ILLUSTRATION BY DAVID PARKINS

Growth of genome screening needs debate

There could be unexpected consequences if greater understanding of disease genetics gives parents more choice in what they pass to their children, says **David B. Goldstein**.

Twenty years ago, at the outset of the human genome project, tens of genes were known to cause Mendelian diseases when disrupted. These rare conditions are usually caused by mutations in single genes, and are passed on from one or both parents according to simple inheritance laws. Now, nearly 3,000 of these genes have been mapped. Advances in screening mean that prospective parents could in principle find out whether they are carriers of each disease-causing mutation in any of these genes before choosing a reproductive partner or before conceiving. Couples could also find out whether an embryo created through *in vitro* fertilization carries such mutations, or whether a fetus does. Indeed, a fetus's entire DNA sequence can now be determined by sequencing the fragments of fetal DNA in the mother's blood[1,2].

Screening will not stop here. Until recently, the idea that you could identify very strong genetic predictors of a person's risk of developing common diseases — such as epilepsy or type 2 diabetes — through screening seemed unlikely because of the presumed complexity of the underlying genetics. Evidence now suggests that numerous genetic variants, each rare in the general population, have a strong influence on which common diseases people get and when. Over the next five years, the sequencing of hundreds of thousands of human genomes is likely to identify many gene variants that, individually or in combination with a few other variants, have a strong effect on disease predisposition.

Societies and governments are ill-prepared for the imminent availability of this information. We must consider now the extent to which we want to dictate the genomes of our children, the individual and societal implications of doing so, and where the authority for such decisions should rest — with governments or parents?

Following the Second World War, a consensus emerged among biologists that the genetic bases of most common diseases are fundamentally different from those of Mendelian ones. Many thought that these diseases, instead of being caused by severe rare disruptions to genes, were strongly influenced by the combined effect of numerous common variants — mutations found in more than, say, 1% or 5% of the population. Each of these mutations was thought to have either small effects on a carrier's risk of developing a disease or nuanced effects — conferring problems in some environments and perhaps benefits in others.

There was comfort in complexity in this world view. Although screening might be appropriate to curb rare Mendelian conditions such as Tay-Sachs disease and cystic fibrosis, such an approach seemed inconceivable for common 'complex' diseases.

In the past few years, support for this

picture has waned. Genome-wide association studies interrogate a set of known variants, most of which are strongly associated with others. By investigating the standardized set, geneticists can obtain information about virtually all the common variants in the human genome. Some studies have scanned tens of thousands and, recently, hundreds of thousands of genomes. Yet for most diseases, only fractions of the genetic control have been explained. What's more, in cases where geneticists have identified many variants, each having a minuscule effect, it is difficult to determine which ones have a causal role.

An even stronger challenge to the idea that numerous common variants underlie common diseases comes from the study of copy-number variants. These deleted or duplicated stretches of DNA sometimes involve scores of genes. They are far more similar than expected to Mendelian-disease mutations — both in being obviously harmful, and in having large effects on a carrier's risk of developing a disease. A small but rapidly growing number of very rare copy-number variants have been identified as definitive risk factors for several common diseases, including autism and epilepsy[3,4].

In other words, at least some common diseases may turn out to be caused by numerous rare genetic mutations, each with considerable effect, that differ from person to person.

HARD TO TREAT

Many in the medical-genetics community stand by the idea that common variants are the primary driver of common disease[5,6]. Yet the perspective I've outlined here — that some common diseases are strongly influenced by rare high-impact mutations — has gained considerable support over the past four years[7].

To me, the most troubling implication of this is the inevitable expansion of screening that will happen once these rare mutations are discovered.

One of the most sobering lessons from the study of Mendelian diseases is that identifying underlying genetic defects rarely leads to the rapid development of effective treatments. Success stories exist: the painful bone lesions and anaemia of enzyme deficiencies such as Gaucher's disease, for example, can be greatly reduced by injecting patients with artificially synthesized enzyme. But many more diseases remain incurable even though their genetic bases have long been known. In some cases, such as cystic fibrosis, care regimes have relieved symptoms and extended lifespan, but these advances are not cures and so far have not been much informed by knowledge of the responsible gene.

Finding treatments for non-Mendelian diseases could prove just as difficult. In the meantime, the demand for screening to give prospective parents the option of not transmitting mutations is likely to soar — especially given the plummeting costs of sequencing entire genomes. (The US$4,000–$5,000 needed today roughly matches the cost of some widely used medical imaging procedures.)

Currently, there is no consensus on which mutations should be identified through screening. Tests are routinely offered in the United States and Europe for mutations causing early onset, serious Mendelian diseases such as Tay Sachs, Down's syndrome and cystic fibrosis. Indeed, since the late 1970s, screening — carried out either before conception, before an embryo is implanted or during pregnancy — has reduced the number of children born with Tay Sachs in the United States by 90%. Even screens for later-onset conditions such as Huntington's disease are offered in some US fertility centres. Yet no screens are available for the *APOE4* variant that confers a dramatically increased risk of late-onset Alzheimer's disease.

"Many diseases are incurable even though their genetic bases have long been known."

Testing for variants that may not necessarily lead to disease, or that underlie diseases of adulthood or old age, may seem less urgent than testing for ones that mean a child will die young. But some of the people who carry the *APOE4* allele today would like to be sure they don't transmit it.

Today, decisions about what should be tested for tend to be made by government organizations, such as the UK Human Fertilisation and Embryology Authority, or by medical practitioners in fertility clinics, as in the United States. The German parliament is considering allowing prenatal genetic testing in only a few situations, for instance when pregnancy would probably result in stillbirth or miscarriage. I am supportive of the rights of parents to choose whether they wish to transmit variants such as *APOE4* that are strongly associated with risk of disease, although this inevitably raises the question of where to draw the line.

TOUGH CHOICES

Within the next few years, our ability to identify pathogenic and potentially pathogenic mutations — as well as the huge number of mutations that no one can vouch for as dangerous or safe — will almost certainly outstrip our ability to act on the information. For example, if parents using *in vitro* fertilization wanted to avoid transmitting five mutations, physicians would have to screen scores of embryos to have a reasonable chance of finding one that carried none of the mutations. Likewise, parents would have to terminate an unfeasible number of pregnancies to be assured that their fetus was unaffected.

Such constraints are unlikely to apply indefinitely, however. It is already routine for researchers to selectively 'edit' DNA sequences in certain kinds of cell. This cannot yet be done in human sperm and eggs, but several technological advances that are generally expected would permit the effective editing of gamete DNA[8]. This would allow a qualitatively different kind of screening.

Rare variants are more likely to damage genes than common ones[9]. Data generated from various whole-genome sequencing studies carried out at the Center for Human Genome Variation at Duke University in Durham, North Carolina, suggest that every person carries hundreds of distinct protein-changing variants that exist in less than 1% of the general population. Might some parents choose not to transmit any such rare variants to 'play it safe' if they could?

One potential problem with this is that numerous genetic risk factors will have diverse and unexpected effects — sometimes causing disease, sometimes being harmless and sometimes perhaps being associated with behaviours or characteristics that society deems positive. Even for simpler Mendelian diseases, up to 30% of the mutations originally termed pathogenic have turned out to be apparently harmless[10]. Wholesale elimination of variants associated with disease could end up influencing unexpected traits — increasing the vulnerability of populations to infectious diseases, for instance, or depleting people's creativity.

There are no clear-cut answers to the questions of what should be screened for and to what end, but we must at least begin the debate. ■

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CORRECTION

The Comment article 'The unplanned impact of mathematics' (*Nature* **475,** 166–169; 2011) credited Andrew Odlyzko with publishing results on kissing numbers in 8 and 24 dimensions. This work was done jointly with Neil Sloane.