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Common medical conditions in which genes play a role

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Genes influence every aspect of a person's health, from the ability to resist infection with a pathogen, to how medication is metabolised, to mental health and behaviour. Diseases have historically been defined by what a clinician sees, rather than the root cause of the pathology. In rare diseases, we know that genetic defects affecting different components of the same biological pathway can produce very similar clinical problems. However, understanding the factors contributing to common disorders is considerably more complex. In general terms, common diseases lie somewhere on a spectrum between multifactorial disorders, in which the key features are caused by the cumulative impact of many minor genetic variations plus environmental factors and, at the other end, many rare genetic defects producing very similar clinical problems. Given the enormous scope of this subject, in this chapter, two of the most common conditions worldwide will be considered, to explore how their presentation can be influenced both by rare, damaging mutations and commoner, more subtle genetic changes acting together with environmental factors.

Searching for genetic contributions to rare versus common disease

From a clinical point of view, variations in the DNA code are described in one of three ways. Mutations are clear mistakes in a gene that have some deleterious effect on the RNA and protein product; these are rare in the population. In contrast, polymorphisms are normal genetic variants, commonly seen in the population. Single nucleotide polymorphisms, or SNPs, represent a change in a single letter of the DNA code. A variant of unknown significance is a deviation from the reference sequence for which there is currently insufficient evidence to know whether it is a mutation or polymorphism.

In general terms, the less common a disease and the more unusual the associated clinical features, the easier it is to identify a genetic cause for this. As genetic sequencing technologies and bioinformatics techniques have developed, it has become more straightforward to interrogate all known genes in the search for changes that are likely to be damaging, and are also either unique to an affected individual or extremely rare. Distinct clinical features allow the identification of other affected patients who can be tested for mutations in the same gene. As the clinical presentation in a rare genetic disorder is caused by a mutation in one or both copies of a single gene, the effect of any identified changes can be evaluated experimentally and may be recapitulated in animal models. This is the reason for the current explosion in rare disease research.

In common diseases, many subtle variations in multiple genes, together with environmental factors, can conspire to produce an individual's clinical presentation. It is therefore a much greater challenge to identify any genetic contributions to development of a common disease, and to tease apart the role that each plays. The main technique used to evaluate subtle

genetic contributions in common diseases is the genome-wide association study. These studies rely on very large populations to identify SNPs that are enriched (with statistical significance) among those affected by a disease when compared with unaffected control subjects. Often, a SNP that is associated with a common disease does not confer the risk, but represents a genetic factor nearby that has been inherited alongside it. In some ways this is the genetic equivalent of looking out of a window and seeing the trail from an aeroplane: you know there must be an aircraft nearby to have caused the trail, but it isn't clear what type the aircraft is, or just how close it might be. A secondary challenge in any common disease is to recognise when an individual's clinical problems actually have a rare genetic cause. This is especially important as, in this situation, the risk to other family members may be well defined, allowing for appropriate counselling and risk management, including reproductive counselling. In some circumstances, identifying a rare manifestation of a common disease may also allow for tailored therapy.

Cardiovascular disease: multifactorial pathology

Cardiovascular diseases are the major cause of illness and death worldwide and an excellent example of how many different genes and environmental factors interact. In 2015, ischaemic heart disease was the leading cause of death in Australia, accounting for 12.4% of all deaths. Cerebrovascular disease was third, causing 6.8% of all deaths. These diseases also account for a significant proportion of hospital admissions and interventions, in addition to ongoing medical therapy. In 2008–09, these two disease groups alone accounted for around $2.7 billion, or over 4%, of the Australian expenditure on health. The core feature of these diseases is atherosclerosis, which is a progressive inflammatory problem in which a fatty streak in the wall of

an artery develops into a trapped pool of fat-rich material covered by a fibrous cap. As these lesions develop, the cap becomes thinner and the fat-rich material within can leak into the vessel, encouraging formation of a clot. This impedes blood flow, and restricts the supply of oxygen to the tissue fed by that vessel (ischaemia). In the heart, this manifests as angina if the occlusion is short-lived or incomplete, or a myocardial infarction (heart attack) if the blockage is more serious. In the brain, the equivalent processes are a transient ischaemic attack (TIA or mini-stroke) and an ischaemic stroke.

There are well known environmental and lifestyle associations with ischaemic cardiovascular diseases. The INTERHEART study, which reported in 2004, assessed factors involved in the development of coronary heart disease in around 15,000 individuals admitted for myocardial infarction against a similar number of age- and sex-matched controls. Daily consumption of fruit and vegetables and regular physical activity were found to be protective. Smoking was found to almost triple the likelihood of developing coronary heart disease. Having diabetes mellitus increased the risk by a factor of 2.38, high blood pressure by 1.91 and obesity by up to 1.67. An increased ratio of apolipoprotein B100 (ApoB100) to apolipoprotein A1 (ApoA1) in blood was found to have the largest effect, increasing the chance of developing coronary heart disease by up to 3.25 times. Apolipoproteins are an important component of the particles that carry fats through the bloodstream. ApoB100 forms part of the very low, and low density lipoprotein (VLDL/LDL) complexes that deliver fats, including cholesterol, to cells, and these therefore promote atherosclerosis. Conversely, ApoA1 forms part of the high density lipoprotein (HDL) complexes that are involved in removing fats from cells and tissues, including areas of atherosclerosis in arterial walls.

We also recognise that cardiovascular diseases sometimes appear to run in families. The INTERHEART study found that, compared with some other risk factors, a family history of early-onset cardiovascular disease was associated with a relatively modest increase in the risk of developing coronary heart disease, by a factor of 1.45. However, it is estimated that between 30% and 60% of all factors associated with atherosclerotic disease are heritable, and so it is worth considering genetic influences on each of these in their own right. As we will see, these risk factors are not mutually exclusive, but influence each other through a complex network of interactions.

Genetic factors influencing smoking

With a major influence on the development of cardiovascular disease and chronic lung disease, including cancer, health professionals routinely advise against smoking. However, quitting is a real struggle for many smokers, despite clear personal health and economic benefits, and an entire industry that has developed around smoking cessation. But why is it so difficult to give up? One of the major neurotransmitter molecules used to pass messages between nerves is acetylcholine. Nicotine can bind and activate many of the receptors for this molecule, known as nicotinic acetylcholine receptors (nAChRs). Acetylcholine or nicotine binding to these receptors in the brain results in the activation of a network of pathways involving a number of other neurotransmitters in a complex counterpoint of positive and negative feedback. Dopamine and glutamate play particularly prominent roles. Stimuli that activate dopamine pathways are perceived as pleasurable, and so the increase in dopamine levels in response to smoking acts to reward this behaviour. Glutamate is the major excitatory neurotransmitter in the central nervous system and plays a role in reinforcing and motivating smoking behaviours.

In order to understand factors influencing smoking behaviours, genome-wide association studies have been performed. While dopamine and glutamate receptors are not consistently identified in such analyses, these studies highlight a role for the nAChRs. These are pentameric proteins — formed from a combination of five subunits, encoded by many different genes. A cluster of three of these genes, *CHRNA5*, *CHRNA3* and *CHRNB4*, lies on chromosome 15 in a region that has been highly correlated with the amount smoked per day, nicotine dependence, and age at which smoking commenced. The greatest influence within this gene cluster is a single SNP in the *CHRNA5* gene (referred to as rs16969968), which is associated with a 1.39 times increased likelihood that an individual will be a heavy smoker (more than 20 cigarettes per day) rather than a light smoker (less than 10 cigarettes per day). While many SNP associations identified through GWAS have intangible effects, this is a functional variant that results in a single amino acid substitution in the CHRNA5 protein subunit, reducing negative feedback in the brain that normally acts to limit nicotine consumption.

It is important to remember that although genome-wide association studies have identified several nAChR subunit genes contributing to smoking behaviours, such studies' ability to detect associations are dependent upon the characteristics of both the study population and controls, including the number of participants and their ethnicity. For example, in Caucasian populations, the rs16969968 SNP is found in both copies of the *CHRNA5* gene in just under 20% of individuals, and in one copy in another 40%. In Gujurati Indians and those of Mexican heritage, these figures are halved, and halved again in the Maasai. In Han Chinese and Japanese populations, rs16969968 is found in one copy of the gene in less than 10% of the population and rarely in both copies.

Diabetes mellitus

Diabetes mellitus (DM) is a common disease in its own right — or rather a group of common diseases in which affected individuals develop high blood glucose levels, which can cause damage to a range of tissues, notably blood vessels, if left untreated. Insulin normally acts to promote the movement of glucose from the bloodstream into cells. In type 1 DM, the pancreas fails to produce enough insulin, and this is treated by providing additional insulin by subcutaneous injection. In type 2 DM, cells respond suboptimally to insulin, and this is often a consequence of someone becoming overweight and not exercising enough. This can be treated with diet and exercise, or medication that either increases the responsiveness of cells to insulin, or reduces the amount of glucose produced by the liver. In some cases, the condition may progress to require insulin administration. It is perhaps a little counterintuitive that family history plays a more prominent role in type 2 DM than in type 1, although twin studies do indicate that there is also an element of genetic predisposition in the latter. In genome-wide association studies for both type 1 and type 2 DM, most variants that reach statistical significance increase the likelihood of having the disorder only a little, in the order of 1.1 to 1.3 times compared with controls. Some of the apparent increased heritability may relate to confounding variables, such as dietary and exercise-related behaviours learned from family members, or other genetic factors influencing these.

In addition to type 1 and type 2 DM, there are a number of rarer, autosomal dominant causes of DM. Maturity onset diabetes of the young (or MODY) accounts for most of these. MODY is a non-insulin dependent form of DM, which usually occurs before 25 years of age and is often misdiagnosed as types 1 or 2. In contrast to type 2 DM, affected individuals are

typically lean. Mutations in at least 11 genes are known to cause MODY, although around four of every five diagnoses are due to mutations in one of three genes: *GCK*, *HNF1A* and *HNF4A*. *GCK* encodes glucokinase, an enzyme that is expressed only in the liver and in insulin-producing cells of the pancreas. This plays an important role in maintaining the balance between circulating glucose and insulin secretion. Mutations in *GCK* cause increased blood glucose levels from birth when an individual is fasted. However, blood glucose levels are only modestly raised and affected individuals display none of the symptoms of DM. In most cases, no treatment is needed and the condition is not progressive. A notable exception to this is in pregnant women with *GCK* mutations. If the baby has not inherited the mutation, increased blood glucose from the mother can cause the baby to grow larger than expected towards the end of pregnancy, which can lead to difficulties at birth. Treatment with insulin may be required to help avoid this. *HNF1A* and *HNF4A* encode transcription factors that regulate the activity of a variety of other genes. Genome-wide association studies have previously identified a SNP in *HNF1A* as being associated with an increased risk of coronary heart disease, though this is only 1.08 times greater than in controls. However, having a mutation in either of these genes causes a progressive problem with insulin secretion, and the increased blood glucose levels associated with this can lead to vascular disease if untreated. Establishing that MODY is caused by mutations in *HNF1A* or *HNF4A* is also especially useful for management, as affected patients respond well to sulphonylurea, an oral medication that increases insulin release from the pancreas.

High blood pressure

Hypertension (high blood pressure), like diabetes mellitus, can itself be associated with a variety of lifestyle and environmental

factors, such as lack of exercise, being overweight, poor diet and stress. There are two main components to blood pressure: the systolic blood pressure, which is the maximum value in the arteries when the heart is contracting, pumping blood into them, and the diastolic blood pressure, which is the resting arterial pressure between contractions. The difference between the two is described as pulse pressure. Values for systolic and diastolic blood pressure are influenced by many factors, including how much blood is pumped out of the heart each time it contracts, the force associated with this, and the volume of blood in the vascular system at any time. Arterial stiffness also has an effect on blood pressure and increases with age as tissues become less elastic. This means that arteries in older people are less able to stretch to absorb the force of blood each time the heart pumps, resulting in higher systolic blood pressure.

As 25% of the blood pumped from the heart is delivered to the kidneys, and these are responsible for excretion of certain types of waste and managing water retention or loss, any disease affecting kidney function can influence blood pressure. Over 200 genes have been linked to rare inherited disorders affecting the kidneys, mostly in very specific ways. Some genetic conditions cause gross structural abnormalities of the kidneys, such as the polycystic kidney diseases. There are several disorders that cause the filtration apparatus (glomeruli) within the kidney to fail. Other groups of diseases alter the way that sodium, potassium or other molecules are processed to maintain steady concentrations of these in the blood, either by affecting the channels responsible for reabsorbing these molecules, or by altering the hormonal regulation of kidney function.

A recent genome-wide association study identified 107 SNPs that correlated with the presence of hypertension, some of which were associated with only diastolic blood pressure, systolic

blood pressure or pulse pressure, while others were associated with two or three of these blood pressure parameters. Effects in this cohort were modest, but the researchers used their findings to develop a genetic risk score, separating study participants into quintiles based on their combination of contributory SNPs. Individuals with a genetic risk score in the top 20% had around a 2.4 times increased likelihood of having hypertension compared with those in the lowest 20%. This genetic risk score also correlated with a 1.3- and 1.4-fold increase in the likelihood of stroke and coronary artery disease from the lowest to highest scoring groups.

Lipid metabolism

Maintaining the balance of circulating lipids (fats) is extremely important, not only for cardiovascular health but for health generally. Diet affects the availability of fats and how these are stored and utilised, and genetic factors influence this and the transport of lipids around the body. Familial combined hyperlipidaemia is characterised by high total cholesterol and/or triglycerides (molecules made of three fatty acids joined together) in blood. This condition is considerably more common among those with cardiovascular disease compared with the general population. While first-degree relatives (parents, siblings or children) of those affected often have abnormal blood lipids, profiles vary widely even within the same family, and single gene causes of the condition are rarely found. In one recent study of Finnish families affected by hyperlipidaemia, single gene defects known to be associated with hyperlipidaemia only accounted for 7% of affected cases. However, the researchers found that among affected family members, variants were significantly more common in a number of genes, including those associated with lipid management (for example, *APOA5*, *APOE* and *LIPC*), which is involved in the breakdown of intermediate

density lipoprotein to low density lipoprotein (LDL). This data was used to construct a polygenic lipid score, with one third of those with hyperlipidaemia scoring above the 90th centile for the population.

Among the genetic contributions to hyperlipidaemia are several rare single gene conditions. Extremely high levels of LDL cholesterol and total cholesterol are seen in familial hypercholesterolaemia. If untreated, men have a 50% chance of experiencing a coronary event by 50 years of age, and women have a 30% chance by 60 years. Very high cholesterol can lead to abnormal deposition of cholesterol in tissues (termed xanthoma), such as a ring of cholesterol in the cornea in the eye (corneal arcus), yellowish collections of cholesterol in the skin, often around the eyes (xanthelasma), or deposits within tendons (tendinous xanthoma). Most cases are caused by an autosomal dominant mutation in the *LDLR* gene. This gene encodes the LDL receptor, which is a cell surface protein that recognises ApoB100 on the surface of LDL particles, allowing these to be internalised. A specific defect in ApoB100 that prevents interaction with the LDL receptor has the same effect. The balance between LDL/VLDL and HDL particles is also clinically important. Autosomal dominant mutations in the *APOA1* gene result in reduction or absence of the ApoA1 protein and a significant reduction in HDL cholesterol levels. Affected individuals also develop xanthomas, in addition to an increase in atherosclerosis and predisposition to cardiovascular disease. A similar clinical picture, complicated by peripheral nerve problems causing muscle weakness and wasting, and loss of temperature and pain sensation, occurs with autosomal recessive mutations in the *ABCA1* gene, which encodes a transporter that pumps cholesterol out of cells to be collected by HDL complexes; this is known as Tangier disease.

It seems logical that mutations reducing ApoB100 levels might be beneficial for cardiovascular risk. Autosomal dominant mutations in the *APOB* gene that reduce levels of ApoB100 also result in reduced LDL cholesterol in blood and there has been no evidence of cardiovascular disease in those affected, although the number of individuals studied has been small. The *APOB* gene therefore appears to be an attractive target for therapy. However, cholesterol and lipids are essential components of many cells and tissues, and some vitamins are lipid- rather than water-soluble and so require an effective lipid delivery system to reach their destination. Autosomal recessive mutations in *APOB* and the *MTP* gene, which is involved in the assembly of ApoB100-containing lipoprotein complexes, can cause extremely low levels or absence of the ApoB100 protein respectively, leading to retinal degeneration, neuropathy (nerve damage) and a tendency to develop blood clots. Affected individuals also develop a fatty liver, as lipids from dietary sources are not effectively transported to other sites in the body.

While very low levels of ApoB100 may be harmful, there are therapeutic options that can make the balance of ApoB100:ApoA1 more favourable. Medications called statins are the mainstay of therapy for high cholesterol; these decrease VLDL/LDL cholesterol and ApoB100 production, while increasing levels of HDL cholesterol and ApoA1. Insulin has been found to reduce secretion of ApoB100 from the liver, and regular exercise has also been associated with an increase in HDL apoliproteins, as well as increased sensitivity to insulin.

The epilepsies: many overlapping presentations, many genes

Seizures are the result of abnormal electrical activity in the brain, and epilepsy is a condition characterised by recurrent seizures. Different seizure types have been recognised for as

long as the condition has been documented. Ancient Babylonian texts describe seizures as being caused by demonic or ghostly possession. A number of seizure types were defined in these texts that we would still recognise today, such as generalised tonic-clonic (GTC, formerly grand mal) seizures, absences (petit mal), nocturnal seizures and complex partial seizures (involving only part of the brain and associated with impaired awareness). In GTC seizures, there is loss of consciousness and jerking of the limbs. In absence seizures there is very brief loss of consciousness without jerking of limbs; the individual may appear to 'phase out' briefly. The specific seizure type was thought to be dependent upon the possessor, or the context in which the possession took place. Moving four millennia on, our understanding of the basis of epilepsy has changed considerably, though there is still a great deal to learn.

Taken together, the epilepsies are among the commonest neurological diseases. The World Health Organization estimates that around 50 million people are affected worldwide, with studies suggesting that between 4% and 14% of the general population have active epilepsy at any time. Only one quarter of those affected living outside high income countries are thought to receive the treatment they require. The causes of epilepsy are diverse, and in many affected individuals, no clear cause will be identified. However, the condition may be acquired through serious head injury or in association with brain tumours, brain damage due to periods of low oxygen delivery (for example, due to birth trauma or following cardiac arrest) or infections involving the brain. Epilepsy may also occur as a consequence of genetic abnormalities that cause metabolic disorders, or influence brain development, or the transmission of electrical signals along or between nerves. Although there are well recognised associations between seizure disorders and chromosome abnor-

malities (duplications or deletions of genetic information) or genetic syndromes, these currently make up only a small proportion of the epilepsies. In contrast, idiopathic (meaning that the condition occurs spontaneously or the cause is not known) epilepsies account for almost one third of all diagnoses. Heritability is thought to be around 80%, with a first-degree relative (parent, sibling or child) of an affected individual having up to a 9% chance of also developing epilepsy. At present, many of the factors underlying heritability in the idiopathic generalised epilepsies remain to be discovered.

So, how does a clinician set about determining whether an individual's epilepsy is likely to be genetic, and how do they decide what testing is appropriate? Careful clinical assessment to exclude acquired causes of epilepsy is essential. A clear family history of one distinct form of epilepsy is an obvious sign that genetics is likely to be at work. However, familial presentations are rarely so simple. Penetrance in any particular disorder — the proportion of individuals with the same genetic defect who exhibit clinical signs of a condition — is often incomplete (that is, not everyone develops clinical problems). There may also be variable expression — the disorder may manifest in different ways, even within the same family. Both incomplete penetrance and variable expression represent the influence of other, often undetermined, genetic factors, together with environmental factors, in modifying the downstream effects of a genetic defect. Many individuals with epilepsy have no related family history. A good rule of thumb is that the earlier the onset of seizures, the more likely it is that a clear genetic cause for the epilepsy will be found. A recent review of 400 referrals to the North East Thames Regional Genetics Service in the United Kingdom for genetic testing in early onset epilepsy and/or severe developmental delay identified a

genetic cause in 39% of infants developing seizures before two months of age, as compared with 18% for those with seizures in the cohort as a whole.

When seizures occur in the context of a chromosomal abnormality or genetic syndrome, there are often additional clues as to the underlying diagnosis, with affected individuals having characteristic physical features, and/or additional developmental or medical problems. This is also true of some single gene causes of epilepsy. Careful clinical evaluation by an experienced clinician remains extremely important in identifying possible causes of epilepsy, particularly in children, so that testing can be focussed where possible and so that families are counselled appropriately regarding diagnosis, management and any potential risks to other family members, including future offspring. In the absence of further clues, the clinical overlap between different genetic causes of epilepsy is such that focused testing becomes impossible. Increasingly, clinicians are adopting a blunderbuss approach to testing: sequencing as many epilepsy-associated genes as possible, and using bioinformatics, the published medical literature and family studies to help identify the likely cause of an individual's disorder. This approach confers a number of benefits. It is less time consuming for clinicians than trying to identify candidate genes on the basis of clinical features alone, and less time consuming and costly for laboratories than phased testing, examining and excluding candidate genes in a stepwise manner. However, the greater the number of genes tested, the greater the likelihood that variants of unknown significance will be identified in multiple genes. If these cannot be appraised and excluded as the cause of a condition, this potentially complicates interpretation of any results and diminishes the value of testing in the immediate management of affected patients and their families.

Chromosome abnormalities associated with epilepsy

Deletions and duplications of genetic information occur in everyone. These are collectively referred to as copy number variants; most have negligible clinical effect and can be considered part of the normal genetic variation seen in the general population. Historically, deletions and duplications that were visible on microscopic examination of chromosomes often contained enough genetic information to result in characteristic medical and/or developmental problems in affected individuals. As technology has progressed, smaller chromosomal changes have become more readily detectable, and many of these are associated with variable clinical features, including among members of the same family. Epilepsy is often seen as part of these chromosomal disorders. In a recent study of 15,767 children with intellectual disability and/or developmental delay, nine of the ten commonest microdeletions identified were associated with recurrent seizures in at least a proportion of cases. These are summarised in Table 1.

While particular seizure types or disorders are seen more frequently in some of these chromosomal disorders, such as infantile spasms in 1p36 deletion syndrome, there are few clear associations between seizure type and copy number variation. Benign familial infantile epilepsy/infantile convulsions with choreoathetosis (irregular, writhing movements) is caused by an individual having a mistake in one copy of the *PRRT2* gene, which lies within the 16p11.2 deletion syndrome region. While this gene explains the unusual seizure disorder seen in 16p11.2 deletion syndrome, it remains unclear why only a small proportion of those with the deletion are affected. Among frequent microdeletions, those with milder clinical features are worth special mention in the context of the idiopathic generalised epilepsies. Chromosome 15q13.3 microdeletions, encompassing

Table 1: Commonest microdeletions identified with recurrent seizures

Chromosome microdeletion	Epilepsy/ seizures	Epilepsy or seizure type	Common other features
1q21	16%	GTC, absence, partial; also a severe epilepsy condition — Lennox-Gastaut syndrome	Unusual facial features (variable), mild-moderate developmental delay/learning difficulties, small head, short stature, eye abnormalities
1p36	44–58%	May be generalised or partial, with no specific type; 20% have infantile spasms with typical EEG	Typical facial features (straight eyebrows, deeply set eyes, cheekbones set further back giving a concave appearance to the face, depressed nasal bridge, unusual ears, pointed chin), developmental delay/learning difficulties, low tone and difficulty feeding as a baby, brain abnormalities on MRI, congenital heart defects
2q13	≤18%	Absences, GTC, nocturnal temporal	Unusual facial features (variable), developmental delay/learning difficulties, low tone as a baby, disrupted sleep, mild genital abnormalities in boys
9q34 (Kleefstra syndrome)	30%	Absences, GTC, complex partial	Typical facial features (brachycephaly — reduced distance from front to back of head, cheekbones set further back, wide-spaced eyes, protruding tongue, prominent jawbone), moderate-severe developmental delay/learning difficulties, very little speech development, congenital heart defects, genital abnormalities in boys.
15q11.2	26%	Absence, GTC, myoclonic	Variable learning difficulties (may need support at school), speech delay, ADHD, autism spectrum features; relatives with no problems may share the deletion
15q13.3	28%	Absences, GTC, myoclonic	Developmental delay/learning difficulties, ADHD, autism spectrum features; relatives with no problems may share the deletion
16p11.2	20%	In some, febrile seizures only; benign infantile epilepsy, infantile convulsions with choreoathetosis (a form of involuntary movements)	Mild developmental delay/learning difficulties, expressive speech delay, familial autism spectrum features, large head, spine abnormalities, tendency to obesity from late childhood into adulthood; rarely inherited.
22q11.2 (includes Di George syndrome)	7%	Often related to low calcium levels .	See chapter 4 for a description of this condition
22q13 (Phelan McDermid syndrome)	25%	Absences, GTC, partial	Subtle facial features (wide forehead, large prominent ears, long eyelashes, bulbous nose, appearance of weak muscles) moderate-profound developmental delay/ learning difficulties, absent or severely delayed speech, decreased sweating, lymphoedema leading to swollen limbs, sleep distubance, gastro-oesophageal reflux

the *CHRNA7* gene, are found in 1–2% of all such diagnoses. A recent study of 1,234 unrelated individuals with idiopathic generalised epilepsies, compared with over 3,000 control subjects, also found that those with microdeletions at chromosome 15q11.2 and 16p13.11 were, respectively, 4.9 and 7.4 times more likely to have epilepsy than controls.

Brain malformation disorders and epilepsy

The cerebral cortex is responsible for the higher functions of the brain, including consciousness, perception and thought. It comprises six layers of cells that are formed during develoment by carefully orchestrated neural migration. This is referred to as grey matter — hence Hercule Poirot's references to the little grey cells in Agatha Christie's novels. The projections (axons) from these cells through the brain form what is described as white matter, due to the myelin (fatty) sheath that insulates each nerve from the others that surround it, in much the same way that plastic is used to insulate wires in electrical circuits. The cortex is divided into a number of distinct lobes, and discrete areas perform different functions — for example, the occipital cortex (at the back of the head) is responsible for vision. As the optimal surface area of the human cerebral cortex is somewhat larger than the inside surface of the skull, a complex pattern of folds, or gyri, also develop. Normal electrical activity in the cortex is controlled through the complex interplay of positive and negative signalling, both in response to external stimuli and through feedback loops within the brain itself. Developmental abnormalities affecting the arrangement of neurons within the brain can destabilise this fine balance, creating the potential for unintended bursts of electrical activity, which can manifest as recurrent seizure activity, or abnormalities on electroencephalography (EEG).

Areas representing abnormal migration of neurons are referred to as heterotopias, and may occur in combination with other structural brain anomalies. Disorders in which heterotopia is a feature are described according to the appearance on brain imaging. If the cells form islands of grey matter adjacent to the ventricles (fluid-filled spaces in the brain), the condition is described as periventricular nodular heterotopia, with epilepsy in eight of every ten cases, usually in the context of normal learning. An X-linked familial form of this condition is caused by mutations in the *FLNA* gene, which encodes the filamin A protein, involved in manipulating cell structure and promoting cell migration. A rare recessive form of the condition, with severe developmental problems and recurrent infection, is caused by mutations in the *ARFGEF2* gene. In this case, the abnormal gene product interferes with cell migration by impeding normal transport to the cell membrane of molecules required for this activity. If a second line of grey matter appears within the white matter, following the line of the cortex, this is described as subcortical band heterotopia, and may occur together with reduced folding of the cortex — lissencephaly (literally, 'smooth brain'). Abnormalities in several genes have been found to cause different forms of lissencephaly, all playing important roles in neuronal migration during development: *LIS1, DCX, TUBA1A, TUBB2B, RELN, VLDLR* and *ARX*. Of these, *LIS1* and *DCX* cause classic lissencephaly, with a characteristic thick, four- rather than six-layered cortex, and can also cause subcortical band heterotopia. As *DCX* is located on the X chromosome, males with an abnormality in this gene usually develop lissencephaly whereas females tend to have a milder clinical picture, with subcortical band heterotopia. In the very mildest cases, affected girls may have learning difficulties and/or seizures, but no abnormality on brain imaging. A non-

classical form of lissencephaly, with a cobblestone appearance to the surface of the brain, is caused by mutations in genes that, in addition to their role in neuronal migration, play an important role in anchoring the machinery for muscle contraction to the extracellular matrix, which acts as an external scaffold for cells and helps maintain tissue structure. This causes individuals affected by these conditions to also develop congenital or early onset muscular dystrophy.

Abnormal organisation of the cerebral cortex itself can also destabilise the equilibrium between positive and negative signalling. Among the commonest structural cortical problems is polymicrogyria (literally 'many small folds'), which is associated with loss of the normal layering of the grey matter. Regions of polymicrogyria can act as a focus for the initiation of seizures, which are seen in 60–85% of cases, although presentations are very variable and may be influenced by the area of cortex in which the polymicrogyria lies. Non-genetic causes of this malformation occur, such as in response to cytomegalovirus exposure or impaired local blood supply during gestation, again highlighting the need for careful clinical evaluation in affected individuals. The commonest site of polymicrogyria is the perisylvian area, which controls the muscles of the mouth and throat. Those affected typically have problems with speech and swallowing, which results in excessive drooling. Individuals with Worster-Drought syndrome have these clinical features, and a third also have epilepsy; however, perisylvian polymicrogyria is seen only in around 15% of cases. No gene has yet been linked causally to Worster-Drought syndrome, although several have been associated with perisylvian polymicrogyria. To date, mutations in more than 30 single genes have been associated with polymicrogyria. Again, most play a role in neuronal migration and, in some, the site of polymicrogyria is characteristic. Autosomal

dominant mutations in *KIF5C* can cause perisylvian polymicrogyria, whereas autosomal recessive mutations in *GPR56* cause polymicrogyria affecting the frontal and parietal lobes, in *LAMC3* the occipital lobe, and in *FIG4* the temporal and occipital lobes. Schizencephaly (literally, 'split brain') describes a cleft in the brain lined with polymicrogyric grey matter, which is associated with epilepsy in more than half of affected individuals and developmental delay and/or learning difficulties in over 80%. Weakness may be present on the side of the body opposite the schizencephaly. Like polymicrogyria, schizencephaly may be caused by non-genetic factors, such as cytomegalovirus exposure or impaired local blood flow in utero. However, causative genes, such as *SHH*, *SIX3* and *EMX2*, have a supervisory role in organising the cortex, rather than in neuronal migration.

The final group of structural brain disorders are caused by abnormal proliferation of cells within the brain. These may be caused by mutations in genes contributing to growth pathways that converge around the *MTOR* gene. The most startling of these disorders is hemimegalencephaly, in which the cerebral cortex on one side of the head is abnormally formed and much larger than on the other side, which is compressed as a result. The typical features of this condition include early onset seizures that are resistant to treatment, weakness and developmental delay. Another disorder related to the mTOR growth pathways is tuberous sclerosis which, at 1 in 6,000 live births is among the commonest genetic disorders. This is an autosomal dominant condition, caused by mutation in the *TSC1* or *TSC2* genes, and is associated with a variety of abnormalities on brain imaging, in addition to characteristic skin changes. Epilepsy occurs in around 80% of cases and learning difficulties in 65%. The finding for which the condition is named, cortical tubers, represent localised loss of the normal six-layered structure of the

cortex, together with collections of abnormal neurons and large astrocytes, another type of brain cell that mainly supports neurons. Disorders of these growth pathways are particularly exciting at present, as features that develop after birth may be amenable to therapy using a group of medications called mTOR inhibitors.

Tranmission of electrical signals along and between nerves

We commonly talk about electrical activity in the brain, and about electrical impulses moving along nerves. While electrons are passed between metal atoms along wires, the same effect is achieved in neurons by positively and negatively charged ions — sodium (Na+), potassium (K+) and calcium (Ca++), and chloride (Cl-) respectively — moving very rapidly in or out of the cell along its entire length, in a molecular Mexican wave. Defects in the genes encoding channels through which these ions move can, unsurprisingly, interfere with the proper transmission of electrical signals within the brain and predispose affected individuals to developing epilepsy. Mutations in at least five different sodium channels, seven potassium channels and two calcium channels have been found to cause epilepsies with a wide range of seizure types and severity. Genome-wide association studies have also identified SNPs in two chloride channels that are found three times more frequently among individuals affected by epilepsy than in controls.

When an electrical impulse reaches the end of a neuron, this provokes neurotransmitter release, which must be detected by an adjacent neuron for the signal to be passed on. Mutations in the receptors responsible for this can therefore produce a range of epilepsies and seizure types that overlap with those caused by mutations in ion channels. Many of the receptors in which mutations have been identified bind gamma-aminobutyric acid

(GABA), which is an inhibitory molecule, responsible for reducing neuron excitability and thereby fine tuning the cortical response to any stimulus. Impaired function of these receptors can therefore lead to an exaggerated response to excitation with other neurotransmitters, predisposing to epilepsy. Mutations in a number of nAChRs expressed in the brain (*CHRNA4, CHRNB2* and *CHRNA2*) are also specifically associated with a familial form of nocturnal frontal lobe epilepsy.

In epilepsies caused by mutations in ion channels and neurotransmitter receptors, testing large panels of genes becomes desirable, as it can be extremely difficult to tease apart which gene might be responsible for any patient's seizure disorder based on the clinical features alone. At present, there is no cure for these 'channelopathies', but knowing which gene is mutated can help clinicians think about what existing medications might be helpful in treating the condition. For example, GABA signalling can be enhanced by benzodiazepines, phenobarbital, sodium valproate and topiramate — which additionally inhibits glutamate signalling and sodium channel opening. Opening of sodium channels can also be inhibited by phenytoin, carbamazepine and lamotrigine, and potassium channel opening is promoted by retigabine and acetazolamide. However, this represents a very unrefined approach to therapy, as the mechanism of action of each medication will also produce off-target effects that may compromise any channel-specific benefit conferred. As our understanding of the molecular control of neuronal signalling improves, we may be able to adopt a precision medicine approach, with drugs specifically designed to target and modify the behaviour of mutated channels or receptors.

Summary

Understanding the genetic contribution to common disorders and translating this into improvements in care poses a significant

challenge to clinicians and researchers. Disorders may be multifactorial, caused predominantly by the complex interaction of many subtle genetic variations, in combination with environmental and lifestyle factors, such as in cardiovascular disease. In the future, algorithms that combine genetic data, lifestyle factors and clinical findings, such as cholesterol levels, will help determine an individual's risk of developing disease, together with which parameters should be tackled to provide optimal risk reduction. This will allow for therapy and lifestyle advice to be tailored to individual patients and, in the case of national health systems, resources can be targeted towards those who need them most, to ensure equity of care. At the other end of the spectrum are common disorders that largely represent the combined manifestations of many different, less common genetic defects that produce considerable clinical overlap due to the complexity of the system affected. In these disorders, environmental and lifestyle factors are less prominent. Our current understanding of the epilepsies is a good example of this. In reality, all common disorders lie on a spectrum somewhere between the two. For example, we know that uncommon genetic defects can have a significant impact on someone's risk of developing cardiovascular disease, and that it is important for clinicians to be able to identify affected individuals, to ensure that they are managed appropriately, and so that any risk to other family members can be addressed. In the epilepsies, we have excelled at identifying uncommon genetic defects that predispose to seizures. However, most of the identified causes are early onset and/or produce more severe clinical features. An ongoing challenge is to identify the missing heritability in the idiopathic generalised epilepsies, particularly in the adult population and in the context of normal development and learning. Given how finely balanced normal neuronal

activity is in the human cortex, it is reasonable to predict that minor variations in different ion channels, neurotransmitter molecules and their receptors, acting alone or together, will be responsible for at least some of this. Additionally, genetic defects arising after conception may well play a role, and these will be more difficult again to uncover, as they only affect cells descended from the one in which a mutation occurred. For example, a mutation arising in proliferating cortical cells might cause a very localised abnormality of cortex structure or neurotransmitter signalling that could act as a focus for seizure activity, but would not be evident on brain imaging, or detectable on DNA sequencing, due to the small number of cells affected.

While genetic knowledge has advanced rapidly over the last 50 years, our understanding of the genetic contribution to common diseases remains in its infancy. However, increased understanding of the genetic and environmental factors influencing common diseases has the potential to revolutionise care for both individuals and populations in the future.