Genetics of Obesity

Obesity is a major contributor to morbidity and mortality, and its prevalence has increased markedly in the last 30 years. This is thought to have occurred due to the increased availability of energy-dense foods and the reduced requirement for physical exertion during work and domestic life.[1] But there is also a genetic component to obesity. Heritability (the chance that offspring will inherit a trait) for BMI is 50%-70%, while heritability for total body fat is as high as 80%.[2] These numbers, along with twin studies, have demonstrated that obesity is partially genetically regulated. Several methods for finding genes controlling obesity have been employed, with some being more successful than others. Below is a brief summary of what is currently known about the genetics of obesity.

The hormonal and neural networks that regulate adiposity are complex, making the dissection of genetic control difficult. Clues have come from monogenic (variations in one gene) obesity. While this type of obesity is rare, it provides a genetic starting point. Leptin deficiency was the first cause of monogenic obesity to be demonstrated in a human patient.[3] Subsequently, variations other genes in the *leptin-melanocortin* pathway were identified as causative of obesity. *Leptin* and other genes in its pathway encode proteins that regulate appetite.[2] Additionally, mutations in three genes (*SIM1*, *BDNF*, and *NTRK2*) involved in neural development have been shown to cause rare monogenic obesity. These genes partially control the function of the hypothalamus; inactivation of the genes results in hyperphagia and a sense that the body needs to increase its energy intake.[3]

In contrast to rare monogenic obesity, common obesity appears to be polygenic with no simple inheritance pattern and significant contribution from environmental factors.[3] Two genes, *FTO* and *INSIG2*, have been identified by linkage studies to be associated with common obesity.[2] Variants in *FTO* (fat mass and obesity-associated gene) are associated with BMI and increased risk for obesity.[3] Studies demonstrate that *FTO* variations are associated with modestly increased food intake and satiety, and also with decreased lipolytic activity in adipocytes.[3] *INSIG2* encodes a protein thought to regulate the proteins responsible for fatty acid synthesis and adipogenesis.[2] An *INSIG2* variant is associated with increased BMI. Interestingly, variations in the *melanocortin 4 receptor* and in *BDNF*, both identified as causative of monogenic obesity, seem to account for a measurable number of common obesity cases as well.[3]

Phenotype associated with variations in both *FTO* and *INSIG2* is dependent on environmental factors as well. Among homozygous carriers of the variant of *FTO* associated with increased BMI, those who were physically active showed a BMI almost 2 points lower than those who were inactive.[2] In a small study of *INSIG2* variants, physical activity seemed to modify the effects of the genetic variation on BMI.[2]

There are likely several other gene variations that together, account for an increased risk in obesity. Study of these genes is difficult since environmental factors like physical activity and diet are also likely to play a role. However, given the increasing prevalence of obesity, these studies are of high priority.

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2. Andreasen CH, Andersen G. (2009) Gene-environment interactions and obesity—Further aspects of genomewide association studies. *Nutr* 25, 998-1003.
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