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GENE EXPRESSION

A new take on expression

Variation in gene expression can be studied just like any other quantitative genetic trait. This is the conclusion published in *Nature* by Morley, Molony *et al.*, who used a combination of microarray analysis and genome-wide linkage analysis.

Natural variation in gene expression is widespread. Realizing that herein lies the key to the inter-individual phenotypic variation, including susceptibility to complex diseases, the authors set out to see how amenable this variation would be to genetic study. First, they used microarrays to identify the variable loci. To do this, they measured differences in the expression of ~8,500 human genes from immortalized B cells, and selected the 3,554 most variable genes for subsequent mapping. Second, they used a computer program called SAGE to carry out genome-wide linkage analysis in 14 families from the CEPH (Centre d'Étude du

Polymorphisme Humain) panel, which was also the source of the expression data. Using two stringency criteria (genome-wide $p = 0.001$ and 0.05), they detected linkage for 142 and 984 expression phenotypes, respectively.

The regions that are linked to the expression phenotypes — the regulators — can be in *cis* (according to the authors' criteria, these have to lie within 5 Mb of the target gene) or in *trans*. Although most target genes are associated with regulators in *trans*, few have multiple regulators. The authors point out that rather than reflecting a biological phenomenon, this result might simply be due to the difficulty in detecting multiple regulators, as each of them would have only a weak effect on its target.

The authors found what they term 'master regulators of transcription' — transcriptional regulators that influence many expression phenotypes.

Two hot spots of such regulators were found: one on chromosome 14 and one on chromosome 20. Furthermore, some targets of the master regulators showed coordinated levels of expression.

For the handful of genes, the expression levels of which are regulated by determinants in *cis*, the authors used the results of linear regression to estimate the proportion of the variation that can be attributed to these *cis* factors. It turns out that for some genes, they account for more than half the variation in expression. The authors point out that the remainder of the variation is probably caused by a variety of factors, including the environment.

So, the combination of expression profiling and genome-wide mapping has allowed the authors to identify regulatory elements without any previous knowledge of the regulatory mechanism. It also uncovered a complex network of multiple regulators, including master elements. Morley and Molony *et al.* have shown us that it is possible to move beyond the experimental manipulation of gene expression, towards revealing the genetic interactions that underlie natural variation in expression.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Morley, M. & Molony, C. M. *et al.* Genetic analysis of genome-wide variation in human gene expression. *Nature* 21 July 2004 (doi:10.1038/nature02797)

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