Association of Leptin Gene –2548 G/A Polymorphism with Obesity: A Meta-Analysis

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Key Words
Obesity · Leptin · –2548 G/A polymorphism · Meta-analysis

Abstract
Background: A common single-nucleotide polymorphism identified in the 5'‐untranslated region of the leptin gene (LEP –2548 G/A polymorphism) may be associated with obesity, but the existing research findings are inconsistent, so we conducted this meta-analysis. Methods: Medline, Embase and ISI Web of Science databases were searched to identify relevant studies. Meta-analysis of the total and subgroup populations was conducted using allelic, additive, dominant and recessive models, and odds ratios and their 95% confidence intervals were calculated in a fixed-effect model if no heterogeneity (evaluated as I	extsuperscript{2} statistic) existed. Otherwise, a random-effects model was adopted. Subgroup analysis was performed by ethnicity. Meta-regression and the HETRED analysis were used to explore the potential sources of between‐study heterogeneity. Egger’s test and influence analysis were conducted to evaluate the publication bias and study power, respectively. Results: The final selection enrolled 9 studies, including 2,988 subjects (1,372 obese subjects and 1,616 controls). No significant association was identified between the LEP –2548 G/A polymorphism and obesity for all genetic models in the overall population and Caucasians. We found a significant association with allelic, additive and dominant models for subjects of mixed race from South America. Notwithstanding, this significance should be treated cautiously for it is based on a rather small sample (788 involved subjects). Conclusions: In total, the combined analysis of data from current and published studies suggested that the LEP –2548 G/A polymorphism does not contribute to the development of obesity, despite the fact that a significant association exists in a small subgroup from South America. Further studies are needed to elucidate the relationship.

Introduction
The prevalence of obesity has steadily been rising over the past decades in adults and children [1–3], to become a global epidemic and represent a major public health challenge. Obesity is a multifactorial condition influenced by the combined effects of genes, the environment and their interactions [4]. Despite intense effort, the genetic pathways underlying obesity remain elusive.
Leptin, a 16-kDa polypeptide hormone predominantly produced by white adipose tissue [5], has been identified as an important player in the risk of obesity through its effects on food intake and energy expenditure [6, 7]. Plasma leptin concentration is proportional to body adiposity and markedly increased in obese individuals [8]. In addition to the action on satiety through hypothalamic receptors, leptin seems to be implicated in the pathophysiology for other components of the metabolic syndrome such as hypertension and insulin resistance [9, 10].

There is a high variability in the 5′-flanking region in the leptin gene, and a bulk of studies has been conducted on the association between leptin gene variants and the obesity risk. Among the variants studied, a common single-nucleotide polymorphism identified in the 5′-untranslated region of the leptin gene (LEP –2548 G/A polymorphism, rs7799039) is the most studied one. Substantial data indicated that the LEP –2548 polymorphism was associated with the variations in plasma leptin and body mass index (BMI) in both obese and non-obese individuals [11–16]. The mechanism may be that the LEP –2548 G/A polymorphism influences leptin expression, possibly at the transcriptional level, and therefore also adipose secretion levels of the hormone [17]. However, the direct association between the –2548 G/A polymorphism and obesity remains vague. While most current published studies have failed to identify a significant association in various populations [18–24], 3 studies found that the current variant was significantly associated with the risk of obesity (defined as BMI ≥30) in subjects of mixed race (South America) [25] and Caucasians (Turkish and Tunisian) [26, 27]. Additionally, while most pieces of evidence have indicated that the frequency of the GG genotype or G allele is higher in the obesity or overweight group compared to that of the control in various populations [16, 25, 28], Nieters et al. [29] found a sharply contrasting outcome, i.e. that the homozygosity for the A allele is significantly associated with an increased risk of obesity. All these inconsistencies in the magnitude or direction of the association may lead to a poor understanding of the true association between the LEP –2548 G/A polymorphism and obesity.

A single study may be limited by sample size, research design and subject traits (gender, ethnicity, age, etc.), and underpowered to achieve a comprehensive and reliable conclusion. Meta-analysis has the benefit to overcome this limitation by increasing the sample size. The aim of this study was therefore designed to clarify the association between the LEP –2548 G/A polymorphism and the risk of obesity.

### Methods and Procedures

#### Literature Search

Relevant studies, i.e. all publications on the association between the leptin –2548 G/A variant and obesity, were identified by searches of the Medline, Embase and ISI Web of Science databases updated in July 2013, using the key words: ('adipose tissue' or 'obesity' or 'body composition' or 'weight' or 'body mass index' or 'BMI') and ('leptin') AND ('polymorphism' or 'genotype' or 'variant'). We used the search engine Google to find additional articles and conference abstracts suitable for inclusion in our meta-analysis. The search was limited to adult human populations. All languages were accepted. We excluded reviews, case reports, letters, editorials, guidelines and comments. References of retrieved articles were also screened.

#### Study Selection and Data Extract

Articles not on the direct relationship between the LEP –2548 G/A polymorphism and obesity in an adult population, and those examining a highly specific population (e.g. pregnant women or a population with a specific somatic disease) were excluded. The selection criteria of studies for this meta-analysis were as follows: (1) unrelated case-control studies, (2) complete data with genotype and allele frequencies, (3) at least two comparison groups (obesity vs. control group) and (4) using a BMI cut-off point of 30 for obesity. All literature items were reviewed independently by two authors. The flow chart for study selection is shown in fig. 1.

Two authors extracted data independently and in duplicate, and researched all items including author’s last name, journal and year of publication, country of origin, ethnicity of the study population, definition of obesity (BMI cut-off point), genotypes and numbers of cases and controls. The results were compared, and disagreements were discussed and resolved with consensus.

#### Statistical Analysis

Hardy-Weinberg equilibrium (HWE) was tested in control samples of each data set by the \( \chi^2 \) (p < 0.05 was considered statistically significant) method to assess the latent bias resulting from the deviation of the genotype distribution. The pooled odds ratio (OR) and its 95% confidence interval (CI) were estimated to assess the magnitude of the association between the LEP –2548 G/A polymorphism and obesity with 4 models: allelic model (G allele vs. A allele), additive model (G/G vs. A/A), recessive model (G/G + G/A vs. A/A) and dominant model (G/G vs. G/A + A/A). The pooled ORs were calculated by a Mantel-Haenszel fixed-effects model if there was no heterogeneity. Otherwise, a random-effects model was adopted. Subgroup analysis was performed by ethnicity. A sensitivity analysis was conducted to evaluate the effect of potential subject overlapping in two studies on combined ORs.

Statistical heterogeneity across studies was formally tested using Cochran’s test. The \( I^2 >50\% \) was considered significant for the heterogeneity between studies. To better investigate the possible source of between-study heterogeneity, a meta-regression analysis and HETRED (heterogeneity-reducing algorithm) analysis were used to explore the potential sources of between-study heterogeneity. For HETRED analysis [30], we took \( I^2 >50\% \) as the criterion to identify the key studies with substantial impact on between-study heterogeneity. An influence analysis was conducted to describe how robust the pooled estimator is after removal of individual studies. An individual study was suspected of excessive influence if the point estimate of...
its omitted analysis lies outside the 95% CI of the combined analysis. Publication bias was assessed using the Egger regression test and Begg's funnel plot. All analyses were conducted in Stata software (version 11.0; Stata Corporation, College Station, Tex., USA).

Results

Study Characteristics

The flow chart for article screening is shown in fig. 1. In the end, we identified 30 studies to evaluate the association of the LEP –2548 G/A polymorphism with the risk for obesity. Among the articles, 14 were excluded for their discussion of a child or adolescent population, pregnant women or patients under antipsychiatric treatment, 2 for complete overlap [20, 31] and 5 for non-compliance with the BMI cut-offs defined by the WHO (BMI 30). At last, a total of 9 studies were enrolled in this meta-analysis. The detailed characteristics of these studies are shown in table 1. In 9 articles published between 2006 and 2012, 1,372 obese subjects and 1,616 controls were involved from a wide range of regions including Europe [19, 21, 22, 27], South America [18, 23, 25] and North Africa [24, 26]. Of the selected studies, 6 related to a Caucasian popula-
There were 2 studies in which the genotypes in the control group were not in HWE [26, 27]. Two studies were performed by the same investigator [23, 25], and it is not clear whether different individuals were genotyped or whether some individuals were counted twice (the author rejected our inquiry e-mail). Both studies were included in the final analysis, and the influence of a possible partial overlap on the overall OR was assessed by subgroup analysis after excluding the older one [23].

**Association between LEP –2548 G/A Polymorphism and Obesity**

Results of pooled analysis are summarized in detail in table 2. In the overall analysis, this meta-analysis showed no significant association between the LEP –2548 G/A polymorphism and obesity as judged by the ORs and 95% CIs (for allelic model: OR = 0.89, 95% CI = 0.67–1.19; for additive model: OR = 0.86, 95% CI = 0.52–1.41; for dominant model: OR = 0.87, 95% CI = 0.61–1.25; for recessive model: OR = 0.91, 95% CI = 0.64–1.30). Fig. 2 shows the forest plot ORs for obesity in the 4 models. After excluding articles that deviated from the HWE in controls, all the associations in the above-mentioned inherited models were not altered significantly (table 2).

Subgroup analysis was further performed by the type of ethnicity (categorized as Caucasians and Southern Americans of mixed race) to evaluate the effect of the –2548 G/A polymorphism in LEP on obesity susceptibility. In the Caucasian population (including 6 studies), no evidence of association was found for all 4 models, and this outcome remained stable after excluding articles that deviated from the HWE in controls. With the subgroup of Southern Americans of mixed race, the LEP –2548 G/A polymorphism seemed to be related to the risk of obesity, as judged by the analysis with allelic, additive and dominant models, and OR = 1.30 (95% CI = 1.05–1.61), 1.71 (1.07–2.73) and 1.40 (1.05–1.87), respectively. Specifically, the incidences of G allele carrier or GG genotype were higher in the obesity group compared to that in the control and may contribute to the development of obesity.

As we failed to exclude the possibility that two articles (named ‘Hinuy 2008’ and ‘Hinuy 2010’) performed by the same investigator might have some subject overlap, we also conducted sensitivity analysis after excluding the older article ‘Hinuy 2008’ to evaluate whether this partial overlap (if it exists) may impair the robustness of the current meta-analysis (as shown in table 2). The outcomes showed that excluding the article ‘Hinuy 2008’ did not change the degree of the association in any above-men-
HETRED analysis: reducing heterogeneity by omitting the study using the GA/AA. M = Model; F = fixed-effects model; R = random-effects model.

recessive model: G/G + G/A versus A/A; dominant model: GG versus G/A.

overall relevant articles

allelic 1,372/1,616 0.89 (0.67 - 1.19) R 84.1 1,165/1,399 1.08 (0.96 - 1.21) F 30.9 Sahin; Boumaiza
additive 1,372/1,616 0.86 (0.52 - 1.41) R 77.4 1,165/1,399 1.13 (0.89 - 1.44) F 31.1 Sahin; Boumaiza
recessive 1,372/1,616 0.91 (0.64 - 1.30) R 64.3 1,212/1,568 1.03 (0.84 - 1.28) F 45.2 Boumaiza
dominant 1,372/1,616 0.87 (0.61 - 1.25) R 79.8 1,165/1,399 1.11 (0.93 - 1.31) F 23.8 Boumaiza

sensitivity analysis excluding ‘Hinuy 2008’

allelic 1,372/1,448 0.85 (0.63 - 1.16) R 78.6 1,065/1,271 1.09 (0.84 - 1.40) F 35.0 Sahin; Boumaiza
additive 1,372/1,448 0.79 (0.46 - 1.34) R 67.2 1,065/1,271 1.07 (0.86 - 1.34) F 18.2 Boumaiza
recessive 1,372/1,448 0.87 (0.59 - 1.28) R 80.6 1,065/1,271 1.07 (0.90 - 1.28) F 22.4 Boumaiza
dominant 1,372/1,448 0.81 (0.55 - 1.20) R 79.8 1,065/1,271 1.05 (0.93 - 1.19) F 33.1 Sahin; Boumaiza

Caucasian all relevant articles

allelic 972/1,228 0.73 (0.51 - 1.05) R 86.3 765/1,011 0.99 (0.86 - 1.14) F 0.0 Sahin; Boumaiza
additive 972/1,228 0.62 (0.34 - 1.12) R 79.2 765/1,011 0.97 (0.73 - 1.29) F 0.0 Sahin; Boumaiza
recessive 972/1,228 0.74 (0.47 - 1.17) R 70.4 765/1,011 1.00 (0.79 - 1.28) F 0.0 Sahin; Boumaiza
dominant 972/1,228 0.67 (0.42 - 1.06) R 81.6 765/1,011 0.98 (0.79 - 1.21) F 0.0 Sahin; Boumaiza

Mixed race all relevant articles

allelic 400/388 1.30 (1.05 - 1.61) F* 0.0 – – – –
additive 400/388 1.71 (1.07 - 2.73) F* 0.0 – – – –
recessive 400/388 1.44 (0.93 - 2.22) F 0.0 – – – –
dominant 400/388 1.40 (1.05 - 1.87) F* 0.0 – – – –

sensitivity analysis excluding ‘Hinuy 2008’

allelic 300/260 1.29 (1.01 - 1.67) F* 24.4 – – – –
additive 300/260 1.71 (0.97 - 3.00) F 20.2 – – – –
recessive 300/260 1.47 (0.87 - 2.51) F 0.0 – – – –
dominant 300/260 1.36 (0.97 - 1.91) F 21.3 – – – –

Allelic model: G allele versus A allele; additive model: G/G versus A/A; recessive model: G/G + G/A versus A/A; dominant model: GG versus GA/AA. M = Model; F = fixed-effects model; R = random-effects model. HETRED analysis: reducing heterogeneity by omitting the study using the STATA module of HETRED when I^2 ≥ 50%; * p < 0.05. Figures in parentheses indicate 95% CI. Hinuy 2008 = Hinuy et al. [23]; Sahin = Sahin et al. [27]; Boumaiza = Boumaiza et al. [26].

Heterogeneity Analysis

As shown in table 2, strong evidence of heterogeneity between studies existed in all above-mentioned models for the risk of obesity in Caucasians and the overall population. To seek the key factors for this heterogeneity, we conducted a univariate meta-regression analysis, with the covariate sample ratio (ratio of sample size in the case group to that in the control), sample size, gender (ratio of males in percent in the case group to that in the control), age (ratio of mean age in the case group to that in the control), ethnicity (categorized as Caucasians and Southern Americans of mixed race) and HWE (categorized as 0 = accordance with HWE and 1 = deviation from HWE). The statistics recognized the covariate HWE as the only significant heterogeneity factor (p = 0.003, as shown in the online suppl. table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000363392).

From the above analysis, inclusion of the studies deviating from HWE seemingly impaired the robustness of the current meta-analysis. In order to check whether this was the case, we conducted a HETRED analysis to evaluate the change of OR estimates after excluding the key contributors of the article to heterogeneity (judged by the STATA module of HETRED when I^2 was reduced to below 50%). The results showed that inclusion or exclusion of the 2 articles not in accordance with HWE had no substantial impact on any OR estimate (including all 4 inherited models in both overall and Caucasian samples), i.e. inclusion of the two studies does not essentially weaken the efficiency of our meta-analysis (shown in table 2).
### a

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portoles [22], 2006</td>
<td>1.03 (0.84 – 1.25)</td>
<td>12.97</td>
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<tr>
<td>Duarte [18], 2007</td>
<td>1.14 (0.82 – 1.59)</td>
<td>11.62</td>
</tr>
<tr>
<td>Bienertova-Vasku [19], 2008</td>
<td>0.94 (0.61 – 1.46)</td>
<td>10.39</td>
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<tr>
<td>Ben Ali [20], 2008</td>
<td>0.85 (0.65 – 1.11)</td>
<td>12.30</td>
</tr>
<tr>
<td>Constantin [21], 2010</td>
<td>1.26 (0.84 – 1.88)</td>
<td>10.85</td>
</tr>
<tr>
<td>Hinuy [25], 2010</td>
<td>1.54 (1.04 – 2.28)</td>
<td>10.93</td>
</tr>
<tr>
<td>Hinuy [23], 2008</td>
<td>1.32 (0.90 – 1.93)</td>
<td>11.07</td>
</tr>
<tr>
<td>Boumaiza [26], 2012</td>
<td>0.49 (0.36 – 0.67)</td>
<td>11.80</td>
</tr>
<tr>
<td>Sahin [27], 2013</td>
<td>0.22 (0.11 – 0.41)</td>
<td>8.06</td>
</tr>
<tr>
<td>Overall (I² = 84.1%, p = 0.000)</td>
<td>0.89 (0.67 – 1.19)</td>
<td>100.00</td>
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Weights are from random-effects analysis

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### b

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<td>Portoles [22], 2006</td>
<td>1.06 (0.71 – 1.58)</td>
<td>13.66</td>
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<tr>
<td>Duarte [18], 2007</td>
<td>1.26 (0.58 – 2.74)</td>
<td>10.97</td>
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<td>Bienertova-Vasku [19], 2008</td>
<td>0.99 (0.44 – 2.26)</td>
<td>10.61</td>
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<tr>
<td>Ben Ali [20], 2008</td>
<td>0.61 (0.33 – 1.12)</td>
<td>12.22</td>
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<td>Constantin [21], 2010</td>
<td>1.46 (0.68 – 3.13)</td>
<td>11.03</td>
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<td>Hinuy [25], 2010</td>
<td>2.42 (1.04 – 5.64)</td>
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<td>Hinuy [23], 2008</td>
<td>1.71 (0.74 – 3.96)</td>
<td>10.48</td>
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<tr>
<td>Boumaiza [26], 2012</td>
<td>0.29 (0.16 – 0.54)</td>
<td>12.17</td>
</tr>
<tr>
<td>Sahin [27], 2013</td>
<td>0.14 (0.04 – 0.43)</td>
<td>8.40</td>
</tr>
<tr>
<td>Overall (I² = 77.4%, p = 0.000)</td>
<td>0.86 (0.52 – 1.41)</td>
<td>100.00</td>
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Weights are from random-effects analysis

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### c

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<td>Portoles [22], 2006</td>
<td>1.05 (0.77 – 1.45)</td>
<td>16.11</td>
</tr>
<tr>
<td>Duarte [18], 2007</td>
<td>1.18 (0.56 – 2.51)</td>
<td>10.20</td>
</tr>
<tr>
<td>Bienertova-Vasku [19], 2008</td>
<td>1.33 (0.64 – 2.77)</td>
<td>10.45</td>
</tr>
<tr>
<td>Ben Ali [20], 2008</td>
<td>0.61 (0.34 – 1.09)</td>
<td>12.47</td>
</tr>
<tr>
<td>Constantin [21], 2010</td>
<td>1.27 (0.63 – 2.55)</td>
<td>10.84</td>
</tr>
<tr>
<td>Hinuy [25], 2010</td>
<td>1.83 (0.85 – 3.93)</td>
<td>10.05</td>
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<tr>
<td>Hinuy [23], 2008</td>
<td>1.36 (0.63 – 2.93)</td>
<td>9.97</td>
</tr>
<tr>
<td>Boumaiza [26], 2012</td>
<td>0.40 (0.23 – 0.70)</td>
<td>12.75</td>
</tr>
<tr>
<td>Sahin [27], 2013</td>
<td>0.28 (0.10 – 0.79)</td>
<td>7.16</td>
</tr>
<tr>
<td>Overall (I² = 64.3%, p = 0.004)</td>
<td>0.91 (0.64 – 1.30)</td>
<td>100.00</td>
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Weights are from random-effects analysis

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(For legend see next page.)
Influence Analysis
The online supplementary figure S1 presents the result of influence analysis in 4 inherited models after removal of individual studies, and no individual study was found to have excessive influence on the pooled effect. It demonstrated that our results were robust.

Publication Bias
Publication bias among studies in all was evaluated by Egger’s regression test, and no significance was found (p = 0.648 for allelic model, p = 0.990 for additive model, p = 0.973 for recessive model and p = 0.530 for dominant model, respectively). Balance in Egger’s publication bias plots also indicated that there was no publication bias for the overall analysis (fig. 3).

Discussion
Among the variants identified in the 5’-flanking region of the leptin gene, the LEP –2548 G/A polymorphism is the most extensively studied one. However, because of modest sample size, different race, age, gender and study design, these studies had less power to provide us with reliable and comprehensive results. Therefore, a meta-analysis is expected to give a more conclusive answer.

To the best of our knowledge, this is the first meta-analysis to examine the association between the LEP –2548 G/A polymorphism and risk of obesity, which involved 1,372 obese subjects and 1,616 non-obese controls with the average age 42–70 years. As the BMI cut-off point for obesity may affect the strength of association between LEP –2548 G/A and obesity, this meta-analysis only included studies adopting a BMI cut-off point of 30. Indeed, of the studies with a BMI cut-off point of 30, most failed to find a significant relationship between the LEP –2548 G/A polymorphism and obesity risk, while 3 studies (2 studies on Caucasians in Northern America and Europe, respectively, 1 on Asians) which selected severe obesity (with BMI 35 or 40) found a significant association
[16, 28, 29].

In this meta-analysis, the combined analysis suggested that the LEP –2548 G/A polymorphism does not contribute to the development of obesity. Subgroup meta-analysis did not reveal any significant association in Caucasians (including 6 studies and 2,234 subjects) for all models either. Nevertheless, we identified a significant association in a mixed race (South American, including 3 studies and 788 subjects) for allelic, additive and dominant models indicating that the G allele carrier state may contribute to the development of obesity. However, this conclusion is weak, and we should treat this significance cautiously because this was obtained based on a rather small sample (only 788 subjects), and more original data from a population survey is needed to support this finding.

Although the results of our study are negative, future study is still urgently warranted, because a great deal of published evidence has indicated that the LEP –2548 G/A
polymorphism is associated with the BMI in both obesity and health [14, 15], and in different ethnicities including Caucasians and African blacks [32, 33]. On the other hand, the variant has been proved to be related to the development of severe obesity (BMI $\geq 35$) in 3 independent studies as mentioned above [16, 28, 29]. Therefore, it could be explained that the variant might have such a modest effect that it did not reach significance in our meta-analysis and most previous studies, if it had any effects on obesity.

In a polygenic disease such as obesity, with a strong environmental influence, genotype is only one factor in the causal pathway to the disease, and gene-gene and gene-environment interactions can influence the final association genotype/disease and the genetic mode of action. Firstly, it is possible that variation at LEP $-2548$ has effects on obesity, while in the context of the combinations of multiple genes and environmental factors, when leading to disorder in body weight regulation and control, this would not be observed, for environmental factors may predominate in the development of metabolic diseases (especially obesity and type 2 diabetes). Thus, if the variation has a pathogenic effect on obesity, it may take a long time to be observed. Secondly, only a small number of single-nucleotide polymorphisms identified may not fully explain the genetic risk for complex diseases like obesity. There are many undetected modest-risk variants combined, which may serve as an origin of the risk of obesity or control the expression of some risk factors. For example, it has been shown that a linkage disequilibrium existed between the LEP $-2548$ G/A polymorphism and a highly variable tetranucleotide repeat (TTTC)n located...
in the 3′-flanking region of the leptin gene [grouped in class I (short) and class II (long)], with obese individuals having higher frequencies of I/G combined genotypes than non-obese subjects (p = 0.018) [25]. In addition, similar linkage disequilibrium also presents between LEP –2548 G/A and the LEPR Q223R variant [18]. In total, this may give some explanation to our findings, and extended haplotype analysis is needed to explore the contribution of LEP genotypes and some unknown haplotypes to obesity susceptibility.

There are still many limitations in this meta-analysis which should be acknowledged. Firstly, numbers of case-control studies are all medium sized in our meta-analysis, so our results should be interpreted with caution. Secondly, only limited ethnicities (Caucasians and mixed race) have been considered. Including more other ethnic populations would be helpful to further evaluate the association between the LEP –2548 G/A polymorphism and obesity. Additionally, in our meta-analysis, 4 genetic models were adopted, including the allelic, additive, recessive and dominant one, because it is unknown which model is more suitable to identify the association based on available published data. However, this question remains unanswered by the current overall analysis, in total, this study is the first meta-analysis of the association between the LEP –2548 G/A polymorphism and obesity, and our results were reliable because the results of sensitivity and influence analysis did not draw different conclusions. In sum, there is no relationship between the LEP –2548 G/A polymorphism and obesity in the overall analysis, despite an ethnicity-specific significant association in the population of mixed race from South America. More studies with a larger sample size and a better ethnicity specificity with routine obesity diagnostic criteria are needed for a better understanding of the association between the LEP –2548 G/A polymorphism and obesity.

Acknowledgements

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References


