Genetics of common forms of obesity: a brief overview1–4

Helen N Lyon and Joel N Hirschhorn

ABSTRACT
The obesity epidemic is attributable to dietary and behavioral trends acting on a person’s genetic makeup to determine body mass and susceptibility to obesity-related disease. Common forms of obesity have a strong hereditary component, yet genetic pathways that contribute to obesity have not yet been elucidated. Many genetic association studies have been reported, but few have been successfully replicated. New research tools and large studies will lead to an understanding of genes and their interaction to cause obesity, which may help guide successful interventions and treatments. Am J Clin Nutr 2005;82(suppl):215S–7S.

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Obesity has reached epidemic proportions in the United States and developing countries. Although the trend of decreased physical activity and increased caloric intake is probably responsible for the recent rise in obesity, it is important to understand that these trends are playing out on a background of genetic variation in the population. Each individual’s genetic background remains an important determinant of susceptibility to obesity. Discovery of the genes involved in the development of common forms of obesity, thereby identifying pathways that are causal in patients, will guide clinicians and scientists in designing more effective therapies and in identifying high-risk individuals for early intervention (1–4).

It is clear that obesity often tracks in families. Having obese relatives increases one’s risk for obesity, even if the family members do not live together or share the same patterns of exercise and food intake (5–7). Family studies and twin studies yield estimates of the fraction of the variation in the population that can be attributed to inherited variation, or the heritability (h²) (8). Estimates of heritability range from 30 to 70%, with the typical estimate at 50%, meaning about one-half of the variation in body mass within a population is a result of inherited factors (2, 5, 6). Common forms of obesity are not inherited in families in a predictable pattern like cystic fibrosis or Huntington’s disease but rather shows a complex pattern of segregation, meaning that multiple genes are involved. Because of this complex, multifactorial pattern, diseases and traits such as obesity are called complex genetic traits. A few studies have suggested that there are genes that act in a recessive manner and can explain a larger fraction of the variation in body mass. These results have not been consistently observed and may also reflect the patterns seen in early-onset, severe obesity caused by one or few genes rather than the more common polygenic, later-onset obesity observed in the general population. Thus, each of the obesity genes likely makes only a small contribution to body weight, but together inherited variation plays a large role in determining how an individual responds to the environmental factors of diet and physical activity.

What are the inherited DNA variants that affect the susceptibility to obesity? Although humans all have the same genetic material, every person’s genome is slightly different: when comparing any two copies of the same stretch of genome, about one in every 1200 bases will be different (usually a single nucleotide polymorphism (SNP)). Most SNPs identified by comparing two chromosomes are common and shared throughout the world: 90% of such SNPs will be seen again at a frequency of at least 1% (9–11). Most of these common variants probably have no functional consequence and are essentially the equivalent of genetic dialect or random differences in spelling with no real significance. However, a few of these polymorphisms will alter the biologic function of a gene, by either affecting the structure of the protein or altering the location, amount, or time at which the protein is made. Some of these functional alterations will affect susceptibility to obesity and related diseases. A catalog of these causal variants and an appreciation of their interaction with each other and environmental factors will be crucial to designing effective interventions.

It is not yet known what types of variants (missense or regulatory, rare or common) affect complex traits such as obesity. Because most human genetic variation is common, it has been proposed based on theoretic (12, 13) and empirical (14) grounds that common variants contribute to common disease and complex traits. However, rare variants have also been proposed to play a role (15). The relative importance of missense variants has

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4 Address reprint requests and correspondence to J Hirschhorn, Children’s Hospital Boston, Enders 561, 300 Longwood Avenue, Boston, MA 02115. E-mail: joelh@broad.mit.edu.
been debated as well (16). Ideally, to have an unbiased and comprehensive search for variants with a contributory role to common obesity, we would test every variant in the genome, but such a large-scale search through even just the common variants (of which there are estimated to be 11 million) (10) is not yet practical. Thus, approaches must be taken to identify genomic regions or sets of variants that are more likely to contribute to obesity in the general population.

Two approaches have been used to date to find the variants that affect obesity, linkage analysis and association studies. Linkage analysis was used with great success in mapping genes responsible for single gene disorders. Such studies involve using multiple affected relatives to look for shared segments of DNA that are inherited more often than expected by chance, eventually narrowing the shared region to a few genes that can be tested for the presence of recognizable mutations in all of the affected relatives. Linkage studies have been applied to complex disorders such as obesity, but, in general, linkage analysis has been less successful for these multigenic diseases. Although whole genome scans often identify similar regions as being linked to obesity, the results vary greatly, probably because of the low power of linkage to find genes with modest effects or possibly differing study designs or populations. Several studies located a region on chromosome 7q31 that was found to contain the leptin gene, mutations in which cause severe obesity syndromes. Although some regions have been repeatedly implicated by linkage analysis, no genes have been found in these regions that have been seen to contribute to common obesity. As these studies are performed on larger cohorts of people, it is likely that the results will become more refined and that important obesity loci will be mapped with this method.

Association studies are another way to find genes involved in obesity. Genes and variants are selected as candidates if they have either a known or hypothesized role in metabolism, or if they are located within an area of linkage. In the simplest form of such studies, the frequency of a variant allele in a particular gene is compared in obese and non-obese individuals, or in obese individuals and their non-obese relatives. Association studies to test these functional and positional candidates have better power than linkage studies to detect the effects of common alleles of modest penetrance on complex traits such as obesity (17).

Association studies have been successfully used to identify genes for common diseases and complex traits. An example of a now well-established disease association is that of Alzheimer’s disease with the gene encoding the apolipoprotein E (ApoE). The ApoE4 variant encompasses two missense polymorphisms, and, because this genotype is found in 10–15% of the population, it is relatively common. It is found three to four times more often in people with Alzheimer’s disease, conferring a 3-fold increased risk to a carrier of this allele. Because not all people with the ApoE4 allele develop disease (and not all people with Alzheimer’s disease carry ApoE4), the allele is neither necessary nor sufficient for disease but is rather associated with higher risk. Many other associations have been reported, including for common obesity, but few have been consistently reproducible as is seen with ApoE4 and Alzheimer’s disease (3, 18).

There are several possible reasons that association studies are not replicated consistently, and it is critical to discern which is present when interpreting association studies. To explore this issue, we conducted a meta-analysis of published association studies by pooling the results from all of the follow-on studies for 25 reported associations between common genetic variants and common diseases (14). Most of these associations showed no evidence of replication in the follow-on studies. Eight of the associations showed convincing evidence of replication, and, for these, the associated variant conferred a modest effect with a less than 2-fold increase in disease risk. We concluded that most association studies are incorrect, but a fraction of reported associations are likely to be correct yet difficult to replicate with small studies that are underpowered to detect a modest effect.

More than 70 associations between body mass index or obesity and common genetic variants have been reported (3), but none have been consistently replicated. There are many interesting candidate genes in the list, including genes found to be altered in Mendelian or rare obesity syndromes, such as leptin, proopiomelanocortin, melanocortin 4 receptor (MC4R), and Bardet-Biedel syndrome loci. Bardet-Biedel syndrome can be caused by alterations in at least eight genes (3, 19, 20). We are currently investigating these eight genes for common variants, yet none have been reproduced associated with typical obesity. There is a well-established association between rare forms of obesity and mutations in the MC4R, accounting for about 4% of early-onset severe obesity (3, 21), yet mutations in MC4R do not seem to play a prominent role in late-onset, common obesity (3, 19, 20). Rare mutations in the leptin gene cause a deficiency also leading to severe early-onset obesity. Although treatment with leptin successfully reverses this progression (22), leptin has not proven effective in treating common obesity. Identification of such rare mutations in candidate genes identifies pathways that, when disrupted, can lead to severe obesity. This suggests a general hypothesis that common variation in genes underlying severe syndromes may contribute to the common form of the disease. However, no common variants in these genes have been consistently found to be associated with common obesity in the general population.

Functional and positional candidates will continue to be investigated in the search for genes involved in the development of obesity and the related diseases. In addition, animal models will provide lists of new candidates through linkage studies, expression profiling, and transgenic strains, whereas other efforts such as expression analysis and protein interaction studies should also identify candidate genes. New molecular tools are becoming available that should expedite the testing of these genes. The complete sequence of the human genome, as well as full genome sequence in other species, are now known and are a shared resource available to all researchers. Abundant genetic variants (dbSNP) and patterns of common variation elucidated by the human HapMap will also facilitate the selection of variants to test in association studies. The HapMap should pave the way for more comprehensive, genome-wide association studies (10).

Obesity is a common disease caused by multiple factors, with heredity playing a strong causal role. There are sequence variants present in the population that increase or decrease an individual’s risk for obesity in their environment. Although we do not yet understand which pathways are altered by these variations, single gene disorders and animal models suggest a wide variety of possibilities. With new molecular tools and resources, well-powered studies can be undertaken to find common obesity genes in the future. These genes will identify root causes of obesity, potentially suggesting new therapies or interventions, and provide tools for the understanding of how people respond to their environment to become obese or remain lean.
REFERENCES