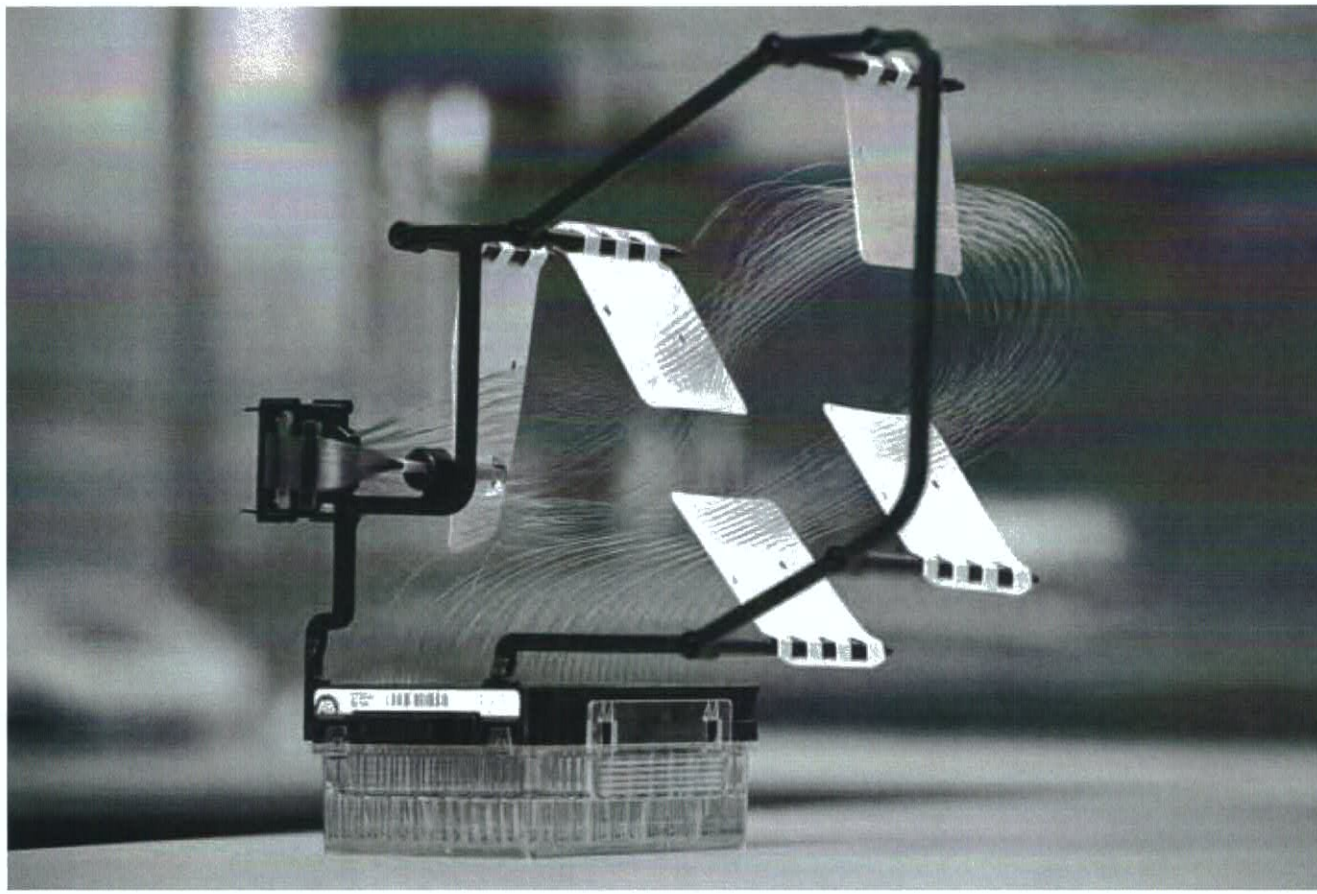


science

DNA variety: the splice of life

The publication of the first draft sequence of the human genome in 2001 was a defining accomplishment; but what has come of it and what does it mean for health care? Alex Wilde reports

You and I have about the same number of genes as the Pinot Noir grape. But the spotlight is no longer on the similarities in our DNA that makes us Homo sapiens and not a Vitis Vinifera, but the tiny differences in our genetic code that makes you You and me Me.

Identifying the function of individual genetic differences – or genetic variation – scientists say, is fundamental to the next step in fulfilling some of the promises of the Human Genome Project; such as determining the contribution of genes to disease and the development of treatments that target DNA alterations in individuals.

There is a conspicuous obstacle, however. The 25,000-30,000 genes that make up the human genome are sequenced, but scientists still don't know how around one third of it – about 10,000 genes – works. This is a question Professor Jeurgen Reichardt, Plunkett Chair of Molecular Biology (Medicine) at the University of Sydney raised recently in *Trends in Biochemical Sciences*.

"There is clearly a lot of promise, but while we may be able to point to a gene that may or may not be involved in a particular disease, if you don't know its function you can't target it," Reichardt says.

"The problem is made worse because there's a lot of human genetic variation out there and we have no idea what it does – tens of millions (of variations, or different versions of the same genes, known as variants or alleles). Some variation may be inconsequential, some may change hair colour, some may be involved in disease."

Genetics to genomics

Before the Human Genome Project, the scientific focus was on identifying genes directly responsible for an estimated 3-4000 relatively rare hereditary diseases – such as dominant or recessive genes that cause Huntington's disease or cystic fibrosis respectively.

Altered genes are known to also play a part in susceptibility to other more common but genetically complex diseases including certain cancers and heart disease, diabetes mellitus and psychiatric disorders. These may also run in families, but tend to stem from genetic predispositions acting in consort with environmental factors, such as stress, diet and lifestyle; interactions that might explain the important health issues of today.

Ron Trent, Professor of Molecular Genetics at the University of Sydney and Director of the Department of Molecular and Clinical Genetics at the Royal Prince Alfred Hospital, says one of the valuable spin-offs from the Human Genome Project is advances in

Above:
A 96 capillary array. (DNA simultaneously flows through the capillaries, a laser beam detects the DNA enabling identification of the sequences.)
Photos: Paul Wright

technology that enable scientists to identify thousands of genes at the same time, which makes analysis more rapid and meaningful.

"If you can look at hundreds of thousands of genes simultaneously you can start to get a better profile of someone. Some people can smoke a pack of cigarettes a day and never develop lung cancer; others get it from passive smoking.

"No doubt if you look at the genetic profile of not just one gene but hundreds to thousands you should be able to identify the risk people have and why they are at risk. Once we understand gene-environment interaction we can talk much more specifically about personalised medicine and preventative medicine."

According to a paper published in *Science* in December 2007, scientists have estimated 15 million places, known as single-nucleotide polymorphisms (SNPs), along the genome where one of an estimated three billion DNA bases or nucleotides, called A (adenine), G (guanine), C (cytosine), and T (thymine), can differ from one person or population to the next. These changes in the sequence of DNA bases are what add variety to the human genome and make everyone's genetic code different.

But finding out how changes in 15 million SNPs impact upon human health takes time. Scientists analyse SNPs to find out which co-occur with disease symptoms, in attempts to link genetic variation to susceptibility to disease. Variants of more than 50 genes have so far been linked to increased risk for more than a dozen diseases including Type 1 diabetes, heart disease, breast cancer, multiple sclerosis, rheumatoid arthritis, colorectal cancer, ankylosing spondylitis, psychiatric illnesses and autoimmune diseases.

In 2001, more than 1.4 million SNPs had been found. By 2007 this had doubled – leaving around 12 million DNA variations to be identified and their function to be discovered.

A quantum leap to clinical medicine

With so much still unknown, applying laboratory genomics to real lives seems a long way off, but Trent believes genomics has already arrived in doctors' rooms. In July 2007, the US Food and Drug Administration approved a genetic test called MammaPrint, which predicts the likelihood of breast cancer returning within five to 10 years after the initial diagnosis.

"This is a very important development; it is the beginning of clinical genomics. Patients who have breast cancer can have a sample of the [tumour] tissue tested. This DNA test looks at 70 genes simultaneously and on the basis of those 70 genes, a prediction can be made about the likely outcome of that tumour," Trent says.

"Presently with breast cancer a lot of people are being detected early and the tumour is removed. But the question is what do you do next – do you put these patients on chemotherapy, radiotherapy or tamoxifen?

"And the difficulty there is that you know some patients, even if you don't treat them, they will do well; but other patients if they don't have these additional treatments they will relapse."

The MammaPrint test is only available via the internet, and to obtain it, patients must go through their health professional such as an oncologist. The oncologist arranges for the tumour sample to be taken and s/he consults with the overseas laboratory to interpret the results.

"I don't know if this test is going to provide all the answers [for women with breast cancer], but it is an approved test and it will provide additional information for the patient and the health professional to make a decision about treatment options," Trent says.

This is one of the reasons why information about individual genetic differences in response to disease and treatment is crucial to understanding the human genome. To fully exploit gains made by the Human Genome Project, a consortium of research has commenced cataloguing all that is known from around the world about human genetic variation in an initiative called the Human Variome Project.

Trent says this database will be vital in making the human genome easier to understand and to find out why individual genetic differences matter.

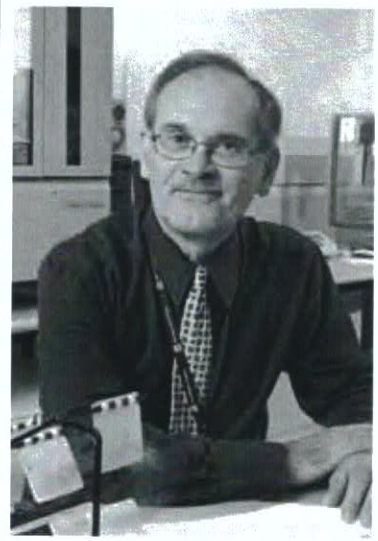
"The Human Variome Project is specifically looking at genetic variation in different populations to try and understand what it means. Why do some people respond well to medication and some not so well? Why do some people get addicted and others do not? It could be environmental and it could be genetic components.

"It was interesting to hear Craig Venter's comment that despite the fact that his genome has been sequenced he still doesn't know much more about himself than he knew before," says Trent. (Craig Venter founded the Institute for Genomic Research and was key to mapping the human genome.)

"All the information is out there," says Trent. "The Nobel Prize will come to the person who develops appropriate bioinformatics software that allows us to understand what the A, T, C and Gs are doing, in what direction, and how they work." SAM

Top: Professor Jeurgen Reichardt, Plunkett Chair of Molecular Biology (Medicine) at the University of Sydney

Below: Ron Trent, Professor of Molecular Genetics at the University of Sydney and Director of the Department of Molecular and Clinical Genetics at the Royal Prince Alfred Hospital



Further information

Human Genome Project
www.genome.gov

Human Variome Project
www.variome.org

MammaPrint
www.agendia.com