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

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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 hyperlipidaemia (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 FCHL 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 *F11R* 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

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WEB SITES

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Päivi Pajukanta's laboratory:

<http://www.research.medsch.ucla.edu/Departments/humgen/faculty.cfm?FacultyKey=3541>