Epidemiologic Reviews
Vol. 29, 2007

DOI: 10.1093/epirev/mxm004
Advance Access publication June 12, 2007

# Genetic Epidemiology of Obesity

**Wenjie Yang[1], Tanika Kelly[1], and Jiang He[1,2]**

[1] Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA.
[2] Department of Medicine, School of Medicine, Tulane University, New Orleans, LA.

*Accepted for publication January 31, 2007.*

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 $kg/m^2$ (underweight), 18.5–24.9 $kg/m^2$ (normal weight), 25.0–29.9 $kg/m^2$ (overweight), 30.0–39.9 $kg/m^2$ (obese), and ≥40 $kg/m^2$ (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

Correspondence to Dr. Jiang He, Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, 1440 Canal Street, SL 18, New Orleans, LA 70112 (e-mail: jhe@tulane.edu).

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 (19). 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 prior 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 GEnetics) 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 causal 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: $\geq$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 Sudy 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 2p22.3 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

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

| DNA marker | Chromosomal location | Study sample | LOD score* | First author, year (reference no.) |
|---|---|---|---|---|
| D2S1788 | 2p22.3 | 66 White families (349 subjects) | 3.08 | Palmer L, 2003 (53) |
| D2S347 | 2q14.3 | 1,249 White European-origin sibling pairs | 4.44 | Deng HW, 2002 (54) |
| D2S347 | 2q14.3 | 53 Caucasian families (758 subjects) | 3.42 | Liu Y, 2004 (55) |
| | 2q37 | 451 Caucasian families (4,247 subjects) | 3.34 | Guo YF, 2006 (56) |
| D3S1764 | 3q22.3 | 1,055 pairs (White, Black, Mexican American, and Asian) | 3.45 (Black) | Wu X, 2002 (57) |
| D3S2427 | 3q26.33 | 507 Caucasian families (2,209 subjects) | 3.3 | Kissebah A, 2000 (58) |
| D3S2427 | 3q26.33 | 128 African-American families (545 subjects) | 4.3 | Luke A, 2003 (59) |
| D3S2427 | 3q26.33 | 1,055 pairs (White, Black, Mexican American) | 3.4 | Wu X, 2002 (57) |
| D3S3676 | 3q26.33 | 128 African-American families (545 subjects) | 4.3 | Luke A, 2003 (59) |
| D4S1627 | 4p13 | 37 Utah families (994 subjects) | 3.4 | Stone S, 2002 (60) |
| D4S3350 | 4p15.1 | 37 Utah families (994 subjects) | 9.2 | Stone S, 2002 (60) |
| D4S2632 | 4p15.1 | 37 Utah families (994 subjects) | 6.1 | Stone S, 2002 (60) |
| D6S403 | 6q23.3 | 27 Mexican-American families (261 subjects) | 4.2 | Arya R, 2002 (61) |
| D6S1003 | 6q24.1 | 27 Mexican-American families (261 subjects) | 4.2 | Arya R, 2002 (61) |
| D7S817 | 7p14.3 | 182 African families (769 subjects) | 3.83 | Adeyemo A, 2003 (31) |
| D7S1804 | 7q32.3 | 401 American families (3,027 subjects) | 4.9 | Feitosa MF, 2002 (62) |
| D8S1121 | 8p11.23 | 10 Mexican-American families (470 subjects) | 3.2 | Mitchell B, 1999 (63) |
| D10S212 | 10q26.3 | 18 Dutch families (198 subjects) | 3.3 | van der Kallen CJ, 2000 (64) |
| Chromosome 10 region | 10q26.3 | 279 White families (1,848 non-Hispanic subjects) | 3.2 | Turner S, 2004 (65) |
| D11S2000 | 11q22.3 | 182 African families (769 subjects) | 3.35 | Adeyemo A, 2003 (31) |
| D11S912 | 11q24.3 | 264 Pima Indian and American families (1,766 pairs) | 3.6 | Hanson RL, 1998 (66) |
| D12S1052 | 12q21.1 | 66 White families (349 subjects) | 3.41 | Palmer L, 2003 (53) |
| D12S1064 | 12q21.33 | 66 White families (349 subjects) | 3.41 | Palmer L, 2003 (53) |
| D12S2070 | 12q24.21 | 260 European-American families (1,297 subjects) | 3.57 | Li W, 2004 (67) |
| | 12q24 | 933 Australian families (2,053 subjects) | 3.02 | Cornes BK, 2005 (68) |
| D13S257 | 13q14.2 | 401 American families (3,027 subjects) | 3.2 | Feitosa MF, 2002 (62) |
| D13S175 | 13q12.11 | 580 Finnish families | 3.3 | Watanabe RM, 2000 (69) |
| D13S221 | 13q12.13 | 580 Finnish families | 3.3 | Watanabe RM, 2000 (69) |
| D13S1493 | 13q13.2 | 1,124 American families (3,383 subjects) | 3.2 | North K, 2004 (70) |
| D19S571 | 19q | 109 French Caucasian families (447 subjects) | 3.8 | Bell CG, 2004 (71) |
| D20S149 | 20q13.31-qter | 92 American families (513 subjects, 423 pairs) | 3.2 | Lee JH, 1999 (72) |
| D20S476 | 20q13 | 92 American families (513 subjects, 423 pairs) | 3.06 | Lee JH, 1999 (72) |
| D20S438 | 20q12 | 103 Utah families (1,711 subjects) | 3.5 | Hunt SC, 2001 (73) |
| D20S107 | 20q12 | 92 American families (513 subjects, 423 pairs) | 3.2 | Lee JH, 1999 (72) |
| D20S211 | 20q13.2 | 92 American families (513 subjects, 423 pairs) | 3.2 | Lee JH, 1999 (72) |

* 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.)

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).

## 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 nonobese 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 $\beta_3$-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 the 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 2. Candidate genes associated with obesity and body composition according to biologic pathways***

| Gene symbol | Gene description |
|---|---|
| | *Central neuronal signaling pathway* |
| *AGRP* | Agouti-related protein homolog |
| *CART* | Cocaine- and amphetamine-regulated transcript |
| *DRD2* | Dopamine receptor D2 |
| *DRD4* | Dopamine receptor D4 |
| *GHRL* | Ghrelin precursor |
| *GPR24* | G protein-coupled receptor 24 |
| *HTR1B* | 5-hydroxytryptamine receptor 1B |
| *HTR2A* | 5-hydroxytryptamine receptor 2A |
| *HTR2C* | 5-hydroxytryptamine receptor 2C |
| *IDE* | Insulin-degrading enzyme |
| *MC3R* | Melanocortin 3 receptor |
| *MC4R* | Melanocortin 4 receptor |
| *MC5R* | Melanocortin 5 receptor |
| *NPR3* | Natriuretic peptide receptor C |
| *NPY* | Neuropeptide Y |
| *NPY2R* | Neuropeptide Y receptor Y2 |
| *NR3C1* | Glucocorticoid receptor |
| *POMC* | Proopiomelanocortin |
| *PYY* | Peptide YY |
| *TH* | Tyrosine hydroxylase |
| *UBL5* | Ubiquitin-like 5 |
| *Y2R* | Neuropeptide Y receptor Y2 |
| | *Adipogenesis* |
| *ACDC* | Adiponectin |
| *ADPN* | Adiponutrin |
| *APM1* | Adipose most abundant gene transcript 1 |
| *APOA1* | Apolipoprotein AI |
| *APOA2* | Apolipoprotein AII |
| *APOA4* | Apolipoprotein AIV |
| *APOB* | Apolipoprotein B |
| *APOD* | Apolipoprotein D |
| *APOE* | Apolipoprotein E |
| *CBFA2T1* | Core-binding factor, runt domain, α subunit 2 |
| *FOXC2* | Forkhead box C2 |
| *GNB3* | Guanine nucleotide binding protein, β polypeptide 3 |
| *INSIG2* | Insulin-induced gene 2 |
| *LDLR* | Low-density lipoprotein receptor |
| *LIPC* | Lipase, hepatic |
| *LIPE* | Lipase, hormone sensitive |
| *LMNA* | Lamin A/C |
| *LPL* | Lipoprotein lipase |
| *MACS2* | SAH† family member, acyl-coenzyme A synthetase for fatty acids |
| *PLIN* | Perilipin |
| *PON1* | Paraoxonase 1 |
| *PPARA* | Peroxisome proliferative activated receptor, α |
| *PPARD* | Peroxisome proliferator-activated receptor, δ |
| *PPARG* | Peroxisome proliferator-activated receptor, γ |
| *SAH* | SA hypertension-associated homolog |
| *SCARB1* | Scavenger receptor class B, member 1 |
| *SORBS1* | Sorbin and SH3† domain containing 1 |
| *SREBF1* | Sterol regulatory element binding transcription factor 1 |
| | *Energy metabolism and thermogenesis* |
| *ACP1* | Acid phosphatase 1 |
| *ADA* | Adenosine deaminase |
| *ADRA2B* | Adrenergic, α-2B−, receptor |
| *ADRB2* | Adrenergic, β-2−, receptor |
| *ADRB3* | Adrenergic, β-3−, receptor |
| *ATP1A2* | ATPase,† $Na^+/K^+$ transporting, α 2 (+) polypeptide |
| *CAPN10* | Calpain 10 |
| *ENPP1* | Ectonucleotide pyrophosphatase/phosphodiesterase 1 |
| *FABP1* | Fatty acid-binding protein 1 |
| *FABP2* | Fatty acid binding protein 2, intestinal |
| *FABP4* | Fatty acid binding protein 4, adipocyte |
| *FASN* | Fatty acid synthase |
| *GAD2* | Glutamic acid decarboxylase 2 |
| *GYS1* | Glycogen synthase 1 |
| *HSPA1B* | Heat shock $M_r$ 70,000 protein 1B |
| *PPARGC1A* | Peroxisome proliferator-activated receptor, γ, coactivator 1 α |
| *PTPN1* | Protein tyrosine phosphatase, nonreceptor type 1 |
| *TUB* | Tubby, mouse, homolog of |
| *UCP1* | Uncoupling protein 1 |
| *UCP2* | Uncoupling protein 2 |
| *UCP3* | Uncoupling protein 3 |
| | *Leptin-insulin signaling pathway* |
| *ABCC8* | ATP†-binding cassette, subfamily C, member 8 |
| *BTC* | Betacellulin |
| *GCGR* | Glucagon receptor |
| *IDE* | Insulin-degrading enzyme |
| *IGF2* | Insulin-like growth factor 2 |
| *INS* | Insulin |
| *IRS1* | Insulin receptor substrate 1 |
| *IRS2* | Insulin receptor substrate 2 |
| *LEP* | Leptin |
| *LEPR* | Leptin receptor |
| *PTPRF* | Protein tyrosine phosphatase, receptor type F |
| *RETN* | Resistin |
| *TBC1D1* | TBC1 domain family, member 1 |
| *TCF1* | Transcription factor 1, hepatic; LFB1, hepatic nuclear factor (HNF1), albumin proximal factor |
| | *Inflammatory cytokines* |
| *IL6* | Interleukin 6 |
| *IL6R* | Interleukin 6 receptor |
| *IL10* | Interleukin 10 |
| *LTA* | Lymphotoxin alpha (TNF† superfamily, member 1) |
| *SERPINE1* | Serine proteinase inhibitor, clade E, member 1 |
| *TNF* | Tumor necrosis factor |
| | *Hormone signaling pathway* |
| *AR* | Androgen receptor |
| *CCKAR* | Cholecystokinin A receptor |
| *CRHR1* | Corticotropin-releasing hormone receptor 1 |
| *CYP11B2* | Cytochrome P450, family 11, subfamily B, polypeptide 2 |
| *CYP19A1* | Cytochrome P450, family 19, subfamily A, polypeptide 1 |
| *ESR1* | Estrogen receptor 1 |
| *ESR2* | Estrogen receptor 2 |
| *GHRHR* | Growth hormone releasing hormone receptor |
| *MAOA* | Monoamine oxidase A |
| *MAOB* | Monoamine oxidase B |
| *MED12* | Mediator of RNA polymerase II transcription, subunit 12 |
| *NR0B2* | Nuclear receptor subfamily 0, group B, member 2 |
| *NCOA3* | Nuclear receptor coactivator 3 |
| *PGR* | Progesterone receptor |
| *SGK* | Serum/glucocorticoid-regulated kinase |
| *SLC6A3* | Solute carrier family 6, member 3 |
| *SLC6A14* | Solute carrier family 6, member 14 |
| *VDR* | Vitamin D receptor |
| | *Renin-angiotensin pathway* |
| *ACE* | Angiotensin I converting enzyme |
| *AGT* | Angiotensinogen |
| *HSD11B1* | Hydroxysteroid (11-beta) dehydrogenase 1 |

**Table continues**

* Please refer to Rankinen et al. (52) for a more comprehensive summarization of obesity-candidate gene associations.

† SAH, SA hypertension-associated homolog (rat) ; SH3, *src* homology-3; ATPase, adenosine triphosphatase; ATP, adenosine triphosphate; TNF, tumor necrosis factor.

sets of tag SNPs that span the genome, greatly facilitating an efficient, linkage disequilibrium-based approach (115).

## 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 multiloci interactions in genome-wide association studies.

Recently, some examples of interactions of known genes on obesity have been reported. Peroxisome proliferator-activated receptor genes (*PPAR*s) 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 (*ADR*s) 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*), *LEP*, ghrelin (*GHRL*), 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 neuromedin 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 $\beta_2$-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 post-transcriptionally 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).

## ACKNOWLEDGMENTS

Conflict of interest: none declared.

## REFERENCES

1. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:i–xii, 1–253.
2. Lei SF, Liu MY, Chen XD, et al. Relationship of total body fatness and five anthropometric indices in Chinese aged 20–40 years: different effects of age and gender. Eur J Clin Nutr 2006;60:511–18.
3. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva, Switzerland: World Health Organization, 1997.
4. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. Circulation 2005;112:e285–90.
5. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Geneva, Switzerland: World Health Organization, 1999.
6. International Obesity Taskforce. About obesity 2005. London, United Kingdom: International Obesity Taskforce, 2005. (http://www.iotf.org/aboutobesity.asp).
7. Haslam DW, James WP. Obesity. Lancet 2005;366:1197–209.
8. Centers for Disease Control and Prevention. What is the prevalence of overweight and obesity among U.S. adults? Atlanta, GA: Centers for Disease Control and Prevention, 2006. (http://www.cdc.gov/nccdphp/dnpa/obesity/faq.htm).
9. Gu D, Reynolds K, Wu X, et al. Prevalence of the metabolic syndrome and overweight among adults in China. Lancet 2005;365:1398–405.
10. Reddy KS, Prabhakaran D, Shah P, et al. Differences in body mass index and waist:hip ratios in North Indian rural and urban populations. Obes Rev 2002;3:197–202.
11. Chan JM, Rimm EB, Colditz GA, et al. Obesity, fat distribution and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961–9.
12. Krauss RM, Winston M, Fletcher BJ, et al. Obesity: impact on cardiovascular disease. Circulation 1998;98:1472–6.
13. Rexrode KM, Hennekens CH, Willett WC, et al. A prospective study of body mass index, weight change, and risk of stroke in women. JAMA 1997;277:1539–45.
14. Kurth T, Gaziano JM, Berger K, et al. Body mass index and the risk of stroke in men. Arch Intern Med 2002;162:2557–62.
15. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev 2004;4:579–91.
16. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. N Engl J Med 2003;348:1625–38.
17. Hu FB, Willett WC, Li T, et al. Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med 2004;351:2694–703.
18. Lee IM, Manson JE, Hennekens CH, et al. Body weight and mortality: a 27-year follow-up of middle-aged men. JAMA 1993;270:2823–8.
19. Dean M. Approaches to identify genes for complex human diseases: lessons from Mendelian disorders. Hum Mutat 2003;22:261–74.
20. Barrett JC, Cardon LR. Evaluating coverage of genome-wide association studies. Nat Genet 2006;38:659–62.
21. Herbert A, Gerry NP, McQueen MB, et al. A common genetic variant is associated with adult and childhood obesity. Science 2006;312:279–83.
22. Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science 1996;273:1516–17.
23. Jorgenson E, Witte JS. A gene-centric approach to genome-wide association studies. Nat Genet 2006;7:885–91.
24. Daly AK, Day CP. Candidate gene case-control association studies: advantages and potential pitfalls. Br J Clin Pharmacol 2001;52:489–99.
25. Carlson CS, Eberle MA, Kruglyak L, et al. Mapping complex disease loci in whole-genome association studies. Nature 2004;429:446–52.
26. Cowley AW Jr. The genetic dissection of essential hypertension. Nat Rev Genet 2006;7:829–40.
27. Stunkard AJ, Foch TT, Hrubec Z. A twin study of human obesity. JAMA 1986;256:51–4.
28. Stunkard AJ, Sorensen TI, Hanis C, et al. An adoption study of human obesity. N Engl J Med 1986;314:193–8.
29. Rice T, Perusse L, Bouchard C, et al. Familial aggregation of body mass index and subcutaneous fat measures in the longitudinal Quebec family study. Genet Epidemiol 1999;16:316–34.
30. Platte P, Papanicolaou GJ, Johnston J, et al. A study of linkage and association of body mass index in the Old Order Amish. Am J Med Genet C Semin Med Genet 2003;121:71–80.

31. Adeyemo A, Luke A, Cooper R, et al. A genome-wide scan for body mass index among Nigerian families. Obes Res 2003;11:266–73.
32. McQueen MB, Bertram L, Rimm EB, et al. A QTL genome scan of the metabolic syndrome and its component traits. BMC Genet 2003;4(suppl 1):S96.
33. Allison DB, Kaprio J, Korkeila M, et al. The heritability of body mass index among an international sample of monozygotic twins reared apart. Int J Obes Relat Metab Disord 1996;20:501–6.
34. Pietilainen KH, Kaprio J, Rissanen A, et al. Distribution and heritability of BMI in Finnish adolescents aged 16y and 17y: a study of 4884 twins and 2509 singletons. Int J Obes Relat Metab Disord 1999;23:107–15.
35. Hsueh WC, Mitchell BD, Aburomia R, et al. Diabetes in the Old Order Amish: characterization and heritability analysis of the Amish Family Diabetes Study. Diabetes Care 2000;23:595–601.
36. Hunt KJ, Duggirala R, Goring HH, et al. Genetic basis of variation in carotid artery plaque in the San Antonio Family Heart Study. Stroke 2002;33:2775–80.
37. Sakul H, Pratley R, Cardon L, et al. Familiality of physical and metabolic characteristics that predict the development of non-insulin-dependent diabetes mellitus in Pima Indians. Am J Hum Genet 1997;60:651–6.
38. Poulsen P, Vaag A, Kyvik K, et al. Genetic versus environmental aetiology of the metabolic syndrome among male and female twins. Diabetologia 2001;44:537–43.
39. Freeman MS, Mansfield MW, Barrett JH, et al. Heritability of features of the insulin resistance syndrome in a community-based study of healthy families. Diabet Med 2002;19:994–9.
40. Wu DM, Hong Y, Sun CA, et al. Familial resemblance of adiposity-related parameters: results from a health check-up population in Taiwan. Eur J Epidemiol 2003;18:221–6.
41. Schousboe K, Visscher PM, Erbas B, et al. Twin study of genetic and environmental influences on adult body size, shape, and composition. Int J Obes 2004;28:39–48.
42. Rice T, Saw EW, Gagnon J, et al. Familial resemblance for body composition measures: the HERITAGE Family Study. Obes Res 1997;5:557–62.
43. Luke A, Guo X, Adeyemo AA, et al. Heritability of obesity-related traits among Nigerians, Jamaicans and US black people. Int J Obes 2001;25:1034–41.
44. Borecki IB, Higgins M, Schreiner PJ, et al. Evidence for multiple determinants of the body mass index: the National Heart, Lung, and Blood Institute Family Heart Study. Obes Res 1998;6:107–14.
45. Fabsitz RR, Sholinsky P, Carmelli D. Genetic influences on adult weight gain and maximum body mass index in male twins. Am J Epidemiol 1994;140:711–20.
46. Davey G, Ramachandran A, Snehalatha C, et al. Familial aggregation of central obesity in southern Indians. Int J Obes Relat Metab Disord 2000;24:1523–7.
47. Farooqi IS, O'Rahilly S. Monogenic human obesity syndromes. Recent Prog Horm Res 2004;59:409–24.
48. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387:903–8.
49. Clement K, Vaiesse C, Lahlou N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998;392:398–401.
50. Krude H, Biebergmann H, Luck W, et al. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet 1998;2:155–7.
51. Vaisse C, Clement K, Guy-Grand B, et al. A frameshift mutation in human *MC4R* is associated with a dominant form of obesity. Nat Genet 1998;20:113–14.
52. Rankinen T, Zuberi A, Chagnon YC, et al. The human obesity gene map: the 2005 update. Obesity (Silver Spring) 2006;14:529–644.
53. Palmer L, Buxbaum S, Larkin E, et al. A whole-genome scan for obstructive sleep apnea and obesity. Am J Hum Genet 2003;72:340–50.
54. Deng HW, Deng H, Liu YJ, et al. A genomewide linkage scan for quantitative-trait loci for obesity phenotypes. Am J Hum Genet 2002;70:1138–51.
55. Liu Y, Xu F, Shen H, et al. A follow-up linkage study for quantitative trait loci contributing to obesity-related phenotypes. J Clin Endocrinol Metab 2004;89:875–82.
56. Guo YF, Shen H, Liu YJ, et al. Assessment of genetic linkage and parent-of-origin effects on obesity. J Clin Endocrinol Metab 2006;91:4001–5.
57. Wu X, Cooper RS, Borecki I, et al. A combined analysis of genomewide linkage scans for body mass index from the National Heart, Lung, and Blood Institute Family Blood Pressure Program. Am J Hum Genet 2002;70:1247–56.
58. Kissebah A, Sonnenberg G, Myklebust J, et al. Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. Proc Natl Acad Sci U S A 2000;97:14478–83.
59. Luke A, Wu X, Zhu X, et al. Linkage for BMI at 3q27 region confirmed in an African-American population. Diabetes 2003;52:1284–7.
60. Stone S, Abkevich V, Hunt SC, et al. A major predisposition locus for severe obesity, at 4p15-p14. Am J Hum Genet 2002;70:1459–68.
61. Arya R, Blangero J, Williams K, et al. Factors of insulin resistance syndrome-related phenotypes are linked to genetic locations on chromosomes 6 and 7 in nondiabetic Mexican-Americans. Diabetes 2002;51:841–7.
62. Feitosa MF, Borecki IB, Rich SS, et al. Quantitative-trait loci influencing body-mass index reside on chromosomes 7 and 13: the National Heart, Lung, and Blood Institute Family Heart Study. Am J Hum Genet 2002;70:72–82.
63. Mitchell B, Cole S, Comuzzie A, et al. A quantitative trait locus influencing BMI maps to the region of the beta-3 adrenergic receptor. Diabetes 1999;48:1863–7.
64. van der Kallen CJ, Cantor RM, van Greevenbroek MM, et al. Genome scan for adiposity in Dutch dyslipidemic families reveals novel quantitative trait loci for leptin, body mass index and soluble tumor necrosis factor receptor superfamily 1A. Int J Obes Relat Metab Disord 2000;24:1381–91.
65. Turner S, Kardia S, Boerwinkle E, et al. Multivariate linkage analysis of blood pressure and body mass index. Genet Epidemiol 2004;27:64–73.
66. Hanson RL, Ehm MG, Pettitt DJ, et al. An autosomal genomic scan for loci linked to type II diabetes mellitus and body-mass index in Pima Indians. Am J Hum Genet 1998;63:1130–8.
67. Li W, Dong C, Li D, et al. An obesity-related locus in chromosome region 12q23-24. Diabetes 2004;53:812–20.
68. Cornes BK, Medland SE, Ferreira MA, et al. Sex-limited genome-wide linkage scan for body mass index in an unselected sample of 933 Australian twin families. Twin Res Hum Genet 2005;8:616–32.
69. Watanabe RM, Ghosh S, Langefeld CD, et al. The Finland-United States investigation of non-insulin-dependent diabetes mellitus genetics (FUSION) study. II. An autosomal genome

scan for diabetes-related quantitative-trait loci. Am J Hum Genet 2000;67:1186–200.
70. North K, Rose K, Borecki I, et al. Evidence for a gene on chromosome 13 influencing postural systolic blood pressure change and body mass index. Hypertension 2004;43:780–4.
71. Bell CG, Benzinou M, Siddiq A, et al. Genome-wide linkage analysis for severe obesity in French Caucasians finds significant susceptibility locus on chromosome 19q. Diabetes 2004;53:1857–65.
72. Lee JH, Reed DR, Li WD, et al. Genome scan for human obesity and linkage to markers in 20q13. Am J Hum Genet 1999;64:196–209.
73. Hunt SC, Abkevich V, Hensel CH, et al. Linkage of body mass index to chromosome 20 in Utah pedigrees. Hum Genet 2001;109:279–85.
74. Ng MCY, So WY, Lam VKL, et al. Genome-wide scan for metabolic syndrome and related quantitative traits in Hong Kong Chinese and confirmation of a susceptibility locus on chromosome 1q21-q25. Diabetes 2004;53:2676–83.
75. Price RA, Kilker R, Li WD. An X-chromosome scan reveals a locus for fat distribution in chromosome region Xp21-22. Diabetes 2002;51:1989–91.
76. Hsueh WC, Mitchell BD, Schneider JL, et al. Genome-wide scan of obesity in the Old Order Amish. J Clin Endocrinol Metab 2001;86:1199–205.
77. Fox CS, Heard-Costa NL, Wilson PW, et al. Genome-wide linkage to chromosome 6 for waist circumference in the Framingham Heart Study. Diabetes 2004;53:1399–402.
78. Chen G, Adeyemo AA, Johnson T, et al. A genome-wide scan for quantitative trait loci linked to obesity phenotypes among West Africans. Int J Obes (Lond) 2005;29:255–9.
79. Lewis CE, North KE, Arnett D, et al. Sex-specific findings from a genome-wide linkage analysis of human fatness in non-Hispanic whites and African Americans: the HyperGEN study. Int J Obes (Lond) 2005;29:639–49.
80. Dong CH, Li WD, Li D, et al. Interaction between obesity-susceptibility loci in chromosome regions 2p25-p24 and 13q13-q21. Eur J Hum Genet 2005;13:102–8.
81. Moslehi R, Goldstein AM, Beerman M, et al. A genome-wide linkage scan for body mass index on Framingham Heart Study families. BMC Genet 2003;4(suppl 1):S97.
82. Meyre D, Lecoeur C, Delplanque J, et al. A genome-wide scan for childhood obesity-associated traits in French families shows significant linkage on chromosome 6q22.31-q23.2. Diabetes 2004;53:803–11.
83. Arya R, Duggirala R, Jenkinson C, et al. Evidence of a novel quantitative-trait locus for obesity on chromosome 4p in Mexican Americans. Am J Med Genet 2004;74:272–82.
84. Lindsay RS, Kobes S, Knowler WC, et al. Genome-wide linkage analysis assessing parent-of-origin effects in the inheritance of type 2 diabetes and BMI in Pima Indians. Diabetes 2001;50:2850–7.
85. Dong C, Wang S, Li W, et al. Interacting genetic loci on chromosomes 20 and 10 influence extreme human obesity. Am J Hum Genet 2003;72:115–24.
86. Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 1995;11:241–7.
87. Altmuller J, Palmer LJ, Fischer G, et al. Genome-wide scans of complex human diseases: true linkage is hard to find. Am J Hum Genet 2001;69:936–50.
88. Loktionov A. Common gene polymorphisms and nutrition: emerging links with pathogenesis of multifactorial chronic diseases (review). J Nutr Biochem 2003;14:426–51.
89. Deeb SS, Fajas L, Nemoto M, et al. A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. Nat Genet 1998;20:284–7.
90. Cole SA, Mitchell BD, Hsueh WC, et al. The Pro12Ala variant of peroxisome proliferator-activated receptor-gamma2 (PPAR-gamma2) is associated with measures of obesity in Mexican Americans. Int J Obes Relat Metab Disord 2000;24:522–4.
91. Ek J, Andersen G, Urhammer SA, et al. Homozygosity of the Pro12Ala variant of the peroxisome proliferation-activated receptor-gamma2 (PPAR-gamma2): divergent modulating effects on body mass index in obese and lean Caucasian men. Diabetologia 2001;44:1170–6.
92. Vidal-Puig AJ, Considine RV, Jimenez-Linan M, et al. Peroxisome proliferator-activated receptor gene expression in human tissues. Effects of obesity, weight loss, and regulation by insulin and glucocorticoids. J Clin Invest 1997;99:2416–22.
93. Marti A, Moreno-Aliaga MJ, Hebebrand J, et al. Genes, lifestyles and obesity. Int J Obes Relat Matab Disord 2004;28(suppl 3):S29–36.
94. Dempfle A, Hinney A, Heinzel-Gutenbrunner M, et al. Large quantitative effect of melanocortin-4 receptor gene mutations on body mass index. J Med Genet 2004;41:795–800.
95. Emorine L, Blin N, Strosberg AD. The human $\beta_3$-adrenergic receptor: the search for a physiological function. Trends Pharmacol Sci 1994;15:3–7.
96. Fujisawa T, Ikegami H, Kawaguchi Y, et al. Meta-analysis of the association of Trp64Arg polymorphism of $\beta_3$-adrenergic receptor gene with body mass index. J Clin Endocrinol Metab 1998;83:2441–4.
97. Kurokawa N, Nakai K, Kameo S, et al. Association of BMI with the $\beta_3$-adrenergic receptor gene polymorphism in Japanese: meta-analysis. Obes Res 2001;9:741–5.
98. Flier JS, Lowell BB. Obesity research springs a proton leak. Nat Genet 1997;15:223–4.
99. Cannon B, Houstek J, Nedergaard J. Brown adipose tissue. More than an effector of thermogenesis? Ann N Y Acad Sci 1998;856:171–87.
100. Fleury C, Neverova M, Collins S, et al. Uncoupling protein-2: a novel gene linked to obesity and hyperinsulinemia. Nat Genet 1997;15:269–72.
101. Vidal-Puig A, Solanes G, Grujic D, et al. UCP3: an uncoupling protein homologue expressed preferentially and abundantly in skeletal muscle and brown adipose tissue. Biochem Biophys Res Commun 1997;235:79–82.
102. Cassell PG, Neverova M, Janmohamed S, et al. An uncoupling protein 2 gene variant is associated with a raised body mass index but not type II diabetes. Diabetologia 1999;42:688–92.
103. Evans D, Minouchehr S, Hagemann G, et al. Frequency of and interaction between polymorphisms in the $\beta_3$-adrenergic receptor and in uncoupling proteins 1 and 2 and obesity in Germans. Int J Obes Relat Metab Disord 2000;24:1239–45.
104. Wang H, Chu WS, Lu T, et al. Uncoupling protein-2 polymorphisms in type 2 diabetes, obesity, and insulin secretion. Am J Physiol Endocrinol Metab 2004;286:E1–7.
105. Walder K, Norman RA, Hanson RL, et al. Association between uncoupling protein polymorphisms (CUP2-UCP3) and energy metabolism/obesity in Pima Indians. Hum Mol Genet 1998;7:1431–5.
106. Oberkofler H, Liu YM, Esterbauer H, et al. Uncoupling protein 2 gene: reduced mRNA expression in intraperitoneal

adipose tissue of obese humans. Diabetologia 1998;41: 940–6.
107. Shen H, Qi L, Tai ES, et al. Uncoupling protein 2 promoter polymorphism -866G/A, central adiposity, and metabolic syndrome in Asians. Obesity 2006;14:656–61.
108. Zurbano R, Ochoa MC, Moreno-Aliaga MJ, et al. Influence of the -866G/A polymorphism of the *UCP2* gene on an obese pediatric population. Nutr Hosp 2006;21:52–6.
109. Marti A, Ochoa MC, Sanchez-Villegas A, et al. Meta-analysis on the effect of the N363S polymorphism of the glucocorticoid receptor gene (*GRL*) on human obesity. BMC Med Genet 2006;7:50−60.
110. Paracchini V, Pedotti P, Taioli E. Genetics of leptin and obesity: a HuGE review. Am J Epidemiol 2005;162:101–14.
111. Lohmueller KE, Pearce CL, Pike M, et al. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nat Genet 2003;33:177–82.
112. Tan NC, Mulley JC, Berkovic SF. Genetic association studies in epilepsy: ''the truth is out there.'' Epilepsy 2004;45: 1429–42.
113. Colhoun HM, McKeigue PM, Smith DG. Problems of reporting genetic associations with complex outcomes. Lancet 2003;361:865–72.
114. Clayton DG, Walker NM, Smyth DJ, et al. Population structure, differential bias and genomic control in a large-scale, case-control association study. Nat Genet 2005;37: 1243–6.
115. De Bakker PI, Yelensky R, Pe'er I, et al. Efficiency and power in genetic association studies. Nat Genet 2005;37:1217–23.
116. Balding D. A tutorial on statistical methods for population associations. Nat Rev Genet 2006;7:781–91.
117. Cordell H, Clayton D. Genetic association studies. Lancet 2005;366:1121–31.
118. Wang S, Zhao H. Sample size needed to detect gene-gene interactions using association designs. Am J Epidemiol 2003;158:899–914.
119. Gaudermann WJ. Sample size requirements for association studies of gene-gene interaction. Am J Epidemiol 2002; 155:478–84.
120. Marchini J, Donnelly P, Cardon L. Genome-wide strategies for detecting multiple loci that influence complex diseases. Nat Genet 2005;37:413–17.
121. Culverhouse R, Suarez B, Lin J, et al. A perspective on epistasis: limits of models displaying no main effects. Am J Hum Genet 2002;70:461–71.
122. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. Endocr Rev 1999; 20:649–88.
123. Collins S, Daniel KW, Rohlfs EM, et al. Impaired expression and functional activity of the β3- and β1-adrenergic receptors in adipose tissue of congenitally obese (C57BL/6J *ob/ob*) mice. Mol Endocrinol 1994;8:518–27.
124. Hsueh WC, Cole SA, Shuldiner AR, et al. Interactions between variants in the $\beta_3$-adrenergic receptor and peroxisome proliferator-activated receptor-γ2 genes and obesity. Diabetes Care 2001;24:672–7.
125. Ochoa MC, Marti A, Azcona C, et al. Gene-gene interaction between PPAR gamma 2 and ADR beta 3 increases obesity risk in children and adolescents. Int J Obes Relat Metab Disord 2004;28(suppl 3):S37–41.
126. Ukkola O, Rankinen T, Weisnagel SJ, et al. Interactions among the α2-, β2-, and β3-adrenergic receptor genes and obesity-related phenotypes in the Quebec Family Study. Metabolism 2000;49:1063–70.
127. Ellsworth DL, Coady SA, Chen W, et al. Interactive effects between polymorphisms in the β-adrenergic receptors and longitudinal changes in obesity. Obes Res 2005;13:519–26.
128. San Millan JL, Corton M, Villuendas G, et al. Association of the polycystic ovary syndrome with genomic variants related to insulin resistance, type 2 diabetes mellitus, and obesity. J Clin Endocrinol Metab 2004;89:2640–6.
129. Proenza AM, Poissonnet CM, Ozata M, et al. Association of sets of alleles of genes encoding beta3-adrenoreceptor, uncoupling protein 1 and lipoprotein lipase with increased risk of metabolic complications in obesity. Int J Obes Relat Metab Disord 2000;24:93–100.
130. Sivenius K, Valve R, Lindi V, et al. Synergistic effect of polymorphisms in uncoupling protein 1 and beta3-adrenergic receptor genes on long-term body weight change in Finnish type 2 diabetic and non-diabetic control subjects. Int J Obes Relat Metab Disord 2000;24:514–19.
131. Li S, Chen W, Srinivasan SR, et al. Influence of lipoprotein lipase gene Ser447Stop and β1-adrenergic receptor gene Arg389Gly polymorphisms and their interaction on obesity from childhood to adulthood: the Bogalusa Heart Study. Int J Obes (Lond) 2006;30:1183–8.
132. Skibola CF, Holly EA, Forrest MS, et al. Body mass index, leptin and leptin receptor polymorphisms, and non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2004;13: 779–86.
133. Stone S, Abkevich V, Russell DL, et al. TBC1D1 is a candidate for a severe obesity gene and evidence for a gene/gene interaction in obesity predisposition. Hum Mol Genet 2006; 15:2709–20.
134. Lissner L, Heitmann BL. Dietary fat and obesity: evidence from epidemiology. Eur J Clin Nutr 1995;49:79–90.
135. Talmud PJ, Stephens JW. Lipoprotein lipase gene variants and the effect of environmental factors on cardiovascular disease risk. Diabetes Obes Metab 2004;6:1–7.
136. Provencher V, Perusse L, Bouchard L, et al. Familial resemblance in eating behaviors in men and women from the Quebec Family Study. Obes Res 2005;13:1624–9.
137. Perusse L, Bouchard C. Gene-diet interactions in obesity. Am J Clin Nutr 2000;72(suppl):1285S–90S.
138. Spitz MR, Detry MA, Pillow P, et al. Variant alleles of the D2 dopamine receptor gene and obesity. Nutr Res 2000;3:371–80.
139. Ukkola O, Bouchard C. Role of candidate genes in the responses to long-term overfeeding: review of findings. Obes Rev 2004;5:3–12.
140. Groot PC, Bleeker MJ, Pronk JC, et al. The human alpha-amylase multigene family consists of haplotypes with variable numbers of genes. Genomics 1989;5:29–42.
141. Collaku A, Rankinen T, Rice T, et al. A genome-wide linkage scan for dietary energy and nutrient intakes: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study. Am J Clin Nutr 2004;79:881–6.
142. Branson R, Potoczna N, Kral JG, et al. Binge eating as a major phenotype of melanocortin 4 receptor gene mutations. N Engl J Med 2003;348:1096–103.
143. Bouchard L, Drapeau V, Provencher V, et al. Neuromedin beta: a strong candidate gene linking eating behaviors and susceptibility to obesity. Am J Clin Nutr 2004;80: 1478–86.
144. Vincent S, Planells R, Defoort C, et al. Genetic polymorphisms and lipoprotein responses to diets. Proc Nutr Soc 2002;61:427–34.
145. Surgeon General's report on physical activity and health. From the Centers for Disease Control and Prevention. JAMA 1996;276:522.

146. Chakravarthy MV, Booth FW. Eating, exercise, and ''thrifty'' genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. J Appl Physiol 2004;96:3–10.
147. Beunen G, Thomis M. Genetic determinants of sports participation and daily physical activity. Int J Obes Relat Metab Disord 1999;23(suppl 3):S55–63.
148. Montgomery HE, Marshall R, Hemingway H, et al. Human gene for physical performance. Nature 1998;393:221–2.
149. Siffert W. G protein β3 subunit 825T allele, hypertension, obesity, and diabetic nephropathy. Nephrol Dial Transplant 2000;15:1298–306.
150. Corbalan MS, Marti A, Forga L, et al. The 27Glu polymorphism of the $\beta_2$-adrenergic receptor gene interacts with physical activity influencing obesity risk among female subjects. (Letter). Clin Genet 2002;61:305–7.
151. Loos RJ, Rankinen T, Tremblay A, et al. Melanocortin-4 receptor gene and physical activity in the Quebec Family Study. Int J Obes (Lond) 2005;29:420–8.
152. Buemann B, Schierning B, Toubro S, et al. The association between the val/ala-55 polymorphism of the uncoupling protein 2 gene and exercise efficiency. Int J Obes Relat Metab Disord 2001;25:467–71.
153. Otabe S, Clement K, Dina C, et al. A genetic variation in the 5′ flanking region of the *UCP3* gene is associated with body mass index in humans in interaction with physical activity. Diabetologia 2000;43:245–9.
154. Prior SJ, Hagberg JM, Phares DA, et al. Sequence variation in hypoxia-inducible factor 1 alpha (HIF1A): association with maximal oxygen consumption. Physiol Genomics 2003;15: 20–6.
155. Rankinen T, Rice T, Boudreau A, et al. Titin is a candidate gene for stroke volume response to endurance training: the HERITAGE Family Study. Physiol Genomics 2003;15: 27–33.
156. Franks PW, Barroso I, Luan J, et al. PGC-1 alpha genotype modifies the association of volitional energy expenditure with [OV0312] O2max. Med Sci Sports Exerc 2003;35: 1998–2004.
157. Bouchard C, Rankinen T, Chagnon YC, et al. Genomic scan for maximal oxygen uptake and its response to training in the HERITAGE Family Study. J Appl Physiol 2000;88: 551–9.
158. Lawrence R, Evans D, Cardon L. Prospects and pitfalls in whole genome association studies. Phil Trans R Soc 2005; 360:1589–95.
159. Clement K. Genetics of human obesity. Proc Nutr Soc 2005;64:133–42.
160. Baranova A, Schlauch K, Gowder S, et al. Microarray technology in the study of obesity and non-alcoholic fatty liver disease. Liver Int 2005;25:1091–6.
161. Challis B, Yeo G. Past, present and future strategies to study the genetics of body weight regulation. Brief Funct Genomic Proteomic 2002;1:290–304.
162. Permana P, Parigi A, Tataranni A. Microarray gene expression and profiling in obesity and insulin resistance. Nutrition 2004;20:134–8.
163. Baranova A, Collantes R, Gowder S, et al. Obesity-related differential gene expression in the visceral adipose tissue. Obes Surg 2005;15:758–65.
164. Gomez-Ambrosi J, Catalan V, Diez-Caballero A, et al. Gene expression profile of omental adipose tissue in human obesity. FASEB J 2004;18:215–17.
165. Thongboonkerd V. Genomics, proteomics and integrative 'omics' in hypertension research. Curr Opin Nephrol Hypertens 2005;14:133–9.
166. Wang J, Li D, Dangott S, et al. Proteomics and its role in nutritional research. J Nutr 2006;136:1759–62.
167. Wildman RP, Gu D, Reynolds K, et al. Are waist circumference and body mass index independently associated with cardiovascular disease risk in Chinese adults? Am J Clin Nutr 2005;82:1195–202.
168. Sempos C, Liu K, Ernst N. Food and nutrient exposures: what to consider when evaluating epidemiologic evidence. Am J Clin Nutr 1999;69(suppl):1330S–8S.
169. Mahabir S, Baer D, Giffen C, et al. Comparison of energy expenditure estimates from 4 physical activity questionnaires with doubly labeled water estimates in postmenopausal women. Am J Clin Nutr 2006;84:230–6.
170. Ionnidis J, Trikalinos T, Khoury M. Implications of small effect sizes of individual genetic variants on design and interpretation of genetic association studies of complex diseases. Am J Epidemiol 2006;164:609–14.
171. Wang W, Barratt B, Clayton D, et al. Genome-wide association studies: theoretical and practical concerns. Nat Rev Genet 2005;6:109–18.
172. Marchini J, Cardon L, Phillips M, et al. The effects of human population structure on large genetic association studies. Nat Genet 2004;36:512–17.
173. Teare MD, Barrett JH. Genetic linkage studies. Lancet 2005;366:1036–44.
174. Botstein D, Risch N. Discovering genotypes underlying human phenoytpes: past successes for mendelian disease, future approaches for complex disease. Nat Genet 2003; 33(suppl):228–37.
175. Laird NM, Lange C. Family-based designs in the age of large-scale gene-association studies. Nat Rev Genet 2006;7:385–94.
176. Hunter DJ. Gene-environment interactions in human diseases. Nat Rev Genet 2005;6:287–98.
177. Manolio TA, Bailey-Wilson JE, Collins FS. Genes, environment and the value of prospective cohort studies. Nat Rev Genet 2006;7:812–20.