Chapter 1

The genetic basis of disease

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Introduction

Individual genetic disorders are rare but, since the advent of antibiotics, they have become the main cause of childhood morbidity and mortality in the developed world. Half of all hospital admissions are due to genetically determined conditions, including polygenic disorders. Genome-wide association studies have demonstrated genetic predispositions to breast and prostate cancer, diabetes, and coronary artery disease. These associations will continue to accumulate with the application of so called single nucleotide polymorphism (SNP) chips. With improving technology, there is also a better understanding of disease mechanisms and the possibility of new therapeutic options.

The human genome

The human genome comprises DNA that carries information for all aspects of embryogenesis, differentiation, growth, development, and reproduction. It is composed of three units: a five-carbon sugar (deoxyribose), nitrogen-containing base (purine or pyrimidine), and phosphate group. These three units polymerize into a long polynucleotide chain held together by phosphodiester bonds between adjacent sugar units. Within the cell, DNA is complexed with protein to form chromatin. During cell division, chromatin condenses and is visible as a chromosome.

A gene is a segment of DNA that codes for a functional protein. In the resting state, DNA is present as a double helix. In the process of protein production, DNA "unzips" so that messenger RNA (mRNA) can be transcribed. RNA is also composed of a five-carbon sugar (ribose), nitrogen-containing base (purine or pyrimidine), and a phosphate moiety. mRNA is produced in the nucleus and is transported into the cytoplasm where it is translated on the ribosomes to form the protein. Not all genomic DNA is transcribed into protein. The segments that are transcribed are called exons. The "silent" regions are called introns.

Members of a pair of chromosomes carry the same genes in the same order along the length of the chromosome (Fig. 1.1). The position of the gene on the chromosome is called the locus. The genes on the locus may be identical or slightly different forms of the same gene (alleles). The genetic composition of an individual is the genotype. The physical manifestation of the genotype is the phenotype.

Rearrangement involving two different chromosomes is called a translocation. A reciprocal translocation is a rearrangement of genetic material between two non-homologous chromosomes. There is usually no net gain or loss of material and no deleterious effect. There is a small risk of gene damage at the breakpoint of the chromosomes. About 1 in 1000 individuals are thought to be carriers of balanced reciprocal translocations. A Robertsonian translocation involves the short arms of acrocentric (Fig. 1.2) chromosomes. The two chromosomes are stuck together. Carriers of Robertsonian translocations are asymptomatic.

The clinical genetics appointment

Patients from all specialties are referred to the genetics clinic to establish diagnosis, arrange relevant investigations, and inform parents or relatives of the likelihood of affected children.

The genetics consultation (Table 1.1) involves a detailed history including antenatal, birth and neonatal

events, developmental progress, loss of skills, at least three generation family tree with attention to inherited disorders, learning difficulties, and cancer. Clinical examination includes anthropometric measurements, risk assessment of recurrence, and management advice.

Genetic disorders

Chromosome abnormalities

Abnormalities of number

The normal chromosome complement of 46 chromosomes is called diploid. Gametes have a haploid (n) set of chromosomes. An exact multiple of the haploid chromosome set is referred to as euploid. This could be triploidy ($3n$) or tetraploidy ($4n$) and such embryos are usually miscarried in the first trimester. Any other abnormality of chromosome number is called aneuploid.

Table 1.1. When to consider an underlying genetic disorder

A child with multiple congenital anomalies
Person with learning difficulties
Family history of learning difficulties
History of recurrent miscarriages or infertility
Family history of cancer
Recognized genetic disorder in the family, e.g. polycystic kidneys

Aneuploidy is the most significant chromosome abnormality occurring in 3%–4% of pregnancies. This may be due to an additional chromosome such as trisomy (three copies) or absence of a whole chromosome (monosomy).

Trisomy 21 (Down syndrome)

The commonest, clinically significant trisomy. The incidence is 1 in 650–1000 live births. The number of babies with Down syndrome is declining, despite increased maternal age. This reflects antenatal screening and termination of affected pregnancies. There is a correlation between the incidence of Down syndrome and maternal age.

Chromosome abnormality 95% of trisomy is due to non-disjunction at meiosis. 5% include translocation and mosaic forms.

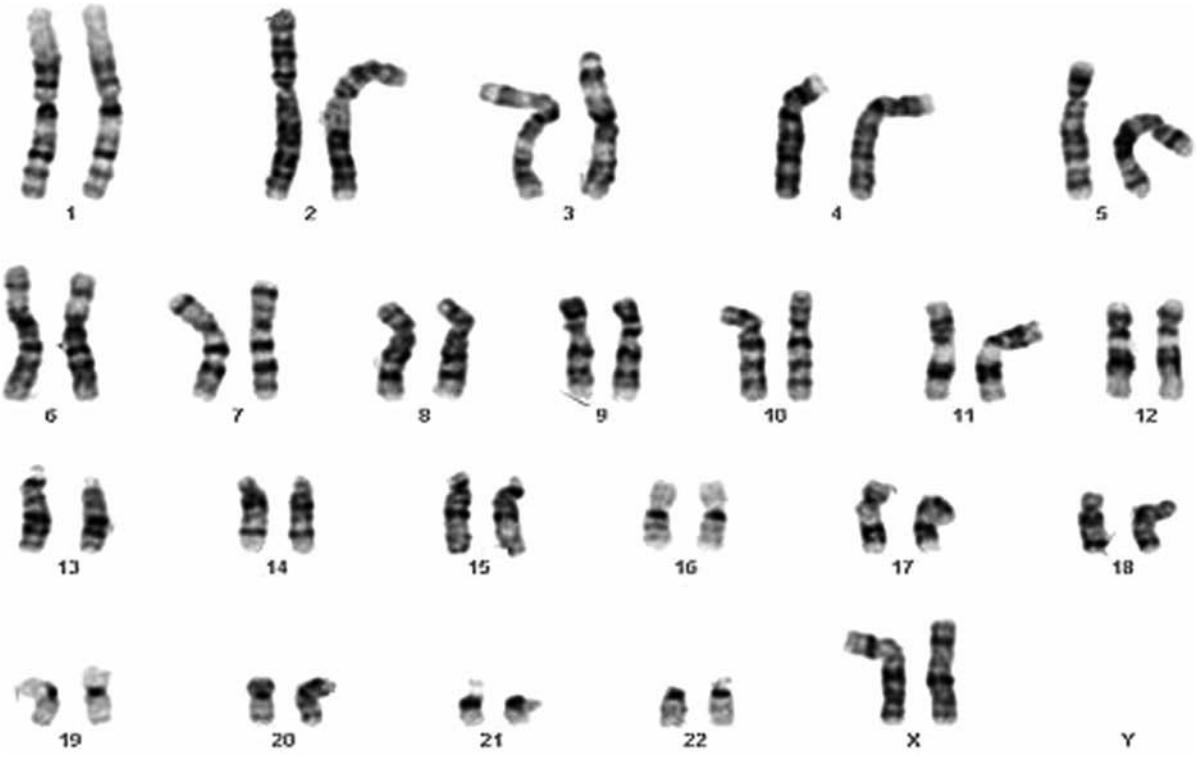

Fig. 1.1. The chromosome complement is called the karyotype. The somatic cells contain 46 (23 pairs) chromosomes. Of these, 22 pairs are common to men and women. These are called autosomes. These are conventionally numbered from 1 to 22 in decreasing order of size. The remaining chromosomes are the sex chromosomes: XX in females and XY in males. Members of the pairs of chromosomes carry matching genetic information.

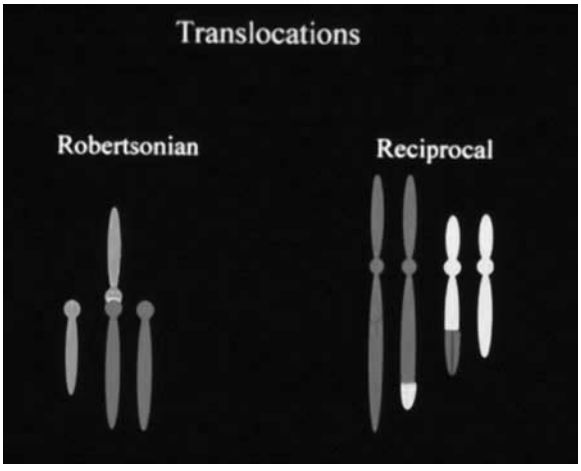

Fig. 1.2. Figurative examples of Robertsonian and reciprocal translocations.

Clinical presentation In infancy, characteristic facial features are evident. Half have congenital heart disease, the most common being atrioventricular and ventricular septal defects (50% and 40%, respectively). One third have intestinal atresia. Hypothyroidism may be a feature. Developmental delay, behavioral and visual problems, obesity, periodontal disease, deafness become apparent in childhood. There is increased risk of acute leukemia between ages 1 and 5.

Puberty proceeds normally. Folliculitis occurs in 50%. Most adults are able to carry out activities of daily living under supervision, but are unable to live independently. Few are employed. Reproduction is rare. The neuropathological changes of Alzheimer's disease usually develop in the fifth decade and 75% over 60 have dementia.

Turner syndrome

Incidence 1 in 2500 live born females. Some conceptions with Turner syndrome are lost in early pregnancy.

Chromosome abnormality Variable.

A majority have 45,X karyotype. Other X chromosome abnormalities include isochromosome Xq (duplication of the q arm of X chromosome) or ring X chromosome. The ring X is associated with a more severe phenotype. There may be more than one cell line – one 45,X and the other may be 46,XX or any of the others above. The presence of cells with different chromosome make-up in the same individual is termed mosaicism.

Infants have low birthweight, lymphedema of the dorsum of the feet, neck webbing, and puffy hands, cardiac, and renal anomalies. Feeding problems cause failure to thrive and short stature in childhood. Ten percent have learning deficits and impaired visuospatial awareness. There is susceptibility to otitis media.

Obesity results from excessive eating. Gonadal dysgenesis occurs and most need estrogen to initiate puberty. Ten percent enter puberty spontaneously, but there is high likelihood of premature ovarian failure especially in mosaic karyotype. Hypertension and hypothyroidism occur in adults.

Klinefelter syndrome (XXY)

Incidence 1 in 1000 male births and mostly unrecognized. Diagnosis is made during prenatal testing for another reason, during the course of investigations for developmental delay or in adulthood during investigation for hypogonadism or infertility.

Increased height velocity occurs in mid childhood. Delayed speech development and reading difficulties arise in many. There is a tendency to obesity in adolescence. Most experience delayed puberty and need testosterone supplements. Half have gynecomastia.

Other sex chromosome aneuploidies

XYY and XXX.

These diagnoses are made either during prenatal testing or during investigation of developmental delay.

XYY – sudden increase of growth in mid childhood resulting in tall stature. 45% have delayed speech and behavior problems.

XXX – small at birth but height velocity increases in childhood and they are tall girls. They may have learning and behavior difficulties.

Microdeletion syndromes

In these conditions, there is deletion of part of a chromosome. The chromosome number is 46 and detailed analysis of the band pattern reveals the deletion. This can be confirmed by fluorescent *in-situ* hybridization (FISH) studies (Fig. 1.3).

Williams syndrome

The incidence is unknown. The diagnosis is based on recognition of the typical facial features and can be confirmed in 99% by FISH studies.

Chromosome anomaly 7q11 deletion.

Features in childhood are broad forehead, periorbital fullness, full cheeks, and a wide mouth with a full lower lip. Fifteen per cent have hypercalcemia. Cardiac lesions occur and supra-valvular aortic stenosis is the commonest (75%). Renal anomalies arise

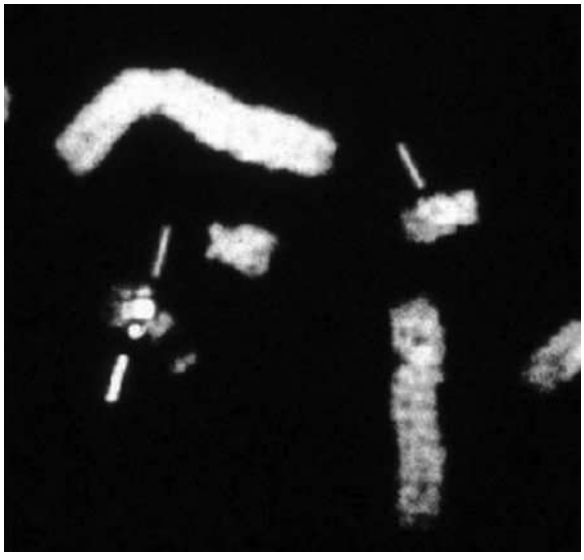

Fig. 1.3. In the FISH study, probes for specific DNA sequences on the chromosome of interest are labeled with a fluorescent dye. The probe is hybridized with the DNA sequences on a slide and analyzed under the fluorescent microscope. In a normal cell, two signals should be detected. If only one signal is present, it denotes missing information or deletion. This can be used to detect deletions at the ends of the chromosomes (telomeres) or within the chromosome (interstitial).

in 20%. There is a typical profile of better verbal and auditory compared with visuo-spatial skills. Most have ligamentous laxity (90%) which affects fine motor skills. Hyperacusis (increased sensitivity to sound) is common. Most adults have learning disability and are unable to live independently. Adult women have decreased bone density. Hypertension occurs in 50%.

Diagnosis FISH studies to look for 7q11 deletion.

Velo-cardio-facial syndrome (also known as Di-George, Shprintzen syndrome)

Chromosome anomaly 22q11 deletion.

Congenital cardiac anomaly and cleft palate, hypocalcemia, immune defects, renal anomalies, typical facial features, and learning difficulties. Incidence 1 in 2000. Individuals present to many specialties including cardiology, immunology, and plastic surgery.

Concurrence of cleft palate and heart disease should raise suspicion. All affected children have learning difficulties and 90% speech delay. Speech has a nasal and indistinct quality (70%). Renal anomalies occur in 35%. Immunodeficiency is due to T cell dysfunction but frequent infections occur even with normal T cells. There is risk of bipolar disorder and schizophrenia in adults (20%). Recurrence risk: children have a 50% chance of inheritance from an affected parent.

Mendelian disorders

Disorders of imprinting

Expression of some regions of the genome depend on whether they are paternally or maternally inherited. Imprinted disorders may result from chromosomal microdeletion or both alleles being inherited from the same parent (uniparental disomy).

Prader–Willi syndrome

Prader–Willi syndrome results from absent expression from the 15q11 region on the paternal allele. Prevalence is 1 in 10 000.

Genetics Microdeletion of 15q11 on the paternal allele is the most common mechanism.

Uniparental disomy Both alleles are maternally inherited.

Hypotonia is followed by childhood obesity due to increased appetite. Growth hormone deficiency may co-exist. Hypogonadism causes incomplete pubertal development. Short stature may respond to growth hormone treatment. All are infertile. Obesity is the major cause of morbidity and mortality. Most adults live in sheltered accommodation. There is a high frequency of psychiatric disturbance.

Diagnosis Deletion of 15q11 region. DNA analysis is needed to check for uniparental disomy.

Angelman syndrome

Incidence is 1 in 10 000–40 000.

Genetics Deletion of 15q11 on the maternal allele – 70%.

Uniparental disomy Two paternal alleles only present – 2%.

Rarer mechanisms *UBE3A* gene mutation, imprinting center defect.

Children have microcephaly and seizures in 80%. Some may be hypopigmented. Hyperactivity and developmental delay are common and none develops speech. Gait is ataxic and EEG characteristic. Mobility decreases due to progressive scoliosis. All adults require supervised accommodation.

Cardiovascular system

Congenital heart defect may be an isolated anomaly or part of a recognizable syndrome such as Williams or velo-cardio-facial syndromes, CHARGE association, or VACTERL association. It is the most common birth defect, affecting 0.7% of live born infants.

Atrial septal defect is mainly an isolated event. It is the characteristic heart disease of Holt–Oram syndrome, associated with an abnormal thumb or radial ray abnormalities. The left hand is affected more than the right. It is autosomal dominant and in some, mutations occur in the *TBX5* gene.

Aortic stenosis

Supravalvular aortic stenosis is seen in 75% of patients with Williams syndrome.

Coarctation of aorta

This anomaly is typically associated with Turner syndrome.

Interrupted aortic arch

About half the patients with this condition have 22q11 deletion.

Pulmonary stenosis

In Noonan syndrome, the commonest cardiac anomaly is valvular pulmonary stenosis due to dysplastic pulmonary valves. Mutations in *PTPN11* gene occur in half.

Peripheral pulmonary stenosis is seen in Alagille syndrome. Features include triangular face, down slanting palpebral fissures, posterior embryotoxon of eyes, "butterfly" vertebrae, and neonatal hepatitis. Deletions and mutations in *JAG1* have been identified. It occurs in 50% of Williams syndrome.

Hypertrophic cardiomyopathy

Is seen in Noonan syndrome and is often septal in nature. Others are familial and inheritance is often autosomal dominant.

Aortic rupture or dissection may follow dilated aorta in Marfan syndrome. Echocardiogram and abdominal ultrasound should be performed regularly.

Respiratory system

Cystic fibrosis (CF)

Autosomal recessive with a carrier frequency of 1 in 25 of Caucasians. More than 30 different mutations occur, the commonest being delta F508 (60–80%).

Failure to thrive requires pancreatic enzyme supplements to ensure weight gain. Respiratory complications start in childhood. Survival beyond the third decade is rare. Accurate prenatal testing is possible if the family mutations are known. This can be done on a CVS (chorionic villus sampling) biopsy or amniocentesis.

Alpha-1–antitrypsin

Alpha-1–antitrypsin deficiency is another autosomal recessive condition. Affected individuals may have emphysema in addition to liver disease and it is associated with the PiZZ genotype.

Table 1.2. Diagnostic criteria for autosomal dominant polycystic kidney disease (ADPKD) have been suggested based on the ultrasound features

Age at assessment	Positive family history	Negative family history
Childhood	Single cyst in both kidneys	
Adult <30 years	Two cysts in one or both kidneys	Five cysts in both kidneys
30–60 years	Four cysts in both kidneys	Five cysts in both kidneys
>60 years	Eight cysts in both kidneys	Eight cysts in both kidneys

Gastro-intestinal tract

Structural anomalies such as gastroschisis or bowel atresia occur as sporadic events or part of a syndrome. Esophageal atresia is seen with VATER association (**v**ertebral–**a**norectal–**t**racheo-**e**sophageal–**r**enal anomalies), small bowel atresia in Down syndrome. Exomphalos or gastroschisis may occur in Beckwith–Weidemann syndrome – an overgrowth syndrome with macroglossia, hypoglycemia, and asymmetry.

Liver disease

Liver involvement may be a feature of Wilson's disease, hemochromatosis or alpha-1-antitrypsin deficiency. Zellweger syndrome presents with neonatal conjugated hyperbilirubinemia, hypotonia, and feeding difficulties. All are inherited as autosomal recessive.

Renal

Structural anomalies

Structural renal anomalies may occur as sporadic events and the recurrence risk is small.

Polycystic kidney disease

Polycystic kidney disease may be a primary disorder or part of other conditions.

Autosomal dominant polycystic kidney disease (Table 1.2)

Incidence is 1 in 1000 live births. Presentation is in adulthood. Severity is variable. There is progressive cyst formation with enlargement of the kidneys. In 25% there are additional benign adenomas. Complications include hypertension, bleeding within cysts, renal impairment, and eventual renal failure. Half develop renal failure by age 60. If an ultrasound is

normal in adulthood, the probability of carrying the faulty *ADPKD* gene is less than 5%.

Sixty percent develop hypertension even if renal function is preserved. A single cyst in a child with a positive family history is adequate for diagnosis.

Two genes are associated: *PKD1* (chromosome location 16p) and *PKD 2* (chromosome 4q). There is no relation between the mutation and clinical picture, which varies within the same family. Molecular testing is not yet possible. Risk of inheritance is 50%. Parental ultrasound should be arranged following diagnosis in children.

Autosomal recessive polycystic kidney disease

Rare with incidence 1 in 10 000.

Genetics Autosomal recessive, mutations in *PKHD1* gene.

Cysts occur in kidney and liver. There may be oligohydramnios in pregnancy and hyperechoic kidneys identified on antenatal scans. Infants develop anuria and renal failure. Hypertension, cardiac hypertrophy, congestive cardiac failure, and renal failure happen early. Hepatic fibrosis and portal hypertension may be seen in survivors.

Mutation screening of the *PKHD1* gene is not available routinely. Linkage analysis is possible and prenatal diagnosis can be performed using this information.

Deafness

Deafness is the commonest sensory impairment worldwide. In the UK, the incidence is 1 in 1000 at birth. Thirty percent are part of a genetic syndrome. In the remaining 70%, deafness is non-syndromic.

Up to 80% of non-syndromic hearing loss is inherited as an autosomal recessive. The commonest gene implicated is *GJB2* (connexin 26). Mutations in this gene are identified in half of European patients. Profound hearing impairment is apparent from early infancy. Autosomal dominant hearing loss may present in late childhood or adults and is not severe. Mitochondrial mutations may also cause hearing loss and may be part of a more extensive neurological phenotype, e.g. MELAS and Pearson syndrome.

Testing for most of the common mutations in the *GJB2* gene is available.

Neuromuscular

Muscular dystrophies are a heterogenous group of inherited disorders characterized by progressive muscle wasting and weakness.

Duchenne muscular dystrophy

The commonest and inherited in an X linked recessive manner. Birth prevalence is 1 in 3500. It is found in affected boys during investigations for delayed walking or progressive muscle weakness in early childhood. They are wheelchair bound by age 12. Respiratory support is required by adolescence and most die in their 20s. A third develop cardiomyopathy. Female carriers require monitoring for cardiac conduction defects (41%) and dilated cardiomyopathy.

Genetics The mutations are in the dystrophin gene – the largest human gene on Xq21. In one-third, mothers are carriers of the mutation. It is possible to detect 98% DMD mutations on molecular testing. Prenatal diagnosis is possible if the molecular defect is known.

Recurrence risk for parents with one affected child where the mother is a carrier is 1 in 4 (half the boys would be affected and half the girls would be carriers). If the mother is not a carrier, there remains a high recurrence risk (10%) probably due to gonadal mosaicism. Affected boys do not reproduce.

Becker muscular dystrophy

This is allelic to DMD and is a milder disorder. The prevalence is 1 in 18 000 males. Affected boys remain ambulant beyond age 16 and often into adult life. Progression is slow but there is risk of cardiomyopathy. Affected men may reproduce. Molecular testing and genetic counseling as for Duchenne muscular dystrophy.

Fascioscapulohumeral muscular dystrophy

Weakness of facial, scapulohumeral, anterior tibial, and pelvic girdle muscles. Many have mild weakness. Some become wheelchair bound. Inheritance is autosomal dominant and both males and females are affected. The relevant gene is linked to chromosome 4 and a large fragment is seen on RFLP analysis.

Huntington's disease

Autosomal dominant neurodegenerative condition of adult onset. Most become symptomatic in their 40s. Age of onset in an at-risk family member cannot be predicted because of anticipation. If the mutation is inherited from an affected father, symptoms may develop in adolescence (juvenile onset HD).

Genetics Autosomal dominant affecting males and females equally. Mutation results from expansion of the CAG trinucleotide sequence in the HD gene. Affected individuals have more than 39 repeats compared with the normal of 30. It is not possible to

predict the severity or age of onset based on the number of repeats.

Genetic counseling Genetic counseling is challenging and awareness of the implications of positive tests is essential. Trained genetic counselors should perform all genetic testing. It is not advisable for young people to have a predictive test before age 21.

Fragile X syndrome

Mental retardation in males and milder features in affected females. It is the most common (1 in 1000 males) cause of severe mental deficiency after Down syndrome. It derives its name from identification of the cytogenetic abnormality on the long arm of X chromosome. The diagnosis is established by demonstrating CGC expansion in the *FMR1* gene.

Genetics It is X linked. The normal allele has fewer than 45 repeats. Affected males have more than 200 repeats. Alleles between 45 and 58 repeats are referred to as intermediate alleles and are not associated with health problems. Repeats between 59 and 200 are in the premutation range and risk instability and expansion to full mutation.

Clinical features Learning and behavior problems in early childhood, high incidence of attention deficit hyperactivity disorder and autism. Premutation carriers show subtle behavior traits characterized by anxiety, obsessional thinking, and depression.

Premature ovarian failure may occur. Males with premutation have progressive intention tremor and gait ataxia (Fragile X related Tremor Ataxia Syndrome). There may be associated peripheral neuropathy. MRI reveals typical symmetrical hyperdense areas in the middle cerebellar peduncles.

Recurrence risks Females who are premutation carriers have a 1 in 4 chance of having an affected son with developmental problems and 1 in 4 probability of having a girl with milder problems.

Prenatal testing is available on a chorionic villus sampling (CVS).

Myotonic dystrophy

Multi-system disorder affecting skeletal muscle, eye, heart, and central nervous system. There is a range of severity including severe congenital or mild adult form with cataracts and mild myotonia.

Genetics Caused by CTG expansion in the *DMPK* gene. It is autosomal dominant and demonstrates anticipation. The normal allele has up to 35 repeats. Increase in the size of the gene to more than 50 repeats results in the disease. The intermediate repeat number is referred to as a premutation.

Neonatal presentation Occurs when inherited from the mother. In the pregnancy, there may be polyhydramnios. The affected child is hypotonic at birth and requires respiratory support. Affected children who survive have learning difficulties.

Mild form Usually presents as cataracts in adults. The diagnosis is often made on extended family studies.

Classic form This usually presents between 20 and 40 years of age. The main complaint is distal weakness. Males report early onset baldness. Almost all develop posterior subcapsular cataracts. Cardiac conduction defects are common. Women predispose to miscarriage and post-partum hemorrhage.

Recurrence risk is 50%. There is risk of the severe congenital myotonic dystrophy if the expansion is maternally inherited.

Prenatal testing is available.

Skeletal

Skeletal dysplasias

Diverse conditions with different patterns of inheritance including autosomal dominant, recessive, and X linked. Detailed family history including family photographs is essential. Assessment involves a full skeletal radiological survey. Prenatal testing is available where the molecular defect is identified.

Marfan syndrome

Incidence is 1–2 per 10 000. Diagnosis is based on clinical criteria (Table 1.3).

Genetics Autosomal dominant with nearly full penetrance. Causative mutations have been identified in the fibrillin 1 gene.

Clinical features Disproportionate tall stature with cardiac and eye abnormalities.

Not all features may be present at the time of diagnosis. Dilatation of the aortic root may not be apparent until adulthood but scoliosis may be manifest in adolescence. Normative data on upper segment–lower segment ratios and aortic root measurements are available for the Caucasian population at different ages. The cardiovascular manifestations of Marfan syndrome are life threatening and require follow-up.

Although mutations have been identified in *FBN1* gene, diagnosis is based on clinical examination. Prenatal testing is not offered routinely.

Recurrence 50% risk to offspring.

Table 1.3. Revised diagnostic criteria for Marfan syndrome

Index case
Major criteria in two different organ systems and involvement of a third system *or*
mutation in FBN1 gene and one major criterion and involvement of a second organ system
Relative of index case
Family history of Marfan syndrome in a first degree relative and one major criterion in one organ system and involvement of a second organ system
Diagnostic criteria (from De Paepe *et al.*)
(i) Skeletal
Major features
pectus carinatum
severe pectus excavatum (req. surgery)
wrist and thumb signs
reduced elbow extension (<170°)
scoliosis >20° or spondylolisthesis
reduced upper to lower segment ratio <0.86
arm span to height ratio >1.05
pes planus
protrusio acetabulae (from AP pelvis X-ray)
Minor features
moderate pectus excavatum
joint hypermobility
high arched palate with crowding of teeth
characteristic facies (dolichocephaly, malar hypoplasia, retrognathia)
Meets major criterion (4 or more major features)
System involved (2 major features or 1 major and 2 minor)
(ii) Cardiovascular
Major features
dilatation of ascending aorta at the sinuses of Valsalva
dissection of the ascending aorta
Minor features
mitral valve prolapse +/− regurgitation
main pulmonary artery dilatation in absence of stenosis
calcification of the mitral valve annulus
dilatation or dissection of the descending thoracic or abdominal aorta <50 years
meets major criterion (1 or more major feature)
system involved (1 minor feature)
(iii) Ocular
Major feature
ectopia lentis
Minor features
abnormally flat cornea
increased axial globe length
hypoplastic iris or hypoplastic ciliary muscle
meets major criterion (ectopia lentis)
system involved (two minor features)
(iv) Pulmonary
Minor features only
spontaneous pneumothorax
apical blebs
system involved (1 minor feature)
(v) Skin [(vi) DURA (not routine)]
Minor features
striae atrophicae with no apparent cause
recurrent incisional herniae
system involved (1 minor feature)
meets major criterion
Major criterion
lumbosacral dural ectasia on CT or MRI

Neurocutaneous syndromes

Tuberous sclerosis (TS)

This is a multi-system disorder affecting 1 in 5000 children at birth due to mutations in one of two genes involved in controlling cell growth, TSC1 and TSC2. It presents in different ways (Table 1.4). Antenatal cardiac rhabdomyoma is associated with an 80% probability of TS. The tumor regresses spontaneously within 6 months without hemodynamic compromise. In 65% infantile spasms develop and EEG shows characteristic hypsarrhythmia. Seizures in childhood, learning difficulties, and autism in 25% are characteristic. SEGA (sub-ependymal giant cell astrocytoma) manifests in late childhood. It causes hydrocephalus.

Facial angiofibromas may be obvious with sparing of the naso-labial groove. Other cutaneous manifestations are hypopigmented macules more often noted on the back over the lumbar region and shagreen patches (raised patches with a well defined margin). Periungual fibromas are fleshy outgrowths from the nail bed.

Eighty percent develop renal angiomyolipomas. These are benign hamartomas but may bleed extra- or intrarenally. Simple cysts occur in 20%. Renal cell carcinoma occurs in less than 1% and at a young age.

Table 1.4. Diagnostic criteria for tuberous sclerosis (from Roach *et al.*)

Major features
(1) Facial angiofibroma or forehead plaque
(2) Non-traumatic ungula or periungual fibroma
(3) Three or more hypomelanotic macules
(4) Shagreen patch (connective tissue nevus)
(5) Multiple renal nodular hamartomas
(6) Cortical tuber
(7) Subependymal nodule
(8) Subependymal giant cell astrocytoma
(9) Cardiac rhabdomyoma – single or multiple
(10) Lymphangiomyomatosis
(11) Renal angiomyolipoma
Minor features
(1) Multiple randomly distributed pits in the dental enamel
(2) Hamartomatous rectal polyp
(3) Bone cysts
(4) Cerebral white matter radial migration lines
(5) Gingival fibromas
(6) Non-renal hamartoma
(7) Retinal achromatic patch
(8) Confetti skin lesions
(9) Multiple renal cysts

Notes:
Definite diagnosis of TS – Either two major, or one major and two minor criteria.
Probable TS – One major and one minor.
Possible TS – Either one major or two or more minor features.

Molecular diagnosis is possible. Parents or relatives of affected individuals can be tested.

There is 50% risk of inheritance. Parents who are clinically normal with no identifiable mutation have a 1%–2% recurrence risk due to gonadal mosaicism.

Neurofibromatosis type 1 (NF1)

A neurocutaneous syndrome characterized by café au lait spots. These are areas of increased pigmentation. Other manifestations include axillary and inguinal freckling. Multiple discrete dermal neurofibromas (tumors of the nerve sheath) may be present. If removed, abnormal scar formation may occur with risk of recurrence. Lisch nodules are hamartomas of the iris detected on slit lamp examination. Less common but more serious are plexiform neurofibromas, optic and other central nervous system gliomas, malignant peripheral nerve sheath tumors, and osseous lesions.

Table 1.5. NIH diagnostic criteria for neurofibromatosis Type 1 (NF1)

(Two or more of the following should be present to make a diagnosis of NF1)
(1) Six or more café au lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
(2) Two or more neurofibromas of any type or one plexiform neurofibroma
(3) Freckling in the axillary or inguinal regions
(4) Optic glioma
(5) Two or more Lisch nodules
(6) A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis
(7) A first-degree relative (parent, sib, or offspring) with NF1 as defined by the above criteria

Genetics NF1 is autosomal dominant. NF1 gene is large and at present, diagnosis is made on clinical examination (Table 1.5). Affected individuals have a 1 in 2 chance of passing it to their children. There is variable penetrance and examination of "normal" parents or siblings for cutaneous manifestations is necessary.

Management is supportive. The plexiform neurofibromata may be disabling and impinge on normal structures necessitating surgery.

Surveillance *In childhood*: affected children should be seen annually for examination of eyes, blood pressure, and scoliosis. Blood pressure should be monitored in adults.

Cancer

Only 5% of cancers are due to a highly penetrant inherited predisposition to cancer. These may be:

(1) defects in tumor suppressor genes, such that a mutation will increase the propensity for cancer;
(2) DNA repair genes where a mutation allows accumulation of new mutations in the DNA within the cell allowing uncontrolled replication;
(3) oncogenes which increase susceptibility by cell proliferation.

These mutations can arise in cancer cells or be inherited in the germ line. It is possible to check for mutations in cancer susceptibility genes. Relatives are

Table 1.6. Guidelines for breast cancer screening. National Institute for Clinical Excellence

	Family history	Screening
Low risk	1 relative diagnosed >40 years	Not required. Clinical examination if concerns
Moderate risk	One first-degree relative diagnosed <40 years *or* One first- and one second-degree relative diagnosed >50 years *or* Two first-degree relatives diagnosed >50 years	Need to be referred for risk assessment Annual screening from 40–50 years of age and then continued screening on the National Breast Screening Program
High risk	*Breast cancer* Two first- or second-degree relatives diagnosed <50 years *or* Three first or second-degree relatives diagnosed <60 years *or* Four relatives diagnosed at any age *or* One first-degree relative with bilateral breast cancer <50 years *Ovarian cancer* One relative diagnosed at any age *and* one first- or one second-degree relative with breast cancer <50 years *or* one relative with ovarian cancer diagnosed at any age *or* two first- or second-degree relatives with breast cancer <60 years *Male breast cancer* One male breast cancer at any age *and* on the same side of family tree. One first- or second-degree relative with breast cancer before 50 years *or* Two first- or second-degree relatives with breast cancer <60 years	Formal risk assessment is necessary. High likelihood of *BRCA1/BRCA2/p53* mutation in family Surveillance tailored according to individual's genotype and family history

often anxious to understand their own risks and seek investigation and surveillance.

Breast cancer

There are about 36 000 new cases annually, 30% of all cancers in women and a rate of 114 per 100 000 women.

One in nine women in the UK will develop breast cancer at some point in their lives. Our understanding of the genetic predisposition is still limited. However, 5%–10% are thought to be due to mutations in the strongly penetrant, inherited predisposing genes, such as *BRCA1, BRCA2*, and p53.

In addition, lower penetrance, modifier genes such as *CHK2* might also influence the risk. This is modified by reproductive history, early menarche, late first pregnancy, low parity and late menopause, oral contraceptive use, hormone replacement therapy (HRT), obesity, and alcohol. A mutation in one copy of the *BRCA1* gene gives an 80% risk. *BRCA1* mutation carriers have a 40% lifetime risk of ovarian cancer and *BRCA2* carriers have a 20% risk.

Genetic testing and mammography screening are prioritized according to risk based on family history (Table 1.6).

Family members can be offered genetic (predictive) testing. Management of women who carry *BRCA1* or *2* mutation includes screening, prophylactic mastectomy, and/or oophorectomy.

Breast screening is offered every 3 years to those aged 50–64, and on request when 65 or over. For *BRCA* mutation carriers, screening is tailored to family history. Ovarian screening has been proposed.

Bowel cancer

Several hereditary autosomal dominant conditions are associated with risk of colorectal cancer. The risk to an individual can be estimated from the family tree.

Some of the genes that predispose to colorectal cancer are known.

Familial adenomatous polyposis (FAP)

This was the first pre-colorectal cancer condition where the gene *APC* was identified. The population frequency of FAP is one in 13 258.

Inheritance Autosomal dominant.

Clinical features It is defined by the presence of 100 or more polyps or microadenomas in the large intestine. Extra-intestinal manifestations may be present. These include CHRPE (congenital hypertrophy of retinal pigment epithelium), sebaceous cysts, desmoid tumors, and gastric adenomas. The association of osseous and other extra-colonic anomalies with FAP is termed Gardener syndrome.

Testing and management: molecular testing can identify the mutation in 60%. Individuals at 50% risk (if no genetic test available) are offered annual colonoscopy with dye spray from age 13–20. If polyps are identified at any stage, total colectomy is offered.