Leptin is an important regulator of the mass of adipose tissue and of body weight; it operates by inhibiting food intake and stimulating energy expenditure. Some polymorphic genes involved in the regulation of leptin—the leptin gene (LEP A19G), the leptin receptor gene (LEPR Q223R, K109R, and K656N), and the peroxisome proliferator-activated receptor-gamma gene (PPARG P12A and C161T)—have been investigated as possible factors associated with obesity. Allelic frequencies of these polymorphisms show ethnic variation. The authors performed a meta-analysis of the available data on the association between these polymorphisms and obesity based on case-control studies. Odds ratios and 95% confidence intervals for obesity associated with leptin polymorphisms were calculated by using both fixed- and random-effects models. Results suggest no evidence of association between the genes under study and obesity. The lack of association could be due to the complex pathogenesis of obesity, which involves a number of genetic and environmental factors. Large studies including testing of multiple genes in both obese and lean subjects, with epidemiologic data on dietary habits in different ethnic groups, are necessary to better understand the role of leptin in regulating weight in human populations.
Many of the genes involved in the regulation of leptin are polymorphic. This paper reviews polymorphisms in three genes—LEP, the leptin receptor gene (LEPR), and the peroxisome proliferator-activated receptor-gamma gene (PPARG)—and their association with obesity.

**BIOLOGY OF LEPTIN**

The structure of leptin consists of a complex of four helices, similar to that of cytokines. Leptin is produced by the white adipose tissue, the most frequent form of adipose tissue in mammals. The white adipose tissue provides a long-term fuel reserve that can be mobilized during food deprivation with the release of fatty acids for oxidation in other organs; it also provides thermal insulation and has a mechanical role for vital organs (2). Leptin is produced in many sites in addition to white adipose tissue, but the amount of body fat is the main determinant of the circulating levels of this hormone. After it is produced, leptin is secreted into the bloodstream, where it circulates attached to proteins, and is transported to the brain, where it stimulates or inhibits release of several neurotransmitters. It down-regulates some orexigenic neuropeptides, such as the neuropeptide Y, melanin-concentrating hormone, orexins, and agouti-related peptide. Leptin up-regulates anorexigenic neuropeptides such as alpha-melanocyte-stimulating hormone, which acts on the melanocortin-4 receptor, cocaine and amphetamine-regulated transcripts, and corticotropin-releasing-hormone (3). Leptin may also directly affect the metabolism and function of peripheral tissues such as the adipocytes, skeletal muscle, ovary, adrenal cortex, and pancreatic beta cells (4, 5).

Leptin is expressed in the adipocytes: both its expression and its secretion are highly correlated with body fat and adipocyte size (4). However, the study of serum leptin levels in relation to several measures of adiposity demonstrates that obesity is not characterized by leptin deficiency but rather by hyperleptinemia; in fact, leptin levels have been found to be elevated in obese patients (6, 7). The inability of such elevated leptin levels to alter the obese state of these persons may be related to “leptin resistance,” an inability of leptin to enter the cerebral spinal fluid to reach the hypothalamus regions that regulate appetite, or it may simply reflect the large amount of fat tissue in these persons (4). Serum leptin levels follow a circadian rhythm, which seems to be predominantly related to an increase in insulin and cortisol rhythm. These two hormones may be among the major regulators of leptin production by the adipose tissue. Compared with males, females have higher leptin levels if leptin levels are expressed as a percentage of body adiposity (8). This difference may be related to the different distribution of adipose tissue in the two genders as well as to hormonal differences. Leptin levels have been shown to differ with medical conditions involving the endocrine system. For example, a comparison between diabetic and nondiabetic subjects shows that leptin levels are lower in the diabetic population (9).

The biologic activities of leptin on target tissues are carried out through selective binding to a specific receptor, LEPR. This gene is found in many tissues in several alternatively spliced forms.

**GENES**

**LEP**

The *LEP* gene encodes for leptin. It has been localized in humans on the 7alpha31.3 chromosome and consists of three exons separated by two introns (10).

It has been suggested that the “obese” promoter is a natural target of CCAAT/enhancer-binding protein-alpha, a transcription factor implicated in the development and metabolic regulation of adipocytes (11). Overexpression of the human *LEP* gene has been found in both subcutaneous and omental adipose tissue of massively obese persons (12).

*LEP* gene expression may be influenced by modulation of CCAAT/enhancer-binding protein-alpha levels or activity (13). Knowledge of the sequence elements and factors regulating *LEP* gene expression as well as the precise definition of the structure of the gene could be relevant when conducting further studies on mutations in this gene that may predispose to certain forms of obesity.

**LEPR**

*LEPR* maps in humans to the 1p31 chromosome and has at least five isoforms. The extracellular and transmembrane domains are identical between the short and the long isoforms; differences are due to changes in the length of the cytoplasmic domain. The long form (*LEPR*) has 302 cytoplasmic residues compared with the short form (*LEPRs*), whose cytoplasmic residues range from 32 to 40 amino acids in length. Another form of the leptin receptor, the soluble form (*LEPr*), is supposed to contain nonintracellular motifs or transmembrane residues, thus consisting entirely of the extracellular domain of the receptor (5).

Isoforms of the receptor have been identified in multiple tissues, such as the pituitary gland, male and female reproductive organs, mammary gland, immune system, gut, kidney, and lung (1). Studies performed on mice showed that the long form, thought to be the most important for transmitting the leptin signal to the cells, is located predominantly in the hypothalamus and not in most other tissues (14), whereas the short forms are expressed throughout the body, especially in the kidney, lungs, and choroid plexus (15).

The structure of the leptin receptor is similar to that of the helical cytokine receptor (class I). Leptin receptors form homodimers, which are capable of activating Janus kinases. The Janus kinase is then able to start activators of the transcription family. Leptin signaling via the Janus kinases–start activators of transcription system is associated largely with the *LEPR* form (16).

**PPARG**

The peroxisome proliferator-activated receptor genes (*PPARs*) are members of the nuclear hormone receptor subfamily of transcription factors that is expressed predominantly in the adipose tissue and the immune system. Such receptors control adipocyte differentiation and regulate glucose and lipid homeostasis (http://www.ncbi.nlm.nih.gov/entrez/). *PPARs* form heterodimers with retinoid X receptors (*RXRs*), which regulate the transcription of various
PPARG2 gene is expressed more than 100 kb. away from the differentiation. The PPARG gene contains nine exons and spans more than 100 kb. PPARG1 is encoded by eight exons and PPARG2 by seven exons (20). Human PPARG is expressed at high levels in adipocytes and at a much lower level in the bone marrow, spleen, testis, brain, skeletal muscle, and liver (21).

**GENES VARIANTS**

**LEP**

A mutation in the mouse LEP gene was first described in 1950 (22): the ob/ob obese mouse shows a nonsense mutation in codon 105 of the original mouse strain (23) resulting in the absence of leptin production. This mutation causes obesity, hyperphagia, hyperthermia, extreme insulin resistance, and infertility. Administration of leptin restores the normal condition. The homologous LEP mutation in humans has not been detected (24). The structure of the LEP gene is preserved in all mammals: human leptin and mouse leptin share 84 percent sequence identity. In humans, a mutation in the LEP gene was reported in two children with the same consanguineous pedigree (25). The homozygous frameshift mutation was the result of deletion of a single guanine nucleotide in codon 133. These children produced a very small quantity of leptin and presented with early-onset obesity and hyperphagia but normal body temperatures and normal plasma cortisol and glucose concentrations. Other variants of the human LEP gene have been reported: a rare mutation at codon F17L, a rare mutation at codon V110M (26), and a polymorphism C(-188)A in the promoter region of the LEP gene (27) have been found. Different microsatellite markers flanking the LEP gene have been also identified, but the possible linkages with obesity are inconsistent. Other studies (28–31) reported a polymorphism in the promoter untranslated exon 1 of the LEP gene (A19G).

**LEPR**

The LEPR gene maps to chromosome 4 of the mouse in regions that contain the db/db and Zucker fa/fa mutations. These mutations cause severe obesity in mice, not reversible by administration of leptin. Human LEPR and the mouse gene share 78 percent homology. Several variants commonly occur, which cause two nonconservative changes: glutamine to arginine at codon 223 (CAG to CGG) in exon 6 (Q223R) and lysine to arginine at codon 109 (AAG to AGG) in exon 4 (K109R); a silent TC change at codon 343; and a silent GA transition at codon 1019. One study found that the leptin receptor is expressed in the hypothalamus of human subjects (32). It has been suggested that the leptin receptor is involved in adipocyte differentiation. No effect of the Q223R, K109R, and K656N polymorphisms of the LEPR gene was observed on the acute decline in leptin after energy restriction (33).

**PPARG**

A screening of the PPARG gene for sequence variants has allowed identification of several genetic variants. P115Q is a very rare gain-of-function mutation associated with obesity (34); V290M and P467L are two loss-of-function mutations reported in three persons with severe insulin resistance but normal body weight (35). Two common polymorphisms are 1) a CG substitution in exon B, resulting in conversion of proline to alanine at residue 12 of the PPARG protein (P12A), which may modify susceptibility to type II diabetes mellitus and obesity (36); and 2) a synonymous CT substitution at nucleotide position 161 in exon 6 (C161T).

The Pro12Ala polymorphism has been shown to prevent insulin resistance and obesity induced by a high-fat diet (37). Expression of the P12A polymorphism is not significantly different in obese subjects carrying one or the other variant of the allele (38).

**META-ANALYSIS**

To examine the frequencies of the polymorphisms in the general population and the association between the various genes involved in regulation of leptin and obesity, we performed a meta-analysis of published studies, following established guidelines (39–41). To investigate the presence of publication bias, funnel plots were created, and their asymmetry was tested statistically: Begg’s adjusted rank correlation (42) and Egger’s regression asymmetry of the Ln( odds ratio) over the standard error (43) were calculated.

To estimate the heterogeneity of the allele frequencies and of the odds ratios, the Cochran Q-test was performed (44). For the meta-allele frequencies of each specific allele and the meta–odds ratios, a fixed-effects model was used if the assumption of homogeneity among studies could be accepted, while a random-effects model was used when heterogeneity across studies was statistically observed (45).

**Population frequencies**

A MEDLINE search was performed up to November 2004 by using different combinations of the keywords “leptin,” “gene,” “polymorphisms,” “leptin gene receptor,” “PPARG polymorphism,” “obesity,” and “BMI.” We also searched for specific polymorphisms of the LEP, LEPR (Q223R, K109R, K656N), and PPARG (C161T, P12A) genes. The search was restricted to articles published in English on human subjects, although we checked the number of articles published in other languages and found that such articles represented 7 percent of the whole relevant literature. The computer search was supplemented by consulting the bibliographies of the articles found through the MEDLINE search. Case-control or cohort, genotype-based studies that
reported allele frequency for polymorphisms of LEP, LEPR, and PPARG genes in healthy subjects (both lean and obese subjects and excluding clinically diagnosed diabetes) were selected, whereas studies including only diabetic or non-healthy subjects and studies on families or twins were excluded. Allelic frequency of the different polymorphisms for each of the above-mentioned genes were evaluated. For each study and for each gene included in the present review, allele frequencies and 95 percent confidence intervals for healthy subjects were calculated. Pooled frequencies were calculated on the whole sample and according to ethnicity.

**Associations**

Case-control studies reporting allele frequency for lean (controls) and obese (cases) subjects were included in the meta-analysis. For each study and for each gene, we calculated crude odds ratios and 95 percent confidence intervals as a measure of the association between a gene polymorphism and obesity. The overall odds ratios and 95 percent confidence intervals for obesity associated with leptin polymorphisms were calculated after pooling the data from the single studies. Forests plots were used to convey the results of the meta-analysis.

**POPULATION FREQUENCIES**

**LEP A19G**

Three studies conducted in Europe (18–20) reported allele frequency in healthy subjects. Table 1 describes the studies. The allelic frequency of 19G for the Caucasian population (375 subjects) was 0.46 (95 percent confidence interval (CI): 0.29, 0.73), with comparable values in France and Italy and higher values in Finland. The Cochran Q-test indicated heterogeneity among studies ($Q^* = 27.88; p < 0.0001$).

**LEPR Q223R**

Frequencies of this polymorphism were reported in 18 articles (46–63), and the studies are described in table 2. Five of the studies were conducted in the United States (46, 59–62), three in Asia (56–58), eight in Europe (47–54), and two in Oceania (55, 63). The allelic frequency varied significantly across different countries and ethnic groups ($p < 0.0001$). In particular, the frequency of the 223R allele for Asians was significantly higher than for other ethnicities. The Cochran Q-test showed heterogeneity among only those studies performed among Caucasians ($Q = 42.70; p < 0.0001$).

**LEPR K109R**

Eleven articles (table 2) were reviewed for this polymorphism (47, 49–54, 56, 58, 60, 61); two studies were conducted in the United States (60, 61), two in Asia (56, 58), and seven in Europe (47, 49–54). The frequency of the 109R allele was significantly different among ethnic groups, being higher in Asians than in other populations (table 2). A significant asymmetry of the funnel plots of the studies performed among Caucasians ($p_{Egger} = 0.03$) indicates the possible presence of publication bias.

**LEPR K656N**

Ten articles (46, 47, 49–54, 56, 61) were included in the present analysis (table 2); two studies were conducted in the United States (46, 61), one in Asia (56), and seven in Europe (47, 49–54). The frequency of the 656N allele showed differences among ethnic groups; the polymorphic allele was more frequent in Caucasians than in Asians (table 2).

**PPARG C161T**

Six articles, described in table 3, were reviewed for this polymorphism (64–69); one study was conducted in the United States on Pima Indians (68), one in Asia (69), three in Europe (64–66), and one in Oceania (67). The 161T allele showed similar frequencies in Caucasians and Asians, while the frequency was higher in Pima Indians (table 3).

**PPARG P12A**

The frequency of this polymorphism in healthy populations was reported in 26 articles (64, 68, 70–93). Table 4 describes the studies. Six were conducted in the United States

**TABLE 1. Studies that included data on the A19G polymorphism of the LEP* gene in healthy subjects**

<table>
<thead>
<tr>
<th>Authors (reference no.), year</th>
<th>Country</th>
<th>Population</th>
<th>Source</th>
<th>No. of subjects</th>
<th>Gender</th>
<th>19G allele frequency</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karvonen et al. (29), 1998</td>
<td>Finland</td>
<td>Caucasian</td>
<td>Weight reduction study, population</td>
<td>206</td>
<td>Mix</td>
<td>0.67</td>
<td>0.61, 0.74</td>
</tr>
<tr>
<td>Hager et al. (30), 1998</td>
<td>France</td>
<td>Caucasian</td>
<td>Hospital</td>
<td>108</td>
<td>Mix</td>
<td>0.36</td>
<td>0.27, 0.45</td>
</tr>
<tr>
<td>Lucantoni et al. (31), 2000</td>
<td>Italy</td>
<td>Caucasian</td>
<td>Hospital</td>
<td>61</td>
<td>Mix</td>
<td>0.38</td>
<td>0.26, 0.50</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>Caucasian</td>
<td></td>
<td>375</td>
<td></td>
<td>0.46</td>
<td>0.29, 0.73</td>
</tr>
</tbody>
</table>

* LEP, leptin gene; CI, confidence interval; $Q$, Cochran Q-test for heterogeneity.
<table>
<thead>
<tr>
<th>Authors (reference no.), year</th>
<th>Country</th>
<th>Population</th>
<th>Source</th>
<th>No. of subjects</th>
<th>Gender</th>
<th>223R allele frequency</th>
<th>95% CI</th>
<th>109R allele frequency</th>
<th>95% CI</th>
<th>656N allele frequency</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver et al. (46), 1997</td>
<td>United States</td>
<td>Caucasian</td>
<td>University weight center, Baltimore Longitudinal Study on Aging</td>
<td>388</td>
<td>Mix</td>
<td>0.45</td>
<td>0.40, 0.50</td>
<td>0.18</td>
<td>0.14, 0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gotoda et al. (47), 1997</td>
<td>England</td>
<td>Caucasian</td>
<td>Population-based epidemiologic study</td>
<td>322</td>
<td>Male</td>
<td>0.44</td>
<td>0.38, 0.49</td>
<td>0.27</td>
<td>0.22, 0.31</td>
<td>0.17</td>
<td>0.10, 0.24</td>
</tr>
<tr>
<td>Quinton et al. (48), 2001</td>
<td>England</td>
<td>Caucasian</td>
<td>Population</td>
<td>88</td>
<td>Female</td>
<td>0.41</td>
<td>0.31, 0.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammes et al. (49), 2001</td>
<td>France</td>
<td>Caucasian</td>
<td>Hospital, unrelated family study</td>
<td>566</td>
<td>Mix</td>
<td>0.44</td>
<td>0.39, 0.48</td>
<td>0.25</td>
<td>0.21, 0.28</td>
<td>0.18</td>
<td>0.15, 0.22</td>
</tr>
<tr>
<td>Wauters et al. (50), 2001</td>
<td>Belgium</td>
<td>Caucasian</td>
<td>Obesity clinic</td>
<td>280</td>
<td>Female</td>
<td>0.48</td>
<td>0.42, 0.54</td>
<td>0.28</td>
<td>0.22, 0.33</td>
<td>0.18</td>
<td>0.14, 0.23</td>
</tr>
<tr>
<td>van Rossum et al. (51), 2002</td>
<td>The Netherlands</td>
<td>Caucasian</td>
<td>Cohorts</td>
<td>582</td>
<td>Mix</td>
<td>0.44</td>
<td>0.40, 0.48</td>
<td>0.27</td>
<td>0.24, 0.31</td>
<td>0.19</td>
<td>0.16, 0.22</td>
</tr>
<tr>
<td>Quinton et al. (52), 2000</td>
<td>Sweden</td>
<td>Caucasian</td>
<td>Cohort study</td>
<td>269</td>
<td>Male</td>
<td>0.50</td>
<td>0.44, 0.56</td>
<td>0.24</td>
<td>0.19, 0.29</td>
<td>0.15</td>
<td>0.11, 0.19</td>
</tr>
<tr>
<td>Rosmond et al. (53), 2000</td>
<td>Denmark</td>
<td>Caucasian</td>
<td>Copenhagen City Heart Study Programme</td>
<td>361</td>
<td>Male</td>
<td>0.41</td>
<td>0.36, 0.46</td>
<td>0.24</td>
<td>0.20, 0.29</td>
<td>0.16</td>
<td>0.12, 0.20</td>
</tr>
<tr>
<td>Yiannakouris et al. (54), 2001</td>
<td>Greece</td>
<td>Caucasian</td>
<td>Students</td>
<td>118</td>
<td>Mix</td>
<td>0.32</td>
<td>0.24, 0.41</td>
<td>0.12</td>
<td>0.06, 0.18</td>
<td>0.24</td>
<td>0.16, 0.31</td>
</tr>
<tr>
<td>de Silva et al. (55), 2001</td>
<td>Australia</td>
<td>Caucasian</td>
<td>Population-based study</td>
<td>335</td>
<td>Female</td>
<td>0.58</td>
<td>0.53, 0.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Caucasian</td>
<td></td>
<td></td>
<td>2,309</td>
<td>Q223R</td>
<td>0.45</td>
<td>0.42, 0.49</td>
<td>0.25</td>
<td>0.23, 0.28</td>
<td>0.18</td>
<td>0.16, 0.20</td>
</tr>
<tr>
<td>Matsuoka et al. (56), 1997</td>
<td>Japan</td>
<td>Asian</td>
<td>Population</td>
<td>115</td>
<td>Mix</td>
<td>0.85</td>
<td>0.79, 0.82</td>
<td>0.78</td>
<td>0.70, 0.85</td>
<td>0.12</td>
<td>0.06, 0.18</td>
</tr>
<tr>
<td>Endo et al. (57), 2000</td>
<td>Japan</td>
<td>Asian</td>
<td>School</td>
<td>553</td>
<td>Mix</td>
<td>0.85</td>
<td>0.82, 0.88</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koh et al. (58), 2002</td>
<td>Korea</td>
<td>Asian</td>
<td>University</td>
<td>220</td>
<td>Male</td>
<td>0.85</td>
<td>0.80, 0.90</td>
<td>0.83</td>
<td>0.78, 0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Asian</td>
<td></td>
<td></td>
<td>888</td>
<td>Q223R</td>
<td>0.85</td>
<td>0.84, 0.86</td>
<td>0.82</td>
<td>0.78, 0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson et al. (59), 1997</td>
<td>United States</td>
<td>Pima Indians</td>
<td>Population</td>
<td>20</td>
<td>Mix</td>
<td>0.25</td>
<td>0.06, 0.44</td>
<td>0.42</td>
<td>0.19, 0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stefan et al. (60), 2002</td>
<td>United States</td>
<td>Pima Indians</td>
<td>Population</td>
<td>452</td>
<td>Mix</td>
<td>0.32</td>
<td>0.28, 0.36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Pima Indians</td>
<td></td>
<td></td>
<td>472</td>
<td></td>
<td>0.32</td>
<td>0.28, 0.36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chung et al. (61), 1997</td>
<td>United States</td>
<td>Mix</td>
<td>Obesity center</td>
<td>194</td>
<td>Mix</td>
<td>0.34</td>
<td>0.27, 0.41</td>
<td>0.21</td>
<td>0.15, 0.27</td>
<td>0.15</td>
<td>0.10, 0.20</td>
</tr>
<tr>
<td>Mattevi et al. (62), 2002</td>
<td>United States</td>
<td>Brazilian European descent</td>
<td>Population</td>
<td>335</td>
<td>Mix</td>
<td>0.40</td>
<td>0.35, 0.46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Silva et al. (63), 1999</td>
<td>Australia</td>
<td>Nauruans</td>
<td>Population</td>
<td>232</td>
<td>Male</td>
<td>0.89</td>
<td>0.85, 0.93</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* LEPR, leptin receptor gene; CI, confidence interval; Q, Cochran Q-test for heterogeneity.
Caucasians showing the highest frequency of this variant allele was statistically different among ethnic groups, with

DISEASE

Obesity is a common condition in industrialized societies and is increasing rapidly; its etiology is complex and results from combined effects of genes, environment, lifestyle, and their interactions (94–99). Obesity is defined as an increase in body fat, while overweight is an increase in weight relative to a standard. In most studies, obesity is defined on the basis of anthropometric measures, mainly height, weight, and waist circumference. Such measurements give information on the degree and distribution of obesity (100). On this basis, subjects are defined as overweight if their body mass index (BMI; weight in kilograms divided by height in meters squared) is equal to or greater than 25 kg/m² and obese if their BMI is 30 kg/m² or more (i.e., weight exceeding 20 percent of the ideal weight), according to World Health Organization indications (101). Several other ways to define obesity have been mentioned in the literature. Some studies have reported waist-to-hip ratio as a rough approximation of body fat distribution (102). In the elderly, sarcopenic obesity has been described, which is defined as an excess of fat with loss of lean body mass (103). Some studies have also described a form of ectopic deposition, which consists of an excess deposition of fat in muscle, liver, and pancreas resulting in insulin resistance and beta-cell dysfunction. The central adipose tissue responds to this unbalance by releasing large quantities of free fatty acids (104).

Body composition can also be estimated by using a variety of technical methods. Included are densitometry methods, such as hydrostatic weighing and plethysmography, bioelectrical impedance analysis, dual energy x-ray absorptiometry, and near-infrared interactance.

Obesity affects 10–25 percent of the European population and nearly one third of the US population, and the number continues to increase (105–107). Each year, obesity causes at least 300,000 excess deaths in the United States (http://www.obesity.org/). Risk factors for obesity include a poor diet consisting of low-nutrient but high-calorie foods, lack of physical activity, medical conditions such as rare hereditary diseases and a hormonal imbalance (e.g., hypothyroid disease), age, genetic factors, ethnicity, and gender (108, 109). Overweight and obesity increase steadily with age in both men and women and occur at higher rates in ethnic minority populations in the United States, such as African Americans and Hispanic Americans compared with White Americans, while the prevalence in Asian Americans is relatively low (110). Women and persons of low socioeconomic status within minority populations appear to be particularly affected by overweight and obesity (111). Cultural factors that influence dietary and exercise behaviors are reported to play a major role in the development of excess weight in minority groups. In these ethnic minorities, rates of several obesity-related diseases (diabetes, hypertension, cancer, and heart disease) are higher than those among Whites (112–115). Obesity is associated with medical conditions that can cause poor health and premature death, among which are arthritis, birth defects, various forms of cancer, cardiovascular disease, diabetes, hypertension, infertility, chronic venous insufficiency, deep vein thrombosis, end-stage renal disease, gout, impaired immune response and impaired respiratory function, liver disease, pancreatitis, sleep apnea, and stroke (116–118).

### TABLE 3. Studies that included data on the C161T polymorphism of the PPARG* gene in healthy subjects

<table>
<thead>
<tr>
<th>Authors (reference no.), year</th>
<th>Country</th>
<th>Population</th>
<th>Source</th>
<th>No. of subjects</th>
<th>Gender</th>
<th>161T allele frequency</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve et al. (64), 1999</td>
<td>Finland</td>
<td>Caucasian</td>
<td>Primary health care</td>
<td>141</td>
<td>Female</td>
<td>0.18</td>
<td>0.12, 0.25</td>
</tr>
<tr>
<td>Meinhaeghe et al. (65), 1998</td>
<td>France</td>
<td>Caucasian</td>
<td>WHO MONICA*</td>
<td>820</td>
<td>Mix</td>
<td>0.15</td>
<td>0.11, 0.18</td>
</tr>
<tr>
<td>Orio et al. (66), 2003</td>
<td>Italy</td>
<td>Caucasian</td>
<td>Volunteer</td>
<td>100</td>
<td>Female</td>
<td>0.07</td>
<td>0.02, 0.11</td>
</tr>
<tr>
<td>Wang et al. (67), 1999</td>
<td>Australia</td>
<td>Caucasian</td>
<td>Heart clinic</td>
<td>133</td>
<td>Mix</td>
<td>0.21</td>
<td>0.14, 0.28</td>
</tr>
<tr>
<td>Overall</td>
<td>Finland</td>
<td>Caucasian</td>
<td></td>
<td>1,194</td>
<td></td>
<td>0.16</td>
<td>0.12, 0.22</td>
</tr>
<tr>
<td>Muller et al. (68), 2003</td>
<td>United States</td>
<td>Pima Indians</td>
<td>Population</td>
<td>330</td>
<td>Mix</td>
<td>0.41</td>
<td>0.36, 0.46</td>
</tr>
<tr>
<td>Ogawa et al. (69), 1999</td>
<td>Japan</td>
<td>Asian</td>
<td>Population</td>
<td>404</td>
<td>Female</td>
<td>0.15</td>
<td>0.11, 0.18</td>
</tr>
</tbody>
</table>

* PPARG, peroxisome proliferator-activated receptor-gamma gene; CI, confidence interval; WHO MONICA, World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (study); Q, Cochran Q-test for heterogeneity.
<table>
<thead>
<tr>
<th>Authors (reference no.), year</th>
<th>Country</th>
<th>Population</th>
<th>Source</th>
<th>No. of subjects</th>
<th>Gender</th>
<th>12Ala allele frequency</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beamer et al. (70), 1998</td>
<td>United States</td>
<td>Caucasian</td>
<td>Population, university weight center</td>
<td>686 Mix</td>
<td>0.11</td>
<td>0.09, 0.13</td>
<td></td>
</tr>
<tr>
<td>Memisoglu et al. (71), 2002</td>
<td>United States</td>
<td>Caucasian</td>
<td>Nurses' Health Study</td>
<td>953 Female</td>
<td>0.11</td>
<td>0.09, 0.13</td>
<td></td>
</tr>
<tr>
<td>Memisoglu et al. (72), 2003</td>
<td>United States</td>
<td>Caucasian</td>
<td>Nurses' Health Study</td>
<td>771 Female</td>
<td>0.13</td>
<td>0.11, 0.15</td>
<td></td>
</tr>
<tr>
<td>Memisoglu et al. (73), 2003</td>
<td>United States</td>
<td>Caucasian</td>
<td>Nurses' Health Study</td>
<td>2,141 Female</td>
<td>0.13</td>
<td>0.11, 0.14</td>
<td></td>
</tr>
<tr>
<td>Franks et al. (74), 2004</td>
<td>England</td>
<td>Caucasian</td>
<td>Medical Research Council</td>
<td>506 Mix</td>
<td>0.11</td>
<td>0.09, 0.14</td>
<td></td>
</tr>
<tr>
<td>Ringel et al. (75), 1999</td>
<td>Germany</td>
<td>Caucasian</td>
<td>Population</td>
<td>310 Mix</td>
<td>0.15</td>
<td>0.11, 0.19</td>
<td></td>
</tr>
<tr>
<td>Koch et al. (76), 2000</td>
<td>Germany</td>
<td>Caucasian</td>
<td>Relatives of diabetic subjects</td>
<td>108 Mix</td>
<td>0.18</td>
<td>0.10, 0.25</td>
<td></td>
</tr>
<tr>
<td>Evans et al. (77), 2000</td>
<td>Germany</td>
<td>Caucasian</td>
<td>Hospital, blood donors</td>
<td>392 Mix</td>
<td>0.15</td>
<td>0.12, 0.19</td>
<td></td>
</tr>
<tr>
<td>Evans et al. (78), 2001</td>
<td>Germany</td>
<td>Caucasian</td>
<td>Hospital</td>
<td>568 Mix</td>
<td>0.14</td>
<td>0.11, 0.17</td>
<td></td>
</tr>
<tr>
<td>Vigourux et al. (79), 1998</td>
<td>France</td>
<td>Caucasian</td>
<td>Unrelated persons</td>
<td>59 Mix</td>
<td>0.06</td>
<td>0.00, 0.12</td>
<td></td>
</tr>
<tr>
<td>Ek et al. (80), 1999</td>
<td>Denmark</td>
<td>Caucasian</td>
<td>Cohort</td>
<td>1,621 Male</td>
<td>0.15</td>
<td>0.13, 0.16</td>
<td></td>
</tr>
<tr>
<td>Frederiksen et al. (81), 2002</td>
<td>Denmark</td>
<td>Caucasian</td>
<td>Health survey</td>
<td>1,951 Mix</td>
<td>0.14</td>
<td>0.13, 0.16</td>
<td></td>
</tr>
<tr>
<td>Valve et al. (64), 1999</td>
<td>Finland</td>
<td>Caucasian</td>
<td>Weight reduction study</td>
<td>141 Female</td>
<td>0.14</td>
<td>0.08, 0.20</td>
<td></td>
</tr>
<tr>
<td>Deeb et al. (82), 1998</td>
<td>Finland</td>
<td>Caucasian</td>
<td>Population</td>
<td>1,306 Mix</td>
<td>0.15</td>
<td>0.13, 0.16</td>
<td></td>
</tr>
<tr>
<td>Niskanen et al. (83), 2003</td>
<td>Finland</td>
<td>Caucasian</td>
<td>Population</td>
<td>119 Mix</td>
<td>0.12</td>
<td>0.06, 0.18</td>
<td></td>
</tr>
<tr>
<td>Mancini et al. (84), 2003</td>
<td>Italy</td>
<td>Caucasian</td>
<td>Population</td>
<td>312 Mix</td>
<td>0.10</td>
<td>0.07, 0.13</td>
<td></td>
</tr>
<tr>
<td>Vaccaro et al. (85), 2000</td>
<td>Italy</td>
<td>Caucasian</td>
<td>Telephone company</td>
<td>375 Mix</td>
<td>0.16</td>
<td>0.13, 0.20</td>
<td></td>
</tr>
<tr>
<td>Gonzalez Sanchez et al. (86), 2002</td>
<td>Spain</td>
<td>Caucasian</td>
<td>Hospital</td>
<td>464 Mix</td>
<td>0.09</td>
<td>0.06, 0.12</td>
<td></td>
</tr>
<tr>
<td>Swarbrick et al. (87), 2001</td>
<td>Australia</td>
<td>Caucasian</td>
<td>Carotid disease study, population</td>
<td>663 Mix</td>
<td>0.14</td>
<td>0.11, 0.16</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Caucasian</td>
<td></td>
<td></td>
<td>13,446</td>
<td>0.13</td>
<td>0.12, 0.14</td>
<td></td>
</tr>
</tbody>
</table>

* PPARG, peroxisome proliferator-activated receptor-gamma gene; CI, confidence interval; Q, Cochran Q-test for heterogeneity.

ASSOCIATIONS

**LEP A19G**

Only one case-control study, which was conducted in Finland (29) and included 141 cases and 65 controls, was available on the association between this polymorphism and obesity. The observed odds ratio was 1.04 (95 percent CI: 0.67, 1.61).

**LEPR Q223R**

Ten studies satisfied the selection criteria and were included in the meta-analysis (46, 47, 49, 53, 54, 56, 59, 61, 62) (table 5). The overall odds ratio was 1.13 (95 percent CI: 0.98, 1.30) (figure 1A), with no evidence of statistical heterogeneity nor of publication bias (figure 2A).

**LEPR K109R**

Seven studies were considered for the meta-analysis (47, 49, 53, 54, 56, 59, 61) (table 5). The overall association between **LEPR K109R** and obesity was 1.05 (95 percent CI: 0.89, 1.23) (figure 1B). The Cochran Q-test showed homogeneity among studies; the funnel plot showed no evidence of publication bias (figure 2B).

**LEPR K656N**

Seven studies were included in this meta-analysis (46, 47, 49, 53, 54, 56, 61) (table 5). The overall odds ratio was 1.02 (95 percent CI: 0.86, 1.21) (figure 1C), with no evidence of statistical heterogeneity nor of publication bias (figure 2C).

**PPARG C161T**

Of seven articles reviewed, none included data for both lean and obese subjects but instead reported information on one or the other of the two categories. Therefore, no formal statistical analysis was performed on these data.

**PPARG P12A**

Six studies were considered in this meta-analysis (70, 80, 88, 85–87) (table 5). The overall association between **PPARG P12A** and obesity was 1.13 (95 percent CI: 0.98, 1.29) (figure 1D). The Cochran Q-test showed that the results of the different studies were distributed homogeneously, with no statistical evidence of publication bias from the funnel plots (figure 2D).

INTERACTIONS

**Gene-environment interactions**

Since leptin is involved in weight regulation, it is interesting to assess whether any interaction exists between leptin polymorphisms and diet or gender. Polymorphisms in the **LEPR** gene have been studied as possible modifying factors of the response to diet (28) or of survival in cancer patients according to their BMI (119), but the associations, if present, represented secondary subgroup analyses of the data.

---

**TABLE 5. Description of the case-control studies included in the meta-analyses and of the polymorphisms tested in each study**

<table>
<thead>
<tr>
<th>Authors (reference no.)</th>
<th>Population</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Obesity definition cutoff</th>
<th>Polymorphisms tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver et al. (46)</td>
<td>Caucasian</td>
<td>281</td>
<td>107</td>
<td>BMI*</td>
<td>Q223R, K656N</td>
</tr>
<tr>
<td>Gotoda et al. (47)</td>
<td>Caucasian</td>
<td>190</td>
<td>132</td>
<td>BMI</td>
<td>Q223R, K109R, K656N</td>
</tr>
<tr>
<td>Mammès et al. (49)</td>
<td>Caucasian</td>
<td>277</td>
<td>289</td>
<td>BMI ≥ 27 kg/m²</td>
<td>Q223R, K109R, K656N</td>
</tr>
<tr>
<td>Echwald et al. (53)</td>
<td>Caucasian</td>
<td>156</td>
<td>205</td>
<td>BMI</td>
<td>Q223R, K109R, K656N</td>
</tr>
<tr>
<td>Yiannakouris et al. (54)</td>
<td>Caucasian</td>
<td>29</td>
<td>89</td>
<td>BMI &gt; 25 kg/m²</td>
<td>Q223R, K109R, K656N</td>
</tr>
<tr>
<td>Matsuoka et al. (56)</td>
<td>Asian</td>
<td>47</td>
<td>68</td>
<td>BMI &gt; 30 kg/m²</td>
<td>Q223R, K109R, K656N</td>
</tr>
<tr>
<td>Endo et al. (57)</td>
<td>Asian</td>
<td>90</td>
<td>463</td>
<td>Obesity index†</td>
<td>Q223R</td>
</tr>
<tr>
<td>Thompson et al. (59)</td>
<td>Pima Indians</td>
<td>10</td>
<td>10</td>
<td>% body fat</td>
<td>Q223R, K109R</td>
</tr>
<tr>
<td>Chung et al. (61)</td>
<td>Mix</td>
<td>167</td>
<td>27</td>
<td>BMI</td>
<td>Q223R, K109R, K656N</td>
</tr>
<tr>
<td>Mattevi et al. (62)</td>
<td>Brazilian</td>
<td>183</td>
<td>152</td>
<td>BMI ≥ 25 kg/m²</td>
<td>Q223R</td>
</tr>
<tr>
<td>Beamer et al. (70)</td>
<td>Caucasian</td>
<td>169</td>
<td>517</td>
<td>BMI</td>
<td>P12A</td>
</tr>
<tr>
<td>Ek et al. (80)</td>
<td>Caucasian</td>
<td>752</td>
<td>869</td>
<td>BMI ≥ 31 kg/m²</td>
<td>P12A</td>
</tr>
<tr>
<td>Vaccaro et al. (85)</td>
<td>Caucasian</td>
<td>95</td>
<td>280</td>
<td>BMI &gt; 35 kg/m²</td>
<td>P12A</td>
</tr>
<tr>
<td>Gonzalez Sanchez et al. (86)</td>
<td>Caucasian</td>
<td>145</td>
<td>317</td>
<td>BMI &gt; 30 kg/m²</td>
<td>P12A</td>
</tr>
<tr>
<td>Swarbrick et al. (87)</td>
<td>Caucasian</td>
<td>292</td>
<td>371</td>
<td>BMI ≥ 30 kg/m²</td>
<td>P12A</td>
</tr>
<tr>
<td>Mori et al. (88)</td>
<td>Asian</td>
<td>169</td>
<td>46</td>
<td>BMI ≥ 22 kg/m²</td>
<td>P12A</td>
</tr>
</tbody>
</table>

* BMI, body mass index (weight (kg)/height (m²)).
† Obesity index = (real weight – standard weight)/(standard weight × 100).
A pooled analysis (120) and a meta-analysis (121) suggested an interaction between gender and the R109R genotype on BMI, although the reported effect was modest. A study in a Brazilian population indicated that the association between LEPR Q223R and BMI was stronger in non-smokers than in the general population (62). The presence of a gene-diet interaction was studied in 592 nondiabetic subjects genotyped for the P12A variant of PPARG (122). Results showed that when the ratio of polyunsaturated to saturated fats in the diet was low, BMI was greater in Ala carriers than in Pro homozygous subjects. The opposite effect was seen when the ratio was high. An analysis of several genes involved in regulation of body weight suggested that the allelic variants of LEP and PPARG might affect diet-related obesity risk (123).

**Gene-gene interactions**

Interactions between polymorphisms involved in regulation of leptin have been reported. An interaction between polymorphisms in the LEP and LEPR genes on the risk of non-Hodgkin’s lymphoma has been suggested (124) and on insulin levels in the population of Nauruans (63). An interaction between the 109R and 223R variants on blood pressure levels was suggested (52), as was one between the K109R and K656N polymorphisms on BMI (120, 121).

**DISCUSSION**

Systematic screenings of the genome have allowed several polymorphisms in the genes involved in leptin regulation to be identified. In this review, we have reported data on the association between obesity and a polymorphism in the LEP gene (A19G), three polymorphisms in the LEPR gene (Q223R, K109R, and K656N), and two polymorphisms in the PPARG gene (C161T and P12A). A meta-analysis performed on the data suggests no evidence of an association between the genes involved in leptin regulation and obesity. The analysis stratified according to ethnicity did not show any variation across populations, in agreement with published literature on this topic (125). Functional data on these genetic variants are very limited and are consistent with a lack of association between these polymorphisms and obesity. The results of our analysis are consistent with those observed in another meta-analysis of 20 studies on 3,263 subjects of different ethnic groups (62 percent of whom were family members of one or more subjects in the data set), which reported no significant effect of the polymorphisms of LEPR on obesity (121). In a meta-analysis by Masud and Ye (126), the P12A polymorphism was associated with BMI in markedly obese persons. It has been suggested that P12A is a functional polymorphism and that substitution of alanine for proline leads to a decrease in PPARG activity, thus reducing its ability to regulate expression of the gene (82). The P12A polymorphism has been associated with diabetes, although the reported effect is modest (126). Our data do not indicate an association between obesity and the P12A polymorphism.

One strength of the present meta-analysis is that, to our knowledge, this is the first such study performed exclusively on unrelated, healthy subjects. A possible limitation is that we could evaluate only the allele frequency of the different polymorphisms, since very few studies reported...
Another limitation is that the number of case-control studies conducted on healthy subjects is still small; several studies reported data on only lean or on only obese persons, but these studies could not be included. The cutoff for obesity, when specified, differed among studies; however, we had to use the definition given by each author, since this was a meta-analysis of published data.

The reported lack of association between leptin polymorphisms and obesity could be due to the complex pathogenesis of obesity, which involves a large number of both genetic and environmental factors. In addition, it should be taken into account that the results were based on studies that used BMI as a marker for the obesity phenotype, while several other methods of defining this condition are available. Therefore, studies including different measures of obesity could be useful in this field.

LABORATORY TESTS

The detailed methods used for determining the different polymorphisms are described in each article. All studies included in the present analysis used genomic DNA extracted from blood. Thirty-one articles reported the use of polymerase chain reaction followed by restriction fragment length polymorphism, 10 used polymerase chain reaction followed by single strand conformation polymorphism; three studies used Southern blot, four studies sequencing, and one hybridization techniques in addition to polymerase chain reaction.

POPULATION SCREENING

Attempts to relate DNA sequence variation in specific genes to obesity phenotypes continue to grow. The obesity gene map shows putative loci on all chromosomes except Y. Overall, more than 430 genes, markers, and chromosomal regions have been associated or linked with human obesity phenotypes (127). However, neither the biologic nor the epidemiologic data on these genes are complete enough to make them candidates for screening in obese people. Before planning a screening program, the association between the gene and the disease should be established with some degree of certainty, and efficacious preventive intervention targeting at-risk subjects should be available. Considering these premises, there is insufficient evidence at present to

FIGURE 2. Funnel plots of the natural logarithm of the odds ratio (LnOR) vs. the standard error (SE) of the natural logarithm of the odds ratio for studies on the association between leptin polymorphisms and obesity. Numbers in parentheses, 95% confidence interval. Q, Cochran Q-test for heterogeneity; p (Begg), p value for Begg’s test for publication bias; p (Egger), p value for Egger’s test for publication bias. Refer to the Associations section of the text for information on parts A–D.
justify population testing for the \textit{LEP}, \textit{LEPR}, or \textit{PPARG} polymorphisms in an obesity screening program in the general population.

\section*{CONCLUSION AND RESEARCH PRIORITIES}

Obesity is a major public health concern given the association of this condition with several chronic diseases. Identification of genetic variants that increase a person’s susceptibility to the common forms of obesity is a critical problem. Several recent studies have made an attempt in this direction (128). The main summary of the literature indicates no association between the genes involved in leptin regulation and obesity. It is also evident from this review that the pathogenesis of obesity is complex and that the interaction between genetic and environmental factors is a crucial event.

Further areas of research include both gene-gene and gene-environment interaction as well as individual genetic and metabolic profiles using the developments occurring in genomics and proteomics (129). Larger studies on both obese and lean subjects are needed, with testing of multiple genes and detailed epidemiologic data on the dietary habits of different ethnic groups, including a better definition of the obesity phenotype.

\section*{INTERNET SITES}

Online Mendelian Inheritance in Man (OMIM). Center for Medical Genetics, Johns Hopkins University (Baltimore, Maryland) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, Maryland), 1999: http://www.ncbi.nlm.nih.gov/omim/

American Obesity Association (AOA): http://www.obesity.org/

\section*{ACKNOWLEDGMENTS}

Conflict of interest: none declared.

\section*{REFERENCES}


92. Kao WH, Coresh J, Shuldiner AR, et al. Pro12Ala of the peroxisome proliferator-activated receptor-G2 gene is...


