The genetics of human obesity

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The heritability of obesity has long been appreciated and the genetics of obesity has been the focus of intensive study for decades. Early studies elucidating genetic factors involved in rare monogenic and syndromic forms of extreme obesity focused attention on dysfunction of hypothalamic leptin–related pathways in the control of food intake as a major contributor. Subsequent genome-wide association studies of common genetic variants identified novel loci that are involved in more common forms of obesity across populations of diverse ethnicities and ages. The subsequent search for factors contributing to the heritability of obesity not explained by these 2 approaches ("missing heritability") has revealed additional rare variants, copy number variants, and epigenetic changes that contribute. Although clinical applications of these findings have been limited to date, the increasing understanding of the interplay of these genetic factors with environmental conditions, such as the increased availability of high calorie foods and decreased energy expenditure of sedentary lifestyles, promises to accelerate the translation of genetic findings into more successful preventive and therapeutic interventions. (Translational Research 2014;164:293–301)

Abbreviations: BMI = Body mass index; CNV = Copy number variants; CPG = cytosine-phosphate-guanine; GCTA = Genome-wide complex trait analysis; GWAS = Genome-wide association study; ITMAT = Institute for Translational Medicine and Therapeutics; MAF = Minor allele frequency; PPARG = peroxisome proliferator-activated receptor gamma; SNP = Single-nucleotide polymorphism; WC = waist circumference; WHR = waist-to-hip ratio

INTRODUCTION

In the search for causes of the recent obesity epidemic, emphasis has been placed on the "obesogenic environment" and lifestyle changes that have resulted in increased access to calories and decreased energy expenditure. Although the hereditary aspects of obesity have long been recognized, the contribution of genetics to this relatively rapid population-wide change is also becoming increasingly evident. The technologic revolution in genotyping that has paralleled the obesity epidemic has allowed investigation of genetic factors in unprecedented detail—from single genes that cause rare forms of obesity to multiple genetic factors involved in more common forms. Such investigations have extended beyond identification of single-nucleotide variants associated with obesity-related traits across populations to rare variants, copy number variations (CNVs), and epigenetic changes that help explain a substantial portion of the heritability of these traits. These technologic advances have also enabled more detailed study of the interaction of the genetic and environmental factors contributing to the obesity epidemic, which promise to point to more effective interventions for both prevention and treatment.

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HERITABILITY

The inherited propensity toward obesity has been supported by numerous family and twin studies, many of which preceded the identification of specific genes by

decades. One early twin study quantifying the heritability of a large number of anthropometric measures, including height, weight, and waist circumference, found body weight to have one of the highest heritability rates of approximately 70%, with nearly equally high heritability of waist circumference of 65%.[1] Although estimates in subsequent studies have varied, the heritability of obesity is now widely accepted as being between 40% and 70%.[2] However, it is clear that the heritability estimates can be dramatically altered by consideration of environmental factors. Physical activity, in particular, has been found to have a powerful influence on the heritability of obesity-related traits. Heritability of fat mass in Finnish twins, for example, has been reported to be 90% among twins with the low physical activity, but only 20% among the most active pairs of twins.[3] Age effects are also striking, with the greatest heritability of body mass index (BMI), for example, manifesting in adolescence (starting around the age of 11 years) and peaking in young adulthood (around the age of 20 years).[4] More detailed exploration of the effects of these and other influences, such as ethnicity and sex, are now being incorporated into studies with increasing emphasis on understanding gene-environment interactions.

MONOGENIC OBESITY MODELS

Although the current focus of obesity genetics research is on the complexity of the multiple genes and gene-gene and gene-environment interactions likely to be involved in common forms of human obesity, the discovery of single genes responsible for obesity in animal models, albeit rare causes of obesity in humans, provided the earliest breakthroughs in identifying mechanisms involved in human obesity. The identification of these genes pointed to the crucial role of hormonal and neural networks in regulating adiposity, particularly in the appetite control centers of the hypothalamus.

The first of these breakthroughs came through an obese mouse strain, ob/ob, which had been discovered at the Jackson Laboratories in 1949.[5] Mice of this strain were found to grow to weights of up to 3 times that of other mouse strains, and early crossbreeding studies revealed that the obesity trait was inherited in a recessive manner. Infusion of blood from normal mice into ob/ob mice resulted in the normalization of the weight of the obese mice, indicating that the inherited alteration involved a lack of a factor present in normal mice.[6,7]

Using positional cloning techniques, Friedman et al[8] identified the specific gene responsible for obesity in the ob/ob mice in 1994. The discovery was followed by the identification of the encoded protein, which when injected into ob/ob mice restored them to normal weight. The protein, named leptin after the Greek "leptos" meaning thin, is released by growing white fat cells and binds to receptors in the hypothalamus resulting in decreased appetite and food intake, consistent with a fed state. Mutations in *Lep* (leptin gene) in mice, and its human homolog *LEP*, lead to a deficiency of leptin and thus a decreased ability to inhibit appetite.

The discovery of *LEP* was followed by the discovery of the gene responsible for obesity in another strain of obese mice with diabetes, db/db.[9] The responsible gene was found to encode the leptin receptor, expressed in the hypothalamus among other regions of the brain, and was named *LEPR*. Other obesity-causing genes in humans similarly discovered from their homologs in obese animal include proopiomelanocortin (*POMC*), prohormone convertase 1 (*PCSK1*), and melanocortin 4 receptor (*MC4R*). Like *LEP* and *LEPR*, these genes are involved in the leptin-melanocortin signaling pathway, wherein leptin acts via its receptors to inhibit food intake through effects on POMC and agouti-related protein—neuropeptide Y neurons in the arcuate nucleus of the hypothalamus. *MC4R* is activated in the paraventricular nucleus through this pathway by α-melanocyte–stimulating hormone, a cleavage product of the *POMC* transcript resulting from the activity of the PCSK1 enzyme to signal satiety.[10]

The identification of leptin and its associated pathways was initially met with enthusiasm for its potential as a therapeutic target for treating all forms of obesity. It subsequently has become apparent, however, that most obese humans are not leptin-deficient, but rather have very high levels of leptin and are leptin-resistant.[11,12] Congenital hypoleptinemia because of mutations of these genes was also found to be rare, affecting only a few families in the world. In these few individuals, however, recombinant leptin therapy has been very effective in treating obesity.[13] And, although not considered an effective treatment for common obesity per se, the use of leptin therapy in diabetes is now being explored.[14]

In contrast to the severe obesity observed in the rare homozygotes for the deleterious mutations in the genes involved in the leptin pathway, heterozygotes for mutations of *MC4R*, *LEP*, *LEPR*, and *POMC* exhibit a less severe and nonfully penetrant form of obesity.[15-19] *MC4R* mutations are the most common, with a population prevalence of at least 0.05% and a prevalence of 0.5%–1% among obese adults and 1%–6% among obese children.[20]

SYNDROMIC OBESITY

Identification of genes involved in human obesity has also been driven by the study of obesity occurring as part of distinct syndromes, such as Prader-Willi