

The Application of Human Genetic Research

- *The Human Genome Project*
- *Diagnostic and Therapeutic Applications*
- *Genetic Testing and Screening*
- *Human Gene Therapy*

Over the past 20 years, developments in biotechnology have greatly facilitated the deciphering of the genetic instructions that control many of the body's processes. Ultimately, it may be possible to determine the complete genetic make-up of a person. Such information is fundamental to understanding how our bodies work and is likely to be of great value to medicine, both in diagnosis and in treatment. However, some aspects of the utilisation of this information raise important social and ethical issues that are receiving increasing attention.

The aim of this briefing paper is to review the scientific developments that have led to current and planned human genetic research together with the important related ethical, social, legal and economic issues. In this context there is the common need for information and understanding about these topics and therefore the overall aim of this briefing paper is to provide balanced information to advance the debate about them.

The paper results from the combined contributions of scientific, industrial, medical, governmental, financial, and genetic support group representatives. It is intended for information and does not represent the views or policy of the European Federation of Biotechnology or any other body.

Scope

Genes, passed from parents to offspring, influence hereditary characteristics such as hair and eye colour. Each gene is comprised of a specific sequence of DNA units (bases) which code for the production of the many proteins essential for life - including those linked with illness and disease. The genes are normally packaged into the 23 chromosome pairs present in each human body cell. In egg and sperm

(germ) cells, the chromosomes are single. When an egg is fertilised by a sperm, the single sets of chromosomes from each parent combine to form the chromosome pairs in the nucleus of our cells. In this way, each parent contributes to the whole of the genetic make-up, or genome, of the next generation. Every human carries essentially the same set of genes, but in every person's DNA there are mutations; it is these that make us individual. Sometimes, if these differences occur in a particularly important stretch of DNA, there may be a disruption of normal biological activity. This is what we speak of variously as a genetic deficiency, disorder, disability or disease.

Diagnosis of genetic disorders is achieved through two methods, testing and screening. Genetic testing aims to detect whether a person or family has, is at risk of, or is a carrier of a genetic disorder (carriers may not be affected by the disorder but may transmit it to their children). Genetic screening involves the testing of whole populations for particular conditions. Knowledge about genetic disposition towards a disorder provides only a prediction of whether a person is at risk of developing a certain condition. Detection of genetic traits other than those responsible for medical disorders, also has applications: for example, forensic genetic fingerprinting and helping to determine paternity and family genealogy.

Some 4,000 specific genetic disorders appear to result directly from the action of single mutant genes. Although many are rare, others are quite common: sickle cell anaemia (Central Africa) and thalassaemia (circum Mediterranean) affect many hundreds of thousands of people, and cystic fibrosis affects one in 2,000 births in Northern Europe.

Single gene mutations are not the only cause of genetic disorders. Disorders

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INFORMATION

For further information concerning Briefing Papers and other publications and activities of the European Federation of Biotechnology, Task Group on Public Perceptions of Biotechnology, contact:

Prof Dr Richard Braun (chairman)
Bio-Link
Postfach 208
CH-3000 Bern 11
Tel & fax: +41 31 832000
Email: rdbraun@bluewin.ch

Dr David J Bennett (secretary)
Secretariat, EFB TGPPB
Oude Delft 60
NL-2611 CD Delft
Tel: +31 15 2127800
Fax: +31 15 2127111
Email: david.bennett@efbpublic.org
<http://efbweb.org/ppb>

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Briefing paper

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Table 1: Areas of Concern

- Confidentiality of testing and screening results
- Scope of genetic testing and screening
- Discrimination and stigmatisation
- Commercial exploitation of human genome data
- Eugenic pressures
- Effects of germline gene therapy on later generations
- Equity of benefits of human genetic research

caused by defects in several genes, together with those involving parts or whole chromosomes, also occur. The environment may also have major effect in these disorders. For example, common diseases such as many cancers, heart disease, stroke, diabetes and some psychiatric disorders may involve the interaction of several genes, combined with many different environmental factors.

The results from human genome research are being used to develop treatments for genetic disorders; some actually correcting the adverse mutations of the sufferer's DNA. New gene-based or gene-directed methods, including gene therapy, are currently being developed for treating conditions such as cystic fibrosis and adenosine deaminase (ADA) deficiency. Such applications, while still in their early stages, are likely to grow.

The early developments in human genome research are promising, but at the same time they have raised questions concerning safety, ethical, social, legal and economic issues, extending to the debate about patents concerning human DNA. Table 1 lists the main areas of ethical concern; which will be discussed below.

The Human Genome Project

The Human Genome Project (HGP) is an international research programme, established with three main aims: to provide a genetic map for the relative positions of the genes; to provide a physical map for the actual gene positions; and to determine the sequence of bases in the DNA. In 1989 an international body, the Human Genome Organisation (HUGO), was formally established, to coordinate research and collaboration as the volume of data generated by participating laboratories grew rapidly and more countries started their own programmes of research. Data from the HGP are stored in a number of databases: for example, gene mapping data in the Genome Database, and DNA sequence data in the US Genbank and the European Molecular Biology Laboratory.

In 1990, it was estimated that sequencing the human genome would cost 6,700-13,300 million ECU. This required individual countries to consider annual budgets of a similar order to those in "big physics" projects such as astronomy and particle physics. Currently, the goal is to have the total human genome sequenced by

the year 2005. A low resolution genetic map now exists for the whole of the human genome, but only less than 1% of the physical map has been completed. Besides improving the resolution of the genetic maps, the project is currently focusing on improving sequencing methods, as outlined in the US' new HGP 5 year plan which devotes half of the budget to this purpose. Priority is also being given to sequence only the genes in the protein coding sections of the genome. This will help the understanding of gene functions and genetic defects, as a starting point for the development of therapeutic treatments.

Issues: Major issues surround the HGP about how the results of research will be applied. In general, these arise from fears that conflicts of interest can occur between the pursuit of knowledge and protection of patients' welfare. The welfare of patients is, however, only possible through the pursuit of knowledge. Beneath is the questioning of the general assumption that scientific progress is inevitably desirable. These issues are discussed in the following parts of this briefing paper.

The expense of the project is another concern: is it cost-effective to sequence the whole genome when a substantial proportion of it is at present believed to have no direct coding function? Such an ambitious project also diverts resources from other important areas of research.

Ethical, legal and social aspects: The social and ethical aspects of the HGP have been the subject of continuing discussion in many quarters⁽¹⁾. US and EU genome programmes include specific projects to explore these issues. The US HGP has devoted 3% of its funding to the study of ethical, legal and social issues (ELSI) arising from data produced by modern genetic research and in relation to diagnosis and treatment of specific genetic disorders. The US National Institutes of Health (NIH)⁽²⁾ and Department of Energy⁽³⁾ have ELSI components strongly connected with genome research. They place special emphasis on promoting public education and defining privacy and confidentiality issues in relation to employment and insurance. Under the Third Framework Programme the European Commission initiated studies on the ethical, social and legal aspects (ESLA) of the HGP in the different Member States⁽⁴⁾. Study groups determined where the problems were likely to lie and what precautions should be taken. Under the Fourth Framework Programme, similar projects will be carried out⁽⁵⁾. At the national level, several countries have established committees whose activities include encouraging public debate, improving public education, developing

advice or guidelines, and linking with their respective parliaments.

Diagnostic and Therapeutic Applications

Increasing numbers of companies (currently mostly in the US) are making use of the information provided by genome research. Commercial developments include: the production of diagnostics; treatments for diseases with multiple genetic and environmental components, such as osteoporosis and rheumatoid arthritis; cloning and sequencing genes, for example, for breast cancer; and the provision of complete genetic counselling and screening services.

Issues: While therapeutic applications have the potential for treating and curing disorders, it is generally still too early to do this. Once developed, however, they will have the potential advantage of being able to treat and cure disorders, rather than solely treating the symptoms. Concerns about commercial applications arise from potentials for conflict between commercial and individual patient interests. This is particularly apparent where companies are being established to provide both treatment and counselling, contravening the principle that counselling should be neutral and independent.

Genetic Testing and Screening

Genetic testing is usually carried out in a context where there is already reason to suppose that a person may have, carry, or be at risk of a disorder. Pre-natal diagnosis for a genetic condition has long been available in the case of Down's syndrome. The increasing range of genetic tests for an increasing range of disorders made possible by human genome research offers parents much greater informed choice of whether or not to continue with a pregnancy. If the pregnancy is continued, it allows the parents to be prepared for a baby with specific needs. Pre-natal diagnosis may have minimal effect on the overall incidence of genetic disorders, but may have a major effect on individuals and their families with a history of a genetic disorder. Some, however, have expressed concern that this may lead to abortion on the basis of gender, minor disabilities, or serious diseases that may or may not develop. Abortion for sex selection already occurs in some cultures, although for example it is forbidden by law in certain Indian states and by new legislation being implemented in China.

Screening for known genetic traits or conditions (such as colour blindness) has been used for many years. The new technologies have made it possible to screen for a wider range of disorders in larger numbers of people more rapidly and

at lower cost. The current speed of human genome research may make it possible to provide people with a genetic “print-out” sometime in the future. It should be recalled, however, that a genetic disposition towards a disorder only forecasts whether that disorder will develop. While it may be possible to identify high-risk individuals and concentrate preventive measures on them, perhaps the main value of this work in the immediate future will be to provide us with a better understanding of the mechanisms of these disorders.

Issues: Benefits of testing and screening are foreseen in the public health area - for instance, the extent of susceptibility to certain disorders could be measured, assisting health-care planning. Concern, however, has been raised about the possible (mis)use of such genetic profiles with calls for restricting the accessibility of this information and ensuring confidentiality. While this issue may not be fundamentally new (eg testing train drivers for colour blindness), it has gained increased significance in the light of the wider range of disorders that can be screened for, and the new predictions that will be possible. Social stigmatisation and discrimination may occur as a result of making personal genetic information available. Insurance and mortgage institutions may wish to minimise their risks by using this information selectively leading to further discrimination. These considerations have also reawakened fears of eugenics, with parents or society being able to specify and alter physical or psychological characteristics to conform to “ideals.”

Many of the issues associated with genetic screening arise because results have important implications not only for the individual but also for their relatives. Genetic tests will increasingly provide early diagnosis before the onset of symptoms of serious, incurable conditions such as Huntington’s disease. In this case an individual may have over 40 years of normal life before onset of this progressively debilitating and ultimately fatal disease. Some persons at risk may wish to exert their undoubted right not to know whether they will succumb to the disease. This may interfere with the wish to know of a partner or relative. It is therefore often argued that genetic testing and screening should be limited to disorders where treatment is available. Others support the availability of such tests on the basis of personal choice, arguing that some individuals will wish to plan their life in the light of a certain diagnosis: for example, they may choose not to have children in order to prevent passing a genetic disorder on to the next generation. For genetic disorders that can be treated, large moral issues are raised: if an individual chooses not to act on information, should he or she,

for example, be denied the right to medical care or social protection?

Ethical, legal and social aspects: These issues are the subject of consideration in many countries, but they rest on questions of human values which are not easily settled by scientific or other expert deliberations.

General international opinion about programmes of genetic testing and screening is represented by the recommendations of the UK Nuffield Council on Bioethics⁽⁶⁾. These include the requirement for informed consent and that all written information should be supplemented with counselling. Individuals, and parents of unborn or young children, should be fully informed of the results of genetic screening and their implications for the family. Genetic screening of employees should only be contemplated when either there is a clear connection between the working environment and the development of the condition screened for, or where the condition seriously endangers the health of the employee or third parties. Insurance companies should not require genetic tests as a prerequisite of insurance. Central coordinating bodies should be established to review genetic screening and testing programmes and monitor their implementation and outcome.

Human Gene Therapy

The term human gene therapy originally referred to proposed treatments of genetic disorders that would involve replacing a defective gene with its normal counterpart. Current usage of the term now extends to include all treatments in which there is an introduction of genetic material into human body cells to treat a variety of diseases.

Gene therapy utilises two theoretically possible approaches:

1 Somatic gene therapy entails the transfer of a gene or genes into body cells other than germ (egg or sperm) cells with effect only on the patient. The new genetic material cannot be passed on to offspring.

Examples of somatic gene therapy have already proven to be clinically effective. The first successful treatments of adenosine deaminase deficiency took place in 1990 in 1991 with two patients aged 4 and 11. Both are thriving with continuing treatment. The first successful treatment of familial hypercholesterolemia, a genetic condition which affects the liver’s regulation of cholesterol in the blood, took place in 1992 of a 29 year old woman. Her improvement was stable for the 18 months of the study and liver biopsy demonstrated

Table 2: The Range of Genetic Treatments

correction of single gene defects (<i>cystic fibrosis, ADA deficiency, familial hypercholesterolemia</i>)
therapeutic use of novel proteins discovered through human genetic research
augmenting deficient levels of normal proteins (<i>melanoma, renal cell carcinoma</i>)
targeting genes coding for proteins toxic to cancer cells or infecting organisms (<i>HIV</i>)
identification of novel targets (eg receptors, enzymes etc) for improved conventional therapies (<i>heart disease, diabetes, rheumatism, cancer</i>)

activity of the inserted gene and no discernible abnormalities. Five patients have been treated as of 1994.

Current research involving somatic gene therapy is focusing on a number of areas. Clinical trials are being performed on a treatment for cystic fibrosis, a chronic genetic disorder. One of its main symptoms is the production of sticky mucus that congests the lungs and airways making them very susceptible to infection. In this genetic treatment, the sufferer inhales a spray containing copies of the CFTR (cystic fibrosis transmembrane regulator) gene, to supplement the defective gene in the airways and thus correct this symptom of the disorder. Several approaches to HIV infection are being developed using gene therapy. Vaccines are being developed to stimulate immunity or to target HIV infected cells with toxic compounds. Reports have also reached the West from China of a gene therapy trial aimed at replacing a defective gene involved in haemophilia, a disease that causes prolonged bleeding from even slight injury.

2 Germline gene therapy would involve the genetic modification of germ cells. Such therapy would change the genetic make up of the egg or sperm of an individual and would be carried on to future generations. This would offer the possibility of removing an inherited disorder from a family line for ever. This could be achieved by other methods, such as, at present, diagnosis when there is a known risk before embryo implantation during IVF. Germline therapy is a remote prospect and general opinion is strongly negative; such therapy is currently illegal in most of Europe.

Gene therapy could offer significant advantages over conventional treatments. The fewer injections required would be preferred by patients, particularly children, and would result in higher compliance with treatments. Potentially, gene therapy would have lower costs than current frequent dosing approaches. Therapeutic affect would be improved due to more constant levels of delivery. Delivery to specific sites, possible by gene therapy, is critical for therapeutic effect in certain conditions.

Table 3: Potential Advantages of Gene Therapies

Category	Potential Advantages
Protein replacement	avoids repeated injections patient preference and improved compliance potential for internal regulation site and/or cell specific delivery
Protein augmentation	
Antisense/ribozyme	
Vaccines/antivirals	broad immunity new antigens possible single injection site and/or cell specific delivery
Other cancer applications	

There are several critical requirements for gene therapies. Safety is of paramount concern and treatments must not endanger public health. Many diseases require long or lifelong therapy and therefore expression of the therapeutic gene must be maintained over extended periods of time.

Issues: Somatic and germline gene therapy raise different issues. Somatic gene therapy offers the prospect of effective treatment and cure for previously fatal disorders. Until now it has only been used experimentally for a small range of genetic disorders; even in these cases treatment is complex, difficult and success uncertain. In terms of the ethical principles involved, adding a single gene by somatic gene therapy does not differ from transplanting an organ or tissue which will contain multiple copies of someone else's genes. It provides a further medical technique which, like all medical interventions, is judged in terms of its effectiveness in treatment and its comparative costs and risks.

The ethical questions raised relate to the ability to modify the human genetic make-up. This will provide opportunities to influence life and health more than any other form of treatment currently available. As with other medical treatments, however, gene therapy will only take place with the free and informed consent of the patient, or in the case of young children, the parents. There exists a strong point for the existence of a basic human right (or a basic organism's right) to an intact (uninjured; under no circumstances touchable) individual genome. Such a proposition, for example, has been brought forward within the realm of the Swiss Academy of Medical Sciences Task Group on Human Gene Therapy.

One cause for concern over human gene therapy is the possibility of non-therapeutic applications: for example, insertion of a gene to increase production of a growth hormone to enhance a person's height. There is general agreement, however, that somatic gene therapy may be used for treating serious disorders, such as those that are life-threatening or cause serious handicap and for which treatment is unavailable or unsatisfactory: decisions on the use of treatment are currently made by medical ethics committees. There are also

fears that it will be hard to limit the application of somatic gene therapy to agreed applications, and prevent its extension to progressively more contentious ones.

Genetic modification of germline cells raises a number of quite new ethical and safety questions. The genetic make-up of members of future generations could be changed without them being able to give consent. There is concern about "interfering" with human evolution for several reasons. Some of the genes responsible for genetic disorders have secondary effects that are potentially beneficial: for example, carriers of the sickle-cell gene have increased resistance to malaria. This is becoming increasingly important as the parasite becomes resistant to progressively more traditional treatments. On the other hand, it is not possible to predict whether a genetic advantage now will hold good in the future with changes in the environment. The technique of germline therapy also raises fears of its potential for use in eugenics.

Most current scientific and medical opinion regards germline gene therapy as technically impracticable, ethically and socially unacceptable, and lacking the understanding needed to evaluate potential risks to future generations. Furthermore there is negligible likelihood in the foreseeable future of being able to influence physical and behavioural traits, such as intelligence, which are determined by many genes in complex interaction with the environment.

Ethical, legal and social aspects: General opinion is that research in somatic gene therapy should be carried out under the following constraints: It must not be used to enhance traits which are not diseases. It should have reverence for life and respect for the dignity and integrity of the person who should have the right to freedom of choice. Any proposal to conduct somatic gene therapy should be subject to scrutiny by a supervisory body on its safety and efficacy, medical and scientific merit, legal implications and wider public concerns.

These principles are reflected, for example, in the recommendations of the UK Committee on the Ethics of Gene Therapy⁽⁷⁾. It is therefore recognised that a period of public debate (as well as technical development) is necessary before germline gene therapy is used as a medical tool.

Patenting Human DNA

The commercial applications of knowledge from the HGP have given rise to controversy about advancing scientific discovery through open collaboration and, at the same time, protecting economic interests through patenting inventions. Much of this debate is common to the commercial development of molecular biology as a whole and is not restricted to the HGP. Companies will be unlikely to develop diagnostic and therapeutic applications by investing financial and other resources unless they have adequate patent protection.

The discussion surrounding the patenting of human DNA has several dimensions. There is the general debate concerning the issue of patenting in biotechnology (Briefing Paper 1) and, more specifically, the patenting of DNA sequences with no known utility and of parts of the human body.

In 1988, the European Commission proposed a Directive on Legal Protection for Biotechnological Inventions in order to harmonise technicalities of patenting legislation across the European Union. This directive has been the subject of protracted debate between the European Parliament, European Commission and the Council of Ministers. The Directive's first measure aims to preclude attempts to patent gene sequences with unknown utility. The issue which most concerned the European Parliament was the patenting of human body parts on ethical grounds. Agreement was eventually reached on 23 January 1995, requiring final approval by the Council and Parliament. This allows patenting of inventions incorporating human body parts obtained in a "technical manner" in such a way that they could not be linked to a specific individual.

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- 4 Mr M A Klepsch, EC DGXII/E-1, 200 rue de la Loi, B-1049 Brussels. Phone, +32 2 2953210; Fax, +32 2 2955365
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