

may have congenital malformations (Fig. 4.14). Even in the absence of structural malformations, a diagnosis of Turner's syndrome may be suspected in a newborn infant because of intrauterine growth retardation and the presence of lymphoedema. This can, on occasions, persist into adulthood (Fig. 4.14).

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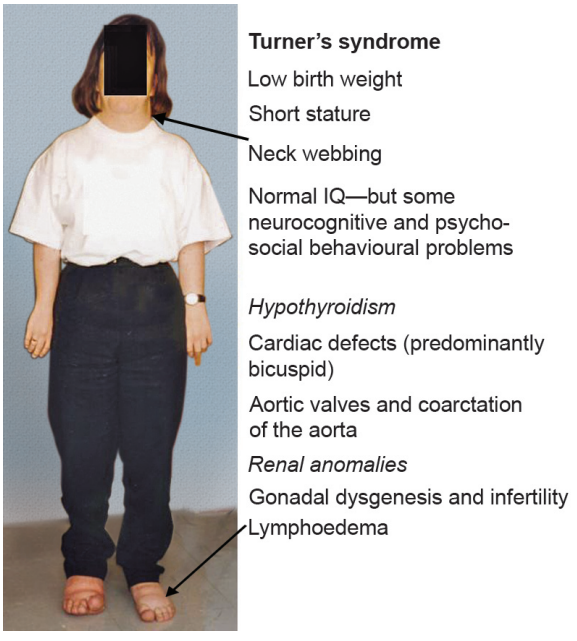

Fig. 4.14: Clinical features of Turner's syndrome

A 47, XYY karyotype is often detected by chance when chromosomes are being checked for an unrelated reason, e.g. a family history of a structural chromosome abnormality, as this chromosome abnormality is not usually associated with any phenotypic effect. There are some studies which suggest that behaviour abnormalities are more common in boys with 47, XYY karyotypes, but this probably just reflects the fact that boys with behavioural abnormalities are more likely to have their chromosomes checked. An additional X-chromosome present in a male (i.e. 47, XXY karyotype) is generally referred to as Klinefelter's syndrome and in a female (i.e. 47, XXX karyotype) is called triple X-syndrome.

In females, with normal karyotypes, only one X-chromosome is active in each cell and the other is condensed into a structure called a 'Barr body'. The X-chromosome which is active varies from cell-to-cell, usually with the maternal X being active in 50% of cells and the paternal X being active in the remaining 50%. If this is not the case it is referred to as 'skewed X-inactivation'. In children with additional copies of the X-chromosome, only one X-chromosome remains activated and the additional copies are inactivated to form extra Barr bodies.

Males with Klinefelter's syndrome are usually diagnosed in adulthood as they are taller than would be predicted from their parental heights and have hypogonadism, resulting in infertility.

Females with triple X-syndrome are also taller than average and some may experience fertility problems. Around 30% of girls with triple X-syndrome have significant learning difficulties and mild learning difficulties may occur in a small proportion of males with 47, XXY or 47, XYY karyotypes. Multiple extra copies of the sex chromosomes can also occur, e.g. 48, XXYY, 48, XXXX or even 49, XXXXY karyotypes. In general higher numbers of additional X-chromosomes are associated with significant learning difficulties.

The frequency of Turner's syndrome is around 1:3,000 female births, while the frequency of Klinefelter's syndrome, triple X-syndrome and 47, XYY is around 1:1,000 live births.

Sex chromosome aneuploidies are not associated with increased maternal age and the recurrence risk for future pregnancies is not increased.

Structural Chromosome Abnormalities

Structural chromosome abnormalities are termed 'unbalanced' if there is loss or gain of chromosomal material and 'balanced' if the overall amount of chromosomal material remains unchanged. Generally speaking balanced chromosome abnormalities are unlikely to cause any adverse effect. The main categories of structural chromosome abnormalities are listed below and illustrated in Figure 4.15.

Robertsonian Translocations

A Robertsonian translocation is the fusion of two of the smaller chromosomes at their centromeres. During this process the short arms of the chromosomes are lost, but as these contain no essential genetic material, no harmful effect occurs. A carrier of a balanced Robertsonian translocation will have a total of 45 chromosomes as the two fused chromosomes are counted as one. Similarly, the correct cytogenetic nomenclature for a person with an unbalanced

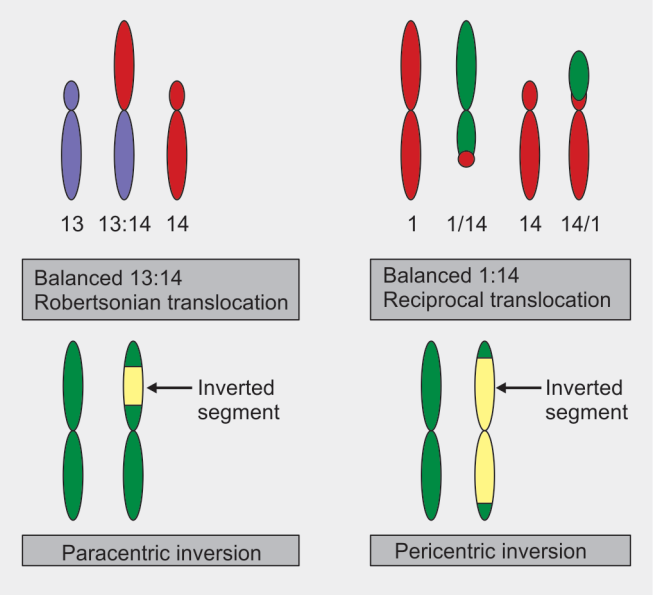

Fig. 4.15: Structural chromosome rearrangements

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Robertsonian translocation, describes them as having 46 chromosomes, but they will of course have three copies of the long arms of one of the chromosomes involved in the translocation.

Carriers of balanced translocations are at risk of having children with unbalanced chromosomes. The actual risk varies depending on: (a) the chromosomes involved in the translocation—highest when chromosome 21 is involved and (b) the sex of the parent who is a carrier—higher when it is the mother. It is important to recognise that all of the children of a carrier of a 21:21 Robertsonian translocation, will be affected by Down's syndrome.

Reciprocal Translocations

A reciprocal translocation is the exchange of segments of chromosomal material between nonidentical chromosomes, usually two chromosomes are involved but complicated exchanges between several chromosomes can occasionally occur. This is detected by there being a disruption to the normal banding pattern along the length of the chromosomes involved.

Carriers of balanced reciprocal translocations are healthy but as they produce a proportion of chromosomally abnormal gametes they may present with infertility, particularly in males, or recurrent miscarriages. Sometimes an individual will be identified as being a carrier of balanced reciprocal translocation following the birth of child with congenital malformations, dysmorphism or learning disability, if investigations reveal the unbalanced form of the translocation in the child. The birth of a live born child with chromosomal imbalance arising from a reciprocal translocation, is more likely to occur if the length of the chromosomal segments involved in the translocation represent less than 5% of the overall length of all 46 chromosomes.

Inversions

An inversion is the term used to describe a segment of chromosome, which has broken away and then rejoined in the same position but rotated through 180°. If the inverted segment is confined to one arm of the chromosome it is termed a 'paracentric inversion' and if the segment spans the centromere it is termed a 'pericentric inversion'. Chromosomal inversions usually have no phenotypic effect, but they interfere with meiosis and again may result in chromosomally abnormal gametes being produced. The chromosome abnormalities arising from paracentric inversions are unlikely to be compatible with survival and are, therefore, more likely to result in recurrent early miscarriages. Pericentric inversions, on the other hand, may result in small chromosomal deletions or duplications and can result in live born children with malformations or learning disability arising from chromosomal imbalance.

Chromosomal Deletions and Duplications

Deletions or duplications of chromosomal segments may arise and most of these are unique to the individuals in whom they are identified. However, there are some regions of chromosomes which are more prone to deletions or other rearrangements. These are termed 'subtelomeric' if they occur at the ends of the chromosomes and 'interstitial' if they occur elsewhere. It is now clear that many of these recurrent rearrangements give rise to recognisable dysmorphic syndromes (Table 4.3 and Fig. 4.16) and that some of the variability in the features of these syndromes is due to the size of the deletion and the number of genes which are missing as a result.

Many chromosomal deletions are visible when observing chromosomes with the light microscope but others are too small to be seen and require a specialised technique, called fluorescent *in situ* hybridisation (FISH) to be detected. FISH is basically a molecular genetic technique (discussed later) whereby a fluorescent probe is attached to the region of interest of the chromosome. In the normal setting two fluorescent signals should be seen, i.e. one on each of the chromosome pair, but if that particular region of chromosome is deleted, only one signal will be seen. In practice two different probes of different colours are used—one purely to identify the particular chromosome of interest and the other for the specific region (Fig. 4.17).

Uniparental Disomy and Imprinting

Uniparental disomy (UPD) is a relatively recently recognised form of chromosome abnormality. It is defined as the 'inheritance of a pair of homologous chromosomes from one parent', with no copy of that chromosome being inherited

Table 4.3: Chromosomal deletion syndromes

Chromosome segment	*Syndrome*
4p16.3	Wolf-Hirschhorn syndrome
5p15.2	Cri-du-Chat syndrome
5q35	Sotos syndrome
7q11.23	Williams syndrome
11p15.5	Beckwith-Wiedemann syndrome
13q14.11	Retinoblastoma
15q12	Angelman and Prader-Willi syndromes
16p13.3	Rubinstein-Taybi syndrome
17p11.2	Smith-Magenis syndrome
22q11.2	DiGeorge/Velocardiofacial syndrome

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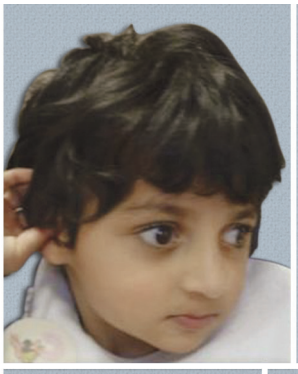
Angelman's Syndrome

Severe learning disability, Happy disposition, Virtually absent speech, Seizures, Hypotonia, Ataxic gait, Microcephaly, Prominent jaw, Large open mouth, Protruding tongue





Prader-Willi Syndrome

Mild-moderate learning disability, Severe neonatal hypotonia, Poor suck and weak cry, Hypogonadism, Hyperphagia and obesity in childhood, short stature, Small hands and feet, Bitemporal narrowing of the skull, 'Almond' shaped eyes, Upslanting palpebral fissures, Stabismus

Velocardiofacial Syndrome

Mild-moderate learning disability, Cardiac defects, Palatal anomalies, Hypocalcaemia, Thymic aplasia, Myopathic facies, Short palpebral fissures, Long nose, Broad nasal tip, Ear anomalies, Long Slender fingers





Williams Syndrome

Moderate learning disability, Characteristic outgoing personality, Heart defects (supravalvular aortic stenosis most commonly), Renal anomalies, Hypercalcaemia, Hyperacusis, Short stature, 'Elfin' facies, Full cheeks, Thick lips, Stellate irides, Features coarsen with increasing age

Fig. 4.16: Clinical features of some chromosome microdeletion syndromes

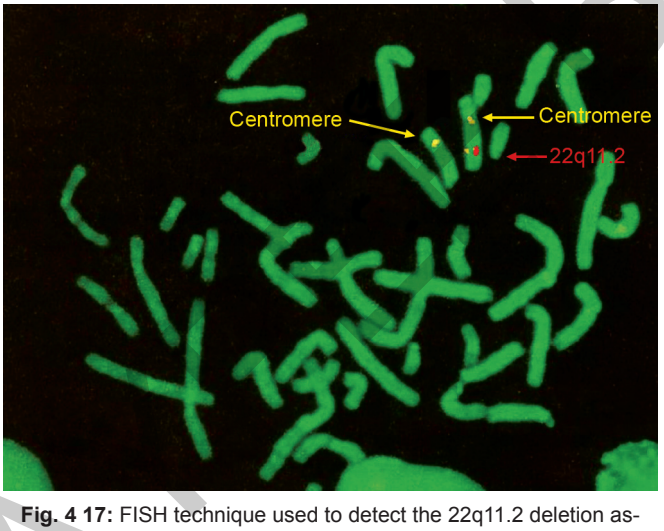


Fig. 4 17: FISH technique used to detect the 22q11.2 deletion associated with velocardiofacial syndrome

from the other parent. There are various mechanisms by which UPD can arise but it is thought that it most commonly occurs as a result of 'trisomic rescue', i.e. the loss of one copy of a chromosome during early cell division in an embryo which was originally destined to be trisomic for that chromosome.

With most autosomal genes, both the paternal and maternal copies of the gene are expressed, but a small number of genes are 'imprinted', which means that only the maternal or paternal (depending on the particular gene) copy is expressed. Therefore, although UPD can occur without clinical effect, for certain chromosomes it can mimic a deletion of an imprinted gene, e.g. Angelman syndrome, can arise as a result of a deletion of the maternal copy of the chromosome region 15q12, but it will also occur if a child has paternal UPD of chromosome 15, since there will be no maternal copy of 15q12 present. Other conditions arising as the result of abnormalities of imprinted genes are summarised in Table 4.4. 'Isodisomy' is a form of UPD where a child inherits two identical copies of the same chromosome from one parent and 'heterodisomy' is the inheritance of a homologous pair of chromosomes from one parent. Thus, another consequence of UPD may be the occurrence of an autosomal recessive disorder in a child, when only one of

Table 4.4: Syndromes due to abnormalities in the expression of imprinted genes

- Angelman syndrome
- Prader-Willi syndrome
- Beckwith-Wiedemann syndrome
- Russell-Silver syndrome
- Transient neonatal diabetes

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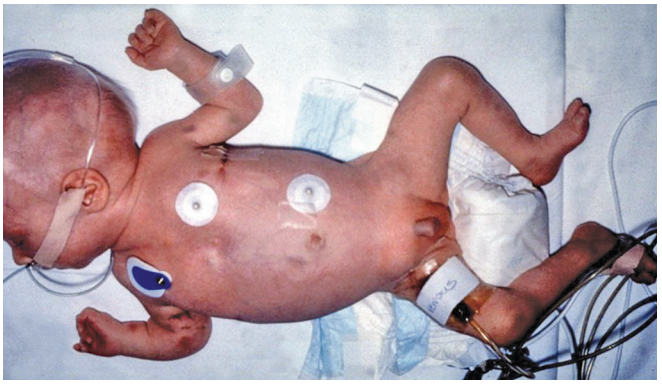

Fig. 4.18: Infant with multiple congenital anomalies due to maternal UPD 16

the parents is a carrier of the disorder. The first case of UPD reported was in fact a child with short stature and cystic fibrosis, which occurred as a result of maternal isodisomy of chromosome 7.

Another consequence of UPD of certain chromosomes is a recognisable pattern of congenital malformations, e.g. UPD of chromosome 16 can give rise to intrauterine growth retardation, cardiac defects, imperforate anus, scoliosis, hypospadias and hernia (Fig. 4.18).

Molecular Genetics

Before discussing the more clinical aspects of molecular genetics, it is useful to review some basic genetic principles. Deoxyribose nucleic acid (DNA) is the genetic template required to construct all the enzymes and proteins, which are necessary for the formation and function of the human body. DNA consists of strands of nucleic acids, containing the bases, adenosine, guanine, cytosine and thymine, held together by a sugar-phosphate backbone (Fig. 4.19). Each DNA molecule exists as two of these strands wrapped around each other to form a 'double helix'. The variable part of the DNA chain is the order of the bases along the backbone and the two strands of DNA are linked by hydrogen bonds between these bases. As a result of their shapes adenine always pairs with thymine and cytosine always pairs with guanine.

It is the order of the DNA bases which form the 'genetic code' required for the production of amino acids and subsequently proteins. The code is a triplet code, as each three bases codes for an amino acid or provides the instruction 'stop' at the end of a peptide chain. As there are 43, i.e. 64 possible combinations of these bases and only 20 amino acids, the code is said to be 'redundant' and more than one triplet may code for the same amino acid. This can obviously be useful when it comes to DNA mutations arising since not all base substitutions will alter the sequence

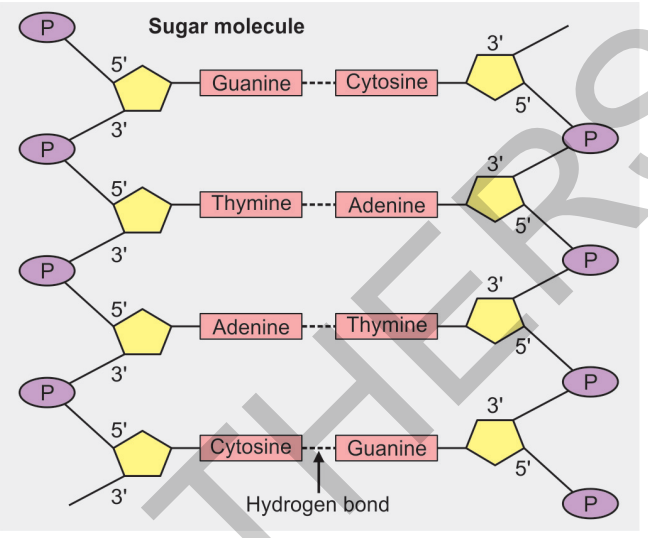

Fig. 4.19: DNA structure

of amino acids in a protein and therefore the protein function will not be lost. Such harmless substitutions are referred to as 'harmless' or 'benign' polymorphisms.

In order to understand how this system works it is necessary to look at the DNA molecule, shown in Figure 4.19, more closely. The deoxyribose sugars of the DNA backbone each have two hydroxyl groups, which occur at the 3 prime and 5 prime positions (denoted 3' and 5' respectively). The phosphate molecules join the sugar molecules together by forming a phosphodiester bond between the 3' hydroxyl group of one deoxyribose molecule and the 5' hydroxyl group of another. This gives the DNA strand a direction, running from the free 5' hydroxyl group of the first deoxyribose molecule to the free 3' hydroxyl group of the last. The two strands of DNA will of course be 'complimentary' in view of the base pairing, with one strand running in one direction an the other in the opposite direction.

DNA replication is an extremely complicated process, whereby the strands of DNA are separated and copied to produce new daughter strands. The process is initiated by the enzyme DNA polymerase and as the initial strands are separated, new deoxyribonucleoside triphosphates are added in a 5' to 3' direction. The process is said to be semiconservative as each new DNA molecule will consist of one of the initial 'parent' strands bound to a new 'daughter' strand.

It was originally thought that genes consisted of a length of DNA providing the triplet code for the necessary amino acids to form a peptide chain. However, it is now recognised that this is not the case and the DNA sequence of each gene contains regions in between its protein coding sequence, known as intervening sequences (IVS). The nomenclature generally used is 'exons' (protein coding sequences) and

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'introns' (intervening sequences). There are particular DNA codes which herald the start (TAG) and end of protein synthesis (TAA, TAG or TGA). Similarily, the dinucleotides GT and AG are found at the start and end of introns, respectively. Other particular nucleotide codes, which may be some distance away from the first exon of a gene, are also important for protein synthesis and are known as promoter regions.

The first stage of protein synthesis is known as transcription and involves the processing of messenger RNA (mRNA). DNA acts as a template for the production of mRNA and is read in a 5' to 3' direction. The process is initiated by enzymes known as RNA polymerases, which separate the strands of DNA. As with DNA replication the order of bases along the strand of mRNA, which is produced, are complimentary to the original DNA bases. The only difference between DNA and RNA is that the backbone sugar is ribose rather than deoxyribose and in RNA the base thymine is replaced by the base uracil. The primary transcript of mRNA, which is produced, contains the entire DNA coding region, including introns and exons. The mRNA then undergoes a number of processing steps, which result in the introns being cleaved out and the exons being spliced together (Fig. 4.20). Finally, the mRNA is modified by the attachment of various adenylic acids and protein molecules, which serve to protect the mRNA as it passes from the nucleus into the cytoplasm, in preparation for protein synthesis.

The process of protein synthesis also involves several different steps, namely 'initiation', whereby the ribosome is assembled on the mRNA, 'elongation', where complimentary tRNA molecules attach to each codon in turn, resulting in the addition of amino acids to the growing peptide chain and finally 'termination' when the polypeptide is released into the cytoplasm.

Not surprisingly with such a complicated process, errors (mutations) can arise and this results in the genetically inherited single gene disorders. There are various different types of mutation and these are summarised in Table 4.5.

Molecular Genetic Investigations

Southern Blotting

This is one of the older techniques used for DNA analysis, but it is still sometimes needed for detecting large genomic rearrangements, such as the large trinucleotide repeats which can occur in patients with myotonic dystrophy. The Southern blotting technique is labour intensive and it can take several weeks to obtain results when this process is used.

Polymerase Chain Reaction

For many single gene disorders 'polymerase chain reaction' (PCR) is now the method of choice for DNA analysis. This process allows the analysis of short sequences of DNA which have been selectively amplified and tests looking for common recurring mutations, such as in cystic fibrosis, or known

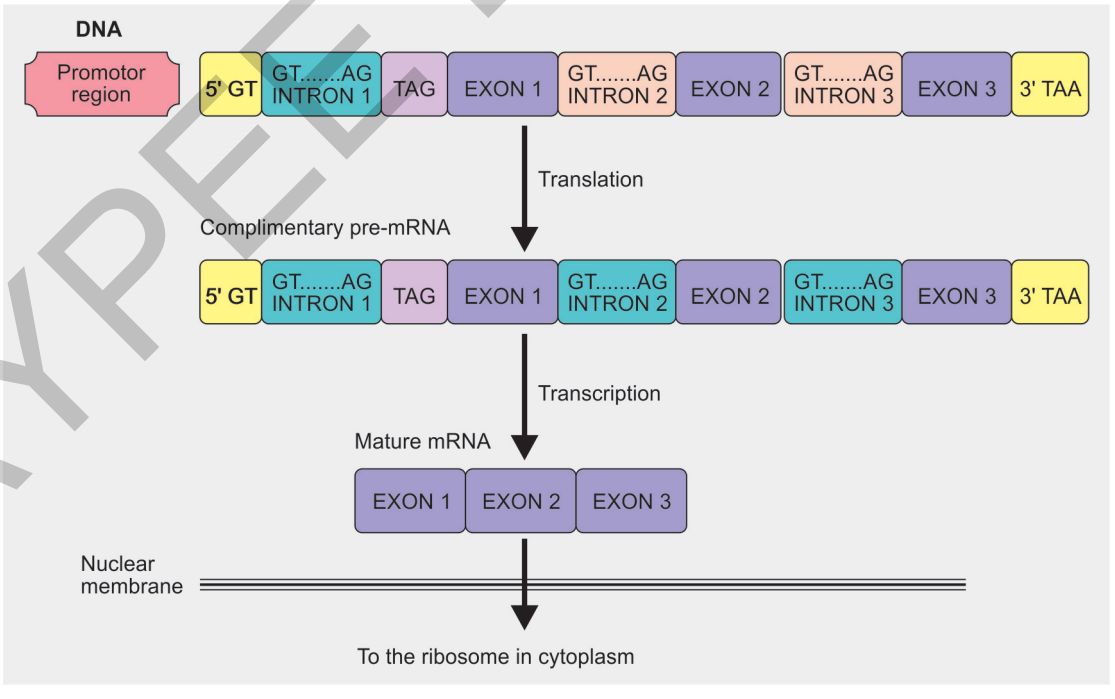

Fig. 4.20: DNA translation and transcription

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Table 4.5: Types of mutation

Type of mutation	*Outcome*
Point mutation:	A single base substitution
a. Missense mutation	Base change results in different amino acid
b. Nonsense mutation	Base change results in 'stop' and a shortened protein
Insertion or deletion	Alteration of the reading frame
	If a complete codon is deleted an amino acid will be missing from the protein, which may or may not affect function
Trinucleotide repeat	After a particular threshold is expansion reached protein function is altered
	Severity of the disorder is generally related to the size of the expansion

familial mutations which have previously been detected by other methods, can provide results within 48 hours.

DNA Sequencing

This type of testing reveals the specific sequence of bases within a region of DNA and compares them to reference sequence data in order to determine if any substitutions, deletions, etc. have occurred. Much of this type of DNA testing is now computerised but it can still take lengthy periods of time to get results, particularly if the gene being investigated is large.

Molecular Cytogenetics

With advancing technology the distinction between cytogenetic tests and molecular genetic tests is disappearing and more and more frequently molecular genetic techniques are being used to detect chromosome abnormalities. The two main techniques used are: (1) Multiple ligand probe amplification (MLPA)—This technique is a new high resolution technique for detecting copy number variation of a large number of DNA segments simultaneously and it can, therefore, be used to provide a rapid screen for deletions and duplications at a number of sites throughout the genome. For instance it can be used to screen for very small chromosomal deletions or duplications in children with learning disability and dysmorphism, in whom conventional cytogenetic testing has failed to reveal any abnormality. (2) Array comparative genomic hybridization (Array CGH)—With this technique a DNA sample from the patient and a 'normal control' DNA sample are labelled with different coloured fluorescent dyes (usually red and green) and spread onto a solid surface, which has previously been spotted with short stretches of DNA. The samples bind to these areas of DNA and where there is no difference between the patient and control samples the 'spots' look yellow and where the patient has additional chromosomal material (i.e. a duplication) the spot looks red or is missing chromosomal material (i.e. a deletion) the spot looks green (Fig 4.21). These spots are subsequently scanned and a computerized analysis is carried out to determine the specific regions of chromosomal imbalance and assess which genes

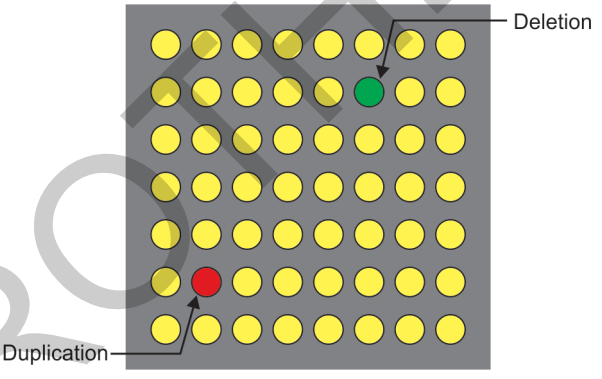

Fig 4.21: Array CGH

are likely be affected by the loss or gain of chromosomal material.

Single Gene Disorders

The clinical features of many of the single gene disorders have been discussed in other chapters throughout this book, but it may be useful to look at a few specific disorders from a genetics perspective.

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) (von Recklinghausen's disease) is one of the most common genetically inherited disorders, having an incidence of approximately 1:3,000. It occurs as a result of mutations in the NF1 gene on chromosome 17 and is essentially fully penetrant, although the phenotype can be extremely variable. In around half of the affected individuals there is a family history of the condition and in the remainder the condition has occurred as a result of new mutations. The main clinical features are: café au lait patches (Fig. 4.22) which are usually present by 5 years of age, cutaneous neurofibromata, iris Lisch nodules and axillary and groin freckling. Most affected individuals are shorter than average and have larger than average head circumferences. Mild to moderate learning difficulties are common. Regular

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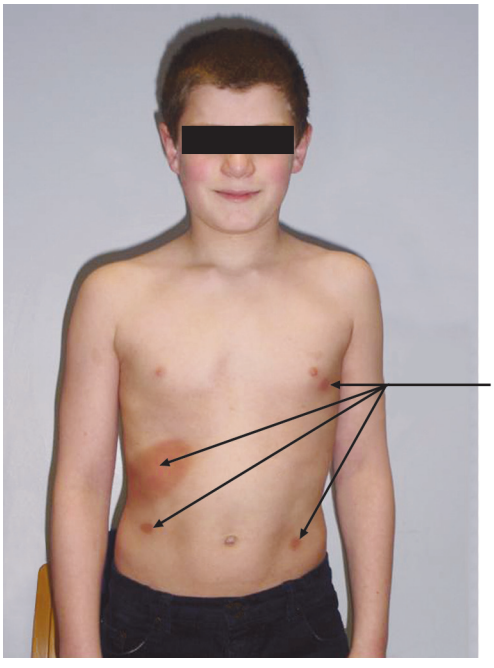

Fig. 4.22: Boy with neurofibromatosis type 1

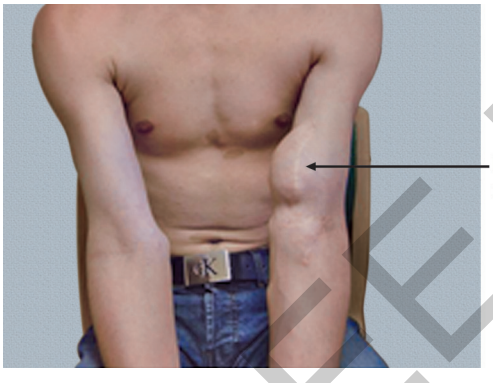

Fig. 4.23: Plexiform neurofibroma

follow-up is required as a small proportion of people with NF1 develop more severe complications such as pseudoarthroses (present from birth), plexiform neurofibromata of the head and neck (usually present within the first year of life), optic gliomata (usually present by 6 years of age), plexiform neurofibromata of other parts of the body as seen in Figure 4.23 (usually present before puberty) and scoliosis (usually present between age 6 years to puberty).

In adulthood, other complications such as hypertension (both essential and secondary to renal artery stenosis or phaeochromocytoma) and malignant peripheral nerve sheath tumours may also occur so follow-up is generally life long.

The NF1 gene is a very large gene and mutation analysis is possible, but as NF1 can usually be easily diagnosed on clinical grounds, genetic testing is rarely necessary.

NF1 should not be confused with neurofibromatosis type 2 (NF2), which is a completely separate disorder due to a gene on chromosome 22. Although patients affected by NF2 may have café au lait patches, they seldom have six or more and they do not have the axillary and groin freckling found in NF1. The most common presenting feature is bilateral vestibular schwannomas.

Tuberous Sclerosis

Tuberous sclerosis complex (TSC) occurs with an incidence of 1:5,000–6,000. It can occur as a result of mutations in two different genes, TSC1 (located on chromosome 9) and TSC2 (located on chromosome 16). The condition is now thought to be fully penetrant and recurrences which have occurred when parents are apparently unaffected are now recognised to be due to one of the parents having minimal clinical features such as periungual fibromata (Fig. 4.24) and the phenomenon of 'gonadal mosaicism', whereby one of the parents is a carrier of the mutation only in their gametes.

TSC is a multisystem disorder with extreme variability in the phenotype, even within one family. The clinical features are divided into major features (facial angiofibromata, ungual and periungual fibromata, forehead plaques, hypomelanotic macules, shagreen patches (connective tissue naevi), multiple retinal hamartomata, cortical tubers, subependymal nodules, subependymal giant cell astrocytomata, cardiac rhabdomyomata, lymphangiomyomatosis and renal angiomyolipomata) and minor features (dental enamel pits, hamartomatous rectal polyps, bone cysts, cerebral white matter radial migration lines, gingival fibromata, non-renal hamartomata, retinal achromic patches, 'confetti' skin lesions and multiple renal cysts). The clinical diagnosis is based on the presence of two major or one major plus two minor features. In the most severe cases TS can present with infantile spasms and such children can remain profoundly

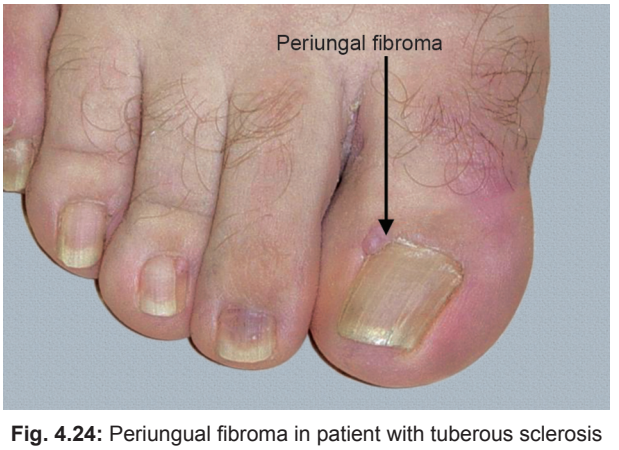

Fig. 4.24: Periungual fibroma in patient with tuberous sclerosis

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handicapped with difficult to control seizures throughout their lives. In milder cases mild to moderate learning disability may be present but some individuals affected by TS have completely normal intelligence. Regular follow-up is again important particularly with regard to the possibility of renal complications.

Mutation analysis is available for both TSC1 and TSC2 and prenatal diagnosis is possible if a mutation is identified.

Marfan's Syndrome

Marfan's syndrome has an incidence of 1:5,000–10,000 and in the majority of affected individuals the condition is due to mutations in fibrillin 1 (FBN1) on chromosome 15. It is a disorder of collagen and is, therefore, also a multisystem disorder affecting primarily the eye, the skeletal system and cardiovascular system. Individuals affected by Marfan's syndrome are usually disproportionately tall with long limbs and arachnodactyly (long fingers and toes) (Fig. 4.25). However, as many people who are tall with long arms and legs do not have Marfan's syndrome it is necessary that patients meet strict clinical criteria, known as the Ghent's criteria, before the diagnosis can be made. The main clinical features included in the Ghent's criteria are: disproportionate stature, pectus excavatum or carinatum, long fingers, flat feet, protrusion acetabulae (an abnormality of the hip identified by X-rays), dental crowding, joint hypermobility, flat cheek bones, ectopia lentis and other eye abnormalities, dissection or dilatation of the ascending aorta, mitral valve prolapse and spontaneous pneumothoraces.

Although the ocular complications and aortic root dilatation and dissection, associated with this condition, are more common in adulthood long-term follow-up is required from the time of diagnosis. The diagnosis of Marfan's syndrome in the past was mainly based on clinical features but mutation analysis can now be used in combination with clinical features and in families where a mutation is identified prenatal diagnosis is possible.

Myotonic Dystrophy

Myotonic dystrophy (dystrophia myotonica) has an incidence of around 1:8,000 and as the name suggests is a muscle wasting disease. However, it too, is a multisystem disorder and can be of very variable severity. The majority of people affected by myotonic dystrophy have myotonic dystrophy type 1 (DM1) due to abnormalities of the DMPK gene on chromosome 19. Myotonic dystrophy type 2 (DM2) is due to abnormalities of the ZNF9 gene on chromosome 3 and is much rarer. DM1 is an example of a condition due to a "triplet repeat expansion". Other trinucleotide repeat disorders which may be encountered in paediatric practice are Fragile X-syndrome, Friedreich's ataxia and juvenile onset Huntington's disease.

In the case of myotonic dystrophy the repeated trinucleotide is CTG and the normal size is 5–35 repeats. In very general terms the age of onset and severity of symptoms relates to the size of the expansion of this repeat, although it is not possible to predict with accuracy an individual's prognosis from their expansion size. Like other triplet repeat disorders, myotonic dystrophy exhibits the phenomenon of anticipation. Anticipation is seen because the expanded trinucleotide region is unstable and therefore expands further

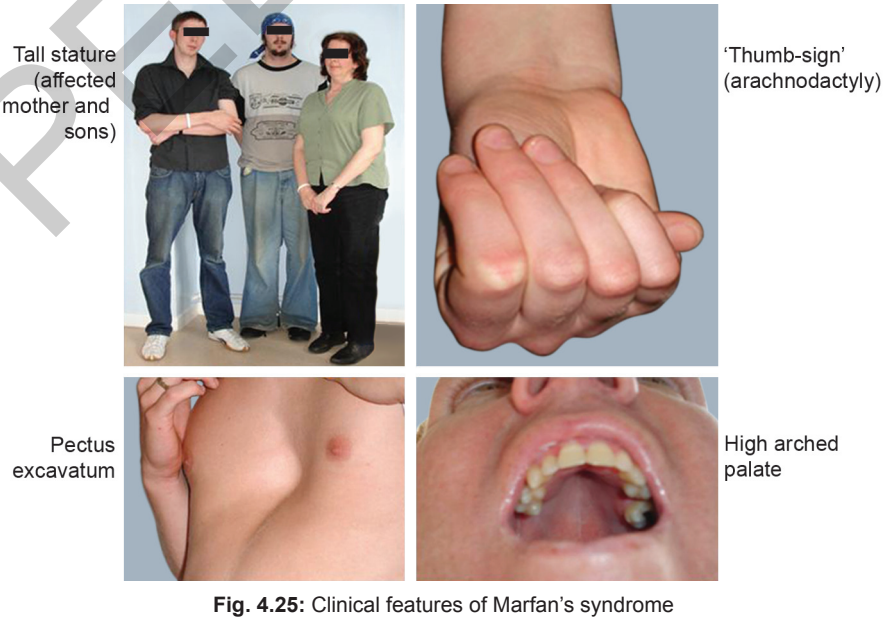

Fig. 4.25: Clinical features of Marfan's syndrome

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as it passes from one generation to the next, resulting in symptoms occurring earlier and with greater severity in each successive generation. For this reason it is particularly important to take a detailed three-generation family history as the older, more mildly affected relatives may only have single symptoms, such as cataracts or diabetes, which may otherwise be overlooked.

The clinical features of DM1 are: muscle disease [muscle weakness and myotonia (difficulty in relaxing the muscles after contraction)], GI tract symptoms (as smooth muscle is also affected patients often complain of constipation, colicky abdominal pain and problems with bowel control), cardiovascular disease (conduction defects may lead to sudden death), respiratory problems (alveolar hypoventilation due to diaphragmatic and probably also a central component, post-anaesthetic respiratory depression can be significant and care should be taken), ocular problems (subcapsular cataracts and retinal abnormalities), CNS (major cognitive dysfunction is unusual with adult onset disease but personality traits such as apathy, with marked daytime sleepiness and stubbornness are well-recognised) and endocrine problems (testicular atrophy—sometimes resulting in male infertility, recurrent miscarriages, diabetes mellitus, frontal balding).

Congenital myotonic dystrophy is a severe form the disorder and almost always occurs when the condition is transmitted by the mother and generally only if the mother has symptomatic disease. Affected neonates have profound hypotonia and usually require prolonged ventilatory assistance. Survivors have learning disabilities in addition to the physical features of the disease.

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HUTCHISON'S
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In this second edition, we seek to provide practical advice about the diagnosis, investigation and management of the full spectrum of childhood disorders, both medical and surgical. We have tried to indicate, and where appropriate to describe, techniques and laboratory investigations which are necessary for advanced diagnosis and up-to-date therapy. Attention is directed to the special problems which often arise in the developing countries. Many chapters in this edition were completely revised, updated and extended with an additional four chapters which are intended to widen the perspective of the book.

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