URLs

NETWORK ANALYSIS

Profiling epistasis

In classical epistasis analysis, the genetic relationship between two mutants is determined by comparing the phenotypes of single and double mutants. The phenotype of the double mutant reflects the epistatic gene, which literally masks the effect of the other gene. Now, Gad Shaulsky and colleagues present a new approach to epistasis analysis, using transcriptional profiles as phenotypes to compare single and double mutants.

Shaulsky and colleagues focused their analysis on the protein kinase A (PKA) signalling pathway within the haploid soil amoeba *Dictyostelium discoideum*. On starvation, this amoeba executes a developmental programme in which single cells combine to form a multicellular organism, a process that depends on the well-studied PKA pathway. To resolve the gene relationships in this pathway, the authors examined 6 genes within the PKA network, comparing single mutants to 3 of the possible 15 double-mutant combinations. Using microarray phenotypes of each mutant, they verified known gene relationships, confirmed two relationships that previously were only suggested by non-genetic studies and reconstructed the PKA pathway.

Using microarrays as phenotypes also allowed a quantitative comparison of the relatedness between two genes. The researchers found that mutants with common morphological defects had similar microarray profiles. They also found that the distance between the profiles of mutants, even those that are indistinguishable by morphology, was always greater than zero. This illustrates the unique effect that the disruption of each gene has on the expression profile, as well as the sensitivity of this approach.

Using transcriptional profiles as a phenotype bypasses the main limitation of traditional epistasis, because there is no need to define a measurable phenotype for each gene. As this approach allows any two genes to be compared without prior knowledge of their function, it could be applied systematically to determine the relationship between genes within an entire interacting network. It will be important to show whether this approach can be applied to other pathways, in particular those for which components might show less distinct phenotypes, as well as to other organisms.

Orli Bahcall, Associate Editor, Nature Genetics

References and links

ORIGINAL RESEARCH PAPER Van Driessche, N. *et al.* Epistasis analysis with global transcriptional phenotypes. *Nature Genet.* 10 April 2005 (doi:10.1038/ng1545)

FURTHER READING Van Driessche, N. *et al.* A transcriptional profile of multicellular development in *Dictyostelium discoideum*. *Development* **129**, 1543–1552 (2002) | Zupan, B. *et al.* GenePath: a system for automated construction of genetic networks from mutant data. *Bioinformatics* **19**, 383–389 (2003)