genes having the lowest rates. The authors propose that recombination might be favoured in regions that are exposed to recurrent selection (for example, from the environment or by pathogens).

Now that the fleshed out HapMap is available, what is the future of the HapMap project? Additional samples and populations will need to be sequenced and genotyped to provide information on rarer variants. Other important goals will involve generating molecular phenotypes for the HapMap samples and integrating SNP information with structural variation.

Magdalena Skipper

ORIGINAL RESEARCH PAPER
The International HapMap Consortium. A second generation human haplotype map of over 3.1 million SNPs. *Nature* **449**, 851–861 (2007)
WEB SITES
International HapMap Project :
http://www.hapmap.org/
dbSNP: http://www.ncbi.nlm.nih.gov/SNP/

colony replicator, making it likely that binary combinations of mutations can be catalogued in a high-throughput manner.

Although the screen designs are not flawless, PEM-2 in particular is quick and easy to implement and can even be extended for use in other organisms. Most of the epistasis data we already have have been collected from the budding yeast, *Saccharomyces cerevisiae*, which is easier to manipulate than *S. pombe*. However, given that many processes in *S. pombe* are more similar to those of higher organisms than to those of *S. cerevisiae*, the interaction maps that it yields will have greater relevance for understanding metazoan biology.

Tanita Casci

ORIGINAL RESEARCH PAPER Roguev, A. *et al.* High-throughput genetic interaction mapping in the fission yeast *Schizosaccharomyces pombe*. *Nature Methods* 23 September 2007 (doi:10.1038/nmeth1098).
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GENE REGULATION

The many paths to coexpression

For gene products to function together, they often need to be expressed together. A new study that explores coexpression in *Ciona* urochordates reveals that the sequence elements involved are remarkably flexible in their architecture.

Brown and colleagues explored the basis of coexpression for 19 genes that function in muscle differentiation in two *Ciona* species. *Cis*-regulatory elements in all of these genes contain three classes of motif that bind different transcription factors and are responsible for directing muscle-specific expression. Within these motif classes there is variation — motifs of each type vary in sequence and, potentially, function.

The authors generated reporter constructs for regulatory elements involved in the expression of the 19 genes, and carried out extensive mutagenesis on them. After generating transgenic embryos expressing the mutagenized constructs, a quantitative whole-embryo gene expression assay was used to explore regulatory element function. This allowed the authors to define the elements that explain the expression of each gene. They then disrupted each of the putative transcription factor binding motifs in each element, either individually or in different combinations, allowing the relationship between the composition and function of the regulatory elements to be explored.

To analyse their results, the authors first needed to be able to determine the contribution of each motif to the expression that was driven by each element. A key question here was whether interactions between motifs are important for element function. This proved not to be the case — an additive model provided a good fit for the data, showing that motif interactions generally affect expression very little and providing a basis for further analysis.

Brown and colleagues then set about exploring how the architecture of different elements contributes to their function. Surprisingly, despite their shared expression pattern, there is a high level of flexibility among the elements that were investigated. First, these elements are diverse in terms of the number and types of motifs that they contain. Also, no rules related to motif spacing, order or orientation seem to explain their regulatory function. So, many different combinations and arrangements of motifs can be used to give rise to the same expression pattern.

Far less flexibility in the architecture of *cis*-regulatory elements is permitted over evolutionary time. When the authors compared orthologues of the coexpressed genes between the two *Ciona* species, they found a high degree of sequence constraint within the regulatory elements. Furthermore, measuring motif function in both species independently revealed that the functional contribution of each motif to the total regulatory activity is extraordinarily well conserved, despite the fact that the two species are diverged enough to have accumulated significant change at these motifs. This constraint seems to be relaxed when genes are duplicated: paralogous genes showed much more flexibility in terms of element use and composition.

As the authors point out, these findings have implications for understanding how genetic variation influences phenotype through polymorphisms in regulatory elements: the effect of alterations on both *cis*- and *trans*-acting factors is expected to vary widely between elements as a result of their diverse architectures.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Brown, C. D., Johnson, D. S. & Sidow, A. Functional architecture and evolution of transcriptional elements that drive gene coexpression. *Science* **317**, 1557–1560 (2007)
WEB SITE
The Sidow laboratory: http://mendel.stanford.edu/SidowLab