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Common genetic conditions

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There are many different ways that faults in the genetic code can occur. Alterations to the genetic code can arise at any level and can affect gene expression leading to human disease. Before reading this chapter, readers might want to remind themselves of some of the terminology that is used to describe the genes and how they are assembled, by looking back at the introductory chapter, Chapter 1. There are many ways in which the genetic code, from the level of the chromosome (the bundles of genes in our cells), right down to a single nucleotide (the individual building blocks that make up our genes), can be disrupted.

One of the common type of faults are differences in the usual number of chromosomes known as 'aneuploidies'. Another variation that can occur are copy number variations such as deletion or duplication of chromosomes — these are large-scale changes that affect multiple genes and can lead to intellectual impairment and congenital malformations. Another mechanism of alteration to the genetic code involves mutations at the nucleotide level, the basic building blocks, which usually affect expression of single genes, or disrupt the function of the encoded protein, leading to genetic conditions that can manifest at any stage of life.

Sometimes a genetic problem occurs because of changes in what are called repeat segments of genes. In some genes there

are repetitive segments that look like the same genetic code of three nucleotides (a triplet) that is repeated over and over. The number of repeats is dynamic and can change in size when transmitted from one generation to another. Research has found that having over a threshold number of triplet repeats leads to genetic conditions that often affect the brain and neurological functions.

More recently, geneticists have come to understand that regulation of gene expression can also occur 'above' the level of the genetic code itself, a concept called 'epigenetics', and these epigenetic changes can lead to alterations in the way a genetic code is read and expressed.

What constitutes a genetic condition?

Many conditions appear to 'run in families', affecting family members in different generations. Examples include cancer, diabetes, mental health issues, cardiovascular disease, intellectual disability or birth defects. This familial clustering can be due to a combination of various reasons, including environmental, diet-related and/or genetic. When considering a genetic contribution to disease, we usually categorise these into those involving a single genetic factor of large effect (e.g. trisomy 21, causing Down syndrome), or a multifactorial model where multiple genetic factors, each of small effect, combine with non-genetic factors to cause disease (e.g. risk of coronary heart disease). This chapter will focus on the former.

In addition to a familial clustering of disease, there are other features that might suggest a genetic condition. The more of these features that are present in an individual or a family, the stronger the likelihood of a genetic condition. These features often prompt medical professionals to seek further assessment and genetic testing (as discussed in the next chapter).

Extreme, or unusual presentation of common conditions

Human diseases often follow a typical pattern of presentation. When exceptions to this pattern occur, such as early age of onset, particularly severe disease, or disease occurring in an individual from a low-risk population, a genetic condition should be suspected. Examples of these include bowel cancer in young people, severe intellectual disability with regression of skills, or breast cancer in a male.

Clustering of anomalies in an individual or family

The presence of multiple anomalies such as congenital malformations, primary cancers, or recurrent miscarriages in one individual or in a family should warrant consideration of a genetic cause. For example, a child with cleft palate, congenital heart defects and developmental delay might have a genetic condition such as what is called the '22q11 deletion syndrome' as the underlying cause. This syndrome is discussed in more detail below.

Rare pathology

Rare or exceptionally abnormal pathology can also be a marker for a genetic condition. For example, a soft tissue sarcoma (a type of cancer that arises in the soft tissues of the body) might arise in an individual with what has been called Li-Fraumeni syndrome, a genetic condition with cancer predisposition. To take another example, a cholesterol level very much higher than the usual range can be a sign of a genetic condition, familial hypercholesterolemia.

Neurocognitive impairment

The finding of developmental delay in a child, or neurocognitive impairment in an adult without a preceding insult, such as

birth trauma or head injury, should prompt consideration of a genetic condition. This is especially so if accompanied by multiple congenital anomalies, developmental regression or, in the case of adult cognitive impairment, an early age of onset.

Chromosomal aneuploidies (more or less than the usual number of chromosomes)

Down syndrome (Trisomy 21)

Having three copies of chromosome 21 (trisomy 21) instead of the usual two causes Down syndrome, the most common and well-known cause of intellectual disability. The features of Down syndrome arise from what can be thought of as an increased dosage of genes on chromosome 21. The prevalence of trisomy 21 at birth is quite common, approximately 1 in 650, but in fact it is higher at conception. The reason for this difference is that there is a high rate of spontaneous miscarriage resulting from a trisomy 21 conception. The prevalence of trisomy 21 also varies depending on maternal age. Although trisomy 21 can occur in the pregnancy of a woman of any age, it is more common with advanced maternal age, especially in those over 40 years.

In most cases, the trisomy 21 arises from incorrect separation of chromosomes during formation of the eggs or less commonly the sperm (a phenomenon known as 'non-disjunction'), but in approximately 5% of cases it arises due to a balanced chromosomal translocation in one of the parents. These rare cases are important to identify because of the increased chance of a recurrence in a future pregnancy. Occasionally, trisomy 21 can occur in mosaic form, meaning that the chromosomal abnormality is only observed in some of an affected individual's cells, but not all. This is due to the non-disjunction event happening at an early stage of the embryo's development after conception. In such

situations, the features of Down syndrome are usually attenuated to varying levels.

People with Down syndrome have a varying degree of intellectual disability, ranging from mild to severe impairment. Affected children are usually developmentally delayed compared to their peers and often have low muscle tone. The facial features of individuals with Down syndrome are often recognisable, including flat facial profile, upslanting eyes with epicanthic folds (a fold of skin over the end of the eye near the nose) and an open-mouthed appearance. Other physical features include short stature, small broad hands with single palmar creases, short and curved fifth fingers, and joint flexibility. Some children with Down syndrome are born with heart defects, which usually require surgery to correct. The risk of leukaemia is much higher in children with Down syndrome compared to unaffected children. Older individuals can develop a dementia similar to Alzheimer disease, with cognitive and emotional decline. Lifespan is usually shortened, although this is increasing with improvements in health care and medical surveillance.

Turner syndrome (Monosomy X)

The clinical features of Turner syndrome were first reported in 1938, but it was not until 1959 that the underlying chromosomal difference was identified. Women with Turner syndrome have only one X chromosome instead of the usual two (45,X). There are variants of this that also lead to similar features of Turner syndrome, including mosaicism, and deletion of part of the X chromosome.

Turner syndrome can be detected prenatally on an ultrasound scan when the ultrasonographer detects increased nuchal fold translucency (increased fluid under skin at the back

of the neck) and sometimes will see additional anomalies including heart defects. Many babies with Turner syndrome are born with tissue swelling, especially over the hands, feet and back of neck. The characteristic features of Turner syndrome include short stature, webbed neck, broad chest, and kidney and cardiovascular anomalies. Most affected individuals have normal intelligence, although some can have difficulties with learning or visuo-spatial processing. The diagnosis of Turner syndrome may also be made in a teenage girl with short stature and delayed puberty. The ovaries are typically underdeveloped and contain 'streaky' tissue, leading to a delay in menstruation and development of secondary sexual characteristics as well as fertility issues. There are rare reports of women with Turner syndrome conceiving, although this often requires assisted reproductive technology, and is more likely in women who are mosaic, having a mixture of cells in the body affected and not affected by the genetic fault.

Klinefelter syndrome (47,XXY)

Klinefelter syndrome is the most common sex chromosome aneuploidy, affecting approximately 1 in 500 to 1 in 1000 males, but many go undiagnosed because of the variable and relatively subtle features. Males with Klinefelter syndrome have an extra X chromosome, resulting in a 47,XXY chromosome complement. This leads to underdevelopment of the testicles with some physical changes to the body and variable effects on learning and emotional development.

Most babies with 47,XXY are indistinguishable from unaffected babies, although undescended testes, small penis or hypospadias (opening of the urethra on the underside of the penis rather than at the end) may be present. Klinefelter syndrome can also be difficult to diagnose in young boys. Affected boys can have low muscle tone, be less outgoing and

more prone to shyness or emotional immaturity compared to their peers. Some boys can have difficulties with language development and writing, or have verbal processing issues. Intelligence is most often in the normal range.

Under the age of 3 years, most boys with 47,XXY will have a height within the normal range. After this time, they tend to be taller than average, and adult body proportions often show relatively long limbs. Klinefelter syndrome is more evident in males after puberty. Testosterone levels are usually low due to insufficient production by their testes, and this results in a lower muscle mass, hips that are more curved, and less body hair. Some males can develop gynaecomastia (extra breast tissue), for which cosmetic surgery might be requested. Truncal obesity can develop in adolescence if low testosterone levels are untreated. Testosterone treatment may be needed to initiate and maintain puberty, and is often continued throughout life to reduce the risk of osteoporosis (thinning of the bones). In untreated men with Klinefelter syndrome, osteoporosis is observed in up to 25%. Other endocrine issues include increased rates of under functioning of the thyroid gland (hypothyroidism) and diabetes (types 1 and 2).

Some males are not diagnosed until they have difficulties with conceiving and are found to have very low sperm counts. Infertility affects most males with Klinefelter syndrome, but a technology called intracytoplasmic sperm injection (ICSI), where a single sperm is injected into a mature egg, has been used successfully to help some men conceive. The success rate of sperm retrieval in men with Klinefelter syndrome is still relatively low, and when sperm can be retrieved, the fertilisation rate is about 50%. Most of the reported live-born offspring of men with Klinefelter syndrome have a normal chromosome complement, but 47,XXY has been reported on a few occasions.

Chromosomal copy number changes

22q11 deletion syndrome

The epomymously named 'Di George syndrome', also called the technical names 'conotruncal anomaly face syndrome' and 'velocardiofacial syndrome', describe the most common 'human microdeletion syndrome'. Such syndromes were only discovered when very small deletions in the genetic code were detected with sophisticated genetic technologies, and the cause of this syndrome was only discovered in 1992. The condition is now most widely and accurately known as the 'chromosome 22q11.2 deletion syndrome'. It is estimated to occur in 1 in 4000 live births, although its prevalence may be higher as some familial cases can go unrecognised.

The most common features observed in individuals with 22q11.2 deletion syndrome include anomalies of the craniofacial region, neurodevelopmental disability and congenital heart disease. Immune, endocrine and kidney anomalies are less common. Distinctive facial features include a tubular nose with full nasal tip, hooding of the eyelids with mildly up-slanting eyes, and small jaw. Minor physical variations of the ears are common. Palatal abnormalities are very common, occurring in up to 70% of affected individuals. These include overt clefting of the palate or uvula (the small tissue/muscle that hangs at the back of the throat), or more commonly, dysfunction of the palate leading to speech and swallowing problems. Feeding issues in infancy with nasal regurgitation of milk, or hypernasal speech in childhood, can be markers of the palate problem called 'velopharyngeal insufficiency'. Chronic fluid build-up of the ears and middle ear infections are also common in children with 22q11.2 deletion syndrome, often exacerbated by palatal dysfunction and underlying immunodeficiency. These often lead to conductive hearing loss (a type of hearing

loss due to a blockage rather a nerve problem), which can have a further impact on speech and language development. This is often treated by insertion of small tubes, called grommets, into the eardrums.

Over 90% of individuals with 22q11.2 deletion syndrome have some degree of neurodevelopmental disability. Low muscle tone and delay of early motor milestones are very common in affected individuals and usually proceed to delays in speech and language development. Augmented communication devices or sign language are often utilised, especially as the affected child may get frustrated at their expressive difficulties. Some individuals can manage mainstream school with additional educational support, but many do better in a special school environment. Intelligence ranges from low-average to severe intellectual disability. Behavioural difficulties such as impulsiveness and autism spectrum disorder are frequently observed. Adolescents and adults with 22q11.2 deletion syndrome are prone to developing psychiatric issues ranging from anxiety and depression to schizophrenia and bipolar disease. Estimates suggest that psychosis and schizophrenia can occur in up to 30% of affected individuals.

Congenital (i.e. a disease that is present at birth) heart disease is identified frequently in children with 22q11.2 deletion syndrome and accounts for most of the early ill health in this condition. The most common defects involve the outflow tract of the heart, and often require corrective surgery. Anomalies can vary from a hole in the wall between heart chambers (ventricular septal defect) through to more complex defects (such as a condition called tetralogy of Fallot).

Less common manifestations are seen in many body systems, and are incredibly variable, even among affected members of the same family. Specific immune defects are reported in children with 22q11.2 deletion syndrome but rarely manifest in life-

threatening infections. Common ear or respiratory infections can be prolonged or recurrent. Some children have low calcium levels, especially in the neonatal period, and this can sometimes lead to tremors, cramping, irregular heart rhythm or seizures. The low calcium is usually a result of low parathyroid hormone levels, a hormone made by some small glands in the neck that regulate bone formation and calcium levels. Genital and/or urinary tract anomalies are identified in up to a third of individuals with 22q11.2 deletion syndrome and include structural defects of the kidneys and urinary tract, or functional problems like backflow of urine in the body's plumbing system between the kidneys and the bladder (called 'vesicoureteric reflux').

Feeding difficulties in children with this condition are common, often due to the underlying velopharyngeal insufficiency (a problem closing off the space between the back of the nose and the mouth), swallowing problems or cardiac disease (including problems with the body's largest vessel called the aorta). These often have an impact on the affected child's growth. Some children also develop growth hormone deficiency, further restricting linear growth, leading to short stature.

The size of the 22q11.2 deletion can vary markedly. Most affected individuals have a 3 Mb (3 million base pairs or building blocks) sized chromosomal deletion, although some can have a smaller or atypical size deletion. When an individual with 22q11.2 deletion syndrome is diagnosed, it is important to test both parents because the manifestations are so variable that the deletion may be found in a parent who is ostensibly unaffected or only mildly affected.

Williams-Beuren syndrome

This condition, often also known as Williams syndrome, is usually diagnosed by recognition of the pattern of distinctive facial features, elevated calcium levels in the blood, and a

specific cardiovascular defect known as 'supravalvular aortic stenosis' (narrowing of the aorta above the aortic valve). Most cases involve the deletion of genes from the chromosome 7q11 region. The incidence of Williams syndrome is estimated to be about 1 in 10,000, and most affected individuals are the only one affected in their family. Parents of affected individuals are almost always unaffected, although familial cases have been reported.

The facial features of affected children are usually recognisable by trained professionals. Distinctive features include a slight narrowing of the temple region, rounded cheeks, fullness around the eyes, a depressed nasal root, broad nasal tip and wide mouth with full lips. Teeth are often small and widely spaced.

Most individuals have mild intellectual disability with some being more severely affected. People with Williams syndrome have a typical cognitive profile, with strengths in verbal and auditory memory, but with weakness in visuospatial awareness. They are often described as having a friendly, sometimes overly familiar loquaciousness, with a 'cocktail party' personality, referring to a superficial conversational style. However, this trait often belies anxiety, which can be a significant issue. Affected adults usually live with their parents or in a partially supervised group home. With vocational training and assistance with daily activities, some individuals can achieve partial independence, but many are employed in sheltered environments. Hyperacusis, or oversensitivity to loud noises, and other phobias can be problematic for affected individuals.

High calcium levels occur in about 15% of people with Williams syndrome, most commonly in infancy, but it can recur in adulthood. Symptoms of high calcium, such as irritability, constipation, and lack of appetite, should be a prompt to check

blood calcium levels in affected individuals. Some affected individuals require a low calcium diet while being closely monitored by their medical professional. Hypothyroidism (low levels of thyroid hormone) can occur at any age in Williams syndrome and should be checked for regularly.

The most common cardiovascular defect in Williams syndrome is supravalvular aortic stenosis (a narrowing above one of the main heart valves), but other vessels such as the pulmonary (lung) artery or renal (kidney) arteries can also be narrowed. Collectively, these are the most significant causes of ill health in Williams syndrome. The underlying cause of the cardiovascular defects in this condition is the loss of the elastin gene (*ELN*), which is in the chromosome 7q11 region, the segment deleted in affected individuals. Elastin is, as the name suggests, a highly elastic protein in the body and allows many tissues in the body to go back to their shape after contracting or stretching. Rarely, there are individuals who have mutations within the *ELN* gene without a chromosome 7q11 deletion, who have only the cardiovascular features but without the other manifestations of Williams syndrome.

Kidney and urinary tract problems are also common in children and adults with Williams syndrome. Structural anomalies include small or absent kidney, or narrowing of the renal arteries. Night-time wetting and urinary frequency are common in affected children. Urinary tract infections are frequently recurrent in many affected individuals, even in adulthood.

Most affected individuals are short for their families, and this growth restriction may be evident even in utero. During infancy and childhood, failure to thrive and feeding issues are common, and these are often complicated by low tone, gastroesophageal reflux and constipation. Compounding problems such as

hypothyroidism and growth hormone deficiency should be checked for, especially if there is a slowing of linear growth in childhood.

Triplet repeat disorders

Fragile X syndrome

Although fragile X syndrome is second to Down syndrome as the most common cause of intellectual disability, it is the most common familial (inherited) form. Its name stems from the observation of a fragile site on chromosome Xq27.3 using special laboratory techniques. Being what is called an 'X-linked condition', it is carried by females and transmitted to their sons; however, females can also be affected. The nature of the fragile X mutation is a dynamic repeat of three DNA bases (CGG), known as a triplet repeat in the *FMR1* gene. The number of repeats determines the likely manifesting clinical features through its effect on a chemical change (known as methylation) in the activity of the *FMR1* gene. The reason why the mutation is referred to as dynamic is because of its ability to expand, or rarely, to contract, when passed from one generation to the next. The size of the triplet repeat tends to correlate with the chance of passing on a full expansion. The higher the number of repeats, the more unstable it is and more likely to expand in size. In fragile X syndrome, expansion of a repeat size is more commonly observed when passed from a mother to her child. The usual number of 'CGG repeats' (this triplet refers to the base pairs in the genetic code) is 5 to 44, and carriers of this number of repeats are healthy and unaffected. Those with repeat size of 45–54 have a 'grey zone' allele (an allele is just one variation of any particular gene). An individual with 55–200 repeats is known as a pre-mutation carrier. When the number of repeats exceeds 200, the result is fragile X syndrome,

with males generally more severely affected than females (owing to the existence of the second X chromosome acting as a 'backup' in females).

Males with a fragile X full mutation have intellectual disability (with an average full-scale IQ in the 40s) and a broad range of emotional and behavioural difficulties. Characteristic physical features include a long face, large or prominent ears, high-arched palate, and flexible fingers. A prominent jaw and large testes become more apparent with age. Joint hypermobility is common, with congenital (present at birth) hip or patellar (knee cap) dislocation, spine curvature and flat feet. Most affected boys will have early developmental delays, with irritability in infancy. In early childhood, attention deficit hyperactivity disorder and autism spectrum disorder or self-injurious behaviours become more prominent. Social anxiety, impulsivity, obsessive and aggressive behaviours are commonly observed. Sensory integration issues and tactile defensiveness are common, so parents are usually recommended to avoid placing their affected children in situations with high sensory stimuli, such as large crowds or noisy environments. Seizures are observed in some children, but are generally well controlled by medications. Most affected individuals stop having seizures by adulthood. Females with a full mutation on one X chromosome are usually also affected with similar neurodevelopmental issues, although generally not as severely as males.

Those with a grey zone gene (45–54 repeats) are healthy and do not have fragile X syndrome, but such genes have a small chance of expanding into the pre-mutation range in subsequent generations. Grey zone genes do not expand to the full mutation range. Pre-mutation carriers do not have fragile X syndrome, and usually have normal intellect and appearance.

Some people with pre-mutations have been noted to have subtle effects, such as learning problems or mild anxiety.

Pre-mutation carriers are at risk of two specific conditions that do not occur in those with full mutation fragile X syndrome. These are the (1) fragile X-associated tremor/ataxia syndrome (FXTAS), which affects movement and memory in an older person, and (2) premature ovarian insufficiency, which affects fertility. FXTAS occurs in later life, usually after age 50, more frequently in men than women. It is characterised by a slowly progressive tremor and unsteadiness of the gait, in addition to cognitive decline and memory loss. Female pre-mutation carriers are at risk of premature ovarian insufficiency, which is defined as a cessation of periods before age 40 years. Knowledge of this in a young woman with a pre-mutation usually leads to a referral to a fertility preservation specialist.

Myotonic dystrophy

Myotonic dystrophy is another triplet repeat disorder, caused by an unstable CTG repeat mutation of the *DMPK* gene. Although the worldwide prevalence is estimated to be about 1 in 20,000, this varies depending on ethnicity and geographic region. It is exceedingly rare in sub-Saharan Africa, but in some regions such as Quebec, Canada, it is more common, thought to be due to what has been called 'the founder effect', which is when there is an increased frequency of a mutation in a small group of ancestors from whom the local population is derived. Although its name refers to the primary symptom of myotonia, which describes a phenomenon where muscles are slow to relax after contraction, myotonic dystrophy is a multi-system disease. It is what is called an 'autosomal dominant' condition, which means that it has a 50% chance of being transmitted to each offspring. As with other triplet repeat disorders, the

number of repeats is unstable and can expand on transmission, particularly from the female. With each successive generation, the repeat size generally increases, with a commensurate increase in the severity of symptoms, referred to as anticipation. It is this phenomenon that sees myotonic dystrophy divided into three categories of clinical presentation.

The mildest form, usually associated with repeat size of 50–100, is late onset (generally in the 50s) of muscle weakness, myotonia and cataracts. The classical form, with onset from childhood onwards, is characterised by more severe muscle weakness, myotonia, apathy, complications involving the gut and other systems, and generally caused by a repeat size of 100–1000. The congenital form is the most severe, associated with a repeat size greater than 1000, with onset at birth with profound low muscle tone and life-threatening breathing difficulties, often requiring ventilation. All three forms of clinical presentation can be seen in different members of the same family.

The classical form of myotonic dystrophy affects multiple systems, including the brain, gut, heart, lungs, eyes and endocrine (hormone) system. Symptoms in childhood include learning difficulties and speech delay with articulation problems due to weakness of the speech muscles. Intelligence is usually in the low-average range. Motor development may be delayed, and children are often clumsy or uncoordinated. Muscle weakness slowly progresses, and many individuals will require a wheelchair in mid adulthood. Myotonia is prominent, and can lead to problems with activities of daily living, such as driving or turning door handles. Many individuals experience swallowing problems, with gastro-oesophageal reflux, as well as constipation. Pneumonia can be due to aspiration of food contents into the lungs, compounded by difficulties with

coughing. Heart rhythm irregularities occur frequently, especially in adulthood. Cataracts can develop, often at an earlier age (30s–40s) than the general population. Facial muscles are often weak, giving an expressionless appearance, and eyelids can also be droopy. Affected men often develop male-pattern baldness. Other issues, such as diabetes, thyroid problems and testicular atrophy, can occur.

Conditions due to mutations in a single gene (monogenic conditions)

Cystic fibrosis

Cystic fibrosis (CF) is the most common 'autosomal recessive' condition affecting northern Europeans, with 1 in 25 individuals being carriers. The incidence is approximately 1 in 3200 live births, but is much lower in other ethnic groups such as Africans and Asians. In order to be affected, an individual requires mutations in both copies of their *CFTR* gene. The CFTR protein plays an important role in chloride transport. The systems most typically affected by CF including the respiratory and gastrointestinal systems, pancreas, male genital tract and sweat glands. Lifespan is usually reduced by the multi-system disease, but modern medicine has led to improvements in management and thus to improved quality of life and lifespan.

Many newborn screening programs now include some form of screening for CF, usually by measuring the immunoreactive trypsin (IRT), which is generally elevated in babies with CF. A newborn found to have a raised IRT usually proceeds to a sweat test, where the sweat chloride is measured. A high level of sweat chloride suggests the diagnosis of CF, and genetic testing is typically undertaken to identify mutations in both copies of the *CFTR* gene.

The clinical manifestations of CF typically involve the respiratory and gastrointestinal systems. The most common respira-

tory symptoms include cough, shortness of breath, thick secretions that are difficult to clear, and chronic infection with bacterial organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa.* Airway obstruction and structural lung damage are major causes of ill health and reduced lifespan in CF. The gastroenterological manifestations of CF include meconium ileus (a condition where the bowel is blocked up with newborn's faeces) in the newborn period, pancreatic insufficiency leading to inability to digest fats, and liver disease. Most children with CF have failure to thrive, with an impact on growth. Most men with CF are infertile due to low sperm count as a result of the vas deferens, the tube that allows sperm to leave the testis into the ejaculate, being absent or underdeveloped.

Neurofibromatosis type 1

Neurofibromatosis type 1 (NF1) is an autosomal dominant condition that affects approximately 1 in 3500 individuals worldwide. Its clinical manifestations are incredibly variable even among affected members of the same family with the same *NF1* gene mutation. The diagnosis can usually be established based on clinical criteria alone, and genetic testing is not often required, except in cases where prenatal diagnosis is requested, or if there is diagnostic uncertainty in adulthood. All affected adults will have evidence of this condition, but individual clinical features may not appear until an individual is older, making diagnosis less straightforward in infancy and early childhood.

NF1 affects the skin, nerves, eyes, brain and bones, and results in a predisposition to tumours. One of the earliest signs of NF1 is the appearance of coffee-coloured spots on the skin known as café-au-lait macules, and having six or more fulfils one of the diagnostic criteria for NF1. The hallmark feature of NF1, after which the condition is named, is the neurofibroma,

which is a benign tumour growth of nerve fibres. These can occur anywhere where there are nerves, but are most commonly observed under the skin. They usually appear in late childhood through to adolescence and adulthood. Plexiform neurofibromas are more complex structures and appear as a diffuse soft swelling under the skin. Freckling in the armpit and/or groin regions is another diagnostic criterion for NF1, usually appearing after the café-au-lait macules. Children with suspected or confirmed NF1 are recommended to have regular eye checks for brown coloured spots on the iris (known as Lisch nodules), and a tumour of the optic nerve (optic glioma), both of which are additional diagnostic criteria. NF1 can also affect the growth of bones in the body, and lead to specific lesions such as pseudoarthrosis (a type of bone fracture that doesn't heal), bowing of the long bones (such as the bones of the legs), and sphenoid wing dysplasia (a deformity of a bone at the base of the skull). Scoliosis (curvature of the spine) is also relatively common in children with NF1.

The *NF1* gene acts as a tumour suppressor, so a mutation that leads to a loss of its function results in an increased predisposition to tumours, both benign and malignant. In addition to neurofibromas and optic gliomas, people with NF1 are susceptible to developing a range of other tumours. These include a number of tumours, including malignant peripheral nerve sheath tumours, rhabdomyosarcomas (muscle tumours), leukaemias and pheochromocytoma (a tumour of the adrenal gland), among others. A person with NF1 who develops high blood pressure (hypertension) is usually investigated further for the possibility of a pheochromocytoma (a tumour in the adrenal glands) or a narrowing (stenosis) of the renal arteries. Essential hypertension (of no known cause) is also more common in individuals with NF1.

Predisposition syndromes

Cancer (breast and ovarian cancer)

Cancer itself is a genetic event at the cellular level, but an inherited cancer predisposition syndrome is a genetic condition affecting the individual and their family members. The most common form of hereditary breast and ovarian cancer affecting all ethnicities is related to a mutation in one of the two copies of *BRCA1* or *BRCA2.* Having a mutation in one of these two genes confers an increased risk for female and male breast cancer, ovarian cancer, as well as other cancers such as melanoma, prostate cancer and pancreatic cancer.

While breast cancer is relatively common in the general population, and the co-occurrence of several cases within a family might occur by chance alone, there are several markers of a hereditary predisposition syndrome. These include young age of onset (e.g. breast cancer diagnosed in a woman in her 30s or 40s rather than over age 55), breast cancer affecting both breasts, breast and ovarian cancer in the same individual, and male breast cancer. Certain tumour characteristics related to the grade of tumour and the receptor status also aid in the assessment of the possibility of a *BRCA1*- or *BRCA2*-related tumour. Ashkenazi Jewish heritage is another 'red flag' due to the presence of founder mutations in this population group.

Having a *BRCA1* or *BRCA2* mutation leading to an increased risk for developing cancer does not necessarily mean that cancer is a foregone conclusion. The chance of having cancer is related to age (the risk is much higher in a mutation-positive 45-year-old than a 10-year-old), and other genetic and non-genetic factors such as lifestyle. Once the first affected individual in the family is identified to harbour a *BRCA1* or *BRCA2* mutation, other family members can be offered predictive testing. This involves the testing of an unaffected individual for

the causative mutation in their relative. International ethical guidelines do not support the testing of a minor for an adult-onset predisposition condition. An unaffected adult woman found to have a causative *BRCA1* or *BRCA2* mutation first identified in her relative is then afforded options of high-risk surveillance with mammograms and magnetic resonance imaging (MRI) and/or risk-reducing surgery such as removal of the breasts, ovaries and fallopian tubes.

As these mutations are heterozygous (affects one of the pair of the gene), the inheritance pattern of the hereditary breast and ovarian cancer syndromes is autosomal dominant. Affected individuals who wish to avoid passing on their *BRCA1* or *BRCA2* mutation usually undertake preimplantation genetic diagnosis (PGD is a reproductive technology used in conjunction with IVF to test the embryo before it is implanted; see Chapter 8) to avoid the ethical minefield of testing an established pregnancy for an adult-onset condition.

Neurodegenerative (Huntington disease)

Predisposition syndromes are not only related to cancer. An inherited form of neurodegeneration is Huntington disease (HD), which is also another triplet repeat disorder. Individuals with a triplet repeat size of 36 or more CAGs in the *HTT* gene are at risk of developing a progressive condition that affects movement with cognitive and neuropsychiatric effects. Like other triplet repeat disorders, the size of the repeat is unstable, but in the case of HD, it preferentially expands when transmitted by the male. In general, the size of the repeat correlates to the age of onset and severity of symptoms. Typically, the average age of onset is in the 30s or 40s, and survival time is usually 10–20 years after diagnosis. HD is more common in Western Europeans (up to 15 per 100,000 individuals) compared to Asians and Africans.

The characteristic movement disorder in affected individuals is called chorea. This is a non-repetitive, jerking movement of the face, limbs and/or trunk, which cannot be suppressed voluntarily. Chorea is continuously present during waking hours, and worsens with stress. As HD progresses, other movement problems, such as clumsiness, stiffness (rigidity, dystonia) or a reduction in movements generally (bradykinesia), become more prominent. Difficulties with speech articulation and swallowing are frequently associated.

All individuals with HD develop a progressive decline in cognition, with symptoms such as forgetfulness, difficulties with planning or executive function, and slowness of thought generally. Early in the disease, affected individuals find it hard to concentrate, with increased distractibility; and language problems such as word-finding difficulties are common in the later stages of progression. Personality changes are common, ranging from aggression, combativeness, apathy, anxiety and obsessive-compulsiveness. Psychiatric issues are common, including depression, psychosis, and substance use. Suicidality, which is a particular risk in the newly diagnosed, occurs more frequently than in the general population.

There is no treatment that has been proven to delay onset or slow progression of HD; however, there are effective treatments for symptoms such as the depression and the involuntary movements. In addition, supportive therapy for the individual as well as their family, especially their spouse or carer, is often very beneficial. Predictive testing of an unaffected individual is not embarked upon lightly, given the profound ramifications of the knowledge of inheriting a genetic mutation that predisposes to a neurodegenerative condition with unknown age of onset and no treatment to delay onset or slow progression.