



# Slow revolution

How the human genome project will change our lives



It might not make a huge difference to you, but their lives will be transformed

LAST year, doctors in Turkey sent a blood sample from a baby who was dehydrated and failing to gain weight to Richard Lifton's lab at Yale School of Medicine. The doctors suspected the boy had a genetic disorder that affects the kidney. Within 10 days, Lifton's team had sequenced all the child's protein-coding genes – about 1 per cent of the genome – and found the mutation responsible for his illness.

Rather than causing kidney problems, though, the mutation affects salt absorption in the intestine. Fortunately, it can be treated simply by administering a carefully balanced solution of glucose and salt every day. So far, the treatment has been a success.

Such a swift diagnosis would have been impossible a few years ago. Not only would it have been time-consuming and costly without the technologies developed as a result of the human genome project, but the mutation could not have been identified without other sequences to compare the boy's with.

The benefits could extend to future generations, too. When the boy grows up, he can – if he chooses – ensure that any children he has do not suffer from the same disorder. It is now routine to test IVF embryos for specific genetic mutations and implant only those that do not carry them. Thousands of parents around the world are already opting for pre-implantation genetic diagnosis to ensure they do not pass on serious diseases.

Few other people have benefited so directly from the human genome project as the boy in Turkey, but that could change dramatically in the next few years. Take "Monica", who had her DNA profiled only because she was once a room-mate of Anne Wojcicki, co-founder of the genetic testing company 23andMe, based in Mountain View, California. When Monica developed a blood clot after a long flight, she was able to tell her doctors that she has a genetic variant that makes her especially sensitive to the blood-thinning drug warfarin, meaning the normal dose could cause excessive bleeding.

Examining people's genes to see how they will respond to drugs – pharmacogenetics – has been talked about for decades, but it is now starting to become a reality. "There are 10 drugs or so that we should be accompanying with genetic tests," says Michael Christman, head of the Coriell Institute for Medical Research, a non-profit organisation in New Jersey. That number is expected to rise to 100 before too long, he adds, because there are a few genes that affect how the body processes a huge number of different drugs.

The best-selling drug clopidogrel (Plavix),

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for instance, is an anti-clotting agent used to prevent heart attacks and strokes. Many people, particularly those with African or Asian ancestry, have variations in an enzyme called CYP2C19 that means less, or even none, of the drug gets converted into the active form in the body. These people need either higher doses or a different drug altogether.

For people with cancer, it is fast becoming the norm to characterise both their normal DNA and the mutations in the cancer. For example, about a third of breast cancers have mutations that result in the overproduction of the HER protein, which can be treated by an antibody called trastuzumab (Herceptin) that blocks HER's effect. Testing ensures patients do not suffer nasty side effects pointlessly, and also saves a lot of money.

## Predicting your future

Testing for one or two common genetic variants is just the first step. Each of us has hundreds of variants that affect how we respond to drugs, and some of these variants may be very rare. Ultimately, sequencing the entire genome may provide the most accurate picture of people's response.

This idea is no longer a pipe dream. Last year, for instance, bioengineer Stephen Quake

of Stanford University in California sequenced his own genome in five days for \$45,000.

It was recently analysed by cardiologist Euan Ashley, also at Stanford, and his colleagues, who predicted Quake's response to a range of drugs based on around 650 genetic variants (*The Lancet*, vol 375, p 1575).

The team also looked at his risk of developing various diseases. For Ashley, the greatest, potentially lifesaving, insight was that while normal medical guidelines would have steered him away from recommending cholesterol-lowering drugs, the genome analysis changed his mind and led him to recommend statins. Quake hasn't yet decided whether he will follow the advice – after all, as Ashley admits, the big question is whether the genome-based predictions are right.

Indeed, until we understand far more about the genome (see page 36), even whole-genome sequencing will be of limited use. And it could still be quite some time before your doctor routinely orders genetic tests before prescribing drugs for you, even for those drugs for which tests are already recommended. One recent survey of 10,000 doctors in the US found that just 10 per cent felt they knew enough to order the right tests and interpret the results. So it's going to be a slow revolution, but it is under way. **Bijal Trivedi**

## HAS THE HUMAN GENOME PROJECT FAILED TO DELIVER?

If, by now, you were expecting to be told exactly what diseases you will develop as you age, and for a plethora of new drugs to be on hand to counteract the effect of your genes and to keep you healthy, then you may believe the human genome project has not lived up to the hype.

In some ways, it has not delivered. Investors who banked on companies such as Celera, Human Genome Sciences and Millennium Pharmaceuticals being able to profit by selling genome-related data felt the first letdown of the genomic age. That business model failed and the companies had to change tack.

Investors who bought into the idea that genome sequencing would revolutionise drug discovery have also yet to see returns. With the development of a drug usually taking decades, though, quick profits were never likely. "It has taken a long time to go from gene to protein to disease to drug. We are just beginning to

see results," says Geoffrey Porges at Bernstein Research in New York City.

Despite this, most researchers involved in the public human genome project, rather than any of the related commercial efforts, dismiss any suggestion that they overhyped the project. Whatever journalists and politicians may have said, as far as they are concerned it was always clear that the sequence was just the first step towards a fuller understanding of what makes us tick, and that it would take a long time for any benefits to materialise.

Those benefits are now starting to trickle in. Back in 2000, Francis Collins, then head of the project, predicted that in 2010 predictive tests would be available for a dozen conditions, that it would be possible to intervene to reduce the risk of some of these conditions and that pre-implantation genetic diagnosis would be widely available. His predictions were pretty much spot on. **BT**

## MEET YOUR ANCESTORS

Want to know more about your genetic roots? Then you are not alone.

Around half a million Americans purchase genetic testing kits each year from one of about 40 companies that promise to find distant relatives, or reveal family ties to such famous ancestors as Genghis Khan or Thomas Jefferson.

Most tests trace your maternal and paternal lines, by examining genetic markers on the mitochondrial DNA, which is passed from mother to child, or on the Y chromosome, passed from father to son. Like the roots of a tree, however, your genetic roots keep branching the deeper you look: tracing just two of these lines tells you nothing about all the others.

So a handful of companies will also analyse the 22 pairs of non-sex chromosomes and report what percentage of an individual's genome is of European, African, Native American or Asian origin. These analyses are more controversial, says Spencer Wells, who leads The Genographic Project, whose ancestry-testing service helps fund its effort to trace ancient migrations.

It's not always clear what it means to tell someone that their DNA is, say, 66 per cent European and 33 per cent African, Wells points out. For someone from Israel or Lebanon, these percentages reflect millennia of mixing. But in a Brazilian, it might tell them something about recent family history.

As we learn more about the genetic make-up of different branches of humanity, through efforts like the 1000 Genomes Project, these ancestry tests should become more informative and reliable. For now, though, the results should be treated with caution. The accuracy of many tests cannot be verified, and supposed connections to famous individuals or particular migrations are only interpretations based on the latest science, a recent paper concluded (*The American Journal of Human Genetics*, vol 86, p 661). **BT**