

Legacy of the code-breakers

SCIENTISTS RECENTLY ANNOUNCED THEY HAD COMPLETED MAPPING THE GENETIC MATERIAL OF DOGS. THE GENOMES OF MORE THAN 100 OTHER ORGANISMS, INCLUDING THE RATHER CURIOUS VARIETY KNOWN AS MAN, HAVE BEEN MAPPED SINCE 1995 AND WORK CONTINUES ON HUNDREDS MORE. **TONY JAMES** LOOKS AT THE HISTORY BEHIND IT ALL AND THE COMPLEX IMPLICATIONS FOR MEDICINE AND SOCIETY OF OUR EVER-EXPANDING GENETIC KNOWLEDGE.

Watson and Crick's model of the DNA double helix, reported in a brief letter to science magazine *Nature* in 1953, is one of the iconic images of the 20th century, paralleling those grainy photos of man's first steps on the moon. Fifty years later (minus 11 days) in April 2003, the International Human Genome Sequencing Consortium announced the successful completion of the Human Genome Project. It had identified 99.9 per cent of the 3 billion pairs of bases that make up a person's DNA, with an accuracy of 99.99 per cent. The missing 0.1 per cent can't be analysed with existing technology.

Watson and Crick's model was a critical step, but certainly not the birth of genetics. Mankind has been selectively

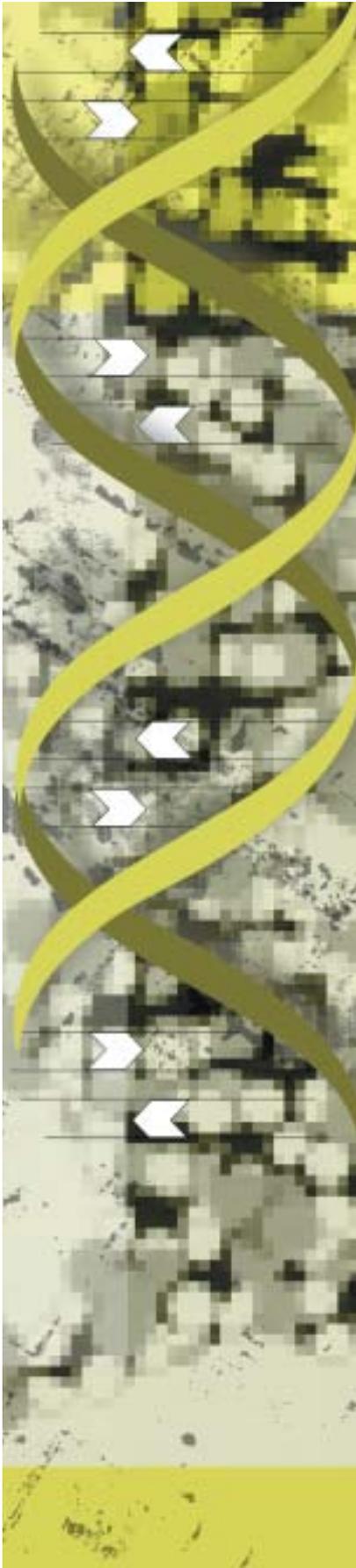
breeding crops and animals for millennia, selecting those that perform best. In the mid-1800s, Austrian priest Gregor Mendel, in experiments familiar to every high-school biology student, established the concept that elements of inheritance are not simply blended from one generation to the next, but preserved intact. Modern statisticians claim his results are suspiciously accurate and he might have "edited" them to support his theories.

Doctors have always paid close attention to inherited aspects of disease. In 1872, the American physician George Huntington showed that the devastating degenerative brain disorder that now bears his name ran in families. By the early 1900s, inherited metabolic

disorders could be diagnosed from byproducts in the urine and blood. Physical inspection of chromosomes has been used for decades in the prenatal diagnosis of conditions such as Down syndrome and Klinefelter's syndrome, in which males are born with an extra X chromosome. Genetic diagnoses have been based on skilled clinicians' interpretations of patients' histories, what they see, and the technology available at the time.

DNA was known to carry genetic information as early as the 1940s, and the race was on to discover exactly how the code was written and how it was used. American James Watson and Englishman Francis Crick, with New Zealand-born physicist Maurice Wilkins

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and working in the Cavendish Laboratories of the physics department at Cambridge, won the 1962 Nobel Prize in medicine and physiology in recognition of their breakthrough. Rosalind Franklin, who produced a crucial high-quality X-ray crystallography image of the DNA molecule, had died by the time and, in accordance with the tradition not to award posthumous prizes, missed out. At least nine more Nobel Prizes in medicine were awarded for work on genetics before the end of the 20th century.

Watson and Crick discovered that DNA is an almost inconceivably long sequence of simple components – the bases adenine (A), thymine (T), cytosine (C) and guanine (G). "A" invariably bonds with "T" to form a pair, and "C"

bonds with "G". Bonds between the complementary bases represent the "steps" in the spiral staircase of the double helix. The mechanism allows the helix to split in two, create strands of messenger RNA to do its work, and then bind with bases to reconstitute the double strand. Even Hollywood knows about bases now: it is no accident a 1997 sci-fi drama about a world populated by genetically modified humans was called *Gattaca*.

Every human cell, except mature red blood cells, includes all 3 billion pairs of bases spread across 23 sets of chromosomes. Three bases in a row (for example, CGG) act as codes for the production of 20 different amino acids, which in turn are connected in sequences to form proteins – the most

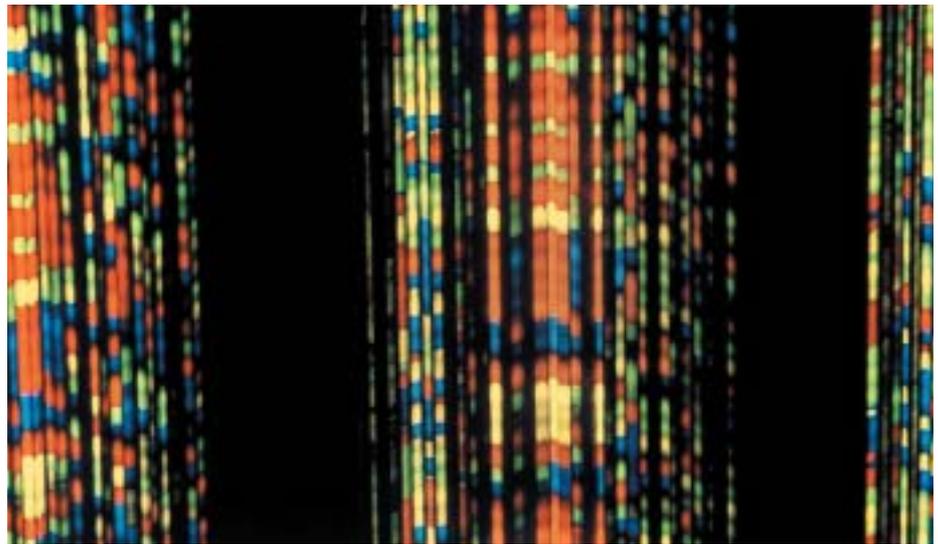
Benefits and dilemmas

A "hypothetical" posed recently in the *British Medical Journal* (July 17) highlighted the intense practical dilemmas that can arise in medical applications of genetic information. A four-year-old boy has been diagnosed with Duchenne's muscular dystrophy – a severe, debilitating and progressive muscle wasting disease that leads to confinement in a wheelchair by the early teens and death in the 20s. This condition is carried by mothers, who have a 50 per cent chance of passing it on to their sons.

The boy's mother, Anne, attends a genetics clinic and is confirmed as a carrier. Her sister Ruth, with whom she doesn't get on, has just become pregnant. Anne doesn't want to tell Ruth about the risk because she would strongly disapprove if Ruth decided to terminate the pregnancy if she discovered she was also a carrier.

The clinic must decide between two models for genetic information. The first is that it resembles a personal account at the bank, and confidentiality to that patient (the "account holder") is paramount. This is the traditional approach in medicine, but is occasionally over-ruled in extreme circumstances such as a particular danger from infectious disease. The second model suggests that genetic information is held in a "joint account" the contents of which other account holders – the other members of the family – have a right to know about. Doctors should not be expected to resolve these ethical dilemmas alone, but need guidance from society.

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important product of genes. One of the surprises from the Human Genome Project is that we have only about 30,000 genes, not the 100,000 expected. Another is that identifiable genes occupy only about 1.5 per cent of the total genome.

Much of the genome seems to consist of genetic "junk", which might have accumulated as redundant material during evolution, but a significant proportion is probably involved in controlling how and when genes are "turned on". Humans share 99 per cent of their DNA with chimpanzees, 95 per cent with mice, and 70 per cent with a humble but well-studied nematode (a primitive worm) called *Caenorhabditis elegans*. The more mysterious parts of the genome almost certainly help determine why we develop into humans rather than mice or worms, but the exact mechanisms are still not understood.

The Human Genome Project, which analysed DNA from a handful of volunteers of varied ethnic origin, was a unique biological project in terms of its size, international collaboration (despite controversies over ownership of data between public and private contributors) and cost. In 1991-value US dollars, the total investment was about \$2.7 billion, or \$0.90 for every base pair. One of the early players in the consortium was the US Department of Energy, which had a long-standing interest in the effects of radiation on genes.

Mapping the human genome, though, was just a part of much wider activity investigating DNA in a wide range of life forms. The first full genome to be described, in 1995, was that of a

humble bacterium: the respiratory tract pathogen *Haemophilus influenzae*. In July this year, the genome of a boxer dog called Tasha was made available. It cost just \$US30 million to identify her sequence of 2.7 billion base pairs. More than 100 other organisms have been completely sequenced, and work is continuing on hundreds more.

"Genomics" is the new science of systematically studying the structure and function of an organism's entire genome. It has spawned other new disciplines including proteomics, which aims to understand the complete set of proteins produced by an organism and the relationships between them. Bioinformatics harnesses computer power to make some sense from the flood of raw data that is becoming available.

Professor Ronald Trent, Professor of Molecular Genetics at the Royal Prince Alfred Hospital and University of Sydney and Fellow of RCPA, says Watson and Crick laid the foundation for molecular medicine. "It allowed us to progress from analysing a patient's phenotype – that is, what we can see or measure – to analysing the genotype, the underlying genetic basis of health and disease," he says. "Genetics has been transformed from a descriptive art of medicine into an exceptionally exact scientific process which we then have to make relevant to the patient's care."

The Human Genome Project will provide answers to questions that haven't even been thought of yet. "We haven't yet appreciated the wealth of information available, and we need to develop the knowledge and skills to

handle the data from a scientific point of view," Professor Trent says.

"The way we practise medicine will inevitably change. Some patients are better informed about their own genetic issues than their doctors, and the health system will probably not be able to support one-to-one genetic counselling that has been provided in the past," he says. This will probably lead to even greater sub-specialisation of medical professionals who take an interest in genetics, a need for continuing education of all health professionals and the public, and the development of tools such as computer-based information packages to guide people in accessing and interpreting their own genetic data.

Access to the full genome has accelerated a pre-existing debate about the legal, ethical, social and practical aspects of dealing with people's individual genetic codes. The eugenics movement of the late 19th and early 20th centuries viewed hereditary characteristics as a tool for understanding a range of social attributes and vices, and for guiding decisions about who should, and who should not, pass on their genes. The UK Eugenics Education Society was founded in 1907 with the aim of encouraging the "fit" to breed more, and the "less fit" to breed less vigorously, but enthusiasm had waned, not surprisingly, by the onset of World War II.

Professor Trent supports the formation of a body similar to the Human Genetics Commission in the United Kingdom, which has assembled panels of professionals and community representatives who can work together

and respond efficiently to new issues as they arise. However, Australia has not ignored the dilemmas provoked by the genetic revolution. For example, the Human Genetics Society of Australia (www.hgsa.com.au) has developed a range of policy statements on genetic testing and provides information on the availability of about 200 genetic tests in local laboratories.

The National Health and Medical Research Council has also produced a number of policy statements and information papers, including one on ethical aspects of human genetic testing. It stresses that genetic information is uniquely personal and can have a great impact on people's perceptions of health and body image, and their worth as individuals, family members and members of society.

The influence of genetic information can extend over a lifetime, and a single sample can be retested to accumulate additional data over time. Decisions that might have to be taken include how much to find out about one's genes in the first place and how to respond to knowledge such as a high risk of future illness.

Some simple genetic tests are highly predictive of future disease. In Huntington's disease, for example, the tragic onset of the illness in a parent suggests each child will have a 50 per cent risk of developing it themselves as they reach middle age. A test that shows the gene is present would allow the young person to plan their lives more accurately, but finding out the gene was absent would provide enormous relief and the prospect of a normal life.

"Information gained from predictive and prenatal tests can prompt profound questions about what constitutes a worthwhile human life," the NHMRC ethics paper states. Genetic susceptibility to an illness does not mean that it is inevitable. The BRCA1 gene predisposes very strongly to breast cancer, leading to cancer in 60 to 85 per cent of women who carry it compared with 7 to 8 per cent of women in the general population. But 15 to 40 per cent will not develop cancer related to the gene.

The fallacy of "genetic determinism" ignores the fact that genes are only one of many factors that influence future health, along with a person's environment, lifestyle choices, complex

and poorly understood interactions between genes, spontaneous gene mutations that occur during life, and chance. "Information from genetic testing can be very precise, but the precision is often unhelpful in predicting future health," the paper says.

In addition, a view of human beings as essentially consisting of their genes could lead to neglect of more traditional determinants of health and quality of life, including the physical, social and

economic environments in which people live. Current attitudes of social solidarity could be threatened by this process of "geneticisation", for example by an expectation that those with genetic susceptibilities should accept the financial responsibility of caring for themselves and their children. "This would challenge concepts of equality of respect for persons and sense of community," the paper says. 🔥

Some medical applications of the 'new genetics'

Diagnostic testing: A DNA test is used to check for a genetically based condition in a patient who already has symptoms. For example, the iron-storage disease haemochromatosis can now be identified in genes isolated from a blood sample instead of requiring a liver biopsy.

Prenatal testing: Checking for chromosomal abnormalities has been routine for decades. Direct DNA analysis from foetal cells can now check for a wider range of conditions. Embryos created during assisted reproduction techniques can be checked for a condition such as cystic fibrosis in a family with a history of the condition, prior to implantation.

Presymptomatic screening: Genetic disorders can be detected before symptoms develop, for example in families with a history of BRCA1-related breast cancer or familial adenomatous polyposis (which poses a high risk of colorectal cancer). Skilled counselling before and after testing is essential.

Screening: For example, checking for a particular gene in an extended family, ethnic group, or even a whole population. As for population screening in other areas of medicine, it is essential to ensure the program is cost-effective and well supported by education and excellent care for those identified at risk.

Medications and diagnostic tools: "New genetics" has had a dramatic impact on treatment. Many "recombinant" medicines and vaccines are becoming available, including hepatitis B vaccine, coagulation factors for people with haemophilia, a range of cancer therapies, insulin and growth hormone. Rapid analysis of the genetic structure of bacteria, viruses or other disease-causing organisms can provide more accurate and faster results than in the past – as in unravelling the cause of the 2003 SARS outbreak.

Gene therapy: In theory, it will be possible to correct genetic defects and restore diseased cells to their normal function. There has been some success with the rare childhood condition of severe combined immunodeficiency, but also some unexpected hurdles in this challenging area.