

## An introduction to genetics and genetic tests

### SUMMARY

The human genome project has determined the sequence of the individual nucleotides that make up our DNA (deoxyribonucleic acid). This will enable our genes to be mapped and increase the understanding of how genetic make-up can influence the development of disease and response to treatment. These advances in genetics knowledge have the potential to impact profoundly on health care, including that delivered in primary care.

In 2003, the Government issued a white paper *Our Inheritance, Our Future*.<sup>1</sup> This outlined the need for health care professionals to be educated and trained in genetics. This *Bulletin* provides a basic introduction to genetics, focussing on genetic and pharmacogenetic testing.



### How do genes influence disease?

A person's genetic make-up is largely determined by the genes received from his or her parents, each parent contributing one of their two copies of their own genes to their offspring.<sup>2</sup> The normal human genome is carried on 23 pairs of chromosomes, one pair of which determines the sex of the individual (XX in females and XY in males). The DNA within all these chromosomes consists of around three billion nucleotides and 30,000 or more genes. These genes determine the production of proteins and related substances in the body, which are needed for tissue and cell structure, metabolism and other important functions.<sup>2,3,4</sup>

The genetic make-up of all humans is 99.9% the same.<sup>1</sup> Slight variations between individuals in the order of their nucleotides lead to gene variants (termed *alleles*),<sup>2</sup> and differences in the way these genes control the production of proteins and related substances. This is what leads to the normal variations in individual characteristics, such as blood group.<sup>1</sup> However, the presence or absence of some alleles of a gene in an individual may influence the production of some proteins or the way genes interact with each other, and this may cause or predispose some individuals to disease.

### Classification of genetic disorders

Each sperm or ovum from an individual contains one of their two copies of their genes. By chance, during conception, each parent may contribute the same allele of a particular gene to his or her child, meaning the child would be *homozygous* for that particular gene. Alternatively, each parent may contribute a different allele of a particular gene, in which case the child would be described as *heterozygous* for that gene.<sup>2</sup>

The pattern of inheritance of specific genes associated with specific conditions or diseases can determine whether and how an individual is affected by those conditions or diseases. Knowledge of the pattern of inheritance can help quantify the risk of an individual being affected by the condition or disease. However, there are some genetic disorders that are not inherited from a parent. These are caused by mutations that occur spontaneously during sperm or ovum production or around the time of conception.<sup>2</sup>

It should also be noted that the presence of a specific gene allele in itself may not always lead to an associated disorder. The presence of some genes is highly predictive of development of a disease (e.g. the gene associated with Huntington's disease).<sup>5</sup> However, in other cases the influence of other genes and environmental factors may significantly influence development of the disease.<sup>5,6</sup> *Gene penetrance* describes the extent to which the presence of a gene leads to expression of the disorder associated with that gene, and this can vary between individuals.<sup>7</sup>

In general, genetic disorders may occur due to abnormalities of single genes, the influence of multiple genes or due to defects at the chromosome level.<sup>4</sup>

### Monogenic disorders

Single gene (monogenic) disorders may be classified in three ways, which describe the pattern of inheritance of these disorders (see **Panel 1** on page 6).

### Polygenic and chromosome disorders

The inheritance patterns and development of disorders that are under the influence of multiple genes (polygenic disorders) are more

*Advances in genetics knowledge have the potential to impact profoundly on health care*

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**Panel 1: Classification of monogenic disorders<sup>2,4</sup>**

With **autosomal dominant** disorders, only one copy of a 'faulty' gene for a specific disease needs to be present in an individual's genetic make-up for the disease to manifest itself clinically (i.e. the individual could be heterozygous or homozygous for that gene, but still develops the disorder). Examples include Huntington's disease and neurofibromatosis.

In **autosomal recessive** disorders, two copies of the 'faulty' gene (one from each parent) are required in an individual's genetic make-up for the disorder to be manifest clinically (i.e. the individual has to be homozygous for that gene for the disorder to develop). Where an individual is heterozygous, the disorder will not be manifest clinically, but the individual will still be a carrier of the faulty gene and can potentially pass this on to future generations. Examples include cystic fibrosis and sickle-cell anaemia.

**X-linked** (sex-linked) disorders involve a recessive 'faulty' gene that is located on the X chromosome. In females, both X chromosomes would have to carry the faulty gene for the disorder to be manifest. However, as males normally only have one X chromosome, the disorder would be manifest in all male carriers of this gene. Female carriers of X-linked faulty genes may pass this gene on to any of their offspring, but male carriers can only pass the gene on to their female offspring. Examples include haemophilia A and Duchenne muscular dystrophy.

**Genetic testing can be used to provide information to help predict future risk of disease**

complicated due to the large number of possible genetic combinations, uncertainties about how different genes interact and the influence of environmental factors. Examples include diabetes, heart disease and some cancers.<sup>1,4,6</sup> Chromosomal abnormalities may involve the addition or loss of an entire chromosome (e.g. Down's syndrome, Turner's syndrome), a section of a chromosome, or the re-arrangement of chromosomes, which leads to disruption of chromosomal material.<sup>2,4</sup>

**What is genetic testing?**

Genetic testing involves the identification of particular genetic characteristics in individuals that are associated with particular diseases, conditions or traits. Depending on the disorder, testing may be carried out on DNA, RNA (ribonucleic acid), chromosomes, proteins or certain metabolites that have been obtained from samples of body tissue (e.g. blood, buccal swabs, amniotic fluid).<sup>4,7,8</sup> Testing may be direct, in that genes or genetic markers (identifiable pieces of DNA) can be detected. In addition, microscopic examination of chromosomes can reveal the presence or absence of chromosomal disorders. Indirect tests, where

the test detects some aspect of the function of the gene, rather than the gene itself (e.g. presence or level of a particular protein), may also be used to indicate genetic status.<sup>4</sup>

Current genetic testing facilities are concerned with single gene or chromosomal disorders, although research is ongoing in polygenic disorders.<sup>1</sup> **Panel 2** highlights how genetic testing is currently employed.

Unlike most conventional medical diagnostic tests, genetic testing can be used to provide information to help predict future risk of disease. Early identification of individuals at risk may enable early informed decisions to be made that otherwise would not be possible, and targeted screening and preventive interventions to be initiated before disease develops. Genetic testing of one individual can also have direct implications for family members who may share the same genes.<sup>9</sup> Therefore, there are a number of clinical and ethical issues associated with genetic testing and these are discussed below.

**What is pharmacogenetics?**

Pharmacogenetics is the study of genetic variability that leads to differences in drug response between individuals.<sup>10</sup> The proteins and enzymes involved in drug action, metabolism and transport are under the influence of genes, and people possessing different alleles of those genes can have different responses to a given drug. Genetic testing to identify which of these alleles an individual possesses (*genotyping*) may potentially enable their response to a particular drug to be predicted.

The clinical consequences of individual variation in drug response can be great.<sup>10</sup> Failure to respond to a drug may lead to delayed effective treatment, prolonged patient morbidity and possibly inappropriate polypharmacy. Adverse drug reactions and drug-drug interactions may cause significant morbidity and mortality. The ability to better tailor drug treatments to individual patients is, therefore, desirable.

Currently, there are only a few examples of the use of pharmacogenetic testing to guide drug use in clinical practice and these are confined to specialist areas. The example in **Panel 3** on page 7 provides an indication of genetic status, but does not involve direct testing of genetic material.

Studies of the application of pharmacogenetic testing to many drug treatments that are commonly used in primary and secondary care are underway. Examples include: statin therapy, which inhibits the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase;<sup>12</sup> nicotine replacement therapy, which exerts

**Panel 2: Current applications of genetic testing<sup>1</sup>**

- To confirm a diagnosis where symptoms already exist
- To indicate whether an individual with a family history of a disease (e.g. Huntington's disease, certain kinds of breast cancer) carries the gene that is responsible for the disease
- To check whether someone is a carrier of a recessive gene that is associated with a disorder (e.g. cystic fibrosis)
- To screen before birth for genetic disorders (e.g. Down's syndrome)
- To screen new born babies for genetic disease (e.g. phenylketonuria)

its effects via dopamine receptors and pathways;<sup>13</sup> and warfarin, which is primarily metabolised by the cytochrome P450 2C9 enzyme.<sup>14</sup> Individual variation in these enzymes and receptors has been shown to lead to variation in drug response, and direct testing of DNA material has been used for genotyping individuals in these cases. However, there are currently a number of limitations to the wide use of pharmacogenetic testing, as discussed below.

### Genetics in primary care

Primary care health professionals are already aware of, and familiar with, some genetics-based services, such as antenatal screening programmes for Down's syndrome. However, genetic and pharmacogenetic testing is increasingly likely to impact across all sectors of health care, and primary care will have an increasing role. It is therefore necessary for all primary care health professionals to have a basic working knowledge of genetics, its influence on disease and the issues involved in testing.

### Challenges and limitations of testing

Availability, speed, reliability and cost currently limit the wider use of genetic and pharmacogenetic testing in clinical practice.<sup>1,7,15</sup> Technological aspects of these limitations will lessen over time but, like any other test, genetic and pharmacogenetic tests will not be 100% sensitive and specific; there will be instances of false positive and false negative results.<sup>1,7,15</sup>

The ability of a test to predict a particular clinical outcome is influenced by these test characteristics and by the penetrance of the gene in question. It is for this reason that using genetic tests to screen large numbers of people (the majority of whom will be at low risk of disease) to identify the few who are actually at risk may not always be appropriate.<sup>1,7</sup>

Other inherent limitations of testing will remain and need to be appreciated. For example, the cytochrome P450 enzyme system is involved in the metabolism and elimination of many widely-used drugs, and is a source of considerable variation between individuals in response to drug therapy. For many drugs, patients may be categorised as poor, intermediate, extensive or ultrarapid metabolisers, based on the activity of their cytochrome P450 enzymes.<sup>16</sup> However, in addition to the genetic status of an individual, environmental factors, such as smoking, diet, and concomitant use of drugs, can significantly influence the activity of these enzymes.<sup>16</sup>

Such issues highlight the fact that testing to determine the genetic status of an individual may not be sufficient to perfectly predict response to drug therapy or the risk of developing disease in every case. If used

### Panel 3: Example of a "pharmacogenetic" test to guide drug use

Trastuzumab<sup>™</sup> is licensed for the treatment of metastatic breast cancer in patients whose tumours overexpress human epidermal growth factor receptor 2 (HER2). HER2 overexpression is observed in 20–30% of primary breast cancers and is associated with shortened disease-free survival. Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against HER2 and only those people whose tumours express HER2 to a certain level are eligible for therapy with the drug. Testing for HER2 overexpression is, therefore, used to target the drug to eligible patients.<sup>11</sup>

appropriately, genetic and pharmacogenetic testing will be able to improve the accuracy of disease risk assessment and make the response to drug therapy more predictable than before.<sup>8,15</sup> However, there will always be some cases where individuals will respond in a particular way to a drug or develop disease in a way that a test predicts otherwise.<sup>15,17</sup> Test results represent probabilities, rather than definitive information, and this will need to be understood and considered when interpreting test results.<sup>15</sup>

### Genetic counselling

Given the limitations outlined above, genetic testing can provide information about future risk of disease. This can have potential benefits and disadvantages for patients. In some cases, genetic test results can be a source of relief, but in other cases they can lead to anxiety about the onset of disease. Testing can lead to decisions being made that otherwise would not be possible and this could include highly emotive decisions, such as whether or not to plan or continue a pregnancy, or consider a particular preventive course of action.<sup>4,8</sup> Testing of one individual can also have direct implications for family members who may share the same genes,<sup>9</sup> so the impact of testing may often extend further than the individual patient. To help understand and deal with such issues, an essential component of the genetic testing process is genetic counselling.<sup>8</sup>

Genetic counselling can involve many activities,<sup>18</sup> including ensuring that adequate family histories are obtained and that appropriate risk assessment is performed.<sup>8</sup> The number of registered genetic nurses and counsellors is increasing,<sup>1</sup> and there are many regional genetics centres in the UK to which patients can be referred (see the websites in the **Resources Panel** on page 4). However, to avoid these services becoming overwhelmed, it will be increasingly important to be able to identify those individuals and families who require referral to specialist services and those who can be appropriately managed in primary care.<sup>19</sup>

A framework for GPs with special interest in genetics has recently been produced,<sup>19</sup> and pilot schemes for genetics nurses and counsellors working in general practice are also underway,<sup>1</sup>

*There will always be some cases where individuals will respond in a particular way to a drug or develop disease in a way that a test predicts otherwise*

*Genetic counselling is an essential part of the genetic testing process*

**Panel 4: Possible issues in gaining consent for genetic testing<sup>21</sup>**

- The use and sharing of information for the benefit of family members
- Sharing of information with other health professionals
- The nature of the test to be undertaken
- The possibility that testing may reveal unexpected results (e.g. about parentage)
- The storage of samples

so these colleagues may increasingly be able to offer support and guidance.

**Ethics, consent and confidentiality**

Genetic testing can in some cases provide information over and above that for which the test was performed. For this reason, some people feel that genetic information is fundamentally different from other forms of medical data. The giving of consent and the sharing of test results with family members and other third parties (e.g. insurance companies) raises ethical issues that require consideration.<sup>20,21</sup>

Draft guidance from the Joint Committee on Medical Genetics, a non-governmental advisory body, identifies possible issues to be discussed in gaining consent for genetic testing (see **Panel 4**).<sup>21</sup> There may also be occasions where gaining written consent is appropriate. These issues may not need to be considered in every case and the final version of the guidance should be consulted when available. It should be noted that, with the exception of test results for Huntington's disease in life insurance policies of over £500,000, the UK has a moratorium on the use of genetic information for the setting of insurance premiums until 2006.<sup>20</sup>

**Conclusion**

Genetics will gradually play an increasing role in all aspects of health care.<sup>22</sup> Genetic and

pharmacogenetic testing has the potential to improve patient care via improved diagnosis, prevention and treatment of disease. However, the increased availability of testing will not in itself lead to improved patient care. Testing will need to be employed appropriately, results will need to be interpreted correctly, and patients will need to be counselled so that informed decisions can be reached. Primary care health professionals will, therefore, increasingly need a working knowledge of the basic concepts behind genetics and its applications, as well as the associated counselling and ethical issues involved.

This *Bulletin* serves only as a basic introduction to genetics and genetic testing. Consideration of the cost-effectiveness of testing and pharmacogenetics-based drug use is beyond its scope. The **Resources Panel** is a starting point for further information.

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**Resources Panel**

**Documents and guides:**

- *Our inheritance, our future*. Available from [www.dh.gov.uk](http://www.dh.gov.uk)
- *Consent and confidentiality in genetic practice — consultation document*. Available from [www.bshg.org.uk](http://www.bshg.org.uk)
- *Genetics services: a guide for primary care trusts*. Available from [www.dh.gov.uk](http://www.dh.gov.uk)
- *General Practitioner with special clinical interest in genetics: framework document*. Available from [www.dh.gov.uk](http://www.dh.gov.uk)

**Websites for health professionals and patients:**

- British Society for Human Genetics — [www.bshg.org.uk](http://www.bshg.org.uk)
- Genetic Interest Group — [www.gig.org.uk](http://www.gig.org.uk)
- Public Health Genetics Unit — [www.phgu.org.uk](http://www.phgu.org.uk)
- Contact a Family — [www.cafamily.org.uk](http://www.cafamily.org.uk)
- GeneReviews — [www.geneclinics.org](http://www.geneclinics.org)
- Oxford Primary Care Genetics Group — [www.dphpc.ox.ac.uk/opcgg](http://www.dphpc.ox.ac.uk/opcgg)

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