GENETICS

Single-cell genetics

Single-cell measurements enable more sophisticated studies of the genetic basis of gene expression phenotypes.

Genomic variants that affect gene expression levels—so called expression quantitative trait loci or eQTLs—are typically identified by their association with changes in average levels of gene expression in the tissue or population of cells in question. But what if average gene expression is not the most relevant phenotype? There is inevitably expression heterogeneity in cells within a population, and at least for single-cell organisms, it is known that heterogeneity can be important. Might it be then that, in more complex organisms too, single-cell measurements would provide a better route to identifying genomic variants that matter?

This is the idea being put forward by Chris Holmes, Quin Wills and colleagues, as part of a collaboration between Oxford University, University College London,

Fluidigm Corporation and UEA Flow Cytometry Services. As Wills puts it, "Just averaging doesn't really mean anything; it's similar to having your head in the fridge and your feet in the oven and saying on average you're OK." In their work, the researchers identified single-cell (sc) QTLs, human genomic variants associated with properties of single-cell gene expression patterns.

Starting with lymphoblastoid cell lines from 15 HapMap individuals, Wills and colleagues used quantitative PCR to measure the expression of 92 genes known to be affected by Wnt signaling, either in unperturbed cells or in cells treated with a Wnt agonist. They did these measurements in close to 1,500 single cells.

The researchers then measured associations of single-nucleotide polymorphisms within 50 kilobases of each gene with either its average gene expression or with several properties of single-cell gene expression,

such as heterogeneity, burst size or burst frequency. They also built networks based on the single-cell data for each individual, and looked for associations between SNPs and properties of these networks. They found 47 significant associations using the single-cell data; this number dropped to 6 when only the average data were considered.

This study identified scQTLs for seven genes that have come up in clinical genome-wide association studies and for which no eQTLs have as yet been defined. As single-cell technology continues to develop, future work will no doubt help define whether scQTLs prove better at providing a mechanistic understanding of the genotype-phenotype connection in health and disease.
Natalie de Souza

RESEARCH PAPERS
Wills, Q.F. *et al.* Single-cell gene expression analysis reveals genetic associations masked in whole-tissue experiments. *Nat. Biotechnol.* **31**, 748–752 (2013).