The key is in the genes, or is it...?

With the human genome project completed, the question is 'What comes next?'

'It's in my genes; my genes are guilty, not me', yelled the convicted criminal as he was led from the courtroom. Will judges in future have to take into account the genetic makeup of the perpetrator when deciding the sentence? As information from various genotyping projects pours in, the longstanding debate on the balance between nature and nurture in the development of phenotypes is being spiced up. Rapid progress in genome sequencing and analysis by public and commercial projects is producing a mountain of data that will be used to explain behavioural traits, and develop new and improved diagnoses and treatments for numerous diseases. But dabble with others' genes at your peril; this information has serious ethical, financial and social implications for the individual and society at large.

Our genes are the last repository of human privacy, and yet they are so easily read

On July 26th, 2000, President Clinton announced the publication of the first map of the human genome: 'Without a doubt, this is the most important, most wondrous map ever produced by humankind.' Knowing 'the language in which God created life' as Clinton put it, scientists and doctors in the field of medical genetics now have the necessary knowledge to enter a completely new era of medical research, one in which researchers will for the first time tackle genetic diseases at their roots. These include some of the most devastating ailments such as Alzheimer's, schizophrenia, Huntington's

and cancer. Scientists have already embarked upon this large and complicated quest by performing genome surveys on population subgroups, but much of the legal framework needed to ensure integrity has yet to be devised. In the eyes of many, our genes are the last repository of human privacy, and yet they are so easily read. It is not surprising, therefore, that the main theme of the ethical debate is protection of privacy.

Genetic material should not be thought of as the sole property of an individual, because it may hold the key to new diagnoses and therapies

Protection of patients' private information was enshrined in the Health Information Declaration of Geneva in 1948 when the genetic code and structure of DNA were still unsolved. Then, a patient was simply a medical entity. Today, a patient may be considered a temporary guardian of a shared genome. Genetic material should not be thought of as the sole property of an individual, because it may, in conjunction with medical data and family trees, hold the key to new diagnoses and therapies that could benefit society. And since it has also become a potential gold mine for industry, we may well ask 'who owns the human genome?'

Clearly, new conventions must be established to allow researchers in academia and industry to use genetic data without violating the privacy of the patient. For this, and other reasons, the World Medical Association wishes to establish a code of ethical principles for database operation. Dr Anders Milton,

Chairman of Council at the WMA, presented the WMA guidelines in May this year at the World Health Organization headquarters in Geneva. Among the more important elements in the document is the requirement that medical databases be owned by non-profit organizations, but top of the list is the patient's right to privacy of information. The WMA plainly seeks to pre-empt all eventualities given the unprecedented scope of distribution of patient data—a resource that may be of interest to academic researchers, health organizations and industry. Indeed, as the words: '...is not intended to criticize any existing or planned database in any country' hint, the WMA might not wholeheartedly agree with the approach taken by some genotyping projects.

Such projects have started springing up in many areas of high genetic homogeneity with good medical and genealogical records, and at least one, deCODE, is commercial. The Icelandic company has frequently been labelled the ugly face of commercialism, but this is probably a backfiring of the policy of its chief executive officer, Kari Stefansson, who has enthusiastically engaged himself in public debate. Having developed its ethical standards in collaboration with the Icelandic authorities, and seeking Institutional Review Board approval for all its projects, deCODE, via a subsidiary, was recently granted the licence to run the Icelandic Ministry of Health database. Furthermore, the decryption key for the subject identity encryption algorithm is held by the Icelandic government authorities, not by deCODE.

Public genotyping projects include the Northern Swedish Health and Disease Study, which involves two facilities, one for sequencing (National Centre for Large Scale DNA Sequencing: <http://www.biochem.kth.se/GenomeCenter/>), the other for disease gene identification (SSF Genotyping

Centre: <http://www.genome.uu.se>), both at Uppsala. The project was begun in 1998, and will run until 2002. Estonia, another region of high genetic homogeneity, has also started a Human Genome Heredity Project with the aim of producing high density SNP (single nucleotide polymorphism) maps from one million subjects between 2001 and 2010 (<http://www.genomics.ee/press.html>). Each project has established its own operating rules in co-operation with the population and authorities concerned.

By mining information from genetically closely related individuals with known family trees these projects seek to correlate genotypes with phenotypes, as documented in a patient's medical records, to

something freely given by you? Both scenarios have recently arisen in the USA. One involves a diagnostic test developed from two men who lack a receptor necessary for HIV entry into T cells, and have therefore remained uninfected despite frequent contact with infected individuals (Connor *et al.*, 1996a,b). In the other case, a hospital research institute obtained a patent on the Canavan disease gene (responsible for a fatal childhood neurological disease), which was discovered by screening Ashkenazi Jews (Kaul *et al.*, 1993). Should patients write their own contracts with researchers, covering the possible patenting of medical advances developed from their DNA? As a report in the *New York Times* recently concluded, it is important that research subjects do not feel cheated and embittered, otherwise they may not participate in genotyping projects that could benefit many others.

Although the study of clinically well-defined genetic diseases has raised a far-reaching ethical debate, this is nothing compared with the ideological quagmire that behavioural geneticists wade through when trying to correlate genotype with phenotype. Invariably the traits they study are complex (involving more than one locus), and are frequently under substantial environmental control. In clinical terms, the hope is that genetics will open the way to the understanding of psychiatric diseases. However, at present even the physiological basis of psychiatric disorders is not well defined. Because the development of a psychiatric phenotype is a complex process, traits often lie on a continuum from normality to clinical significance. Whether a person has a 'disease' is often a very subjective matter.

The latest method for identifying disease genes is whole genome association. By scanning genomes for mutant loci that appear consistently within and between sets of sibling pairs, scientists expect to

identify genes involved in a particular trait. This approach, practised on a Finnish sample group, recently identified a likely predisposing locus for schizophrenia on chromosome 7q22 (Ekelund *et al.*, 2000). However, as witness to the multifactorial nature of the disease, there is additional strong evidence for linkage (though not predisposition) to several other chromosome regions including 5q, 6p, 8p, 9, 13q, 18p, 20 and 22q (Karayiorgou and Gogos, 1997).

Despite the fact that we can now identify more predisposing genes, we must resign ourselves to the fact that they will never be the whole story

As more knowledge about the development of diseases, personality and behaviour is gathered, it also becomes clear that environment and life-style play much larger roles than previously assumed. Cancer is a prime example; intelligence is another. A mouse called Doogie, the creation of Joe Tsien at Princeton University, recently became smarter than the average mouse, demonstrating how genes might influence learning and memory. Sadly, Doogie, as happens to many stars, was misrepresented in the media fame-making machine, demonstrating admirably how, once played out in the media, an emotive topic can become more hype than science. What Tsien really showed was that manipulating the expression of a single gene coding for the subdomain of a neuroreceptor could increase learning ability in mice (Tang *et al.*, 1999). The waters of reality, however, are muddier than the media wish the public to believe: shortly thereafter, another study (Crabbe *et al.*, 1999) showed that genetically identical mice behave differently under *nearly* identical conditions. From this it appears that even small environmental differences can have a profound influence on the development of a trait. So, despite the fact that we can now identify more predisposing genes than before, we must resign ourselves to the fact that they will never be the whole story.

Genes and Society

These and many other issues relating to the sequencing and analysis of the human genome have been extensively discussed at the 'Genes and Society: Impact of New Technologies on Law, Medicine, and Policy' conference on May 10–12, in Cambridge, MA. Information about the conference and its organisers, the Whitehead Institute, can be found at <http://www.wi.mit.edu/news/n&e/policy2000/home.html>.

A joint conference organized by the European Molecular Biology Laboratory and the European Molecular Biology Organization will devote one day to human genetics. 'Science and Society: Developing a New Dialogue', takes place from 10–12 November, in Heidelberg, Germany. The organizers invite scientists, social scientists, journalists and policy makers to discuss the impact of the life sciences on society before a public audience (<http://www.embl-heidelberg.de/Conferences/SciSoc00/>). This represents a rare opportunity for the reporting of a wide-ranging debate on many aspects of public concern and interest.

provide a reliable set of genetic markers for a variety of diseases. This approach promises more efficient and accurate diagnosis, better risk evaluation, and new or improved treatments, and has therefore attracted considerable interest from the pharmaceutical industry.

So imagine you are a patient in a genotyping project. You may have gone through the tribulations of giving consent, and satisfied yourself that your data are anonymous and secure, but what if your DNA proves to be of commercial interest? Researchers may find a genetic marker for your inherited condition and decide to patent it as part of a diagnostic test. Should you be a beneficiary of the patent, or should you, indeed, be outraged that someone is seeking to make money from

And so we are building a mountain of knowledge that at once says much and little. But how do we communicate this to the public? People are still in the process of grasping *Mendelian* genetics; it is a further conceptual step to accept the *complex* genetics and interplay with the environment involved in the development of behavioural traits. While the benefits of medical genetics are important to emphasize, we need to be sensitive to the public's concern for privacy of data and integrity of use of those data. Furthermore, we must acknowledge their fear of the re-emergence of eugenics in the form of prenatal testing for inherited diseases. Knowing and analysing the sequence of the human genome holds great promises as well as great dangers. Knowledge *per se* has no value without a worthy application. It is up to us to develop the promises

and thwart the dangers. As Britain's Prime Minister, Tony Blair, said in his statement on the human genome project: 'With the power of this discovery comes, of course, the responsibility to use it wisely.' Perhaps what he meant was '...must come the responsibility...'

- Connor, R.I., Paxton, W.A., Sheridan, K.E. and Koup, R.A. (1996a) Macrophages and CD⁴⁺ T lymphocytes from two multiply-exposed, uninfected individuals resist infection with primary non-syncytium-inducing isolates of human immunodeficiency virus type 1. *J. Virol.*, **70**, 8758–8764.
- Connor, R.I., Sheridan, K.E., Lai, C., Zhang, L. and Ho, D.D. (1996b) Characterization of the functional properties of env genes from long-term survivors of human immunodeficiency virus type 1 infection. *J. Virol.*, **70**, 5306–5311.
- Crabbe, J.C., Wahlsten, D. and Dudek, B.C. (1999) Genetics of mouse behaviour: interactions with laboratory environment. *Science*, **284**, 1670–1672.

- Ekelund, J. *et al.* (2000) Genome-wide scan for schizophrenia in the Finnish population: evidence for a locus on chromosome 7q22. *Hum. Mol. Genet.*, **9**, 1049–1057.
- Karayorgou, M. and Gogos, J.A. (1997) Dissecting the genetic complexity of schizophrenia. *Mol. Psychiatry*, **2**, 211–223.
- Kaul, R., Gao, G.P., Balamurugan, K. and Matalon, R. (1993) Cloning of the human aspartoacylase cDNA and a common missense mutation in Canavan disease. *Nature Genet.*, **5**, 118–123.
- Tang, Y.P., Shimizu, E., Dube, G.R., Rampon, C., Kerchner, G.A., Zhuo, M., Liu, G. and Tsien, J.Z. (1999) Genetic enhancement of learning and memory in mice. *Nature*, **401**, 63–69.

Andrew Moore

The author is a contributing editor to *EMBO Reports*.

DOI: 10.1093/embo-reports/kvd038

JBIC will pool Japanese genomics research

Japan's efforts to catch up in bioinformatics

Last month, the Japan Biological Informatics Consortium was officially established as an independent, non-profit organization after having reached all of its planned goals within its first 3 years. JBIC is a consortium of academia, government and industry, and its aim is to pool Japan's research resources in bioinformatics. Founded in 1998 by the Japan Biotechnology Association (JBA) with financial support from the Japanese Ministry of

International Trade and Industry (MITI), it will now contract with governmental institutions and biotechnology companies to pursue and support genomics research and application. JBIC is part of a growing Japanese effort to catch up

with the USA and Europe in the rapidly emerging field of bioinformatics.

'There has been no infrastructure for bioinformatics, the interdisciplinary science. Research activities were not integrated. We have to join forces,' Kazuo Katao, director of the Biochemical Industry Division, Basic Industries Bureau of the MITI, explains why the Japanese government decided to provide funding for the establishment of an interdisciplinary organization. To close the gap particularly with the USA, Katao, a former chemical engineer, created JBIC in 1998 with a phone call. 'I called JBA to establish the head of the body to fix the lack of infrastructure in Japan,' he recalls. 'We don't have many [management] resources to invest, so I called on the JBA council,' he explains why MITI was asking the Japanese industry for help.

The industrialization of biotechnology with heavy support from the government is a legacy of the late Prime Minister Kenzo Obuchi and falls under 1999's 'Millennium Project'. However, the intense co-operation between industry and academia has always been an essential

part of the Japanese economy and politics. In the field of biotechnology, it had started half a century earlier with the establishment of the Japanese Organization of Industrial Fermentation in 1942. Its successor, the Japanese Biotechnology Association now comprises a group of 300 companies, 100 public organizations and 1300 academic institutions. Often under the auspices of MITI, these groups focus and drive research and development further, and have a considerable influence on Japanese economic politics.

It is Japan's perception that it has to catch up with other countries in genomics research and bioinformatics

Another impetus for the establishment of JBIC is Japan's perception that it needs

The father of JBIC, Kazuo Katao