THIS WEEK

EDITORIALS

A more personal view

A long-planned effort to examine gene expression and gene regulation in all the major tissues in the human body across many people comes to fruition.

"The observation of and the search for similarities and differences are the basis of all human knowledge," Alfred Nobel once said. From external events to spiritual influence, each culture and time has found its own way to explain how we differ from each other and what we have in common. Today, much biological effort focuses on the similarities and differences between people's DNA, and probing the myriad ways that these can combine, for good or ill, is at the cutting edge of genetics.

This week, geneticists announce the results of one such project. The researchers describe how they have analysed the regulatory code in our genomes. This should help scientists to unpick how genetic variants associated with disease function in different tissues of the body.

The project is called GTEx (genotype-tissue expression) and it catalogues genetic variation and its influence on gene expression in 44 tissues across the human body. The results — published in four papers (see pages 204, 239, 244 and 249) and discussed in an accompanying News and Views article (see page 190) — show how most of these critical regulatory regions are located close to the gene they affect. And they report important differences in gene regulation between tissues and between individuals. These results build on the findings of a pilot study that were announced in 2015.

The project results were a long time coming and were widely anticipated. The GTEx study was first proposed back in 2008. Its goal was to establish a resource database and an associated biobank (holding all major human tissues from 1,000 deceased individuals) that could be used by scientists to study the relationship between genetic variation and gene expression.

That seemed so far beyond technical capabilities at the time that many dismissed the idea as unrealistic. How could that many tissues be sampled from a single donor? How could so many individuals be recruited and be appropriately consented? How could high-quality samples be taken within the required post-mortem interval (different for various tissues)? And would the data even reflect living biology and replicate known findings on gene regulation?

What was not questioned was the scientific need to reach for those goals. Following the Human Genome Project in the early 2000s, the genomics community had continued to establish reference catalogues for human genomes. These characterized genetic variation within and between individuals in populations worldwide, and made it possible to begin to identify functional elements in different cell and tissue types. Geneticists also identified genetic variation associated with a wide range of human diseases, a large proportion of which is found in non-coding regions, suggesting a role for gene regulation.

The GTEx Consortium investigates this link. To do so, project scientists needed a framework to consider ethical, legal and social issues that surround post-mortem donation (as discussed in a News story on page 169). Research on samples from deceased donors is not covered by rules on using humans as experimental subjects, and so does not need consent in the United States, where the project was based. But the GTEx scientists decided to include only samples from people for whom consent had been obtained from next of kin. This is commendable. Presumed consent — a sensible policy for organ donation for transplantation — seems less appropriate for basic research, where the benefits are not as immediate and clear-cut. It is good, too, that some researchers kept in touch with donor families, many of whom have attended project meetings to hear about the ongoing contribution of their loved one to science.

Nearly all donor families have said that they would like some genetic results returned, especially information relevant to treatable diseases. The GTEx study was not designed to do this. Nevertheless, project organizers and other researchers should consider in future studies whether and how they could return results to tissue donors' families.

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Why rely on deceased donors? Previous studies were largely limited to cell lines or blood, but the GTEx project wanted to assess other tissues relevant to disease, for example the heart and kidneys. Combined with the desire to study materials that are not available from living donors, such as the brain, and the need to sample multiple tissues from the same individual, it was clear that the project would have to find a way to source and quickly sample tissue post-mortem. To identify potential donors, the project made use of a network of existing programmes, such as autopsies carried out soon after death, and organ- and tissue-transplantation registers.

In reaching this point, and by providing an open-access database and tissue biobank that is already being widely used in biomedical research, the GTEx project has provided clear guidelines and procedures that are already informing, and providing the groundwork for, a next generation of studies.

These should include, for example, continued expansion of projects such as GTEx to include larger numbers of donors and sampling across different populations to further our understanding of the impact of genetic variation and regulatory differences. Complementary to these studies are projects such as the proposed Human Cell Atlas, which aims to use single-cell sequencing to better resolve cell types and their relationships.

For now, all biomedical researchers should welcome the wealth of data that continues to be released by the GTEx project, and the insights it provides into the regulatory code of our genomes. It is an important step towards the ultimate and ambitious goal of being able to characterize genetic variation and gene regulation in all cells of the human body. ■