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NEWS AND COMMENTARY

Medical genetics

Revenge of the thrift

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Diet-induced obesity and Type II diabetes mellitus are escalating afflictions of Westernised society, and the factors controlling susceptibility, whether life style dependent or genetic, are the subject of intense scrutiny. In a recent issue of Heredity, Hillel *et al* (2005) have addressed the genetics underlying why some rodents are more prone than others to diabetes caused by a high-energy diet. The fat sand rat, *Psammomys obesus*, is an animal model illustrating the 'thrifty gene' hypothesis: the idea that certain gene variants provide an evolutionary advantage by allowing more efficient storage of scarce food energy, in preparation for times of famine. *P. obesus* is a desert-dwelling relative of the domestic gerbil. When its usual sparse diet of saltbush (*Atriplex halimus*) is replaced with higher energy foodstuffs, some individuals are found to be more prone to symptoms of Type II diabetes and excessive weight gain.

A selective breeding programme was undertaken over 10 years ago to separate out those *Psammomys* that are more prone to diet-induced diabetes (DP) from the diabetes-resistant (DR) ones. This study design has been widely used in rats for the separation of simple phenotypes, such as blood pressure, alcohol preference, and plasma glucose. The variability in response to high-energy diet in DP and DR strains provides an opportunity to examine the gene–environment relationship, and to identify which genes are responsive to dietary influence (recently referred to as 'nutrigenomics' (Müller and Kersten, 2003)). In the current study, the resulting DP and DR *Psammomys* lines are crossed to obtain an F1 intercross, and back-crossed with the DP, to give a BC1 generation. A high-energy diet is fed to 232 BC1 individuals who are then phenotyped for plasma glucose and body weight. This resulted in a bimodal distribution of nonfasting blood glucose concentration, with similar numbers of individuals in the susceptible and resistant groups. These results provide good evidence that in *P. obesus*, one major, dominant gene (or tightly linked group

of genes, see Flint *et al*, 2005) imparts resistance to diabetes and obesity induced by high-energy diet.

The authors' proposal that one major gene variant may also initiate Type II diabetes in humans is less clearly supported. The authors cite a 1996 study by Stern and colleagues of a Mexican-American population as an example of a major gene affecting diabetes susceptibility, yet a genome scan of presumably the same or similar population in 1999 identified several loci linked to Type II diabetes and age of onset (Duggirala *et al*, 1999). Many other genome scans for linkage to Type II diabetes have been performed in a wide range of human populations and, to our knowledge, without exception they support polygenic inheritance of diabetes and the relatively modest effects of the underlying gene variants. Several diabetes susceptibility genes have been suggested and replicated in linkage or large-scale association studies, including calpain-10 (Horikawa *et al*, 2000), peroxisome-proliferator activator receptor gamma (Altshuler *et al*, 2000), and ATP-sensitive potassium channel subunit (Gloyn *et al*, 2003).

What will be the next step on the path to cloning the diabetes susceptibility gene in *Psammomys*? Classical QTL mapping studies in the fat sand rat, though not impossible, would be very challenging. While the unique qualities of *Psammomys* make it a good model of DP and diet-induced obesity, this status also gives rise to some difficulties. Genetic and genomic resources for mapping the locus are limited, unless enough rat and mouse microsatellite and SNP markers are identified that will amplify in the fat sand rat. In our hands, approximately 20–30% of mouse microsatellite primers work in the rat; unluckily, gerbils are further removed phylogenetically. One may need to construct genomic or artificial chromosome libraries (PAC, BAC, or YAC) for *Psammomys* and screen them for microsatellite markers by hybridisation or vectorette libraries, which are expensive and laborious tasks. Even if the PCR amplification works, the genetic poly-

morphism rate between the DP and DR strains is likely to be very low, since they were derived from the same outbred stock with a limited pool of alleles differentiating the two strains. Prior experience of selecting rats for high and low responders has demonstrated this problem.

Given these limitations, gene investigation so far would be restricted to candidate studies in this animal model. Walder *et al* (2005) chose a novel tactic to identify new candidate genes in the fat sand rat. They hybridised human microarrays with reverse-transcribed skeletal muscle RNA from either lean nondiabetic or obese diabetic *Psammomys*. One gene with reduced expression in the diabetic animals, presenilins-associated rhomboid-like protein (PSARL), was shown to be correlated with insulin sensitivity in human skeletal muscle. PSARL is located in human chromosome 3q27, a region found to be linked to obesity and Type II diabetes in several genome scans. Walder *et al* (2005) also performed an association study of 1031 individuals from 169 families previously studied for metabolic syndrome, and demonstrated that an amino-acid variant in PSARL is significantly associated with phenotypes related to Type II diabetes.

PSARL may be one of the genes with variants predisposing to diabetic phenotypes in the fat sand rat, but whether PSARL is the major dominant gene identified in the current study of Hillel *et al* (2005) is unknown. Although Walder *et al* (2005) sequenced the gene in *Psammomys*, they do not state whether they compared sequences between the lean nondiabetic and obese diabetic animals to determine whether altered expression was due to a sequence variant or to a secondary effect (however, since the animals are outbred, the results may not have been clearcut). Hillel *et al* (2005) may be able to use their diabetes-prone and DR lines of *Psammomys* to determine whether a sequence variant in PSARL is present that may cause diabetes. They can take this opportunity to exploit their unique resource for detailed physiological studies, which may be critical in determining the precise function of PSARL in susceptibility to Type II diabetes and obesity.

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