The new genetics

Modern genetics will improve health and usher in “designer” children

It may also provoke an ethical storm

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SOMETIME NEXT year, if all goes to plan, a gay male couple in California will have a child. The child in question will have

been conceived by *in vitro* fertilisation. In this case a group of eggs from a female donor are now being fertilised by sperm from both fathers (half from one, half from the other). Of the resulting embryos, the couple will choose one to be implanted in a surrogate mother. An uplifting tale of the times, then, but hardly a newsworthy event. Except that it is.

Where the story becomes newsworthy is around the word "choose". For the parents, in conjunction with a firm called Genomic Prediction, will pick the lucky embryo based on a genetically estimated risk of disease. Such pre-implantation testing is already used in some places, in cases where there is a chance of parents passing on a condition, such as Tay-Sachs disease, that is caused by a single faulty gene. Genomic Prediction is, however, offering something more wide-ranging. It is screening embryos for almost 1m single-nucleotide polymorphisms (SNPs). These are places where individual genomes routinely differ from one another at the level of an individual genetic letter. Individual SNP differences between people rarely have much effect. But add them up and they can raise or lower by quite a lot the likelihood of someone suffering a particular disease. Generate several embryos and SNP-test them, then, and you can pick out those that you think will grow up to be the healthiest.

Great expectations

Much fuss was made last year about a researcher in China, He Jiankui, who edited the genomes of two human embryos in order to try, he claimed, to make them immune to infection by HIV, the virus that causes AIDS. What Genomic Prediction proposes is different. No editing is involved. There is thus no risk of harming a child by putting it through a risky experimental procedure. Whether Genomic Prediction's particular technique will actually deliver super-healthy children remains to be seen. The principle seems plausible, though. History may therefore look back on this moment as the true beginning of "designer" babies. And the tool that has made that possible is called GWAS.

GWAS stands for genome-wide association study. It is the endpoint of a historical process that began in the mid-19th century with Gregor Mendel, a Moravian abbot and amateur botanist. Mendel worked out the first set of rules of heredity. This led to the idea of a gene. And that, when allied with the discovery that the material of heredity is a chemical called DNA, which encodes genetic information in the order of its component units, known as nucleotides, led to the idea of a gene being a particular piece of DNA that carries in its nucleotides the blueprint of a particular protein. This protein goes on to contribute, in combination with environmental effects such as nutrition, to a particular bodily or behavioural characteristic, known as a phenotypic trait.

Since the 1950s, researchers have tried to quantify the relative contributions of genes and the environment to such traits. Mostly, this is in the context of disease. But behavioural characteristics, personality and cognitive ability have also been

matters of interest. GWAS expands this process by looking not just at the effects of individual genes, but across the whole

genome—for protein-coding genes make up only about 2% of a person's DNA.

Comparisons, over several generations of a family, of the prevalence of a particular trait yield estimates of its heritability—a measure of how well individual genetic differences account for variations in that trait in a given population. A heritability of 100% indicates that any differences in a trait between individuals in that population are accounted for solely by genetic factors, while 0% suggests the environment alone is responsible. The phrase "given population" is important. Some populations may be exposed to relevant environmental variables unknown to others. Conversely, genetic factors present in one group (better response to oxygen scarcity in those evolved to live at high altitude, for example) may be absent in another.

An analysis published in 2015 of more than 2,700 studies of heritability shows that its average value, for all traits looked into in those studies, is about 50%. That includes physical traits like susceptibility to heart disease (44%) and eye disorders (71%), and mental ones, including "higher-level" cognitive functions (47%) such as problem-solving and abstract thought.

Other, less obvious traits are heritable, too. The amount of time a child spends watching television was assumed for many years to have a heritability close to zero. In 1990, however, a study led by Robert Plomin, now at King's College, London, compared the habits of adopted children with those of their birth mothers. It found television-watching has a heritability of about 45%. Similar surprisingly heritable traits include a child's tendency to be bullied at school (more than 70%) or to be accident-prone (51%). Even someone's likelihood of being religious (30-40%) or of getting divorced (13%) is heritable.

In 1989 James Watson, the first head of the Human Genome Project, summarised the mood of many by declaring that "We used to think our fate was in our stars. Now we know, in large measure, our fate is in our genes." There was hope then that the genome project would locate those genes. No one was naive enough to think that there existed, say, such a thing as a gene for television-watching. But it was reasonable to believe that there might be a handful of genes which combined to encourage television-watching indirectly. More important, there was an expectation that the heritable causes of things like heart disease might be pinned down to such genetic handfuls. These might then be investigated as drug targets. To everyone's frustration, though, few such genes revealed themselves. And in most cases the contributions they made to a condition's heritability were small. Where, then, was the missing heritability?

Hiding in plain sight

With hindsight, the answer was obvious. The number of variants that play a role in disease risk is far higher than Mendel-blinded researchers had imagined. Though human beings are genetically more than 99.9% alike, they have 6bn genetic letters in their genomes. This is where the SNPs are hidden, for a diversity of less than 0.1% still leaves room for millions of them. And when SNPs' contributions are combined, their effects can be significant. For height, for example, the number of relevant SNPs is reckoned to be about 100,000—each adding or subtracting, on average, 0.14mm to or from a person's adult stature. Furthermore, most of these SNPs are in parts of the genome that do not encode proteins at all. Rather, they regulate the activities of other genes and often have no obvious connection to the trait in question.

To be fair, it was mainly human geneticists who were captivated by the simple Mendelian model of single genes with big effects. According to Peter Visscher of the University of Queensland, Australia, many plant and animal scientists knew of traits' genetic complexity long before the Human Genome Project started. But they were more interested in breeding better crops or livestock than in understanding the biology behind such complexity.

Dr Visscher was one of the first to realise that human studies would need to recruit more participants and screen for many thousands more SNPs if they were to capture in full the genetic components of most traits. In 2007 he and his colleagues used models to show that for a condition with a prevalence of 10% in the general population, approximately 10,000 volunteers are required to identify the SNPs marking the 5% of those at highest risk of developing that condition. Earlier studies, often with just a few hundred participants, had simply not been powerful enough to see what was going on. And

thus was GWAS born.

Ideally, a GWAS would obtain a full sequence of the genome of every participating individual. However, even though the cost of such sequences has fallen dramatically since the completion of the genome project, to about $1,000 a shot, this would still be prohibitively expensive. Instead, researchers use devices called SNP arrays. These detect hundreds of thousands of the most common SNPs for a price of $50 or so.

A combination of SNP arrays, larger samples of volunteers and better computing methods means it is now possible to find millions of variants that contribute to a trait. An individual's score from these variants, known as his polygenic score, can then be calculated by adding up their contributions to give, for example, his risk of developing a particular disease in later life.

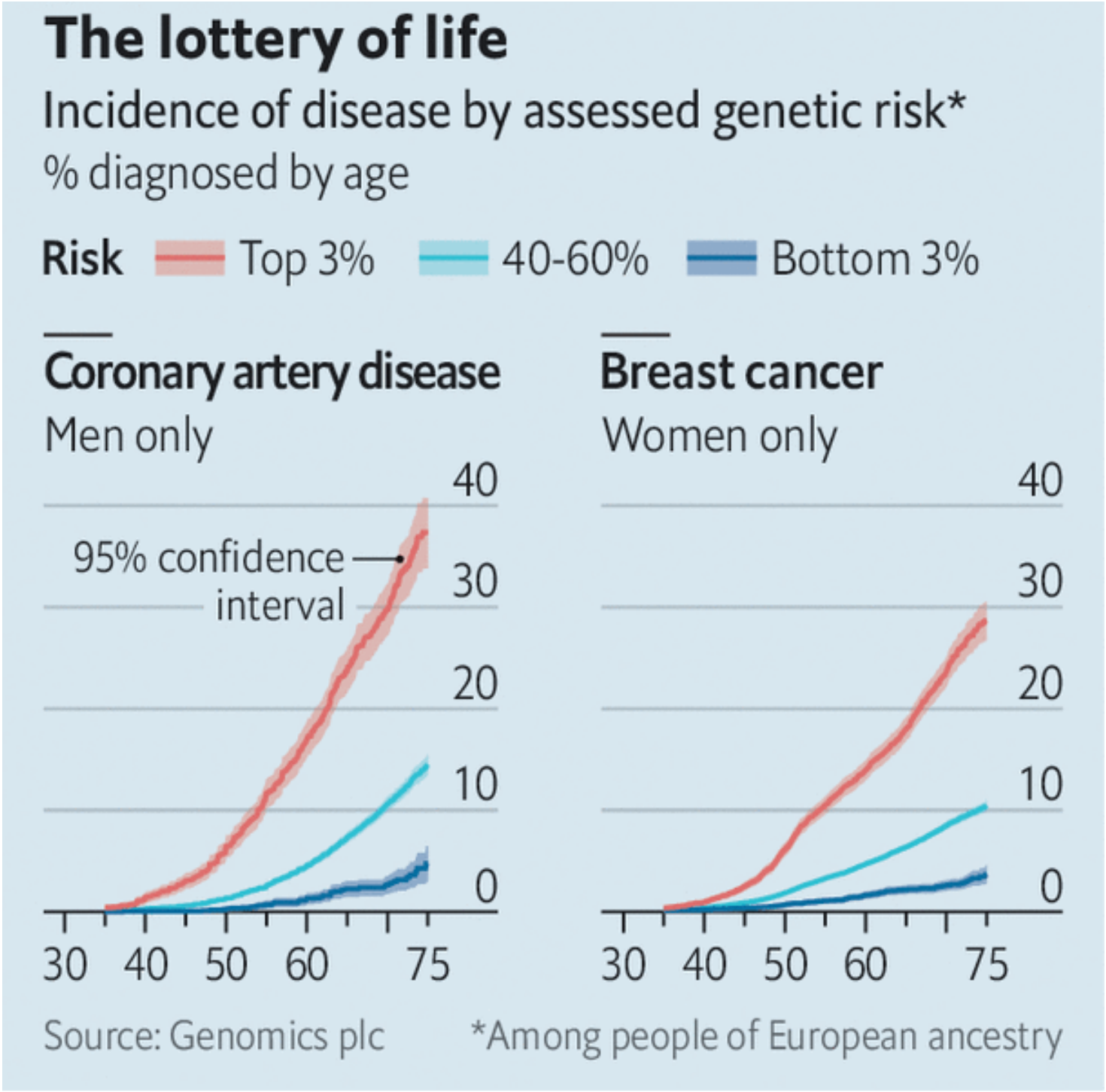
We have the technology

Another advance has been a change in the way volunteers are recruited. Institutions called biobanks have come into existence. These hold both tissue samples from, and a range of medical and other data about, large numbers of people who have agreed to make those data available to researchers who meet the criteria employed by the bank in question.

Among the largest of these repositories is the UK Biobank, in Britain. This has 500,000 depositors. One study that drew on it, published in 2018 by Sekar Kathiresan of the Massachusetts General Hospital in Boston and his colleagues, worked out polygenic risk scores for five diseases, including coronary heart disease and type 2 diabetes. By totting up scores from over 6m genetic variants, they were able to elucidate SNP patterns that identify those who are at a threefold higher risk or worse than the general British population of developing one of these diseases. For heart disease, 8% of the population are at such risk. For type 2 diabetes, 3.5%.

Nasim Mavaddat of the University of Cambridge and her colleagues have similarly calculated polygenic risk scores for breast cancer. These showed that a British woman's average ten-year risk of developing breast cancer at the age of 47 (the earliest that England's National Health Service begins screening for the disease) is 2.6%. The study also found that the 19% of women who had the highest risk scores reached this level of risk by the age of 40. Conversely, the 10% at lowest risk did not cross the threshold until they were 80.

Using these and similar studies, it is possible to draw up lifetime risk profiles for various medical conditions. A British firm called Genomics has done that for 16 diseases (see chart). This will help screening programmes to triage who they screen, by offering their services earlier to those at high risk of developing a condition early in their lives. It will also permit the dispensing of risk-appropriate advice about diet and exercise to those who need it most, and the early offering to those who might benefit from them of things like statins and antihypertensive drugs. In light of all this England's National Health Service announced in July that 5m healthy Britons would be offered free gene tests.



A third study that drew on the UK Biobank is rather different. It was published in October and demonstrated the power of GWAS to reach beyond non-medical matters. It examined patterns of internal migration in Britain, and showed that there has been an outward migration from former coalmining areas of people with SNP patterns associated with high educational attainment—precisely the sorts of individuals economically deprived places can least afford to lose.

Educational attainment also demonstrates how heritability varies with environment. In Norway, for example, heritability of educational attainment increased after the second world war as access to education widened. Since all children now had more or less the same opportunities at school, environmental variation was largely ironed out and the effects of genetic

differences consequently exaggerated.

Both of these examples foreshadow how the sort of genetics made possible by GWAS can have political consequences. The implication of the internal-migration study is that the geographically left-behind are dimmer, on average, than the leavers. The implication of the Norwegian study might likewise be seen by some as suggesting that those who have done well at school and thus snagged the best (and best-paid) jobs are part of a genetic elite that deserves its success, rather than being the lucky winners of a genetic lottery.

And that is just within a country. Start comparing people from different parts of the world and you enter a real minefield. Because most of the genetic data now available come from populations of European ancestry, their predictive power is poorer for people from elsewhere. Alicia Martin of the Broad Institute in Massachusetts and her colleagues scored West Africans for height based on SNPs drawn from studies on European or European-derived populations. The scores predicted that West Africans should be shorter than Europeans. Actually, they are not.

As more people of non-European ancestry are sequenced, these problems may abate. But if group-based differences emerge or persist in the face of better data, that would be cause for concern. Differences between groups in things like height are rarely cause for prejudice beyond a jocular level. For something like educational attainment, by contrast, there is a risk that politically motivated groups would try to exploit any differences found to support dubious theories of racial superiority.

To some historians, this looks horribly familiar. They fear that the old spectre of eugenics risks rising in a new guise. As Nathaniel Comfort of Johns Hopkins University, in Baltimore, observes, "The IQ test was invented in order to identify students who needed extra help in school. But within about a decade, it was being used as a tool to weed out the so-called 'feebleminded', not just from school but from the gene pool." Such fears of genetic stratification would become particularly acute if polygenic scores were applied to embryos for the purpose of selecting which to implant during IVF—as Genomic Prediction is just about to do.

Brave new world

Genomic Prediction and a second firm, MyOme (which is not yet accepting customers), claim to be able to build up an accurate picture of an embryo's genome. That is tricky because the sequencing has to be carried out using the tiny quantities of DNA in a few cells taken from that embryo. A sequence so obtained would normally be full of errors. The two companies say they can deal with this by comparing embryonic sequences with those of the biological parents. All of the DNA in the embryo has come from one or other parent, so blocks of embryonic DNA can be matched to well-established sequences from their parental progenitors and an accurate embryonic sequence established. That makes working out the embryo's SNP pattern possible.

Genomic Prediction thus says it is able to offer couples undergoing IVF a polygenic risk score for each embryo for a variety of diseases including type 1 diabetes, type 2 diabetes, breast cancer, testicular cancer, prostate cancer, basal-cell carcinoma, malignant melanoma, heart attack, atrial fibrillation, coronary artery disease, hypertension and high cholesterol. At the moment it does not offer scores for non-medical traits like height or educational attainment. But there is nothing to prevent it from doing so should it so wish.

Even for medically relevant scores, however, some worry about this approach. One concern is pleiotropy—the phenomenon of the same piece of DNA influencing several apparently unrelated traits. Choosing an embryo with a low risk of heart disease might accidentally give it, say, a higher chance of developing epilepsy. Single-mindedly maximising scores for positive traits like intelligence or height may therefore increase the risk of genetic disorders.

Stephen Hsu of Michigan State University, one of Genomic Prediction's founders, acknowledges the theoretical risk of this, but argues that serious pleiotropic effects are unlikely. "If you looked at a bunch of kids with IQs of, say, 160 or 170," he says, "I doubt you'd find much seriously wrong with them. They'd just be a bunch of geeks." Dr Hsu, who in 2014 predicted that reproductive technologies would soon be used to select for more intelligent offspring, estimates that an IQ gain of between 10 and 15 points would be possible if couples were allowed to choose between ten embryos. He also thinks that further gains would probably accumulate if people selected in this way went on to select their own offspring on the basis of intelligence.

This is plausible. Before 2008, when the first SNP chips for cattle became available, the annual milk yield of dairy cows in America had been increasing at about 50kg per year. After six years of chip-based polygenic selection, the rate of increase had doubled to more than 100kg per year. This suggests the technique is powerful—in cattle at least. Despite Dr Hsu's optimism, however, pleiotropism has reared its head in these animals. They have become less fertile and have weaker immune systems.

In the end, then, it is generally a good idea to remember that human beings have already been optimised by a powerful agent called natural selection. Trade-offs between different pieces of physiology, even in domestic animals, will have been forged in the crucible of evolution and will generally be optimal, or close to it. Genetic tinkering may sometimes improve things. But by no means always.

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