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COMPLEX TRAITS

Old meets new in obesity genetics

Selection studies in model organisms provide a well-controlled evolutionary framework for identifying genes that are responsible for a selected phenotype. Long generation times usually make such studies challenging to carry out in mammals. A new study combines historical long-term mouse selection experiments with modern genomic analyses to identify genetic determinants of body weight.

Chan *et al*. took advantage of multiple independent mouse strains that had been selected for high body weight in the 1970s, some of which had been selected for >150 generations. These strains (and normal body-weight controls) have since been inbred to maximize genomic homozygosity, thus facilitating the identification of genotype–phenotype correlations. In the current study, the authors carried out genome-wide SNP genotyping to identify genetic variants that had been positively selected in independent high-weight mouse lines compared with normal-weight controls. They identified 67 regions of interest encoding 525 genes, achieving superior resolution to typical quantitative trait locus (QTL) studies.

To assess the relevance of this set of candidates, the authors used ontology analyses and found enrichment for genes with putative roles in energy regulation, metabolic signalling and birth-weight determination. Furthermore, gene expression analyses showed that such pathways were differentially active in high-weight compared with normal-weight mice.

The authors prioritized this candidate list by focusing on genes that overlap QTLs for body weight or fat pad weight from previous studies; using this approach, they identified the G-protein-coupled receptor genes *Gpr133* and *Gpr10*. Existing functional data are consistent with a role for these genes in body weight; they are specifically expressed in glands that hormonally control body weight (expression of *Gpr133* in adrenal glands) or that control appetite and metabolic rate (expression of *Gpr10* in the hypothalamus). Furthermore, mice with engineered *Gpr10* deficiency are known to suffer multiple abnormalities, including obesity.

As confirmation that the study findings might be relevant outside experimental settings, the authors found patterns of selection in equivalent genomic regions in naturally selected wild populations of large mice living on remote islands. There was also significant overlap with human QTLs associated with height: another indicator of body size.

This study emphasizes that mammals are useful organisms for classical selection studies and that historical genetic studies can be complemented by modern genomic tools.

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ORIGINAL RESEARCH PAPER Chan, Y. F. *et al*. Parallel selection mapping using artificially selected mice reveals body weight control loci. *Curr. Biol.* 22 Mar 2012 (doi:10.1016/j.cub.2012.03.011)

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