Genetic Epidemiology of Obesity

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Obesity has become a global epidemic and contributes to the increasing burden of type 2 diabetes, cardiovascular disease, stroke, some types of cancer, and premature death worldwide. Obesity is highly heritable and arises from the interactions of multiple genes, environmental factors, and behavior. In this paper, the authors reviewed recent developments in genetic epidemiologic research, focusing particularly on several promising genomic regions and obesity-related genes. Gene-gene and gene-environment interactions of obesity were also discussed. Published studies were accessed through the MEDLINE database. The authors also searched the Obesity Gene Map Database (http://obesitygene.pbrc.edu/) and conducted a manual search using references cited in relevant papers. Heritabilities for obesity-related phenotypes varied from 6% to 85% among various populations. As of October 2005, 253 quantitative trait loci for obesity-related phenotypes have been localized in 61 genome-wide linkage scans, and genetic variants in 127 biologic candidate genes have been reported to be associated with obesity-related phenotypes from 426 positive findings. Gene-gene interactions were also observed in several genes, and some genes were found to influence the effect of dietary intake and physical activity on obesity-related phenotypes. Integration of genetic epidemiology with functional genomics and proteomics studies will be required to fully understand the role of genetic variants in the etiology and prevention of obesity.

body mass index; genes; obesity; overweight

Abbreviations: LOD, logarithm of the odds; SNP, single nucleotide polymorphism; WHO, World Health Organization; WHR, waist/hip ratio.

Obesity is characterized as an excess of adipose tissue. The most commonly used measurement to assess weight status is body mass index, defined as weight (kg)/height (m)². The World Health Organization (WHO) recommends the following body mass index cutpoints to classify weight status in adults 20 years of age or older: <18.5 kg/m² (underweight), 18.5–24.9 kg/m² (normal weight), 25.0–29.9 kg/m² (overweight), 30.0–39.9 kg/m² (obese), and ≥40 kg/m² (extremely obese) (1). Although it is by far the most commonly used index for classifying general obesity in an adult, body mass index cannot distinguish obese from muscular individuals, such as athletes, who have more lean muscle than body fat. Body fat mass and percentage body fat, which are measured by dual energy x-ray absorptiometry, can provide a more accurate estimate of obesity status. Percentage total body fat is calculated as fat mass/(fat mass + lean mass + bone mineral content) (2). The WHO-recommended cutoff point for obesity corresponds to a percentage body fat of 25 percent and 35 percent in men and women, respectively (3). Waist circumference and waist/hip ratio (WHR) are other indicators commonly used to determine abdominal obesity status. The American Heart Association and the National Heart, Lung, and Blood Institute recommend waist circumference cutpoints for determining abdominal obesity status as ≥102 cm in men and ≥88 cm in women of non-Asian origin and ≥90 cm in Asian men and ≥80 cm in Asian women (4). According to guidelines from the WHO, abdominal obesity status can be identified as a WHR of >0.90 in men and >0.85 in women (5).

Obesity is becoming an increasingly important clinical and public health challenge throughout the world. Recently, the International Obesity Taskforce estimated a total of 1.1
billion overweight, including 320 million obese, adults worldwide (6). Economically developed regions have a higher prevalence of overweight and obesity compared with developing regions of the world (7). For example, results of the 1999–2002 National Health and Nutrition Examination Survey indicated that an estimated 65 percent of US adults aged 20 years or older (over 131 million people) were either overweight or obese and that 30 percent of adults (over 60 million people) were obese (8). Despite these estimates, the developing world actually faces a larger absolute burden of overweight and obesity because of a larger population size (9, 10). Obesity is a major risk factor for type 2 diabetes, cardiovascular disease, stroke, some types of cancer, and premature death (11–18).

Human obesity arises from the interactions of multiple genes, environmental factors, and behavior, and this complex etiology makes management and prevention of obesity especially challenging. While a genetic basis for obesity exists, defining the genetic contribution has proven to be a formidable task. Genetic epidemiologic methods for the gene discovery of complex traits, such as obesity, can be divided into two broad classes: hypothesis-free (genome-wide linkage and genome-wide association) and hypothesis-driven (candidate gene and biologic pathway) approaches.

The hypothesis-free approach does not involve any specific biologic hypothesis about the trait of interest. Genome-wide linkage analysis, typically using a 10-centimorgan (cM) (or denser 2-cM) marker density usually containing 400 (or 2,000) microsatellite markers evenly covering the entire human genome, identifies broad intervals of several megabases that might contain hundreds of susceptibility genes for diseases of interest. This method has been remarkably successful in identifying disease genes for monogenic disorders (9). When applied to the common complex disease, however, linkage analysis has less power, and success has been limited. In addition, relatively high costs and the family-based data requirement make linkage analysis more restricted in practice. Falling genotype costs and the recent advancements in the International HapMap Project have made genome-wide association studies of complex disease popular (20). For example, the first genome-wide association study of obesity conducted by Herbert et al. (21) identified a common genetic variant near the insulin-induced gene 2 (INSIG2) associated with obesity in Framingham Heart Study participants. Genome-wide association studies have been expected to be more powerful than linkage studies because of their resolution and ability to narrow down the genomic target region more precisely and to detect even small gene effects. In addition, the number of genotyped variants could be dramatically reduced, taking advantage of linkage disequilibrium between variants (22). The practical necessity of having a fixed set of genome-wide association markers has obvious advantages. For example, a linkage disequilibrium-based set of tag single nucleotide polymorphisms (SNPs) can maximize the amount of variation captured per SNP by 300,000 SNPs of Illumina HumanHap300 BeadChip or by 500,000 SNPs of Illumina HumanHap500 BeadChip (Illumina, Inc., San Diego, California). A set of SNPs that ignores linkage disequilibrium patterns can be selected to distribute approximately randomly across the genome available from Affymetrix 111,000 and 500,000 array sets (Affymetrix, Inc., Santa Clara, California). A combination of these two methods is also a good choice, consisting of a set of “random” SNPs augmented by a carefully chosen fill-in set. Therefore, a research group should make decisions about which genome-wide association genotyping platform to use in order to balance efficiency, redundancy, and completeness regarding the different marker panels and populations being studied (23).

The hypothesis-driven approach (candidate gene or biologic pathway analysis) needs an a priori hypothesis that the genetic polymorphisms in a candidate gene or a biologic pathway being studied are causal variants or in strong linkage disequilibrium with a causal variant for a particular phenotype of interest. This approach is now considered to be an efficient strategy for identifying genetic variants with small or modest effects that underlie susceptibility to common disease, including obesity. The selection of candidate genes (or biologic pathways) should consider both the relevance of the candidate gene (or biologic pathway) to the pathogenesis of the disease of interest and the functional effects of a particular polymorphism (24). Candidate gene analysis is an indirect test of association to examine the relation between a dense map of SNPs and disease, while candidate SNP analysis is a direct test of association between putatively functional variants and disease risk (25). The advantage of indirect association is that it does not require prior determination of which SNP might be functionally important; however, the disadvantage is that larger numbers of SNPs need to be genotyped (25). A combination of functionally important SNPs with a collection of tag SNPs covering the entire candidate gene has been used in many candidate gene association studies. Genetic variants in multiple candidate genes within the same biologic pathway can be examined, and their interaction can be tested in pathway analysis. It also makes sense to do fine mapping in significant linkage peaks by association analysis with the knowledge of candidate genes that reside in these regions and are involved in biologic pathways for developing the disease of interest. One of the main weaknesses of candidate gene analysis is that it depends on an a priori hypothesis about disease mechanisms, so that the discovery of new genetic variants or novel genes is precluded by previously unknown pathways (26).

This paper reviews recent developments in genetic epidemiology research of obesity in human populations and includes current information from heritability studies, genome-wide linkage studies, and candidate gene association studies, focusing particularly on several important genomic regions and obesity-related genes. Gene-gene and gene-environment interactions of obesity are also discussed.

HERITABILITY OF OBESITY

Twin, adoption, and family studies have established that obesity is highly heritable, and an individual’s risk of obesity is increased when one has relatives who are obese (27–29). Heritability estimates ranged from 16 percent to 85
percent for body mass index (30–34), from 37 percent to 81 percent for waist circumference (35–37), from 6 percent to 30 percent for WHR (38–40), and from 35 percent to 63 percent for percentage body fat (40–43). The Framingham Heart Study reported a moderate heritability estimate for body mass index (40–50 percent) (32). In contrast, the National Heart, Lung, and Blood Institute family heart study and twin studies observed higher estimates of heritability for body mass index (40–80 percent), and they also reported a heritability of 70–80 percent for weight gain (27, 44–46). Davey et al. (46) reported that the heritability estimate exceeded 90 percent for abdominal fat accumulation in an Indian population, while a family study in an Old Order Amish community showed a heritability of 37 percent for waist circumference and 13 percent for WHR (35). A twin study and HERITAGE (HEalth, RIsk factors, exercise Training, And GEneetics) Family Study reported similar heritabilities of 63 percent and 62 percent, respectively, for percentage body fat (41, 42), while the maximal heritability estimate in a Taiwanese population was 35 percent (43).

MONOGENIC OBESITY

In recent years, molecular approaches have advanced the understanding of some forms of monogenic obesity in humans. These forms of obesity are rare and very severe, generally starting in childhood (47). For example, mutations in human genes coding for leptin (LEP), leptin receptor (LEPR), proopiomelanocortin (POMC), and melanocortin-4 receptor (MC4R) have been associated with juvenile-onset morbid obesity (48–51). To date, 176 human obesity cases due to single-gene mutations in 11 different genes have been reported, 50 loci related to Mendelian syndromes relevant to human obesity have been mapped to a genomic region, and causative genes or strong candidates have been identified for most of these syndromes (52).

GENOME-WIDE LINKAGE STUDIES

Obesity is a complex, heterogeneous group of disorders, which develops predominantly from a polygenic multifactorial trait, with interplay of genetic and environmental factors. As of October 2005, 253 quantitative trait loci for obesity-related phenotypes have been localized from 61 genome-wide linkage studies in human populations. A total of 52 genomic regions harbor quantitative trait loci supported by two or more studies (52).

The genome-wide linkage studies have linked body mass index to almost every chromosomal region except Y. Table 1 lists studies that showed evidence for the presence of linkage with body mass index (logarithm of the odds (LOD) score: > 3) (36, 53–73). The strongest linkage evidence was observed in a multipoint analysis with a LOD score of 9.2 in Utah pedigrees (60).

Few studies have found evidence of linkage with waist circumference or WHR (74–76). A LOD score of 3.71 was observed for waist circumference, which was located at 1q21-q25, in the Hong Kong Family Diabetes Study, and evidence of linkage with waist circumference was shown in the 6q23-25 region in the Framingham Heart Study (74, 77). Suggestive linkage was found in European Americans and African Americans, both with LOD scores of 2.7 at the Xp21.3 and Xp11.3 regions (75).

Some studies have found evidence of linkage with percentage body fat (56, 67, 72, 78–80). LOD scores of 4.27 and 4.21 were observed with the same genetic marker, D21S1446, in chromosome 21q22.3 by Li et al. (67) and Dong et al. (80). The HyperGEN Study reported a LOD score of 3.0 for men in chromosome 15q25.3 with marker D15S655 and 3.8 for women in chromosome 12q24 with markers D12S395–D12S2078 in non-Hispanic Whites and African-American populations (79), while in the same year, a LOD score of 3.8 was observed in chromosome 12q24 with marker D12S2070 in European-American families (80).

Most reports of chromosomal regions linked to obesity and body composition are not robust; only a few regions have been replicated in some studies. As for body mass index, the most promising genomic regions (in chromosomes 2, 3, 6, 11, 13, and 20) were replicated in multiple studies. For example, two studies reported linkage in the 2q14.3 region with marker D2S347 (54, 55), and two studies obtained evidence of linkage in the 2p2.2.3 region with marker D2S1788 (53, 81). Three studies reported evidence of linkage at chromosome 3q26.33 with marker D3S2427 (57–59). In chromosome 6, two studies found linkage in the 6q22.31 region with marker D6S462 (71, 82). In chromosome 11, three studies showed evidence of linkage or suggestive linkage in the 11q24.3 region with marker D11S912 (60, 66, 81), and three studies observed suggestive linkage (LOD scores of 2.3, 2.7, and 2.8, respectively) in chromosome 11q24.1 with marker D11S4464 (60, 83, 84). Li et al. (67) and Dong et al. (80) reported two regions with suggestive linkage located at 13q21.32 and 13q32.2 with the same markers, D13S800 and D13S779, respectively, and North et al. (70) found evidence of linkage at 13q13.2 with marker D13S1493, which was also reported by Li et al. (67) with suggestive linkage. In chromosome 20, at the 20q12 region with marker D20S438, one study observed linkage, and another study found suggestive linkage (60, 73). As for waist circumference, two studies observed evidence of linkage in the 12q24.21 region with marker D12S2070 (67, 80). As for percentage body fat, aside from chromosomes 12q24 and 21q22.3, suggestive linkage was reported at the chromosome 20q13.31-qter region with marker D20S149, which has already been observed by Lee et al. (72) and Dong et al. (85).

The general lack of replication of genome scan results across data sets has been an ongoing concern for genetic epidemiologic studies. The inconsistency between studies may be attributed partially to varying sample sizes from study to study. Relatively small study sample sizes tend to limit the power of genome scans to detect linkage. In addition, the multiple statistical tests performed in each scan increase the risk of type I error. The problem of false positives could be solved by applying more stringent statistical significance criteria (86). The study population is also an important issue when considering inconsistencies of results. Population heterogeneity decreases the power to detect the
true linkage signals within studies and makes it difficult to compare them across studies (87). The genome-scan meta-analysis method would be useful for combining evidence from multiple studies and could confirm evidence for regions highlighted in more than one scan or identify new regions where weak but consistent evidence for linkage has been seen across studies (87).

### TABLE 1. Evidence for the presence of linkage with body mass index

<table>
<thead>
<tr>
<th>DNA marker</th>
<th>Chromosomal location</th>
<th>Study sample</th>
<th>LOD score*</th>
<th>First author, year (reference no.)</th>
</tr>
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<tbody>
<tr>
<td>D2S1788</td>
<td>2p22.3</td>
<td>66 White families (349 subjects)</td>
<td>3.08</td>
<td>Palmer L, 2003 (53)</td>
</tr>
<tr>
<td>D2S347</td>
<td>2q14.3</td>
<td>1,249 White European-origin sibling pairs</td>
<td>4.44</td>
<td>Deng HW, 2002 (54)</td>
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<tr>
<td>D2S347</td>
<td>2q14.3</td>
<td>53 Caucasian families (758 subjects)</td>
<td>3.42</td>
<td>Liu Y, 2004 (55)</td>
</tr>
<tr>
<td></td>
<td>2q37</td>
<td>451 Caucasian families (4,247 subjects)</td>
<td>3.34</td>
<td>Guo YF, 2006 (56)</td>
</tr>
<tr>
<td>D3S1764</td>
<td>3q22.3</td>
<td>1,055 pairs (White, Black, Mexican American, and Asian)</td>
<td>3.45</td>
<td>Wu, X, 2002 (57)</td>
</tr>
<tr>
<td>D3S2427</td>
<td>3q26.33</td>
<td>507 Caucasian families (2,209 subjects)</td>
<td>3.3</td>
<td>Kissebah A, 2000 (58)</td>
</tr>
<tr>
<td>D3S2427</td>
<td>3q26.33</td>
<td>1,055 pairs (White, Black, Mexican American)</td>
<td>3.4</td>
<td>Wu, X, 2002 (57)</td>
</tr>
<tr>
<td>D4S1627</td>
<td>4p13</td>
<td>37 Utah families (994 subjects)</td>
<td>3.4</td>
<td>Stone S, 2002 (60)</td>
</tr>
<tr>
<td>D4S3350</td>
<td>4p15.1</td>
<td>37 Utah families (994 subjects)</td>
<td>9.2</td>
<td>Stone S, 2002 (60)</td>
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<tr>
<td>D4S2632</td>
<td>4p15.1</td>
<td>37 Utah families (994 subjects)</td>
<td>6.1</td>
<td>Stone S, 2002 (60)</td>
</tr>
<tr>
<td>D6S403</td>
<td>6q23.3</td>
<td>27 Mexican-American families (261 subjects)</td>
<td>4.2</td>
<td>Arya R, 2002 (61)</td>
</tr>
<tr>
<td>D6S1003</td>
<td>6q24.1</td>
<td>27 Mexican-American families (261 subjects)</td>
<td>4.2</td>
<td>Arya R, 2002 (61)</td>
</tr>
<tr>
<td>D7S817</td>
<td>7p14.3</td>
<td>182 African families (769 subjects)</td>
<td>3.83</td>
<td>Adeyemo A, 2003 (31)</td>
</tr>
<tr>
<td>D7S1804</td>
<td>7q32.3</td>
<td>401 American families (3,027 subjects)</td>
<td>4.9</td>
<td>Feitosa MF, 2002 (62)</td>
</tr>
<tr>
<td>D8S1121</td>
<td>8p11.23</td>
<td>10 Mexican-American families (470 subjects)</td>
<td>3.2</td>
<td>Mitchell B, 1999 (63)</td>
</tr>
<tr>
<td>D10S212</td>
<td>10q26.3</td>
<td>18 Dutch families (198 subjects)</td>
<td>3.3</td>
<td>van der Kallen CJ, 2000 (64)</td>
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<tr>
<td>Chromosome</td>
<td>10q26.3</td>
<td>279 White families (1,848 non-Hispanic subjects)</td>
<td>3.2</td>
<td>Turner S, 2004 (65)</td>
</tr>
<tr>
<td>D11S2000</td>
<td>11q22.3</td>
<td>182 African families (769 subjects)</td>
<td>3.35</td>
<td>Adeyemo A, 2003 (31)</td>
</tr>
<tr>
<td>D11S912</td>
<td>11q24.3</td>
<td>264 Pima Indian and American families (1,766 pairs)</td>
<td>3.6</td>
<td>Hanson RL, 1998 (66)</td>
</tr>
<tr>
<td>D12S1052</td>
<td>12q21.1</td>
<td>66 White families (349 subjects)</td>
<td>3.41</td>
<td>Palmer L, 2003 (53)</td>
</tr>
<tr>
<td>D12S1064</td>
<td>12q21.33</td>
<td>66 White families (349 subjects)</td>
<td>3.41</td>
<td>Palmer L, 2003 (53)</td>
</tr>
<tr>
<td>D12S2070</td>
<td>12q24.21</td>
<td>260 European-American families (1,297 subjects)</td>
<td>3.57</td>
<td>Li W, 2004 (67)</td>
</tr>
<tr>
<td>D13S257</td>
<td>13q14.2</td>
<td>401 American families (3,027 subjects)</td>
<td>3.2</td>
<td>Feitosa MF, 2002 (62)</td>
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<tr>
<td>D13S175</td>
<td>13q12.11</td>
<td>580 Finnish families</td>
<td>3.3</td>
<td>Watanabe RM, 2000 (69)</td>
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<td>D13S221</td>
<td>13q12.13</td>
<td>580 Finnish families</td>
<td>3.3</td>
<td>Watanabe RM, 2000 (69)</td>
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<tr>
<td>D13S1493</td>
<td>13q13.2</td>
<td>1,124 American families (3,383 subjects)</td>
<td>3.2</td>
<td>North K, 2004 (70)</td>
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<tr>
<td>D19S571</td>
<td>19q</td>
<td>109 French Caucasian families (447 subjects)</td>
<td>3.8</td>
<td>Bell CG, 2004 (71)</td>
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<tr>
<td>D20S149</td>
<td>20q13.31-qter</td>
<td>92 American families (513 subjects, 423 pairs)</td>
<td>3.2</td>
<td>Lee JH, 1999 (72)</td>
</tr>
<tr>
<td>D20S476</td>
<td>20q13</td>
<td>92 American families (513 subjects, 423 pairs)</td>
<td>3.06</td>
<td>Lee JH, 1999 (72)</td>
</tr>
<tr>
<td>D20S438</td>
<td>20q12</td>
<td>103 Utah families (1,711 subjects)</td>
<td>3.5</td>
<td>Hunt SC, 2001 (73)</td>
</tr>
<tr>
<td>D20S107</td>
<td>20q12</td>
<td>92 American families (513 subjects, 423 pairs)</td>
<td>3.2</td>
<td>Lee JH, 1999 (72)</td>
</tr>
<tr>
<td>D20S211</td>
<td>20q13.2</td>
<td>92 American families (513 subjects, 423 pairs)</td>
<td>3.2</td>
<td>Lee JH, 1999 (72)</td>
</tr>
</tbody>
</table>

* LOD score: In genetics, a statistical estimate of whether two loci (the sites of genes) are likely to lie near each other on a chromosome and are therefore likely to be inherited together as a package. “LOD” stands for logarithm of the odds (to the base 10). (A LOD score of three means that the odds are a thousand to one in favor of genetic linkage.)

### CANDIDATE GENE ASSOCIATION STUDIES

Obesity is a complex trait, which does not show a typical Mendelian transmission pattern and may depend on several susceptibility genes with low or moderate effects. There is firm evidence that genes influencing energy homeostasis and thermogenesis, adipogenesis, leptin-insulin signaling transduction, and hormonal signaling peptides play a role in the
development of obesity (88). The number of studies reporting associations between DNA sequence variation in specific genes and obesity phenotypes has increased considerably, with 426 findings of positive associations in 127 candidate genes. A promising observation is that 22 genes are each supported by at least five positive studies (52). A selective list of candidate genes according to biologic pathway is presented in table 2 (52).

It is necessary to clarify the biologic mechanism underlying the putative pathogenic association despite the level of statistical evidence in favor of an allele-obesity association. For example, SNP Pro12Ala of the peroxisome proliferative activated receptor, gamma gene (PPARG), is responsible for the association with elevated body mass index in some studies (89–91). The lower trans-activation capacity of the Ala variant of PPARG suggests a potential molecular mechanism underlying the association of this allele with lower body mass index and higher insulin sensitivity. The Ala isoform may lead to less efficient stimulation of PPARG target genes and predispose individuals with this variant to lower levels of adipose tissue mass accumulation, which in turn may be responsible for improved insulin sensitivity (92).

Recently, the best evidence for a causal role in the etiology of obesity, other than the rare autosomal recessive forms of obesity, stems from findings pertaining to diverse mutations in the melanocortin 4 receptor gene (MC4R), of which more than 40 mutations have been detected so far (93). The MC4R V103I polymorphism has been found to be negatively associated with obesity in a meta-analysis encompassing over 7,500 individuals, which revealed that, among obese cases, the carrier frequency is about 2.0 percent, whereas in non-obese controls the rate is 3.5 percent (94). These results indicate that large-scale association studies are most likely required to pick up such small effects, particularly among alleles with frequencies below 5 percent.

The β3-adrenergic receptor gene (ADRB3) is predominantly expressed in adipose tissue and regulates lipid metabolism and thermogenesis (95). Therefore, an impairment of ADRB3 function may lead to obesity through its effect on energy expenditure of fat tissue. A meta-analysis including 31 studies with more than 9,000 individuals demonstrated a significant association of the Trp64Arg polymorphism of the ADRB3 gene with body mass index (96). For the first time, an association among diverse population groups exhibited a relatively similar strength, and the ADRB3 locus has been shown to be a genetic factor associated with body weight in a universal manner. More recently, another meta-analysis conducted in Japanese populations supported the hypothesis that the ADRB3 gene Trp64Arg polymorphism is associated with body mass index (97).

Uncoupling proteins, designated as “UCPs,” are a family of proteins whose function is to uncouple oxidative phosphorylation of adenosine diphosphate to adenosine triphosphate, leading to the generation of heat (98). Three different proteins have been discovered. Uncoupling protein 1 (UCP-1) is expressed in brown adipose tissue (99), uncoupling protein 2 (UCP-2) is expressed in most tissues including white adipose tissue, and uncoupling protein 3 (UCP-3) is expressed in skeletal muscle (100, 101). The 3′ insertion/deletion (I/D) polymorphism in the UCP-2 gene had a reported association with obesity and body mass index in different populations (102–105). This variant might have an effect on UCP-2 messenger RNA stability. This, in turn, could affect protein expression and determine body weight by influencing energy expenditure and thermogenesis, which was supported by a study that found reduced UCP-2 messenger RNA levels in the visceral fat of obese but not lean subjects (106). Although several studies had conflicting findings about the −G866A polymorphism of the UCP-2 gene with obesity, results from one group indicated that this polymorphism may increase the risk of central obesity in Chinese and Indian men (107), and results from a Spanish population indicated that the presence of the A allele increased the likelihood of developing obesity in the future (108).

Other genes, such as the LEPR gene and the glucocorticoid receptor gene (GRL), have been reported to be associated with an increased body mass index, an increased weight gain, or obesity in some populations. However, findings from two recent meta-analyses indicated that there was no compelling evidence of an association between these two genes and obesity (109, 110).

Although genetic association studies offer a potentially powerful approach to detect genetic variants that influence susceptibility to common disease, the failure to replicate findings across these studies is a serious concern of this approach. Several possibilities have been proposed to explain the inconsistent findings from association studies (111). First, the association may be due to false positive results. Recently, a meta-analysis suggested that the false positives were probably responsible for many failures to replicate associations between common variants and complex traits; similarly, the estimate of the genetic effect in the first positive report was always biased upward (111). Second, a true association may fail to be replicated in an underpowered replication attempt (false negative), especially for complex diseases with modest genetic effects (112, 113). Third, population stratification results in inconsistency in replication, reflecting different ancestral history that includes responses to natural selection, migration patterns, and founder events (111, 112). Thus, a true association in one population is not true in another population because of heterogeneity in genetic or environmental background. Unmeasured factors, selection bias, and differential misclassification of exposure may also be responsible for some nonreplication in association studies (114).

In light of the seemingly high proportion of false positive reports in the literature, more stringent criteria for interpreting association studies are needed (111). A single, nominally significant association should be viewed as tentative until it has been independently replicated in other studies. In addition, large association studies should be encouraged, with collaborative efforts probably required to achieve the sample size of many thousands of case-control pairs that is necessary for definitive studies of common variants with modest genetic effects. Finally, using large samples to test previously reported associations, perhaps focusing initially on those associations that have already been replicated at least once, would probably identify a significant number of variants that affect the risk of common disease, such as obesity. The International HapMap Project has identified appropriate
<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene description</th>
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<tbody>
<tr>
<td>AGRP</td>
<td>Agouti-related protein homolog</td>
</tr>
<tr>
<td>CART</td>
<td>Cocaine- and amphetamine-regulated transcript</td>
</tr>
<tr>
<td>DRD2</td>
<td>Dopamine receptor D2</td>
</tr>
<tr>
<td>DRD4</td>
<td>Dopamine receptor D4</td>
</tr>
<tr>
<td>GHRP</td>
<td>Ghrelin precursor</td>
</tr>
<tr>
<td>GRP82</td>
<td>G protein-coupled receptor 24</td>
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<tr>
<td>HTR1A</td>
<td>5-hydroxytryptamine receptor 1A</td>
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<tr>
<td>HTR2A</td>
<td>5-hydroxytryptamine receptor 2A</td>
</tr>
<tr>
<td>HTR2C</td>
<td>5-hydroxytryptamine receptor 2C</td>
</tr>
<tr>
<td>IDE</td>
<td>Insulin-degrading enzyme</td>
</tr>
<tr>
<td>MC3R</td>
<td>Melanocortin 3 receptor</td>
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<td>MC4R</td>
<td>Melanocortin 4 receptor</td>
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<td>MC5R</td>
<td>Melanocortin 5 receptor</td>
</tr>
<tr>
<td>NPR3</td>
<td>Natriuretic peptide receptor C</td>
</tr>
<tr>
<td>NPY</td>
<td>Neuropeptide Y</td>
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<tr>
<td>NPY2R</td>
<td>Neuropeptide Y receptor Y2</td>
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<td>NR3C1</td>
<td>Glucocorticoid receptor</td>
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<td>POMC</td>
<td>Propiomelanocortin</td>
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<tr>
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<td>Peptide YY</td>
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<tr>
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<td>Tyrosine hydroxylase</td>
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<td>UBL5</td>
<td>Ubiquitin-like 5</td>
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<tr>
<td>Y2R</td>
<td>Neuropeptide Y receptor Y2</td>
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<tr>
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<td>Adiponectin</td>
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<td>Adiponutrin</td>
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<tr>
<td>APM1</td>
<td>Adipose most abundant gene transcript 1</td>
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<tr>
<td>APOA1</td>
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<tr>
<td>APOA2</td>
<td>Apolipoprotein A2</td>
</tr>
<tr>
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</tr>
<tr>
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<td>Apolipoprotein B</td>
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<td>Apolipoprotein D</td>
</tr>
<tr>
<td>APOE</td>
<td>Apolipoprotein E</td>
</tr>
<tr>
<td>CBF2</td>
<td>Core-binding factor, runt domain, α subunit 2</td>
</tr>
<tr>
<td>GNB3</td>
<td>Guanine nucleotide binding protein, β polypeptide 3</td>
</tr>
<tr>
<td>INSIG2</td>
<td>Insulin-induced gene 2</td>
</tr>
<tr>
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<td>Low-density lipoprotein receptor</td>
</tr>
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<td>Lipase, hepatic</td>
</tr>
<tr>
<td>LIPE</td>
<td>Lipase, hormone sensitive</td>
</tr>
<tr>
<td>LMNA</td>
<td>Lamin A/C</td>
</tr>
<tr>
<td>LPL</td>
<td>Lipoprotein lipase</td>
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<td>MACS2</td>
<td>SAH family member, acyl-coenzyme A synthetase for fatty acids</td>
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<td>Paraoxonase 1</td>
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<tr>
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<td>Sterol regulatory element binding transcription factor 1</td>
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<tr>
<td>ACP1</td>
<td>Acid phosphatase 1</td>
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<tr>
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<td>Adrenergic, β-2- , receptor</td>
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<tr>
<td>ADRB3</td>
<td>Adrenergic, β-3- , receptor</td>
</tr>
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<td>ATPase, Na+/K+ transporting, α 2 (β) polypeptide</td>
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<td>Calpain 10</td>
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<td>FABP1</td>
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Table continues
GENE-GENE INTERACTION IN OBESITY

The risk of obesity is determined by not only specific genotypes but also significant gene-gene interactions. There is a growing awareness that the failure to replicate single-locus association studies for obesity may be due to underlying genetic interactions between genes. Unfortunately, difficulty in detecting gene-gene interactions is a common problem for current epidemiologic studies. Certain association study designs have been shown to be more effective in identifying gene-gene interactions compared with others. For example, case-only and unmatched case-control studies have been shown to be more powerful than matched case-control studies and family-based designs for detecting interaction; however, both of these study designs are particularly sensitive to population stratification (116–118). Additionally, study sample sizes are often calculated with the purpose of capturing the main effect of the candidate gene and are therefore underpowered to detect any gene-gene interactions (119). Moreover, if an association study fails to detect the marginal effect of a single locus, subsequent identification of interactions including that locus may be unlikely (120, 121). A recent paper by Marchini et al. (120) illustrates the utility of two- and three-locus models for identifying multi-loci interactions in genome-wide association studies.

Recently, some examples of interactions of known genes on obesity have been reported. Peroxisome proliferator-activated receptor genes (PPARs) are ligand-activated nuclear receptors implicated in adipocyte differentiation and lipid and glucose metabolism (122), whereas the ADRB3 gene is expressed in adipocytes and mediates the rate of lipolysis in response to catecholamines (123). A gene-gene interaction was reported between Pro12Ala of the PPARG2 gene and Trp64Arg of the ADRB3 gene, where subjects with both gene variants had significantly higher body mass index, insulin, and leptin levels than those with only the PPARG2 gene variant in Mexican Americans (124); a synergistic effect between these two polymorphisms was also found for obesity risk in a Spanish population (125).

In the Quebec Family Study, gene-gene interactions were observed among the markers in the α2-, β2-, and β3-adrenergic receptor genes (ADRs) contributing to the phenotypic variability in abdominal obesity (126). An interaction was also found in women between the β1- and β3-adrenergic receptors. Women with Gly/Gly genotypes at the β1-adrenergic receptor gene (ADRB1) and carrying at least one β3-Arg allele showed notable increases in body mass index (127). Additionally, the simultaneous existence of the ADRB1/ADRB3 gene with the UCP-1 gene and/or the lipoprotein lipase gene (LPL) might play a role in the development of obesity or weight gain and have synergistic effects when combined with each other (128–131). Genetic interactions between LEP –G2548A and LEPR Q223R may promote immune dysfunction associated with obesity (132).

Some potential chromosome regions have also been detected by allowing for interaction between obesity-susceptibility loci, such as chromosome regions 2p25-p24 and 13q13-21, 20q and chromosome 10 centromere, and the TBC1 domain family member 1 gene (TBC1D1) and the 4q34-q35 region (80, 85, 133).

GENE-ENVIRONMENT INTERACTION IN OBESITY

The rapidly increasing prevalence of obesity, in spite of an unchanged gene pool, makes it interesting to search for responsible environmental factors that increase the susceptibility for obesity at the individual level. Migration studies help support the impact of environmental factors on obesity development. For example, Japanese people who have migrated to Hawaii and California are more overweight than their relatives who remained in Japan (134). Perhaps the genetic background of most people is not prepared for the current abundance of food and sedentary lifestyle. However, even in the obesity-promoting environment, not every individual becomes obese. Therefore, the importance of a gene-environment interaction is demonstrated when an individual with a high-risk genetic profile enters a high-risk environment, and the effects on risk are so great that obesity develops (135).

GENES AND DIET INTERACTION

Eating behavioral traits aggregate in families. The familial environment seems to be the major determinant of correlations in weight status between parents and their offspring, although a genetic contribution cannot be excluded (136). At the population level, people with high risk of obesity could benefit from early diet intervention. However, it is well documented that there are considerable interindividual differences in the response of plasma lipid concentrations to alterations in the amount of fat and cholesterol in the diet (137). Therefore, in tailoring prevention and treatment programs for eating behavior, both an individual’s genetic makeup and family environment should be considered.

Some potential susceptibility genes, which relate to energy homeostasis, appetite, satiety, lipoprotein metabolism, and a number of peripheral signaling peptides, may be involved in variable responses to diets (138). Genes regulating energy homeostasis and thermogenesis include neuropeptide Y (NPY), agouti-related protein (AGRP), melanocortin pathway factors (MC4R), uncoupling proteins (UCPs), and fatty acid binding protein (FABP) (80, 138). Diet intake control may be affected by genes encoding taste receptors and a number of peripheral signaling peptides, such as insulin (INS), leptin (GHR), and cholecystokinin (CCK) (138). Levels of uncoupling proteins (UCP-2 and UCP-3) were reported to increase during starvation without changing heat production (85). LEPR genes showed an association with energy balance in an overfeeding experiment (139). Clusters of α-amylase genes (AMY1A, AMY2A, and AMY2B), involved in the digestion of starch, and the insulin-like growth factor 1 gene (IGF1) may be linked to carbohydrate and protein intakes (140, 141). The MC4R gene and the neurenomed beta gene (NMB) were identified as having an association with the control of eating behavior (142, 143).
Some genes have been identified and linked to variable responses to diet in the lipoprotein metabolism pathway, including apolipoprotein E (APOE), apolipoprotein B (APOB), apolipoprotein AIV (APOA4), apolipoprotein CIII (APOC3), low-density lipoprotein receptor (LDLR), FABP, LPL, microsomal transfer protein (MTP), cholesteryl ester transfer protein (CETP), and hepatic lipase (HPL) (144). For example, the subjects with APOA4 T allele showed a better reduction in low-density lipoprotein cholesterol under dietary intervention, and subjects with the FABP 54Thr allele exhibited a much better lowering of triglyceride with dietary intervention (144).

GENES AND PHYSICAL ACTIVITY INTERACTION

Physical activity is a determinant of energy and substrate metabolism. However, recent cultural changes have engineered physical activity out of the daily lives of humans. More than 60 percent of American adults are not regularly active, and 25 percent are sedentary (145). Physical activity deficiency is predicted to disrupt the optimized expression of the “thrifty” genes and genotype for the physical activity-rest cycle. Some of these “thrifty” genes could have been initially selected to conserve glycogen stores by oxidizing greater quantities of fatty acids to maximize survival during famine and exercise. Therefore, the present sedentary lifestyle has led to discordance in gene-environmental interactions (146).

A review showed heritability coefficients between 0.29 and 0.62 for daily physical activity, suggesting significant genetic effects (147). Some genes have been reported to influence human physical performance and physical activity, such as the angiotensin I converting enzyme gene (ACE), the guanine nucleotide binding protein, beta polypeptide 3 gene (GNB3), the β-adrenergic receptor gene (ADRB2), MC4R, the cocaine- and amphetamine-regulated transcript gene (CART), UCP-2, and UCP-3 (148–153). For example, duration of exercise improved significantly for those with the II and ID genotype of the ACE gene but not for those with DD genotype (148). Furthermore, the CART gene may modify the effect of the MC4R genotype (151). The hypoxia-inducible factor 1 gene (HIF1) and the titin gene (TTN) were associated with maximal oxygen consumption after aerobic exercise training (154–156). Linkage studies also discovered some genes related to maximal oxygen uptake in the sedentary state and in response to training: these included the following: the skeletal muscle-specific creatine kinase gene (CKMM), the β-sarcoglycan gene (SGCB), the syntrophin β-1 gene (SNTB1), the γ-sarcoglycan gene (SGCG), the dystrophin-associated glycoprotein 1 gene (DAG1), the lamin A/C gene (LMNA), the liver glycogen phosphorylase gene (PYGL), the guanosine triphosphate cyclohydrolase I gene (GCH1), and the sulfonylurea receptor gene (SUR) (157).

FUTURE DIRECTIONS

With the completion of the Human Genome Project and recent advancements in the International HapMap Project, our capability in understanding the genetic mechanisms underlying human obesity is rapidly increasing. High-throughput genotyping and decreased genotyping costs have made whole-genome association studies a feasible option, and future studies will likely utilize this method for identification of novel genes involved in obesity pathogenesis (158). However, complete elucidation of this complex trait will require the integration of many disciplines, combining advances in genetic epidemiology with the fields of functional genomics and proteomics. The advent of the DNA microarray has made gene-expression profiling a powerful tool for simultaneous investigation of the expression of a large number of genes that may provide more clues regarding the molecular basis of obesity with its continued use (159–161). Several studies have already examined gene expression in adipose tissue in obese and nonobese subjects, identifying some novel genes of interest along with genes mapped to regions with suggestive linkage to obesity (162–164). Rodent models may also play an important role in not only identifying novel genes for further exploration in human populations but also testing the functional effects of candidate genes already identified in studies from human populations (26). Additionally, because a gene can be posttranscriptionally or posttranslationally modified into many different protein products, other methods of studying the molecular mechanisms of obesity must be used. The recent emergence of proteomics, defined as the analysis of proteins and their interactions in an organism, holds great promise as an adjunct technique for unraveling the pathogenesis and pathophysiology of this complex trait (165, 166).

CONCLUSIONS

The global emergence of obesity is one of the greatest challenges in public health research today. Unhealthy diet and physical inactivity have been identified as primary determinants of the increase in the incidence of obesity. It is likely and reasonable to assume that acute changes in behavior and the environment have contributed to the rapid increase in obesity and that genetic factors may be important in determining an individual’s susceptibility to obesity. Its complex etiology makes the prevention and treatment of obesity especially challenging. While exciting advancements in molecular technology are rapidly expanding the field of genetic epidemiology and the capabilities of the genetic epidemiologist, it should be noted that limitations of genetic epidemiologic studies of obesity still exist. For example, body mass index is the most widely used phenotype for defining obesity status; however, recent epidemiologic studies have indicated that it is not the best predictor for the risk of cardiovascular disease compared with other obesity measures (167). Moreover, common confounders such as diet and physical activity are very difficult to measure accurately, which can result in residual confounding in examining the association between candidate gene and obesity-related phenotypes (168, 169). Additionally, the effect size of individual genetic variants on a polygenic disorder such as obesity is typically moderate to small; therefore, very large sample sizes may be necessary to detect these effects, particularly...
when adjusting for other confounders or when examining gene–gene or gene–environment interactions (170). With the increasing utilization of large-scale case-control studies of unrelated individuals, special attention to population stratification is also warranted (114, 171). While methods of genomic control have been established to correct for population substructure, recent evidence has shown that these methods may not always be adequate, and, therefore, issues of population stratification should be considered in the study design phase (172). Finally, with the advances in genotyping technology and the emergence of genome-wide association studies, statistical methods for correcting for multiple comparisons have become challenging.

Generally speaking, researchers must always understand the limitations and potential pitfalls of their study. However, with careful planning and attention to study design, methods, conduct, and analytical issues, genetic epidemiologic studies of obesity can yield important and valid results. For the novice researcher initiating a linkage study, information from Teare and Barrett (173) and Botstein and Risch (174) would be helpful, and important guidelines for interpreting and reporting linkage results have been illustrated by Lander and Kruglyak (86). Moreover, recently published reviews have demonstrated design and statistical issues involved in population-based or family-based association studies that should also be kept in mind (116, 171, 175). In addition, gene–gene and gene–environmental interaction methodological reviews can also be useful references (118, 119, 176, 177).

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REFERENCES


