MULTIFACTORIAL GENETICS

A winning combination

It's a regrettable fact faced by many scientists that some projects can only be carried out with backbreaking hard work. Although a geneticist can dream, it's unlikely that machines will ever take on the burden of, say, dissecting 50,000 mutagenized animals, scoring their phenotype and classifying them into complementation groups. That said, for some projects it wouldn't be naive to hold out hope. The road from quantitative trait to causative gene has always been a long one. However, by combining the more traditional QTL (quantitative trait locus) mapping approach with the recently developed microarray technology, Wayne and McIntyre have moved towards making this particular road a shorter and more efficient one.

A QTL study would typically begin by identifying two populations that differ in the quantitative trait of interest, mixing the two genomes by genetic crossing and then looking for genomic regions that segregate with differences in the quantitative phenotype. The expensive and time-consuming step then follows: as a QTL region can be very large, the march to the gene in that QTL can mean sifting through hundreds, sometimes thousands, of candidates. Wayne and McIntyre have thought to simplify this step by applying microarrays to detect genes in the QTL interval that vary in expression between the parental lines. What's more, they have successfully translated theory into practice by identifying candidate genes that underlie a quantitative and evolutionarily relevant trait in *Drosophila* — ovariole number. There are usually ~20 ovarioles — the parallel filaments in which oogenesis takes place — in each fly ovary, but their number can vary and is related to female fecundity and therefore to their fitness. This was a particularly apt system to study: despite the importance of the ovary, not much is known about its developmental genetics.

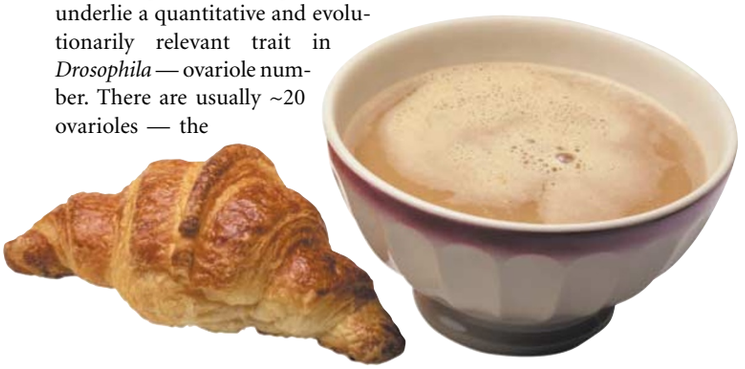
The initial QTL mapping for this trait uncovered 5,286 potential loci. As these were clearly too many to work with, the authors narrowed down the list by applying a tool that is widely used in flies — deficiency mapping. Lines of flies in which large, but defined, chunks of the genome are deleted were useful in identifying which parts of the candidate QTL regions contained informative genes. This reduced the number of positional candidate genes to 548. The microarray step was introduced next: using Affymetrix whole-genome microarrays chips, 34 genes were identified, in the region uncovered by the deficiencies, that differed in expression between the parental lines. Among these candidates were five genes that had not been annotated and that, therefore, would probably have been ignored in a more traditional QTL study.

The authors have shown that there is an efficient and objective means of homing in on candidate QTL while dodging the hard slog of fine mapping and candidate-gene study. In the process, they have confirmed the increasingly recognized role of regulatory gene changes — not simply structural ones — in evolution.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Wayne, M. L. & McIntyre, L. M. Combining mapping and arraying: an approach to candidate gene identification. *Proc. Natl Acad. Sci. USA* **99**, 14903–14906 (2002)



IN BRIEF

CANCER GENETICS

A Robertsonian translocation suppresses a somatic recombination pathway to loss of heterozygosity.

Haigis, K. M. & Dove, W. F. *Nature Genet*. 25 November 2002 (10.1038/ng1055)

The C57BL/6 *Apc*$^{Min/+}$ mouse, which carries a germline mutation in the tumour-suppressor gene *Apc* (adenomatous polyposis coli), is a model for the colon tumorigenesis initiated by loss of human APC. The authors have shown that loss of heterozygosity of mouse *Apc* occurs principally by somatic recombination between homologous copies of the gene — a process that is suppressed by a (7; 18) Robertsonian translocation. General genomic instability might therefore not be required generally for tumour progression.

MOUSE MODELS

IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice.

Holzenberger, M. *et al. Nature* 4 December 2002 (10.1038/nature01298)

Mutant studies in several invertebrate species have found that members of the insulin or insulin-like signalling pathways are involved in regulating lifespan. The authors have confirmed this hypothesis in mammals by inactivating the *Igf1r* (insulin growth factor 1 receptor) gene in mouse. Animals that are heterozygous for an *Igf1r* knockout mutation live, on average, 26% longer than wild type, but are otherwise normal.

COMPARATIVE GENOMICS

Whole-genome analysis of photosynthetic prokaryotes.

Raymond, J. *et al. Science* **298**, 1616–1620 (2002)

Photosynthesis is one of the biological processes that have had the greatest impact on life on earth, but its origin is unclear. The authors carried out a whole-genome comparison of representatives from each of the five photosynthetic groups of bacteria and have found that many orthologues, including photosynthesis-specific genes, have undergone substantial lateral gene transfer. The fact that different genes have had very different evolutionary histories explains the inconsistent phylogenies that have been built using more limited gene sets.

EVOLUTION

Dobzhansky–Muller incompatibilities in protein evolution.

Kondrashov, A. S. *et al. Proc. Natl Acad. Sci. USA* **99**, 14878–14883 (2002)

By analysing the fitness landscape of 32 proteins, the authors find that ~10% of human pathogenic missense mutations are residues that occur naturally in the non-human orthologues. This observation suggests that the proteins in non-human species frequently (and rapidly) accumulate mutations that compensate for the otherwise deleterious variant. The authors' study further shows that these compensatory mutations usually fall in the same protein.