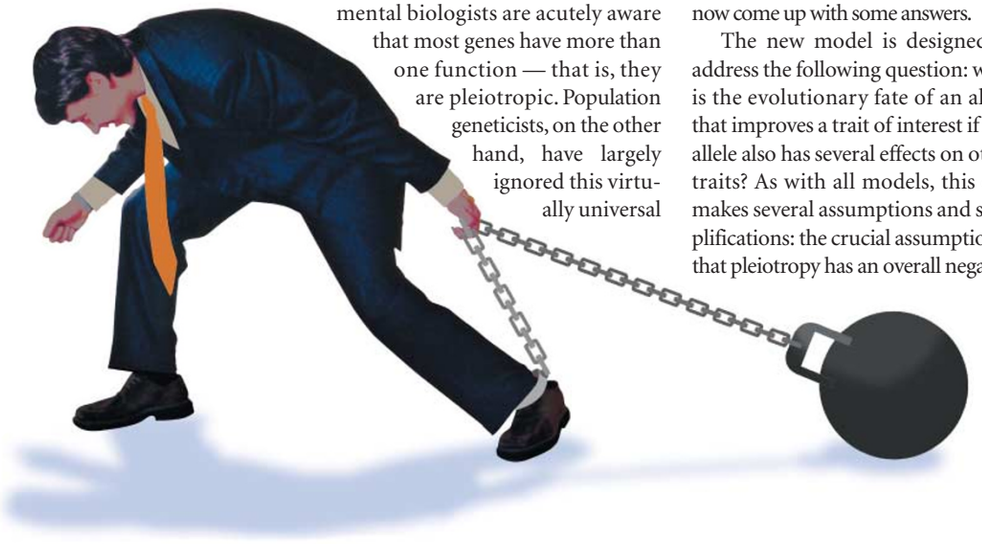
POPULATION GENETICS

Pleiotropy — what a drag



Whether they like it or not, developmental biologists are acutely aware that most genes have more than one function — that is, they are pleiotropic. Population geneticists, on the other hand, have largely ignored this virtually universal feature of genes, principally because of the difficulty of incorporating it into mathematical models: if a gene influences many traits, how does one of its functions evolve without this process disrupting its other roles? By developing a model that quantifies the effect of pleiotropy on selection, Sarah Otto has now come up with some answers.

The new model is designed to address the following question: what is the evolutionary fate of an allele that improves a trait of interest if this allele also has several effects on other traits? As with all models, this one makes several assumptions and simplifications: the crucial assumption is that pleiotropy has an overall negative impact on fitness — that is, the success of an allele that improves the trait of interest is hindered by virtue of that gene having other functions. To simplify the model, Otto then focused on conditions in which the negative effects of pleiotropy are strong relative to the allele's favourable effect on the trait of interest. From this model, some surprisingly general results emerged.

The model predicts that pleiotropy halves the total selection on alleles that spread within a population relative to the case in which evolution proceeds unencumbered by pleiotropy — that is, for every two steps in fitness that evolution takes a population forward when a favourable allele spreads, pleiotropy takes it one step back. And this just describes the effects of pleiotropy on those alleles that do succeed in spreading within the population. A large fraction of alleles that favour a trait of interest do not even spread because their benefit is overwhelmed by deleterious side effects.

DEVELOPMENTAL GENETICS

Rooting around for genes

Large-scale mutagenesis programmes are becoming the standard means of gene discovery, but the elegant identification of a novel gene that is involved in plant root development illustrates how natural variation can be equally useful for isolating interesting genes.

In one of the best examples yet of this approach, Céline Mouchel and colleagues exploited natural variation in the morphology of the root system in 44 accessions (samples) of *Arabidopsis thaliana*. One accession — Uk-1 — was particularly unusual: roots arose in unusual locations more often than in the others, it had a shorter primary root than average and its root system was generally more branched at later stages. Crosses of Uk-1 to another accession (Sav-0) with an average primary root length allowed standard segregation analysis of one of the traits that is peculiar to Uk-1: the short primary root phenotype.

The segregating locus — *BREVIS RADIX* (*BRX*) — was located to a 45-kb section of chromosome 1. Analysis of candidate genes in this region eventually identified the variant that leads to shorter primary roots as a base-pair substitution that causes a premature stop codon in an ORF, designated At1g31880 in the annotated *Arabidopsis* genome. Quantitative trait loci (QTL) analysis of 206 recombinant inbred lines derived from the Uk-1 x Sav-0 crosses showed that *BRX* accounts for approximately 80% of the variance in this trait.

Unlike previous genes involved in root growth that were identified through mutagenesis studies, *BRX* activity is specifically required in the root. Further phenotypic analyses also showed that variation at *BRX* affected both the number and the size of the primary root cells, the former accounting for two-thirds of the root length difference between Uk-1 and Sav-0.

The authors went on to identify other members of the plant-specific gene family to which *BRX* belongs. By analysing single- and double-null mutants of these genes, they found that *BRX* is likely to be the only member of the family that is involved in root development. Subsequent experiments that indicated that expression of *BRX* is localized to the nucleus and can activate transcription led the authors to speculate that members of this gene family encode a novel group of transcription factors.

This neat study from Christian Hardtke's group confirms that natural variation within species can be a great source of 'mutants' for gene discovery. Closely related species (see the article by Kocher on page 288 of this issue) or domestic animals breeds that vary from each other will be similarly potent sources of 'pre-selected' quantitative mutants. However, few QTLs will have as strong an effect as *BRX*, and few species have genomes that are as well-characterized as *Arabidopsis*, so we still have some way to go before the genetic dissection of natural variation becomes routine.

Nick Campbell

References and links

ORIGINAL RESEARCH PAPER Mouchel, C. F. *et al.* Natural genetic variation in *Arabidopsis* identifies *BREVIS RADIX*, a novel regulator of cell proliferation and elongation in the root. *Genes Dev.* 15 Mar 2004 (doi:10.1101/gad.1187704)
FURTHER READING Andersson, L. & Georges, M. Domestic-animal genomics: deciphering the genetics of complex traits *Nature Rev. Genet.* **5**, 202–212 (2004)
WEB SITE
Christian Hardtke's laboratory:
http://ww2.mcgill.ca/biology/faculty/hardtke_website/index.html

The main problem with any model that involves pleiotropy is that no-one knows what pleiotropy is really like. For example, what distribution does the size of pleiotropic effects follow? Despite our ignorance, Otto believes that some inferences about the process of evolution with pleiotropy are possible as, remarkably, certain calculations hold true no matter what shape this distribution takes.

Finding the right conditions to test the model's prediction will not be simple as natural selection is impossible to reproduce. However, previously published artificial selection experiments seem to hint that Otto's numbers are telling the truth.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Otto, S. P. Two steps forward — one step back: the pleiotropic effects of favoured alleles. *Proc. R. Soc. Lond. B* 23 Feb 2004 (doi:10.1098/rspb.2003.2635)

WEB SITE

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HUMAN GENETICS

Fat chance

One-fifth of the large number of people who get premature coronary heart disease also have familial combined hyperlipidaema (FCHL). Characterized by high total cholesterol and/or triglycerides, FCHL has been linked to a locus on 1q21-q23, which is also implicated in type II diabetes. Päivi Pajukanta and colleagues have now explored this region in detail and discovered that FHCL is associated with the gene that encodes upstream transcription factor 1 (USF1), a protein that is involved in the regulation of several genes for glucose and lipid metabolism.

The team scrutinized 4 functionally relevant candidate genes on 1q21 in 60 Finnish families. These genes encoded thioredoxin interacting protein (TXNIP), retinoid X receptor gamma (RXRG), apolipoprotein A-II (APOA2) and USF1 itself. Although *TXNIP* underlies an equivalent condition in mice, sequence analysis in 60 FCHL probands revealed no such association in humans. Similarly, none of the SNPs that were found in *RXRG* or *APOA2* proved to be relevant to the condition. Examination of *USF1* was more productive. The common alleles at 2 SNPs (usf1s1 and usf1s2) that are separated by 1,239 bp were linked to and associated with FCHL and high levels of serum triglycerides. A further 4 SNPs were related to elevated triglycerides in males, which brought the size of the associated region up to 46 kb. This region also includes the neighbouring F11 receptor gene (*F11R*). The authors established that *USF1* is implicated in the complex FCHL phenotype, rather than in elevated triglycerides alone, by demonstrating an association of the usf1s1–usf1s2 combination with increased apolipoprotein B, increased total cholesterol and small low-density lipoprotein peak particle size.

The researchers then moved on to look at gene expression in fat biopsies from individuals with the *USF1* 'risk' haplotype, using the 'protective' haplotype for comparison. Interestingly, genes that are involved in fat metabolism were upregulated more often than expected in those with the 'risk' haplotype, whereas the downregulated genes included components of the immune-response machinery. With nearly 100 differentially expressed genes altogether, it seems that the *USF1* risk haplotype is responsible for changes in gene expression in these samples.

As steady-state expression levels of *USF1* itself proved to be similar in 'risk' individuals and individuals not carrying the risk haplotype, the authors suggest that there is no direct effect of the associated allele on *USF1* transcription, at least in adipose tissue. Turning to the genomic sequence that flanks the risk haplotype, the team found a highly conserved 60-bp sequence element that is present in 91 human genes. A reporter assay indicated that this was possibly a new *cis*-acting regulatory element.

Although further studies are needed to understand the mechanics of the connection between *USF1* alleles and the FCHL phenotype, this work ties the gene into the complex genetic network of this disorder and hints also at a role in diabetes.

Ruth Kirby,
Nature Publishing Group

References and links

ORIGINAL RESEARCH PAPER Pajukanta, P. *et al*. Familial combined hyperlipidemia is associated with upstream transcription factor1 (USF1). *Nature Genet.* 29 Feb 2004 (doi:10.1038/ng1320)

WEB SITES

Leena Peltonen's laboratory:
http://www.research.medsch.ucla.edu/Departments/humgen/faculty.cfm?FacultyKey=422

Päivi Pajukanta's laboratory:
http://www.research.medsch.ucla.edu/Departments/humgen/faculty.cfm?FacultyKey=3541