

November 2014

Galton Institute
Occasional Papers
Third series, No 4

Genetics in Medicine

2. Adult life

By

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Published November 2014 by

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In association with

The Manchester Centre for Genomic Medicine
Manchester Academic Health Science Centre
Central Manchester University Hospitals NHS Foundation Trust and The University of Manchester

Acknowledgements

Picture credits
National Genome Research Institute/EMBL-EBI
Heart UK
Professor Steve Humphries, University College London
Professor Bill Newman and Dr Kay Metcalfe, Manchester Centre for Genomic Medicine
Professor Simon Lovestone, The University of Oxford

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Front cover image

A genetic consultation at the Manchester Centre for Genomic Medicine

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Genetics in Medicine 2. Adult life

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Introduction

This is the second booklet in a series dealing with genetics in medicine. The first booklet – *Genetics in Medicine 1. Conception and Early Life* – focussed on the implications of genetics for the health of infants and children. Here we focus on the ways genetic variants can affect health in adult life. The genetic mechanisms described in the first booklet apply equally to later life, and the clinical genetic services described there cater in the same way for infants or adults. In the first booklet we established that:

- The human **genome** determines the nature of all our inherited characteristics.
- The genome consists of about three thousand million (3×10^9) letters of **DNA** code, organised into 23 packages called chromosomes. About 1.2% of the DNA makes up **genes** coding for around 20,500 proteins. Much of the rest is involved in regulating when and where a protein-coding gene is switched on (**expressed**).
- When a protein-coding gene is expressed, first an **RNA** copy of the gene is made (a messenger RNA) and this is then used as a guide to assemble the correct **amino acids** into the relevant protein, according to the **genetic code**.
- Comparing the genomes of two unrelated individuals, there are around 3-4 million differences.
 - ◇ A few of these determine a distinct measurable or identifiable change in a characteristic. Characteristics determined in this way are called **mendelian** or **monogenic** and follow the inheritance patterns illustrated here on page 8.
 - ◇ Many variants act with other genes and environmental factors to contribute towards a change in an overt characteristic, but do not alone determine it (we used the example of cleft lip and palate).
 - ◇ The great majority have no apparent biological effect.
- Cells contain *two* genomes (in 23 pairs of chromosomes, giving in total 46),

one from the mother and one from the father. Thus every cell has two copies of almost every gene.

In addition, every cell contains mitochondria – known as the batteries of the cell, responsible for energy production – inherited from the mother in the **cytoplasm** of the egg. Mitochondria contain their own small genomes that encode 37 genes in 16,569 letters of DNA.

Some disorders present almost exclusively in childhood and are not further considered here. These include chromosomal abnormalities, caused by having whole chromosomes or large sections of a chromosome extra or missing. Other examples are rare recessive conditions that are seen with increased frequency in consanguineous (cousin) marriage.

Although genetic conditions were regarded as untreatable in the past, that is far from the truth for many conditions today. Progress in understanding has enabled doctors to anticipate and treat complications and to develop treatments for a wide range of genetic disorders.

How genes can influence adult health

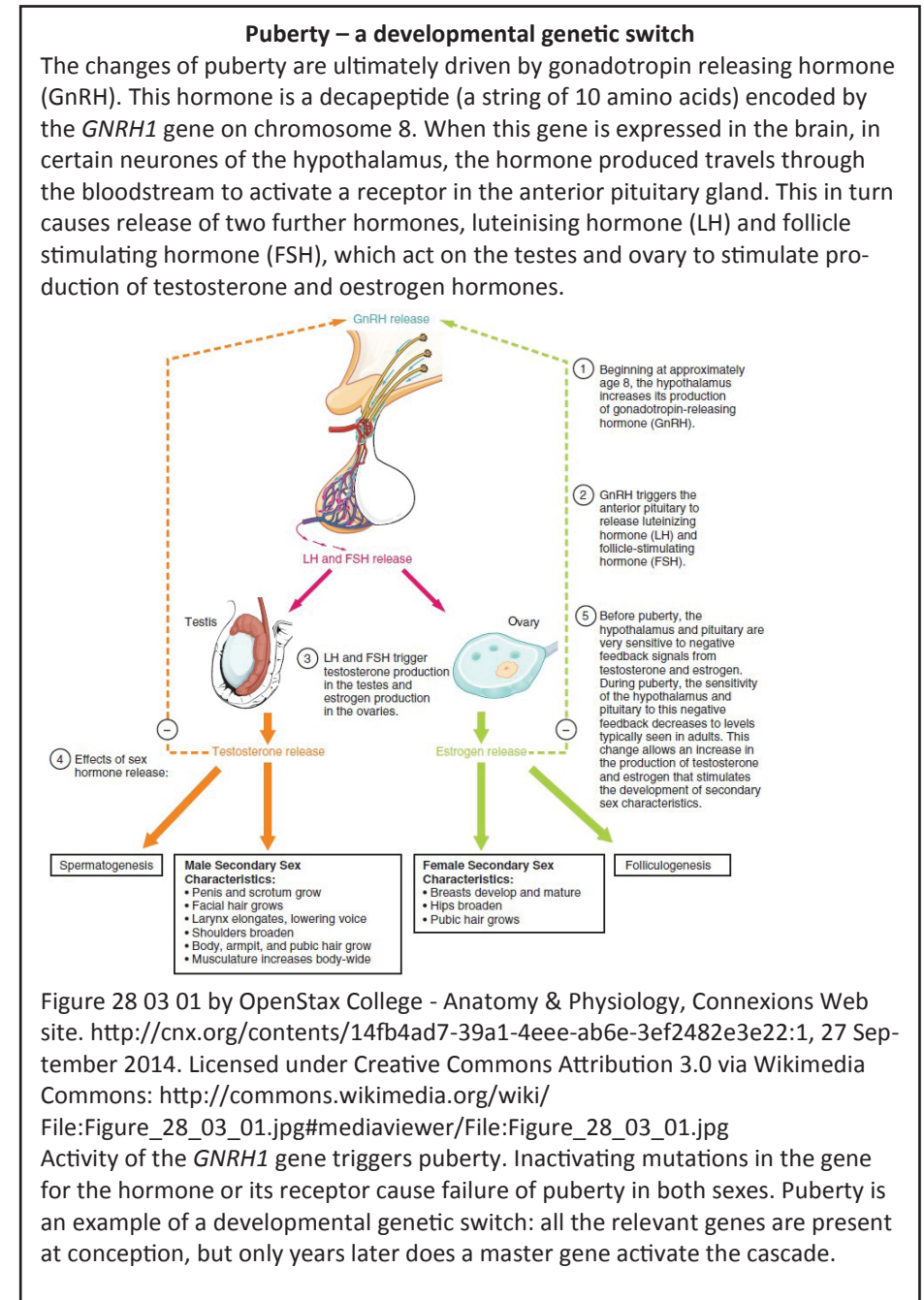
Genes play a role in almost every disease of adult life. This happens through two mechanisms:

- A genetic variant present at conception may first show an effect many years later.
- A novel genetic variant may be acquired through a mutation that happens after conception.

Many genes are developmentally regulated. Though present from conception, they are only normally expressed at the time and in the tissues where the protein product is required, and not before or elsewhere. The genes responsible for puberty (see page 7) are an obvious example. Other genes may be active from early in life, but the effect of a variant may not become apparent until much later. It might make a tissue or organ unusually sensitive

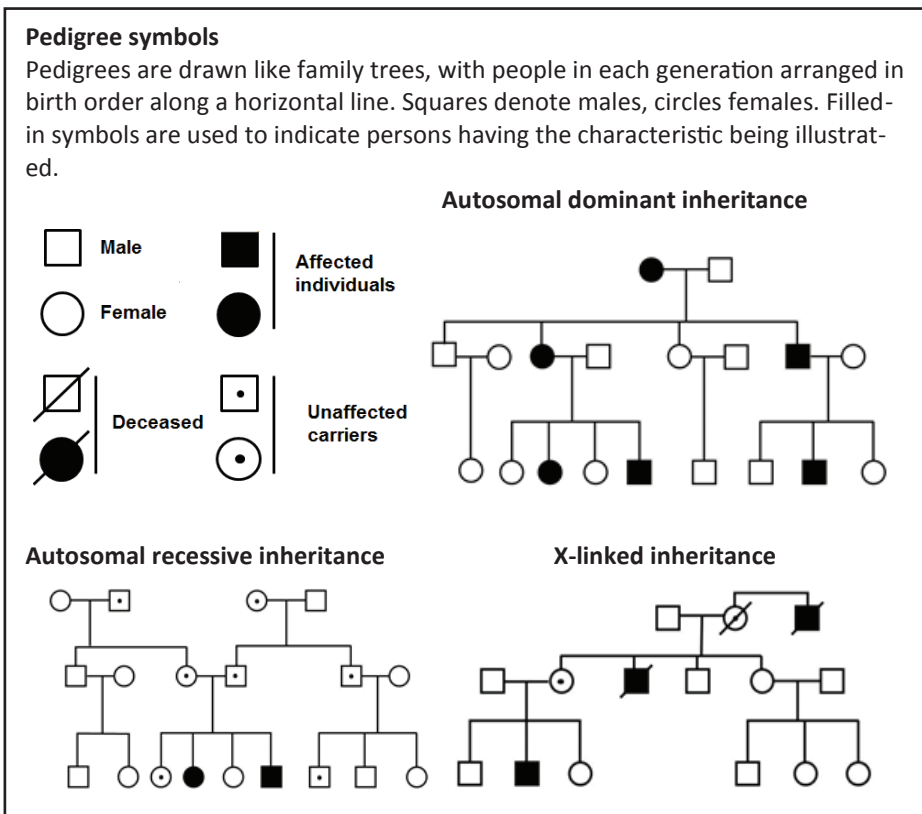
to normal wear and tear. Age-related macular degeneration is the leading cause of blindness in people aged over 55 in the UK and other Western countries. Certain genetic variants make the ageing retina more vulnerable to stress caused by factors such as smoking, poor diet and sunlight, as well as several other factors. In other conditions a genetic variant may function well enough under normal circumstances, but may fail when the person suffers exceptional stress. The sudden death **syndromes**, described later (page 19) are examples. Slow accumulation of a toxic product is another way a genetic variant may precipitate disease after a long period of apparently normal function. In Huntington disease the variant gene encodes an abnormal protein that slowly kills neurones. The result is a gradual neurodegeneration that first becomes clinically apparent in middle life, typically in the fourth to sixth decades.

All these are examples of adult-onset diseases caused by inherited genetic variants that were present at conception. Alternatively, variants that arise by new mutation in a cell of the body some time after conception (**somatic mutations**) may cause problems later. The DNA in a cell suffers constant damage and needs constant repair. Damage may come from external agents such as cosmic rays or – in exposed skin cells – ultraviolet light, but mostly it results from chemical actions within a cell. Reactive oxygen species (chemical molecules generated as a by-product of normal **metabolism**) are highly damaging to DNA. Other damage may result from mistakes in DNA replication when a cell divides. All these forms of damage must be repaired if the cell is to remain healthy. Cells possess several independent DNA repair systems which, between them, repair most damage so effectively that, for the most part, we are completely unaware of the constant activity. However, they are not infallible. As the years go by there is a slow accumulation of unrepaired damage which, eventually, may prove harmful. Cancer is the prime example of a group of diseases caused by accumulation of somatic mutations – see page 28.



Simple versus complex inheritance

In our first booklet we described the pedigree patterns that are seen when a single genetic variant is both necessary and sufficient to cause a disease. These are briefly summarised below.



However, in real life the situation is often not so clear-cut. For the more severe dominant or X-linked conditions, familial (inherited) cases may conform to these patterns, but many cases occur as fresh mutations, without any previous family history. In many other cases a genetic variant will have some role in determining a characteristic, but will not be the sole factor. Other genes often play some part. The genetic contribution towards a characteristic will fall

somewhere along a spectrum between monogenic (single gene) and polygenic (many genes, with no single major determinant) mechanisms.

Environmental factors also play a role. When a condition is governed by many genetic and environmental factors, it can be described as **multifactorial**. An important first step to establish the genetic contribution to a multifactorial condition is to determine its **heritability** (the proportion of variation in the condition that is due to genetic factors). This can be done through **family, twin or adoption studies**. For most adult diseases the heritability is less than 100%. When one gene largely, but not entirely controls a character, deviations from the simple patterns shown opposite are accommodated by two concepts:

- **reduced penetrance** is seen when a person carries a genetic variant that normally results in a certain characteristic, for example a disease, but in that individual does not do so.
- **variable expression** is seen when individuals carrying the same gene variant manifest the relevant condition to different degrees – some more severely than others – or with a wider involvement of different body systems.

Reduced penetrance and variable expression reflect the roles of additional ('modifier') genes and/or environmental factors.

As the influence of other factors increases, use of the terms describing monogenic inheritance patterns becomes increasingly questionable. Haemochromatosis, for example, is a condition of iron overload. Affected individuals absorb too much iron from their food, resulting in damage to their livers. They are always **homozygous** for variants in the *HFE* gene – but many homozygous individuals remain healthy all their lives. Women are seldom clinically affected because blood loss from menstruation keeps the iron level under control. In fact, no more than 5% of **homozygotes** are clinically affected. Clearly other factors are having a major influence on the development of clinical disease, so it is questionable whether haemochromatosis is best described as an autosomal recessive rather than a multifactorial condition.

Most of the major diseases of adult life are best described as **complex**. The term implies that different cases of the same condition may have different causes, which might include monogenic, multifactorial and in some cases maybe purely non-genetic causes. We will see examples in diabetes and breast cancer.

School biology lessons can easily leave the impression that most genetic effects are inherited in a simple fashion – like monogenic disorders – and that multifactorial or complex inheritance is strange and exceptional. Actually, exactly the reverse is true. For a single DNA sequence variant to reliably produce a certain **phenotype**, regardless of all of a person’s other genes or their environment, history and lifestyle – the prerequisite for simple mendelian inheritance – is strange and exceptional. Our general appearance and health are the result of many genes acting together and responding to our environment. Most genetically-influenced characteristics are multifactorial or complex, and this is especially true of most of the common diseases of later life. Multifactorial conditions still tend to run in families, because relatives share genes, but we no longer see the simple inheritance patterns characteristic of monogenic diseases.

Complex inheritance and family risks

We all share some specific versions of genes with others because of our common human ancestry, but relatives share gene variants to an extra extent. The degree of sharing depends on the relationship:

- **First-degree relatives** are parents, children and siblings (brothers or sisters). Parents and children share half their genes; siblings do so on average, but may share more or fewer of their genes in individual cases.
- **Second degree relatives** are grandparents, grandchildren, uncles, aunts, nephews, nieces and also half-siblings (that is, children who share one parent but not both). Second-degree relatives share on average one quarter of their genes.
- **Third degree relatives** are mainly first cousins. Note that the term ‘cousin’

has a precise and limited meaning in genetics, even though it may be used in a wider sense in some other contexts. In genetics two people are (first) cousins if they are the offspring of siblings. Third degree relatives share, on average, one eighth of their genes.

As relatives share genes, a relative of a person affected by a genetic or part-genetic condition will also be at increased risk of the condition. Although complex diseases are much more frequent than monogenic diseases such as HD or CF, the risk to relatives, and hence the degree of family clustering, is much less (see the Table below).

Disease	Lifetime risk in the UK (to age 80)	Relative risk for sibling of patient
Monogenic conditions		
Huntington disease (HD)	0.01%	5,000
Cystic fibrosis (CF)	0.05%	500
Complex diseases		
Coeliac disease	1%	10
Multiple sclerosis	0.15%	18
Type 1 diabetes	0.3%	18
Type 2 diabetes	16%	3
Alzheimer disease	17%	3
Breast cancer	12%	2
Schizophrenia	1%	12
Bipolar disorder	1%	7
Autism (Autism spectrum disorder)	1%	5
Congenital heart defect	0.7%	4

Both monogenic and complex diseases tend to run in families The relative risk is the increased risk to a sibling of an affected person above the population risk. Quoted risks are for illustrative purposes and vary between populations.

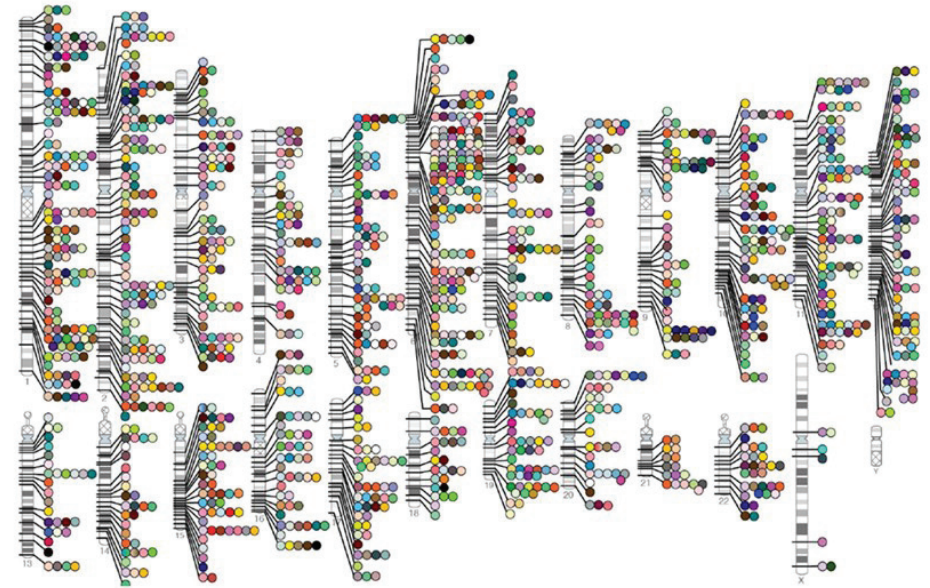
Genetic prediction in complex disease

Because of the overwhelming importance of these and similar conditions to healthcare systems, great efforts have been devoted to understanding their causes in the hope that this will point the way to better prevention and treatment. Despite the less clear-cut genetics, compared to monogenic conditions, family, twin and adoption studies show that each of these conditions has a substantial genetic element in its causation. Hence it has become a major research goal to identify the genetic factors that contribute to susceptibility to each of the many common complex diseases

Suppose we wished to identify genetic variants that increase a person's risk of developing Type 2 diabetes. We might collect DNA from 1,000 people with the condition (the 'cases') and 1,000 ethnically matched healthy people (the 'controls'). We would type each person for a very large number of **single nucleotide polymorphisms or SNPs**. These are places in the genome where two alternative DNA 'letters', say A or G, are both common in the population. Several million SNPs have been documented by researchers, and the technique of **microarrays** allows hundreds of thousands of them to be typed in a single relatively simple operation.

In the case where a single variant is – on its own – neither necessary nor sufficient to cause the disease, but where a variant increases the *risk* of a disease, we would expect people with the disease to be more likely than controls to have that variant. Having collected all our data we would look for statistically significant **associations** between SNP variants and diabetes. Over the past decade genome wide association studies (**GWAS**) have been used with great success to study a huge range of common diseases. Genetic risk factors have been identified for virtually every common disease of adult life. The figure opposite gives an impression of the wealth of data generated, although the details are not visible at this magnification.

GWAS have been extremely successful in identifying innumerable genetic susceptibility factors. But GWAS identify only the common variants that have



The fruits of GWAS. Each small circle represents an identified genetic risk factor, colour coded for the disease concerned and superimposed on a diagram of the 24 chromosomes (22 **autosomes**, an **X** and a **Y chromosome**) to indicate its position in the genome. From www.ebi.ac.uk/fgpt/gwas/ See this website for full details and a key to the colour coding.

probably existed in the population for thousands of years, and fail to detect recent mutations predisposing to disease susceptibility, since such new mutations have not yet become common in the general population.

Furthermore, the impressive results from GWAS conceal a problem in potential clinical applications of the new knowledge: natural selection operates on all of us all the time; it has made us who we are and shaped our genomes. So how can variants that predispose to disease have survived in the population for so long? Why has natural selection not eliminated them? There are several possible explanations - a variant might be pathogenic only in conjunction with modern lifestyle factors (smoking, lack of exercise etc, or poor diet), or it might tip the balance of physiology such that it increases the risk of one disease but provides a compensating resistance against another. Moreover, most of the common diseases that are studied by GWAS afflict us *after* we have had

children, so any selective pressure is minimal. However, much the major reason is that these ancient variants - the risk factors identified by GWAS - have only a very small effect on disease susceptibility. Typically they might increase the risk by a few percent. They almost never double the risk and seldom increase it by even 30%. For a disease that affects only a few percent of the population, the extra absolute risk conferred by such a factor is very small.

Genetic risk and clinical practice

As we have seen, susceptibility to common complex diseases depends on the cumulative effect of a whole range of factors, genetic and environmental. Each individual genetic factor, identified through GWAS, may have only a small effect, but maybe collectively they can be used to predict who will develop a disease and who will remain free of it? The idea seems intuitively plausible – but both current experience and theoretical predictions suggest this will seldom be the case. Although GWAS have successfully identified numerous genetic risk factors, and often helped illuminate the mechanisms that cause a condition, hopes that this research would lead to wholesale breakthroughs in prediction and prevention of disease have not so far been realised. The typical example of Type 2 diabetes is discussed below (page 15).

Consequently, NHS genetic services for common complex diseases have *not* been revolutionised by the progress of GWAS. Genotyping for risk factors is not routinely offered to people concerned about their risk of common diseases; the results do not offer useful options for predicting or modifying the risk, and diet and lifestyle will often influence risk far more than any genetic information. Even so, internet-based companies have leapt into the breach and offer to perform the analysis in return for a fee. You spit into a tube and send it off to a company, which extracts your DNA from the saliva, analyses it on a microarray for a panel of known risk variants and reports back the results. All this is done outside the NHS and usually without taking into account all the other pointers to risk (your clinical picture, family history, diet, weight and lifestyle). Your GP is unlikely to thank you for bringing along a printout of your results.

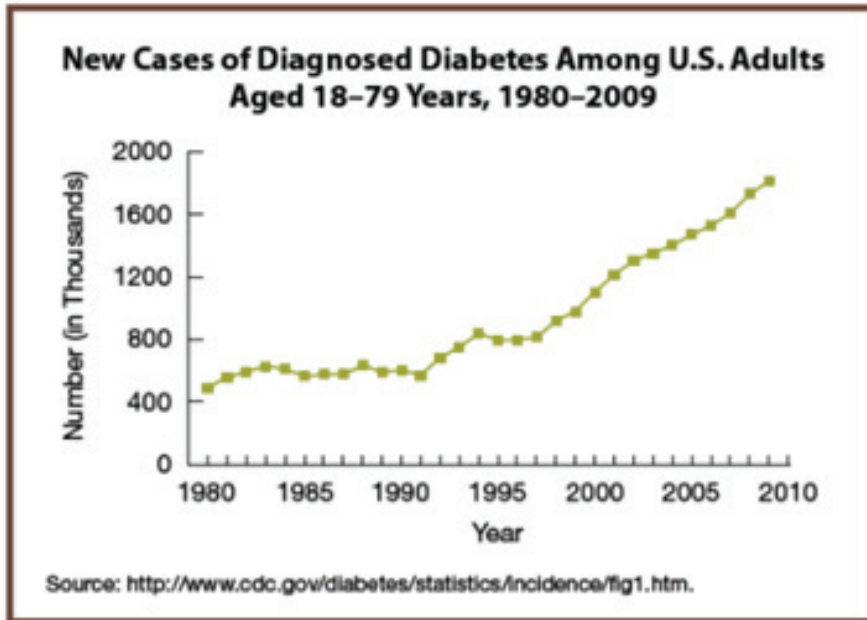
Adult medicine: the big challenges

In the following pages we look at the role genetic factors play in some of the major causes of adult illness and death in the UK and other developed countries. Despite the generally pessimistic conclusions we reached above about the overall potential of genetics to predict or prevent complex diseases, when we survey the major diseases of later life we will find that in many individual cases genetic services have a lot to offer. Frequently we will note the importance of identifying monogenic subsets of these common complex conditions.

Diabetes

The label 'diabetes' covers two quite different conditions:

- **Type 1 diabetes** is a lifelong disease, with onset in childhood or adolescence. Unknown triggers, possibly viral infections, induce the body's immune system to mount an attack against the insulin-producing cells in its own pancreas. This leads to a chronic inability to produce the protein hormone insulin – essential for metabolising glucose (a sugar) in the bloodstream – which would otherwise induce extreme lethargy, thirst, frequent urination and weight loss, so that survival depends on constant lifelong injections or infusions of insulin. Recent research that has used human embryonic stem cells to create insulin-producing beta cells in large quantities has offered future hope of transplantation for people with Type 1 diabetes.
- **Type 2 diabetes** is caused by a combination of reduced production of insulin and reduced response of the end organs to such insulin as there is. It mainly affects older adults. Generally it can be controlled by drugs taken in tablet form, but the impact on health can be severe, with increased risks of blindness and heart disease.



Type 2 Diabetes: a classical complex disease

Type 2 diabetes affects over three million people in the UK, and its incidence is rising worldwide (see figure above). Obesity and physical inactivity are strong risk factors, and weight control and exercise are powerful protective measures. The rapidly increasing incidence and strong association with unhealthy lifestyles show that environmental factors are important in determining risk. Nevertheless genetic factors are also significant. Typically for a complex disease, there are both multifactorial and single gene subsets. Risk tends to run in families. If your sibling has the condition, you have three times the risk of developing it, compared to an unrelated person. These are average figures, but in about 1-2% of cases the genetic factors are very strong: affected people are young (onset is typically before age 25) and the usual lifestyle risk factors are absent. This variant is called MODY (maturity-onset diabetes of the young). MODY is inherited as an autosomal dominant condition (page 8), so other family members are at high risk of inheriting the

same gene variant. It can be caused by variants in any one of at least seven genes; identifying the cause is extremely important because MODY patients with variants in certain genes respond very well to specific drugs that can be taken by mouth, and these patients do not need insulin injections.

The commoner age-related form of Type 2 diabetes has been a major target for GWAS. A whole panoply of genetic risk factors have been identified. Some of these overlap with risk factors for obesity and for the metabolic syndrome, a combination of insulin resistance, hypertension and abnormal blood lipids that may represent a pre-diabetic state. Most of these risk variants are in the **non-coding DNA** but are believed to be linked to the regulation of the activity of nearby genes. Looking at the functions of those genes, we can see how they might be involved in Type 2 diabetes. There are genes controlling the formation or function of the insulin-secreting pancreatic cells, genes involved in controlling blood glucose levels and genes involved in fat metabolism and weight control.

Can we use this knowledge to help predict who will develop diabetes, and maybe persuade them to reduce their risk by adopting more healthy lifestyles? A number of long-term studies have addressed this question. Large cohorts of healthy people were recruited; baseline clinical and lifestyle data recorded, and study subjects were then followed for many years to see who developed diabetes. As expected, age, sex, body mass index and fasting glucose level are, in combination, reasonably good but not perfect predictors of the risk. How much better would the prediction have been if genetic risk factors were taken into account? One way of doing this is through family history, and this does indeed improve the prediction. What about specific genetic risk factors? The evidence from several independent studies is that genetic testing adds very little to predictive power, even when many genetic risk factors are taken in combination. Thus the major role of genetic services in Type 2 diabetes is in identifying people with MODY, the subset caused by single changes in one of several genes.

Heart disease

Coronary Heart Disease

Coronary heart disease (CHD) occurs due to narrowing of the arteries that supply oxygen and blood to the heart. CHD is usually caused by atherosclerosis – hardening of the artery walls. This is a complicated process involving accumulation of fatty substances with a resulting inflammatory response and thickening in the artery walls (known as **plaques**). The narrowing can restrict blood flow causing angina or a heart attack. Whilst an unhealthy lifestyle – such as smoking, drinking and obesity – plays a major part in causation, hereditary factors also play a role since risks for adopted children bear more relationship to the medical history of their biological parents than their adoptive parents. Because CHD is such a major cause of death and ill health there have been many large scale studies to identify potential genetic factors. Apart from familial hypercholesterolemia which is a monogenic cause of CHD (see below) no major genetic predisposing factors are known. Currently about 40 genetic variants associated with CHD have been identified by GWAS studies but none of these are of great effect and cannot be used in prediction for individual patients. However further research may highlight how these variants cause their effects and lead, in time, to new types of treatment.

Hypertension

Hypertension (high blood pressure) has many causes including obesity, diabetes and kidney disease and predisposes a person to coronary heart disease and **stroke**. Whilst it is very common in the population and the incidence increases with age, there is still a family tendency, with a risk three times the population risk if a person has two or more affected relatives.

Familial hypercholesterolaemia

High cholesterol levels in the blood can lead to atherosclerosis and coronary heart disease. In some people, a high cholesterol is present from birth and is caused by an inherited genetic variant that considerably increases their risk of early heart disease; this is known as familial hypercholesterolaemia (FH). FH affects at least 1 in 500 people in the UK, yet fewer than 10% of the 120,000

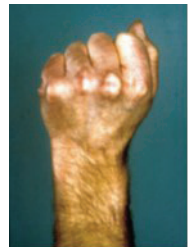
people affected have been identified. Early identification of FH means that people can make changes to their lifestyle and be given cholesterol-lowering drugs – known as statins – to help prevent heart disease.

The disease shows an autosomal dominant pattern of inheritance, so that siblings and children of a person with FH have a 50% risk of inheriting the condition (page 8). Because of this, DNA testing of all first degree relatives of an affected individual is recommended. A mutation in any of three known genes can lead to elevated blood cholesterol levels, but relevant variants are identified in only 40% of patients with a clinical diagnosis of FH. So it is likely that there are additional genes for both monogenic and polygenic causes of high cholesterol.



Corneal arcus (fatty deposits appearing as a ring around the edge of the iris)

Tendon xanthoma (a build-up of fatty deposits on the tendons over the knuckles)



Typical symptoms of high cholesterol seen in individuals with FH

Genetic causes of sudden death in adults

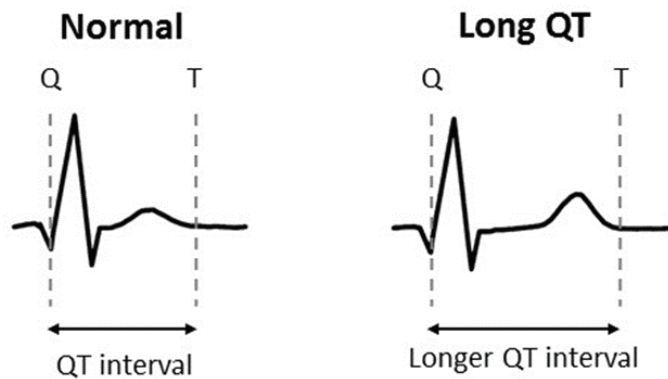
The sudden unexpected death of a young adult whilst asleep, in the swimming pool or on the football pitch is a tragedy which we now know can have a genetic cause, which, if identified, can lead to preventative treatment for at-risk relatives. Many specialised cardiogenetic clinics are now established for survivors and close relatives for assessment of cardiac function and for specialised genetic investigations followed by appropriate treatments.

Arrhythmia

Sudden cardiac death can occur because of a disturbance in the heart's regular rhythm (an arrhythmia) due to an error in the way electrical impulses are transmitted from the pacemaker in the heart. This can result in the heart ceasing to beat; this is termed a cardiac arrest.

Arrhythmia due to chemical imbalance

Electrical charge is carried through heart muscle via charged sodium and potassium **ions**; these ions pass through the muscle cell membrane via special protein channels which regulate the flow and control the electrical impulse. Mutations in the genes for the components of these channels are linked to inherited conditions called 'channelopathies'; for example, long QT, short QT, Brugada, CPVT (Catecholaminergic polymorphic ventricular tachycardia). Some of these can be diagnosed by a characteristic electrocardiogram (ECG) pattern (see below) but many manifest by a history of blackouts, palpitations, dizziness or cardiac arrest. Once the relevant genetic variant is identified, family members can be tested and appropriate treatment – including medicines and an implantable cardioverter defibrillator (ICD) – can be offered.



ECG of a normal individual (left) and of a patient (right) who was screened following the sudden death of his teenage child

Arrhythmia due to abnormalities of heart muscle

Arrhythmias and sudden death may also be caused by disorders of the heart muscle, known as 'cardiomyopathies'. Hypertrophic cardiomyopathy (HCM) is where the heart muscle becomes thickened (or 'hypertrophied') and dilated cardiomyopathy (DCM) when the heart enlarges (or 'dilates'). Symptoms include shortness of breath, palpitations, chest pain and fainting.

In HCM, the contracting cells of the heart increase in size resulting in thickened muscle. Disruptions of the electrical functions of the heart also occur that can lead to sudden death. In DCM the dilatation of the heart causes impaired contraction.

Patients with HCM and DCM can have mutations in a wide variety of genes; mutations in some genes can result in either of the two clinical pictures. Most commonly affected are genes encoding one of the many heart muscle proteins. Treatments vary according to the type of cardiomyopathy and the symptoms. For HCM, medication to improve heart function or an interventional procedure to reduce obstruction caused by the increased muscle bulk may help. For DCM, medication is given to increase efficiency of the pumping action of the heart and to decrease its workload. For both HCM and DCM an ICD may be sometimes be necessary.

Identifying the precise genetic variant in a patient can guide treatment, help define the prognosis and allow screening of relatives to identify which ones are at risk and which ones are free of the family mutation.

Neurodegenerative diseases

Neurodegenerative diseases (see below) are caused by a gradual loss of neurones in the central and/or peripheral nervous system. The causes can be genetic, environmental or any combination of the two, and the symptoms depend on the rate and extent of loss and the location and functions of the affected neurones. Some, but not all, of these disorders are associated with dementia – a loss of memory, changing personality and impaired reasoning. As examples we will discuss Huntington and Alzheimer diseases.

Disease	Prevalence in UK
Alzheimer disease	20% by age 80
Fronto-temporal dementia	20% of pre-senile dementia
Huntington disease	1 in 10,000
Motor neurone disease	1 in 2-5,000
Parkinson disease	1% aged 60+; 3% aged 80+
Spinocerebellar ataxias	1 in 3,000 overall (many types)

Examples of neurodegenerative diseases

Huntington disease (HD) was first described by George Huntington, a country doctor in the USA, in 1872. His unsurpassed description is a fine example of the value of observant clinicians in advancing science.

THE
MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.


By **GEORGE HUNTINGTON, M. D.,**
Of Pomeroy, Ohio.

Essay read before the Med. and Surg. Academy of Medicine at Middleport, Ohio, February 15, 1872.

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempts to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of



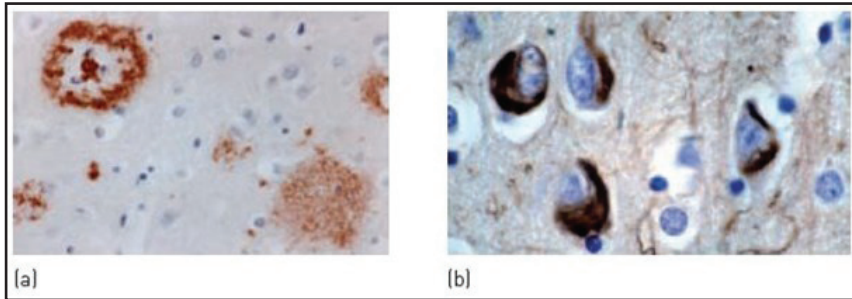
HD typically affects people in mid-life, though the onset can be at any age. The first symptom is chorea – involuntary movements of the face and limbs. This progresses to an increasingly severe movement disorder and often some degree of personality change, depression and dementia, leading to death typically 10-15 years after the first onset. It is inherited as an autosomal dominant condition. In the family of an affected person, siblings and offspring are at 50% risk of developing the condition. The knowledge and attendant uncertainty can cast a major cloud over the lives of such people.

The gene responsible was identified in 1993. Called *HTT* and located on the short arm of chromosome 4, it encodes a protein, named huntingtin, that is expressed in neurones. The mutant version produces an abnormal form of the protein that has a tendency to form clumps. In ways not fully understood, this clumping is toxic to the affected neurones.

Because the gene and mutation are known, it is possible to test healthy but at-risk family members to see whether they carry the mutation. Testing follows an agreed protocol to ensure that consent is truly informed, and is conducted in specialist genetic centres where support is available afterwards. In practice, only a minority of those at risk choose to be tested, mainly because there is currently no effective treatment, should they test positive. However, with the hope offered by the many current active clinical trials of new interventions, this may change in the future.

Alzheimer disease (AD) is the most common form of progressive dementia in the elderly. There is a characteristic picture when the brain cells are looked at under a microscope (see overleaf). Of course, these can only be observed after death, so diagnosis rests on clinical and psychiatric assessment.

AD is usually divided into early onset (before age 65) and late onset. Early onset AD is rare, and in some cases the cause is a single mutation in one of three genes (*APP*, *PSEN1*, *PSEN2*). In those families AD is inherited as an autosomal dominant condition and genetic testing can be offered, as in HD.



The characteristic pathology of Alzheimer brain (a) amyloid plaques
(b) neurofibrillary tangles

Most early onset, and all late onset AD, however, is not so simple genetically. No single genetic variant has been identified that causes late-onset AD, although a number of variants are known to influence the risk. Chief among these is a variant called E4 in the gene for apolipoprotein E (APOE). Importantly, the E4 variant on its own is neither necessary nor sufficient for developing AD (in other words, some E4 carriers will never develop AD however long they live, and many AD patients do not have the E4 variant), but it is a significant risk factor. Rare individuals who are homozygous for the E4 variant are at 12-15 times the risk of those who lack E4 of developing Alzheimer. Testing the *APOE* gene is controversial; it is not available on the NHS because the results are poorly predictive and – currently – do not lead to any useful preventative action.

As with HD, AD involves abnormal formation of protein clumps (called plaques) in the affected neurones. It is generally supposed that this clumping (or ‘aggregation’) is somehow a cause of the neuronal death, rather than a side-effect of a different underlying cause, but the exact mechanism is not well understood. Abnormal protein aggregation is also a feature of Parkinson disease and some rarer neurodegenerative conditions. There is considerable interest in developing drugs that could inhibit protein aggregation.

Disorders of mental health

Psychiatric disorders are common in the population and, although they are classified into separate categories, there is considerable clinical overlap. Family, twin and/or adoption studies have demonstrated a significant genetic influence on susceptibility, and in each case GWAS have identified some specific genetic variants. However, each condition is complex and the known genetic susceptibility factors account for only a small part of the overall risk.

Schizophrenia and bipolar disorder

Schizophrenia is the most severe psychiatric disorder with a prevalence of 1%. Symptoms include hallucinations (eg: hearing voices), false beliefs (delusions), disordered thoughts and behaviour, and emotional and cognitive impairment. Although people with schizophrenia might not know which thoughts and experiences are real and which are not, the vast majority are not violent, contrary to popular myth. They are however at increased risk of suicide. Generally, the onset is in young adulthood; some individuals recover completely although others suffer recurrences. Medication is effective in ~70% of cases, often in conjunction with psychological treatments. In particular, **cognitive behavioural therapy (CBT)** is used increasingly in schizophrenia.

Bipolar disorder, once known as manic depression, affects a similar age group and also has a prevalence of 1%. It manifests with episodes of elevated and agitated mood (mania) alternating with episodes of low mood (depression) sometimes with delusions. People with bipolar disorder are also at a greater risk of suicide. Most patients with bipolar disorder respond to mood stabilising drugs, as well as medication to treat the symptoms. Talking therapies can also be helpful. Typically bipolar disorder occurs in episodes, usually with full recovery in between. Some patients will only have a couple of episodes in their lifetime, but many will have several episodes.

Inherited factors play a role in both schizophrenia and bipolar disorder. The relative risk to a sibling of a person with schizophrenia is 12 times the risk to a

member of the general population, and for bipolar disorder the risk is sevenfold. GWAS identified many risk factors of low effect which are shared between patients with schizophrenia and bipolar disorder. However, several **copy number variants (CNVs)** that confer a much greater risk have been identified in a few patients. These are also common to both schizophrenia and bipolar disorder but are also found in patients with disorders such as autism, attention deficit disorder and intellectual disability – and in their parents – and may mark some sort of neurodevelopmental vulnerability.

COMT, cannabis and schizophrenia

There is a clear link between heavy cannabis use and schizophrenia, though the nature of the link is open to debate: some propose cannabis causes schizophrenia; others argue that people with schizophrenia use cannabis to self-medicate; still others propose a ‘vulnerability’ mechanism by which cannabis use is a trigger for individuals already at risk. COMT (catechol O-methyl transferase) is one of several **enzymes** that degrade chemicals involved in transmission of nerve impulses in the brain. One particular variant in the *COMT* gene affects cognitive tasks; and *COMT* gene variants are also relevant to emotional processing in the brain. There is some evidence that the variant *COMT* gene could predispose someone to developing schizophrenia later in life, maybe in combination with cannabis use, but this is a controversial finding.

Depression

10-15% of the population suffer clinical depression during their lifetime. Depression is not just feeling unhappy or fed up for a few days; symptoms include continuous low mood, hopelessness and low self-esteem. Depression is a feature of many chronic illnesses and of bipolar disease. Treatment for depression usually involves a combination of antidepressant medicines, talking therapies, exercise and self-help. The risk to a first degree relative of a person with depression is two to three times the risk to a member of the general population. GWAS studies have identified many risk alleles of small effect and have particularly concentrated on genes relating to transmission of signals

between neurones. No association with CNVs has been shown.

Addiction

Addiction refers to a physical or psychological need for a habit-forming substance, such as heroin, crack cocaine, nicotine or alcohol. In physical addiction the body adapts to the substance being used and gradually requires increased amounts to reproduce the original effects. If addicts suddenly stop taking the substance, they will experience the effects of withdrawal, which can be severe and life threatening; eg: withdrawal from alcohol can cause craving, shaking, hallucinations, seizures, confusion, anxiety, sweating and nausea. In 2011-12 there were an estimated 293,879 opiate (eg: heroin) and/or crack cocaine users in England. In 2013, ~9% of men in the UK and 4% of women show signs of alcohol dependence. Treatments include drugs to relieve the symptoms of withdrawal, to help re-establish normal brain function and to prevent relapse. Behavioural therapies are also helpful.

As addiction can run in families, there have been many studies to look at potential genetic factors. There are over ten examples of genes where one variant is more common in addicts. However, as with other mental health conditions, these variants alone are neither necessary nor sufficient to cause addiction. In other words, a person can have an ‘addiction’ variant without ever becoming an addict; environment and experience play an important role.

Genetic studies of mental health conditions are not pursued to inform ‘nature-nurture’ controversies, which are generally agreed to be obsolete and based on failure to appreciate the interdependence of genes and environment. Rather, the hope is to achieve a better classification of these conditions. The labels ‘schizophrenia’, ‘bipolar disorder’, ‘depression’ etc probably each cover a host of different conditions with different causes that might respond to different drugs or other treatments. In the future, genetic tests might be used to determine which medications are likely to be most effective based on an individual’s specific genetic profile. Identifying the gene products involved could also suggest targets for possible new drugs.

Cancer

Everything we have discussed so far relates to your genome as fixed at conception by the DNA in the sperm and egg that made you. This original genome was copied at each of the successive cell divisions that produced the ten million million or so cells of your body, such that each cell carries in its nucleus a copy of that original genome. However, the copies may not be totally perfect. Any change in a single cell, the result of an error in copying the genome, or DNA damage that escaped repair, will be passed on to all the descendants of that cell.

We all have innumerable such changes (called somatic mutations), scattered around the various cells of our body. For the most part they are of no significance. They will not be passed on to offspring because they are not in the sperm or egg (the **germ cells**). They are unlikely to cause clinical problems: if a cell in a person's finger happens to pick up the Huntington disease mutation, it does not matter because it is an isolated cell in a tissue that is irrelevant to the disease. However, there are two circumstances in which a somatic change may be significant:

- If it happens to a cell in an early embryo, such that the progeny of that cell end up making up a significant part of the whole adult organism.
Depending on the particular mutation, this can produce a person with a significant part of their body showing features of a genetic disease.
- If the mutation confers a growth advantage on the cell and its progeny.
This is the genetic basis of cancer.

Cancer – a product of evolution

Natural selection acts among the cells of our body just as it acts in populations of whole organisms. If one cell acquires a somatic mutation that allows it to divide a little faster than the surrounding cells, then we would expect its progeny to take over. Thus multicellular organisms have a natural tendency to develop tumours. To resist this, cell division is very tightly

controlled. Cells are allowed to divide only in order to replace cells that have died, or as part of bodily growth as the fertilised egg develops into a 3 kg baby and then a 70 kg adult. Cancer is not a genetic disease, in the sense that it is not usually transmitted through families (see below for exceptions), but it *is* a genetic disease in the sense that it is the result of somatic genetic changes in the cells that make up the tumour that allowed them to escape the controls.

Multiple mutations are needed to escape all the different controls on cell division, and these can involve any of a large number of genes. Cancer cells usually have destabilised genomes and high mutation rates, spawning innumerable random irrelevant 'passenger' mutations in addition to the so called 'driver' mutations that drive cancer development (or 'tumorigenesis'). In some types of cancer, catastrophic scrambling of certain chromosomes (known as chromothripsis) is associated with accelerated malignancy. No two tumours are genetically identical. Large international projects are working to document the changes in cancer patients by comparing the genomes of their tumour cells with the genomes of their healthy cells (their **constitutional genome**). The results allow a new classification of cancers, by their molecular mechanisms instead of just by their tissue of origin. This new knowledge is helping define the prognosis and identify the best treatment.

Familial cancers

Cancer is a common disease and so it is quite common for several members of a family to all develop cancer. Even if we limit ourselves to one cancer type, it is far from rare to find families where there is more than one case of breast or colorectal cancer. Most such families are just chance co-occurrences of common cancers – pure bad luck. But there are some 'cancer families' where multiple members develop particular cancers. Often there is also an unusually early age of onset and, with breast cancer, there may be bilateral cases (cancers in both breasts) or cases of male breast cancer. The table overleaf lists some of the major familial cancer-prone syndromes.

Examples of single gene cancer-prone syndromes

Cancer syndrome	Gene name
Familial breast ± ovarian cancer	<i>BRCA1</i>
Familial breast cancer	<i>BRCA2</i>
Familial adenomatous polyposis coli (a type of bowel/colon cancer)	<i>APC</i>
Lynch syndrome (non-polyposis colon cancer)	<i>MSH2, MLH1</i>
Li-Fraumeni syndrome (sarcomas , breast + other cancers)	<i>TP53</i>
Neurofibromatosis 1 (skin neurofibromas , optic gliomas etc.)	<i>NF1</i>
Neurofibromatosis 2 (acoustic neuromas)	<i>NF2</i>
Gorlin syndrome (basal cell carcinomas)	<i>PTC</i>
Retinoblastoma (tumours of the retina in the eye)	<i>RB1</i>
Multiple endocrine neoplasia (MEN) 1 (tumours of hormone producing glands)	<i>MEN1</i>
Von Hippel-Lindau (VHL) syndrome (kidney and other tumours)	<i>VHL</i>

Familial cancer syndromes are rare, but they played major roles in developing our understanding of cancer. The genes that are mutated in these conditions have crucial roles in restricting cell division. An affected person inherits a non-functional copy of the relevant gene. Every cell of their body has a single mutant gene, but the other copy is still functional. Thus the controls on cell division still work normally and the person is healthy. However, if one cell in a relevant tissue happens to acquire a new somatic mutation that inactivates the remaining functional copy, the brakes on division of that cell are now ineffective. It becomes the founder of a **clone** of abnormally proliferating cells – in other words, a tumour.

Mutation testing to identify patients with one of the monogenic syndromes is important for clinical management. For example:

- If a woman's breast cancer is due to a *BRCA1* or *BRCA2* mutation, her

relatives are at increased risk compared to the general population; they should undergo risk assessment regarding their risk of breast and other cancers and be offered predictive genetic testing.

- People with von Hippel-Lindau syndrome are usually diagnosed following detection of a tumour associated with VHL in the eye, brain, adrenal gland or kidney. First degree relatives are offered testing, if available, and, if necessary, are entered into a screening programme. The clinical geneticist is often the person who co-ordinates the screening programme.

Exploiting genetic knowledge for treatment of cancer

Traditional anticancer drugs simply target and attack all dividing cells. Not surprisingly, the side-effects of chemotherapy with these drugs are extremely severe. A newer generation of drugs specifically target chemical signalling systems that are dysfunctional in tumour cells. Each drug is highly effective against tumours that carry the particular abnormality that it targets – with few side-effects in normal tissues – but is completely ineffective against similar tumours that do not. These are also extremely expensive drugs. Thus before such a drug is prescribed the genetics laboratory must test a tumour biopsy to check what mutations it carries. Tailoring the treatment to the individual patient is called stratified medicine, and this has been one of the recent success stories of cancer treatment. However, as mentioned above, tumours are genetically unstable and rapidly evolving, so sooner or later a tumour usually develops resistance to the drug. Hopefully, using combinations of drugs may make it much more difficult for tumours to become resistant.

Other conditions affecting adults

It is beyond the scope of this booklet to describe all the disorders where genetic factors play a role, but the table below gives some examples of disorders in various body systems where genetic influences have been identified.

Organ or system	Condition	
	Simple inheritance	Complex inheritance
Kidney	Adult polycystic kidney disease (multiple cysts in the kidneys; half of patients go into renal failure by age 60)	Kidney stones
Liver	Polycystic liver (multiple cysts on the liver)	Cirrhosis (scarring due to damage from alcohol abuse, infection etc)
Endocrine	VHL, and MEN (see page 30)	Thyrotoxicosis (excess thyroid hormones in the bloodstream)
Skin	Epidermolysis bullosa (EB) simplex (blistering of the upper layer of the skin)	Psoriasis (a skin condition that causes red, flaky, crusty patches of skin)
Eye	Retinitis pigmentosa (RP; leading to progressive loss of vision and blindness)	Age-related macular degeneration (an eye condition that usually leads to the gradual loss of sight)
Hearing	Autosomal dominant deafness	Oto-sclerosis
Skeleton	Osteogenesis imperfecta (OI) Type I ('brittle bone' disease)	Osteoporosis (a condition that weakens bones, making them fragile and more likely to break)

Disorders that arise through mutations in the mitochondrial genome

Mitochondria are small structures in cells that produce much of its energy; they contain a small amount of DNA (mtDNA). Mutations in mtDNA can cause a range of rare but serious diseases that can present at any age. Whilst some of these only affect a single organ (eg, eyes), many individuals with mtDNA mutations show a cluster of features that fall into discrete clinical syndromes. However, there is great variability and many patients do not fit neatly into one category. Common clinical features of mitochondrial disease include deafness, diabetes, muscle weakness, other neurological symptoms and vision loss. Since mitochondria are derived from the cytoplasm in the egg, inheritance of these disorders is exclusively from the mother.

Genetics and drug responses

We have seen how treatment of cancer has been greatly advanced by the development of drugs that target the specific genetic variants present in a particular tumour. Treatment of many other conditions can similarly be improved by tailoring the choice or dose of drugs to the individual patient's genetic constitution. People respond differently to drugs: a drug that is effective in one person might not work in another, or require a much higher dose to work; a drug that is well tolerated in most may trigger a side effect in a small number of people. Ineffective drugs waste time and money and delay relief for the patient. Adverse drug reactions are a major cause of sickness in patients and also a drain on NHS resources (see below).

The importance of adverse drug reactions (ADRs)

Pirmohamed and colleagues studied 18,820 admissions to two large UK general hospitals in 2001-2. They found that 6.5% of all admissions were related to ADRs. 2% of patients admitted for ADRs died. They estimated the annual cost to the NHS was up to £466 million.

Source: *Pirmohamed et al, BMJ 329: 15-19; 2004*

A variety of factors contribute to the variable responses of patients to a drug. These include the patients' general health, other diseases they may have and other drugs they may be using; their age, sex and weight, and lifestyle factors (smoking, drinking, diet etc.); but a major influence is genetics. The study of the role of genetic variants on the safety and efficacy of drugs is called pharmacogenetics. In some cases, as with the cancer drugs described above, genetic variants in the molecule that is the target of the drug's action determine the response. Often, however, the different responses are the result of differences in the rate at which a drug is metabolised. Our bodies possess elaborate sets of enzymes whose job is to detoxify and eliminate potentially harmful compounds present in our diet. The same enzymes act to metabolise drugs. People vary quite widely in the efficiency of the different enzymes, and as a result they also vary quite widely in how rapidly they eliminate particular

drugs. Somebody who eliminates a drug very rapidly will need a higher dose of the drug to be effective, while somebody who eliminates it very slowly will be exposed to the drug much longer, and may suffer overdose effects when given the standard dose. Warfarin (see below) illustrates some of these effects.

Warfarin

Warfarin is a very widely prescribed anti-coagulant used, amongst other things, for prevention of blood clots that can cause strokes and **pulmonary embolisms**. 1% of the entire UK population (600,000 people), and 6% of those over 80, are on warfarin. The dose required varies widely from individual to individual. If it is too low the drug will not be effective, and dangerous blood clots can still form; if it is too high, there is a risk of internal bleeding and death (it is used in this way as a rat poison!). The overall risk of major bleeding averages 7-8% per year. In the US, warfarin is by far the greatest cause of adverse drug reactions leading to emergency hospitalisation.

Differences in warfarin response depend on several genetic factors. The activity of the key enzyme for eliminating warfarin, CYP2C9, varies greatly between normal people, while the target of warfarin's action, an enzyme called VKORC1 that is involved in blood clotting, varies in its sensitivity to warfarin. Genetic tests to identify a patient's particular variants of CYP2C9 and VKORC1 allow doctors to better estimate the right dose of warfarin for their patient.

Some drugs require the activity of one or another of these enzymes to generate the active molecule. Codeine, for example, is active only after an enzyme, CYP2D6, has converted it into morphine. People with a very low activity variant of CYP2D6 gain no benefit from codeine. A further complication is that many drugs themselves activate or repress certain of the drug-metabolising enzymes. As a result one drug can affect the metabolism of another, so that certain combinations of drugs are either ineffective or dangerous. As we age some of us require more drugs to keep us going, so these problems are particular concerns for older adults. Details of all these effects can be found in the PharmGKB database (<https://www.pharmgkb.org>).

Adverse drug reactions usually involve an exaggerated response to a standard dose of a drug, because of variants that make an individual particularly sensitive to that drug. Occasionally, however, ADRs are unrelated to the normal action of

the drug and are the consequence of some quite unexpected interaction. Carbamazepine is one such case. This is one of the most commonly prescribed drugs for the treatment of epilepsy. As well as predictable side-effects, 5-10% of UK patients taking carbamazepine suffer hypersensitivity reactions such as skin rashes with liver problems and fever. Usually these are mild, but 1-6 per 10,000 patients suffer an extreme form, the rare but very serious Stevens-Johnson syndrome (SJS). This is a severe inflammatory condition of the mucous membranes leading to ulceration and scarring. It is fatal in 5-15% of cases, and survivors often have long term problems, especially with their eyes. For unknown reasons, carbamazepine triggers SJS only in individuals of certain ethnic groups who have particular genetically determined **tissue types**: East Asian people with the tissue type *HLA-B*1502* or Europeans with *HLA-A*3101*. By tissue-typing patients before prescribing carbamazepine, a major clinical risk can be avoided.

An increasing number of drugs are prescribed with a 'companion diagnostic', a genetic test to determine how the patient will respond. The main factor holding back wider application of such tests is the time delay in getting the test result: both patients and doctors want a quick consultation leading to an immediate prescription. The development of bedside genetic testing devices promises to eliminate this obstacle.

Treatments of genetic disorders in adults

In modern medicine, almost all clinical specialties use genetic knowledge in the management and treatment of patients. Genetic tests for monogenic disorders confirm diagnoses and allow appropriate management, whether by treating symptoms or preventing complications. Genetic clinical and laboratory specialists take part in many multi-disciplinary team meetings to decide on the best clinical management for individual patients, as well as contributing to clinical trials of new treatments based on knowledge of gene changes. Genetic information is used increasingly in treatment decisions, whether after testing a tumour or to find out how a person's metabolism processes certain medicines. Some examples of genetic knowledge-based treatments are listed below.

Management guidelines for rare diseases

Most genetic diseases are rare. This presents a challenge to doctors and families since so little evidence exists about the disease course and effective management. An important job of specialist centres with professional knowledge of a condition is – often as part of an international network – to develop clinical management guidelines to help doctors anticipate and prevent complications. In this they work together with the patient support groups, an often undervalued repository of expert knowledge pulled together from many years of families' experience.

Management and treatment of cancer

As described above, genetics now plays a major role in management and treatment of cancer. Identifying patients who have the rare single-gene cancer syndromes is crucial for the patient and family, whilst treatment often depends on identifying the specific mutations in a patient's tumour.

Replacing defective genes – gene therapy

In principle, knowledge of the defect in a genetic condition might allow scientists to correct the defect by replacing the non-functioning genes with

working versions. Unfortunately, delivering the replacement gene to the correct tissue, and keeping it functioning in the long term, proved much more difficult than expected. Thus the high expectations during the 1980s and 1990s for such gene therapy have not been realised. However, progress has been made and there are now many patients who have benefitted from gene therapy for some of the genetic defects of the immune system (eg: the severe combined immunodeficiencies (SCIDs)), and active gene therapy trials are underway for a number of eye diseases such as Leber's amaurosis. Furthermore, a large trial by the UK cystic fibrosis gene therapy consortium has been completed in 2014, and the results are awaited. Numerous other clinical trials are underway with a large range of conditions. New experimental technologies for very precise genetic engineering in the patient's own cells in culture – followed by re-implantation of the corrected cells – are just emerging; these techniques might revolutionise this field in the next decades.

Treatment based on genetic knowledge

Cancer is not the only condition where knowledge of the specific mutation in a patient can guide treatment. Advanced genetic engineering techniques can potentially correct mutated genes. For example, some patients with Duchenne muscular dystrophy who have certain specific mutations are enrolled in trials of drugs that can enable the defective gene to produce a functional protein.

Identifying the gene, or even the metabolic pathway involved in a patient's disease may allow targeted treatment. As mentioned above, identification of the genes involved in rare monogenic types of diabetes such as MODY allows more specific treatments to be prescribed and insulin therapy to be stopped. Patients with Marfan syndrome, an autosomal dominant condition characterised by skeletal, heart and eye problems, have dilatation of the aorta which can result in rupture and sudden death. The discovery that this is caused by over-activity of particular chemical signals in the cell has led to successful use of long-established drugs – originally developed to treat high blood pressure – to correct the over-activity.

Metabolic diseases, due to absence of a specific enzyme, are mostly diseases of childhood, where they have been successfully treated by replacing the missing enzyme, or by diet, drugs or bone marrow transplants. However some, such as Gaucher disease Type 3, are not detected until adult life. In this disease the body does not store fatty materials correctly due to deficiency of the enzyme glucocerebrosidase. Fatty deposits build up around the liver, spleen, lungs, bones, and brain. Enzyme replacement is effective in slowing down progression of the disease and prolonging active life.

The future of genetics in medicine

It is very likely that medicine of the 21st century will have a much greater genomic basis than in the past. Its success will rely on ever closer collaboration between geneticists, scientists and other specialist clinicians to treat patients based on knowledge of the specific genetic components of their illness and understanding of its effects.

Whilst all the evidence to date suggests that genetics will have a major role to play in medicine for those individuals who already have an illness or a family history, the situation is less clear for healthy people in the population without known risk factors. We don't yet know whether genetic screening of healthy adults to predict and prevent complex diseases will be feasible in the near future. And this is not a deliberation for clinicians alone: ethicists, bioinformaticians, scientists, politicians and members of the public will all be a part of the discourse that will result in such decisions.

Glossary

- Acoustic neuroma** – a non-cancerous tumour on the acoustic nerve in the brain.
- Adoption studies** – if adopted children bear more similarity to their biological parents than their adoptive parents for a health condition, this signifies that there is an inherited element to the condition.
- Autosome** – any chromosome except the sex chromosomes (X and Y).
- Association** – A statistical observation. A and B are associated if they happen together significantly more often (or maybe less often) than predicted by chance. This may be because A causes B, because B causes A, or because something else, X, causes both A and B.
- Amino acids** – organic compounds that are the building blocks of proteins.
- Basal cell carcinoma** – slow-growing, locally invasive epidermal skin tumours.
- Clone** – a DNA sequence, cell or organism that is an exact genetic copy of another.
- Coding DNA** – DNA containing the genetic code for a protein.
- Cognitive behavioural therapy (CBT)** – a talking therapy for patients with mental health conditions that can help them change the way they think, feel and behave.
- Complex condition** – a condition that can have different causes, or combinations of causes so that no single genetic model or mode of inheritance can fit it.
- Constitutional genome** – a person's genomes as inherited from the parents.
- Copy number variants (CNVs)** – where the number of copies of a particular gene(s) or sequence of DNA varies between individuals.
- Cytoplasm** – the substance of a cell between the cell membrane and the nucleus.
- DNA** – deoxyribonucleic acid, the ultimate repository of genetic information.
- Enzyme** – a protein which acts as a catalyst to bring about a specific biochemical reaction in a living organism.
- Expressed gene** – a gene that is 'switched on' to produce the protein it encodes.
- Family studies** – if a disorder tends to run in families, this indicates there could be an inherited susceptibility.
- Gene** – the unit of heredity, comprising a sequence of DNA, which is transferred from a parent to child and determines a single characteristic.
- Genetic code** – the information encoded within the DNA of the genome that is translated into proteins by living cells.
- Genome** – the totality of genes or genetic material of an individual.
- Genotype** – the genetic constitution of an individual (at one or more loci, or over the whole genome).
- Germ cells** – the line of cells that produce the gametes (the sperm and egg cells).
- GWAS** (genome-wide association study) - a large case-control study in which many SNPs scattered across the genome are each tested for association with a condition.
- Heritability** – the proportion of variation in a condition that is genetic.
- Homozygous/homozygote** – of an individual, having identical versions of a particular gene.
- Ion** – an atom or molecule with a positive or negative electrical charge.

Mendelian – of a character, determined by a single gene locus (= Monogenic).

Metabolism – the chemical processes that occur in a living cell or organism.

Microarray – a glass slide or similar, divided into many cells like the pixels of a picture. In each cell thousands of copies of a particular short DNA molecule are anchored. Used to genotype multiple regions of a genome.

Monogenic – of a character, determined by a single gene locus (= mendelian).

Multifactorial – in genetics, describes a characteristic that is determined by several genes and environmental factors.

Neurofibroma – a benign nerve tumour.

Non-coding DNA – DNA that does not code for protein.

Nucleotide – the basic unit of DNA or RNA.

Optic glioma – tumour of the optic nerve, connecting the eye with the brain.

Penetrance – the probability that a particular genetic variant will produce the phenotype associated with it.

Phenotype – the observable properties or behaviour of an organism (as distinct from the **genotype**).

Plaques – build-up of biological matter in a specific location.

Pulmonary embolism – a clot in the blood vessel that carries blood from the heart to the lungs, which is potentially life threatening, as it can cause a blockage.

Reduced penetrance – where a gene does not always manifest itself by conferring an associated phenotype; can cause a dominant condition to appear to ‘skip’ a generation.

RNA – ribonucleic acid – closely related to DNA, deoxyribonucleic acid.

Sarcomas – rare cancers that develop in the muscle, bone, nerves, cartilage, tendons, blood vessels and fatty and fibrous tissues.

Single nucleotide polymorphism (SNP) – a small, normally non-pathogenic DNA sequence variation where two alternative DNA ‘letters’ are both frequent in the population at a particular position in the genome.

Somatic cell – a body cell, as distinct from a **germ-line** cell. The genotype of somatic cells is not transmitted to the next generation.

Somatic mutation – a mutation that takes place in a somatic cell.

Stroke – the sudden death of brain cells due to inadequate blood supply, either due to a blood clot in an artery to the brain, or to bleeding from a vessel in the brain.

Syndrome – a combination of clinical features which occur together and are due to the same underlying defect or factors.

Tissue type – the set of individual-specific protein molecules on a person's cells or tissues that control recognition of cells as self or non-self.

Twin studies – if identical twins (with 100% genes in common) are more similar than non-identical twins (with, on average, only 50% genes in common) for a given health characteristic, this suggests that genes play a role in the development of the characteristic.

Variable expression – the variable phenotypic effect of a given genetic variant.

X chromosome, Y chromosome – the sex chromosomes. Males have one X and one Y, females have two Xs.

Further information

Background resources

<http://learn.genetics.utah.edu/>

<http://www.dnalc.org/>

<http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22:1>

Information on individual conditions

<http://www.nhs.uk/> and search Health Encyclopaedia

<http://www.rcpsych.ac.uk/healthadvice.aspx> for information on mental health conditions

<http://www.cancerresearchuk.org/> for information about cancer

<http://www.bhf.org.uk> for information about heart disease

Some support groups

Autism <http://www.autism.org.uk/>

Cancer <http://www.macmillan.org.uk/>

Coeliac disease <https://www.coeliac.org.uk/coeliac-disease/>

Cystic fibrosis <http://www.cysticfibrosis.org.uk/>

Dementia <http://www.alzheimers.org.uk/>

Diabetes <http://www.diabetes.org.uk/>

Huntington disease <http://hda.org.uk/>

Mental health conditions <http://www.mind.org.uk>

Genome wide association studies

<http://www.ebi.ac.uk/fgpt/gwas/>

Genetics and drug responses

<https://www.pharmgkb.org>

<http://www.geneticseducation.nhs.uk/courses/courses/pharmacogenetics/>

All websites accessed 19 October 2014

Genetics in Medicine - 2. Adult life

This is the second booklet in a series dealing with genetics in medicine. The first booklet focussed on the implications of genetics for the health of infants and children. The second booklet concerns the way that genes play a role in almost every disease of adult life.

