

# Genetics, health and medicine

Advances in genetics are driving a revolution in health care, promising greater understanding of disease, superior tools for prevention and diagnosis, and novel treatments. No one can afford to ignore genetics. In this article, **Philippa Brice** and **Simon Sanderson** outline essential knowledge for pharmacists, and consider the immediate and possible long-term impact of genetics on health

The term “genetics” has a range of possible meanings. In the traditional sense, it refers to the study of biological inheritance — how characteristics are transmitted from one generation to another — including the inheritance of diseases. More broadly, genetics encompasses the cellular and molecular basis of this biological information, in terms of DNA (deoxyribonucleic acid), genes and chromosomes, and their function in normal and disease states. Genetics is sometimes also used to refer to genetic technology, from basic techniques in molecular biology to specialised applications such as genetic engineering or gene therapy. Panel 1 (p54) summarises the key knowledge underpinning all aspects of genetics.

It is important to remember that, in terms of health and disease, inherited biological information does not act in isolation — all individuals are subject to unique environmental as well as genetic influences that affect their susceptibility to disease. No two people ever experience precisely the same environment, even those who live together and share similar lifestyles. This is evident from the fact that even genetically identical twins brought up together are unlikely to have identical health records. Environmental factors include a vast range of variables, from dietary intake and exercise to aspects of our physical and social surroundings and also individual behaviours. Nevertheless, there is great interest in determining precisely how genetics influences health, with a view to estimating and minimising individual disease risks and of developing new drugs and other therapeutic interventions.

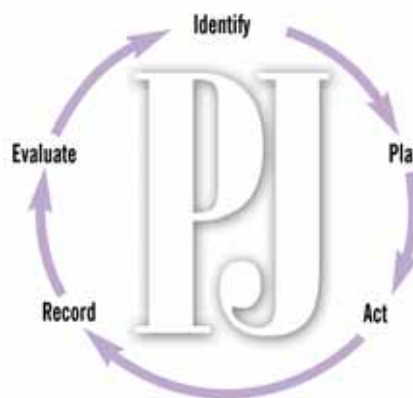
## Genetic variation

Human genetic variation has arisen due to the process of mutation; an alteration in the normal DNA sequence. The scale of a mutation can vary from alteration of a single base in the DNA sequence to large changes involving deletion, movement or duplication of whole sections of chromosomes. Mutations constantly arise during DNA and cellular replication and sometimes also as a result of exposure to environmental agents such as ultraviolet radiation or viruses, but most are recognised and repaired by the cell. Of those that go uncorrected, some may affect genes by disrupting a protein coding or regulatory DNA sequence. The biological impact of this could be catastrophic (rendering a crucial protein non-functional, for example, could cause serious disease), neutral, or even beneficial.

If a mutation occurs in cells that give rise to sperm or egg cells, it can be passed on to the next generation. This is the basis of evo-



Humans have 23 pairs of homologous chromosomes



## Identify knowledge gaps

1. What factors influence health in an individual?
2. What is the difference between genotype and phenotype?
3. Can you give three examples of genetic variants associated with disease risk or drug response?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in “Plan and record”, (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to “keeping abreast of issues affecting pharmacy”.

lution: genetic alterations that increase reproductive fitness (or at least do not decrease it) will tend to persist and spread in a population. Over time, humans have accumulated subtly different normal variants of a DNA sequence, termed polymorphisms. This explains why individuals are not identical and is known as polymorphism. Most genetic variants are single base-pair differences, known as single-nucleotide polymorphisms or SNPs. Any two randomly selected humans will share 99.9 per cent of their genomes; on average, one base in every 1,000 will differ between the two complete DNA sequences. However, these relatively small variations in genetic information can have significant impacts on our appearance, personality and health.

The Human Genome Project, which began in 1990, set out to determine the sequence of all three billion bases in the human genome, and to identify all the genes. A reference sequence was completed in 2003, but work continues to characterise all human genes for their function in health and disease. The project, combined with technical advances, has already facilitated the identification of many mutations associated with rare dis-

**Philippa Brice, PhD**, is science policy and dissemination manager for the Public Health Genetics Unit (part of the Cambridge Genetics Knowledge Park). She previously worked in biomedical intelligence in the pharmaceutical industry. **Simon Sanderson, DPH, FFPHM**, is clinical lecturer in primary care genetics in the Department of Public Health and Primary Care, University of Cambridge and public health physician at the Public Health Genetics Unit

## Panel 1: Genes and gene expression — the basics

Genetic information is stored inside each cell of the body as DNA (deoxyribonucleic acid). DNA has two main features: it is a code for directing the formation of proteins (key components of cell structure and function) and it is reproducible. The special double-helix structure of DNA, two twisted parallel strings of bases (or nucleotides), is essential for both these functions. There are four different bases: adenine (A), cytosine (C), guanine (G) and thymine (T). Bases A and T form pairs, as do bases G and C. A sequence of DNA that contains the information to code for a protein is called a gene.

Every cell in the body contains a complete set of DNA instructions for all the millions of different proteins the body needs; this is the genome. The human genome contains three billion base pairs; current estimates predict that there are 22–25,000 genes in all, representing 1–2 per cent of the total genome. The functions, if any, of most of the rest of the genome are not known. Evidence is emerging that some regions of non-coding DNA are involved in regulating the function of genes but, at present, it is thought that much of the genome is probably non-functional.

DNA is wound up tightly in cells to form chromosomes. Humans have 23 pairs of homologous chromosomes, having inherited one member of each pair from their mother and the other from their father. This means that every individual has two copies of each gene. The sex chromosomes form one of the 23 chromosome pairs; women have two X chromosomes, while men have one X and one Y chromosome.

Different versions of the same gene on homologous chromosomes are known as alleles; some alleles are identical in their action, but others produce different effects (eg, two alleles specifying eye colour might specify different colours). An individual with two copies of the same allele is said to be homozygous for that allele, whereas someone with two different alleles is said to be heterozygous.

The set of alleles that a particular person has is known as their genotype, while the set of observable characteristics that they have is known as their phenotype. The phenotype is the result of the interaction between the genotype and environmental factors.

**Gene expression** To use the information stored in DNA, a cell needs to express it (ie, it must produce the proteins encoded by the genes). Different types of cells (eg, blood, liver or skin cells) contain the same DNA, but have different characteristics because they have expressed different sets of genes. To convert the information carried in the DNA into protein, the cell reads the DNA code. The code instructs the cell how to build the protein, by dictating which of 20 different amino acids to link together and in what order. A set of three bases (known as a codon; for example, AGC or TTA) specifies one amino acid. There are one or more codons representing each amino acid, and some signal the start or end of a protein.

eases. There is also particular interest in the genetic variation between individuals.

A second initiative, the international Haplotype Map Project, is creating a database of sets of common human genetic polymorphisms (haplotypes) by analysing genome sequences from unrelated individuals from a range of different populations. The intention is that this resource will facilitate discovery of genetic variants involved in susceptibility to more common diseases and individual responses to therapeutic agents.

### Genetic diseases

The link between genetics and disease was once confined to traditional “genetic diseases” — familial disorders, such as cystic fibrosis or Huntington’s disease, inherited in a recognisable pattern. Although these classic single-gene diseases are still a major focus of modern clinical genetics, it is now recognised that there are also significant genetic components to all forms of disease, including cancer, cardiovascular disease, asthma, diabetes and depression. Such conditions do not show an obvious pattern of inheritance because they are the product of a range of different genetic and environmental factors.

**Single-gene disorders** There are several thousand inherited diseases known to be associated with mutations in single genes. Individually, most of these diseases are rare, but collectively they are significant, affecting about 1 per cent of newborn babies.

There are three main classes of single-gene disease, based on the pattern of inheritance: dominant, recessive and X-linked. Dominant diseases are conditions where possession of one disease-linked allele is sufficient to confer disease (eg, myotonic dystrophy and polycystic kidney disease), whereas in recessive diseases, two disease-linked alleles are necessary for clinical disease. Individuals with just one copy of a recessive disease allele are asymptomatic carriers of that condition (eg, thalassaemia, sickle-cell anaemia and cystic fibrosis). X-linked diseases, such as haemophilia and Duchenne muscular dystrophy, are caused by disease gene variants present on the X chromosome; these conditions are seen more often in men than women because men have only one X chromosome and hence will always have the disease if they inherit a disease allele, whereas women with a disease allele will only be affected if the disorder is a dominant one.

**Chromosomal disorders** Many chromosomal disorders are caused by errors during the formation of reproductive cells and are, therefore, technically inherited from a parent, although the parent has normal chromosomes. Down’s syndrome is caused by possession of an entire extra copy of chromosome 21, but most chromosomal disorders involve the gain, loss or rearrangement of smaller chromosomal subsections.

**Common complex diseases** In developed nations like the UK, complex diseases, such as diabetes and cardiovascular disease, represent leading causes of ill-health and death. Although susceptibility to many common diseases is known to have a genetic component, the association between gene variants and disease is much less obvious than for diseases that show a discernible pattern of inheritance. This is because multiple different genes may be involved, and the risk of disease is influenced by interactions between these genes and multiple environmental factors, making it difficult to identify genuine links between a given genetic variant and susceptibility to a disease.

There are, in fact, thousands of putative gene-disease associations, but only a small proportion of these have been shown to be reliable. Without well-designed large-scale studies to produce statistically significant results, reproduction of these results in independent trials and, ideally, some evidence of a relevant function for the gene concerned, there is often insufficient evidence to conclude that a polymorphism is definitely associated with disease, and so reports must be viewed with caution. Examples of validated gene associations include ApoE4 (one of three common variants of the apolipoprotein

**It is hoped that as the number of valid gene-disease associations increases, eventually it will be possible to target disease prevention and health promotion**



E gene), which has been linked with a significantly higher risk of developing late-onset Alzheimer's disease. Another example is the Factor V Leiden mutation, a blood coagulation gene variant linked with an increased risk of deep vein thrombosis.

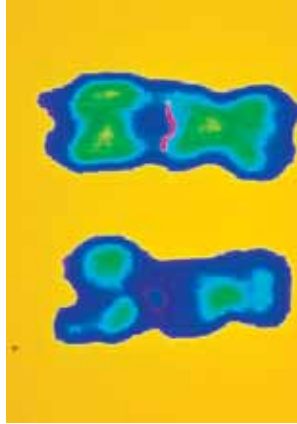
It is hoped that, as the number of valid gene-disease associations increases, eventually it will be possible to target disease prevention and health promotion efforts to individuals at high risk because of their genetic make-up. The UK Government Genetics White Paper of 2003 visualised a future in which individuals could be assessed for a whole range of polymorphisms associated with disease susceptibility, and a personalised health plan worked out taking their genetic profile into account. For example, smoking is known to increase the risk of coronary heart disease for all individuals, but there is evidence that those with the ApoE4 gene variant may be at even greater risk. A physician will always advise people to stop smoking to reduce the risk of heart disease, but this recommendation might carry greater weight for individuals who learn that they are also at an increased genetic risk.

**Single gene subsets of common diseases**

Although common diseases generally result from the combined effects of multiple genes interacting with environmental factors, there are exceptions. Some families show an abnormally high prevalence of disease, often affecting individuals at an earlier age than usual, and this suggests the existence of a single mutation that confers a high risk of disease. Identification of such a mutation allows fairly reliable prediction of the disease risk in individuals who carry that genetic variant. Well characterised examples include familial hypercholesterolaemia, and familial breast and ovarian cancer (BRCA1 and BRCA2 genes). Single gene subsets of common diseases typically represent less than 5 per cent of the total disease burden.

**Cancer** Cancer arises from the accumulation of several harmful mutations that disrupt the normal control of cell growth. Some mutations are particularly common in cancerous cells, and these have proved valuable in research into the biological processes underlying cancer, and in the design of therapeutics targeting cancer cells.

Recently, there has been growth in the area of targeted tumour therapeutics. Genetic analysis of tumour DNA can identify the presence or absence of specific genetic characteristics that, in turn, dictate the likely efficacy of a given treatment. For example, trastuzumab (Herceptin) is an effective immunotherapy agent for advanced breast tumours that show raised levels of expression from the HER2/neu gene. Testing for HER2 status (ie, looking for increased copies of the gene or increased levels of the HER2 protein in tumour cells) is, therefore, essential to determine whether or not trastuzumab should be used for a patient.



Custom Medical Stock/Science Photo Library

The BRCA1 gene (red) has been linked with breast cancer

**Definitions**

**Gene expression** The process by which the information in the DNA sequence of a gene is turned into protein.

**Genome** All the genetic material of an organism.

**Genotype** The specific genetic constitution of an individual.

**Heterozygous** Carrying two different alleles of a particular gene.

**Homozygous** Carrying two identical copies of a particular gene.

**Phenotype** The observable traits of an organism, resulting from a combination of genetic and environmental factors.

**X-linked inheritance** Males have only one allele of (almost) every gene on the X chromosome, so a recessive mutation in one of those genes can cause disease. Inheritance of the disease is said to be X-linked.

**Infectious disease** The impact of infectious disease is much less significant in developed countries compared with the global burden, but human genetics has important applications in this area. The study of microbial genetics is allowing researchers to identify key genes associated with microbial virulence and drug resistance, which allows the development of novel antibiotics and other antimicrobial interventions.

However, there is also interest in the human genes involved in resistance and susceptibility to infection. Perhaps the best-known example is of the Δ32 mutation in CCR5 gene, which encodes a blood cell surface receptor used by HIV to facilitate cellular entry. The CCR5 Δ32 variant, which is common among Caucasian populations, confers a significant degree of resistance to HIV infection.

**Genetics of drug response**

The study of genetic variations that affect responses to drugs is already of immense importance to the pharmaceutical industry — it is, for example, being used in the drug development process to help select promising candidate compounds. However, direct applications to patient care are currently limited.

The concept of “personalised medicine” is exciting. It could mean that an individual would be tested for genetic variants associated with drug response in order to select the optimal therapeutic agent (providing maximum efficacy with minimum risk of side effects). It is, however, going to be some years before this will impact on primary care. This is because (as with complex diseases) drug responses are influenced by multiple genetic and environmental factors, making it hard to identify key genetic polymorphisms. Nevertheless, pharmacogenetics is a broad ranging and fast-moving field.

**Genetic testing**

Genetic testing is a broad term used to cover tests to reveal the presence of abnormal genetic variants, that may influence the occurrence of disease or specific clinical outcomes (including response to drugs or other therapeutic agents). This could be by examination of whole chromosomes or selected DNA sequences, but could also involve tests for biochemical markers. Genetic tests are already widely used in prenatal and newborn screening programmes. They are also used to reveal the presence of disease associated mutations in children and adults for diagnostic or predictive purposes, and to identify healthy individuals who carry a deleterious gene that could be passed on to their offspring.

In the future, applications of genetic testing are likely to widen. In particular, as it becomes possible to test quickly and cheaply for genetic variants associated with susceptibility to common disease and individual responses to drug treatments, the context in which tests are administered will grow more varied, extending from the hospital setting to primary care centres and pharmacies.

## Future applications of genetics

Genetic technology is being used for a wide range of novel therapeutics and diagnostics that are beyond the scope of this article; it is sufficient at this stage to be aware that stem cell medicine (see *PJ*, 3 December 2005, pp695–8), gene therapy and DNA microarray diagnostics (to name but a few) are already beginning to move into clinical practice.

### Resources

- Our inheritance, our future — realising the potential of genetics in the NHS. 2003 UK Government White Paper. Available at: [www.dh.gov.uk](http://www.dh.gov.uk) (accessed 16 May 2006).
- Medical genetics information (including gene testing, genetic counselling and pharmacogenomics) from The US Department of Energy human genome website is available at [www.ornl.gov](http://www.ornl.gov) (accessed 16 May 2006). The site also provides links to a range of additional articles and other resources.
- The US Genetic Science Learning Center website (<http://gslc.genetics.utah.edu>) provides a simple but entertaining resource for further information on basic genetics and an introduction to topics such as stem cells, cloning, pharmacogenomics and gene therapy.
- An animated tutorial on DNA, genes and heredity ("DNA from the beginning"), with multimedia links and background

## Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Treat media reports of links between genes and disease with caution; be aware they will not necessarily be proven in the long term.
2. Read the Genetics White Paper for an insight into possible future trends in genetic medicine, and consider how they might impact on pharmaceutical practice.
3. Revise your knowledge of human genetics and medicine by working through the online exhibit, "Human Genetics and Medical Research" at <http://history.nih.gov/exhibits/genetics>.

## Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

A further CPD article looking at pharmacogenetics will be published in the 22 July issue of *The Journal*.

information is available at: [www.dnafb.org/dnafb](http://www.dnafb.org/dnafb) (accessed 16 May 2006).

- The Public Health Genetics Unit website ([www.phgu.org.uk](http://www.phgu.org.uk)) provides constantly updated news and information about advances in genetics and their impact on public health and the prevention of disease.

# Pharmacy training specialist: putting learning into practice

**Helen Middleton is a continuing professional development manager and training specialist at London Pharmacy Education and Training (LPE&T). She is responsible for developing and delivering a strategy to support CPD implementation in pharmacy departments in NHS organisations across London, Hertfordshire and Essex, and developing and delivering study days on the LPE&T annual programme. Her hobbies include travelling, reading and cooking.**

**Reflection** When I joined LPE&T almost three years ago, I was confident as a trainer because I had gained experience of training and facilitating staff development throughout my career, and had attended a number of short courses for trainers as part of my CPD. However, I wanted to learn more educational theory to undertake a training specialist role.

**Planning and action** I read training books in the LPE&T library and used an online encyclopaedia of educational resources ([www.infed.org](http://www.infed.org)). I found out about different learning theories and more creative ways of training. This increased my knowledge, but the challenge was putting my learning into practice so I decided to try using a new theory or technique at each training session I ran.

**Evaluation** I realised that I had identified an enormous learning need and this made my overall CPD record difficult to evaluate (see below). Nevertheless, I have definitely improved my knowledge and am more confident as a result. It was easier to evaluate the records I had written after each training session and looking back at these after sometime enabled me to see changes in the way I handle situations. I am now a more flexible trainer and have moved from a trainer-focused to learner-focused approach. I identified more specific learning needs, for example, learning more about group dynamics as a result of training some challenging groups and this formed part of further CPD.



**Recording** I recorded my original learning need as "I want to have more theoretical knowledge of educational models" using the "Plan and record" template for learning that starts at reflection. My learning from the training sessions where I tried different training methods was recorded using the "Plan and record" template for learning that starts at action.

I started recording my CPD in 1999 using a portfolio provided by LPE&T but have used "Plan and record" since 2002. I find the online version easy to use and I write a CPD record at least once a month. It was difficult, initially, to make the transition from a less structured way of recording CPD but I have realised that "Plan and record" can be used flexibly, and that I can choose the level of detail I include.

Supporting individuals with their CPD is one of my key roles. I think some people struggle with CPD because they either choose something so huge that they find it difficult to achieve or they choose so many small things that they feel overwhelmed when trying to record them. Thinking of a tree can help. If the learning need is the size of a tree trunk you need to break it down into branches and focus on the branch-sized learning. In addition, if the learning need is the size of a twig is it really important enough to record?