Genetic factors in human obesity

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Accepted 24 November 2006

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Keywords: Genetics, monogenic, obesity.

Background

The recent increase in the prevalence of obesity in many parts of the world is clearly driven by secular changes in exposure to environmental factors, including the increased availability and reduced costs of energy-dense food and a reduction in physical activity during work and leisure time (1,2).

The speed with which this 'obesity epidemic' has occurred has led to the widespread misconception that heritable factors play an insignificant role in determining which humans become obese. In fact, measures of fatness (also known as adiposity) are among the most heritable of human traits (3). Multiple studies of families, adoptees, twins and, most powerfully, adopted twins (4,5) have all confirmed that heritable factors are likely to be responsible for 45-75% of the inter-individual variation in body mass index (the commonly used measure of adiposity) (3,6-8). These heritable factors are likely to be multiple and are likely to operate through the full range of potential mechanisms, including energy intake, energy expenditure and the partitioning of nutrients between fat and lean tissue. Paradoxically, there is a danger that the effects of such hereditary influences on weight will be downplayed at a time when we are beginning, for the first time, to have a genuine understanding of the molecules involved in the control of body weight and how genetic variation in them can influence human obesity.

Why search for human obesity genes?

The discovery of obesity genes will undoubtedly lead to health benefits. These will come in at least three ways. First, some genetic obesity syndromes are very severe, occur at a young age and are associated with other developmental and clinical manifestations (9). Knowledge of the underlying genetic defect in these syndromes will greatly aid genetic counselling. A demonstrated by the dramatic benefits of recombinant leptin in congenital leptin deficiency (10), such discoveries may also lead to the development of mechanism-based forms of effective therapy for these uncommon disorders. Second, genetic studies can help reveal novel molecular pathways controlling human energy balance and thereby clarify the relevance of such pathways as targets for pharmacological intervention in more common forms of obesity (11,12). Third, it is possible that, by recognizing common genetic variants that predispose to obesity through different mechanisms, we may be able to classify obese subjects into subgroups that might have particularly beneficial responses to specific diets and/or exercise regimes, drugs or surgery.

What progress have we made?

Monogenic obesity

Progress to date has mostly been in more severe familial forms of obesity presenting in childhood. Although these
only represent a small fraction of those with obesity (albeit a group with disproportionate physical and psychosocial morbidity and health costs), the implications of these discoveries have been profound. The genetic defects found to date all impair satiety, affecting the function of appetite control centres in the brain rather than being due to a 'slow metabolism' (13). This indicates that we must think of human food intake not as an entirely voluntarily controllable phenomenon but one driven by powerful biological signals from relatively primitive brain areas. When these basic signalling mechanisms are severely disrupted, it is very difficult to overcome the drive to eat. Importantly, the discovery of these genetic disorders has helped de-stigmatize human obesity and allowed it to be seen as a biomedical disorder and not simply a moral frailty. In one case, discovery of the causative genetic defect has led to dramatically successful therapy in a few individuals (10,14). Finally, mutations in one gene, the melanocortin 4 receptor, may be responsible for tens of thousands of cases of obesity in the UK alone (15,16). Knowledge of the specific molecular mechanisms in this and other genetic disorders should lead to better mechanism-directed pharmacotherapy in the future.

'Polygenic' contribution to obesity

Given the undoubted environmental influences on obesity in the general population, the multiple molecular mechanisms that could influence adiposity and the unknown genetic architecture of obesity susceptibility, it is unsurprising that progress in the identification of genes influencing susceptibility to common forms of obesity has been slower. It is not yet clear whether the genetic architecture of common obesity will conform more to the 'common variant–common disease' model, in which some relatively common polymorphisms have modest but widespread effects on risk, or the 'multiple rare variants–common disease' model, where multiple different rare alleles underlie genetic susceptibility (17).

Polymorphisms in multiple candidate genes, selected by virtue of their known biological function and/or their role in the causation of monogenic obesity syndromes in humans or animal models, have been examined in population and case–control studies to determine whether they influence the risk of adiposity. The Trp64Arg variant in the Beta-3 adrenergic receptor gene has been the subject of more than 60 independent studies and four meta-analyses (18–22) and, while evidence does point to some effect, especially in Asian subjects, this effect does not seem to generalize to other populations. The Val103Ile variant in the MC4R receptor, present in only 2–3% of the general population, has been studied by Heid et al. in their large KORA study and found to reduce the risk of obesity (23). This conclusion has been supported by a recent meta-analysis (N. J. Wareham, personal communication). Recently, single nucleotide polymorphisms (SNPs) in pro-opiomelanocortin, a precursor peptide, have been found to associate with obesity-related variables in a Hispanic population (24). Thus, as is the case with common forms of type 2 diabetes, it does appear that subtle variants in genes, which when mutated result in severe early onset obesity, are likely to contribute to susceptibility to obesity in the general population.

Multiple linkage studies have been undertaken on family-based datasets, with some chromosomal regions (e.g. on chromosomes 2p, 3q, 10p, 20q) showing positive results in more than one study (25,26). For a comprehensive list of all linkage studies performed, see Human Obesity Gene Map (http://obesitygene.pbrc.edu/). Some of these regions have been subjected to intensive 'second phase' analysis. Using these approaches, Froguel et al. identified a region on chromosome 10p12 that showed significant linkage with obesity in several populations. Examining candidate genes within the region, they tested GAD2, the gene encoding glutamic acid decarboxylase 65, an enzyme involved in gamma aminobutyric acid (GABA) synthesis. They found significant associations of a particular GAD2 SNP in both case control and family-based studies (27). However, Swarbrick et al. subsequently reported no association of GAD polymorphisms with obesity in several populations (28).

Uncertainty remains regarding the role of GAD2 polymorphisms in susceptibility to human obesity. Meyre et al. identified a region on chromosome 6q16.3-q24.2 that was associated with significant Logarithm of Odds (LOD) scores in relation to obesity and diabetes phenotypes (29). An SNP in ENPP1, a gene in this region which encodes an ecto-phosphatase, was found to associate with childhood obesity and also with insulin resistance (30). Further studies in other populations will be required to establish the reproducibility of these observations. The pace of discovery will change with the advent of genome–wide association studies (31). Very recently, using such an approach, Herbert et al. (32) have identified an SNP close to the Insl2 gene which, when present in homozygous form, increases the odds ratio for obesity by 1.2–1.3.

Future progress

Studies of the genetics of human obesity will continue to aid scientific understanding and fuel clinical advances in a number of ways.

Genetics will continue to provide new knowledge regarding the normal physiology of energy balance. The recent explosion in knowledge regarding the control of mammalian energy balance has been largely driven by genetics, both rodent and human (33). It is likely that further discovery of causative genetic defects in humans and experimental animals will continue to highlight other molecular
elements of the control pathways for body weight. Thus, genetics will continue to teach us how the normal systems controlling energy balance are wired up and how they function.

Genetics will increasingly aid drug development and better drug targeting to specific patients. Molecules discovered to be involved in energy homeostasis through genetics will immediately become therapeutic targets, the pharmacological manipulation of which may be of use in the treatment of obesity. In this way, genetics will continue to provide therapeutic targets for the pharmaceutical industry and aid their development of novel compounds for the treatment of obesity. Genetics may also help to guide drug use in particular patients, so-called ‘pharmacogenomics’, as individuals with specific types of molecular defect are likely to respond differentially to different drugs. So genetics will also help us to better target drug therapy.

Genetics will improve the targeting of behavioural/dietary strategies for the prevention and treatment of obesity. It is likely that common genetic variants will selectively influence an individual’s response to environmental stimuli and that those of a particular genotype, for example, will be less likely to respond to particular subtypes of dietary intervention than others. There are already examples of interactions between genes and dietary factors (34) in the determination of metabolic status, and knowledge of gene–environment interactions will increasingly play a role in the improved targeting of behavioural interventions for the prevention of obesity.

Conclusion

The past decade has been a remarkable time for the genetic study of human obesity. We have seen the first definitive descriptions of genetic mutations leading to obesity in man, the identification of a subtype of genetic obesity that is dramatically responsive to mechanism-based therapy, the discovery of a monogenic form of obesity that is one of the commonest single-gene disorders in humans, and the first convincing reports of the identification of common genetic variants predisposing to obesity in the wider population. We have learned that genes can powerfully influence human eating behaviour and that obesity, at least in part, is a genetically determined disorder of appetitive behaviour. The pace of discovery is escalating and human genetics will play a crucial role in improving our understanding of basic energy regulation, in aiding the discovery of new effective drugs and optimizing their use, and in targeting behavioural strategies to those who will benefit most from them. Any scientific strategy designed to understand and combat human obesity will need to have firmly embedded at its core a deep understanding of, and engagement with, human genetics.

Conflict of Interest Statement

No conflict of interest was declared.

References


This paper was commissioned by the Foresight programme of the Office of Science and Innovation, Department of Trade and Industry
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Journal compilation © 2007 The International Association for the Study of Obesity


