Association between -174G>C polymorphism in the IL-6 promoter region and the risk of obesity

A meta-analysis

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Abstract

Background: Many researchers have suggested that the -174G>C polymorphism in the interleukin-6 (IL-6) promoter region contributes to the risk of obesity; however, this hypothesis is still inconclusive. Therefore, we conducted a meta-analysis to combine the data from several studies to arrive at a conclusion regarding the association between -174G>C polymorphism and the risk of obesity.

Methods: The PubMed and Embase databases were searched up to February 20, 2018. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using a random-effects model. Subgroup analysis and sensitivity were also performed.

Results: Ten eligible studies involving 7210 cases were performed to identify the association strength. The association strength was measured by the ORs and 95% CIs. By pooling the eligible studies, we found a significant association between the -174G>C polymorphism and obesity risk (C vs G: OR = 1.37; 95% CI, 1.08–1.74; \(P_{\text{heterogeneity}} < 0.01\)). Overall, individuals with the variant CC (OR = 1.58; 95% CI, 1.09–2.28; \(P_{\text{heterogeneity}} < 0.01\)) and GC/CC (OR = 1.61; 95% CI, 1.13–2.29; \(P_{\text{heterogeneity}} < 0.01\)) were associated with a significantly increased risk of obesity.

Conclusion: The meta-analysis results suggested that the polymorphism -174G>C in the IL-6 promoter region was associated with a significantly increased risk of obesity.

Abbreviations: BMI = body mass index, HWE = Hardy–Weinberg equilibrium, IL-6 = interleukin 6, SNP = single nucleotide polymorphism.

Keywords: -174G>C polymorphism, IL-6, obesity

1. Introduction

Obesity-related disorders have become a major public health problem worldwide and can lead to metabolic disorders. Obesity is caused by several genetic, metabolic, social, and environmental factors. Among these internal and external factors, the contribution of genetic factors has been recognized widely, but the genes involved have not been fully elucidated.\textsuperscript{[1,11]}

Interleukin (IL)-6 is a cytokine that has dual roles, namely, it exhibits both inflammatory and anti-inflammatory effects.\textsuperscript{[2]} IL-6 is critical in the inflammatory signaling pathway and is involved in the development of obesity and insulin resistance.\textsuperscript{[3]} High circulating IL-6 concentration has been associated with obesity and the visceral adipose tissue.\textsuperscript{[4]}

Genetic variants, especially functional polymorphisms in the promoter region of genes, may alter the function and expression of genes associated with energy intake and energy expenditure. Several indications of the linkage between single nucleotide polymorphisms (SNPs) and obesity phenotypes have been found.\textsuperscript{[5,6]}

The functional IL-6–174G/C promoter polymorphism has been shown to affect IL-6 transcription.\textsuperscript{[7,11]} The IL-6–174C mutation change is expressed at a lower level in cellular constructs relative to the 174G construct.\textsuperscript{[9]} The human IL-6 gene is located on chromosome 7p21, and the -174G/C polymorphism consists of a single nucleotide change from G to C at position -174 in the promoter region.

In recent years, the association of the IL-6–174G/C polymorphism with obesity risk has been evaluated in several genetic studies. Some studies have suggested that IL-6–174G/C increased the obesity risk;\textsuperscript{[10,11]} while some found no association between IL-6–174G/C and obesity.\textsuperscript{[12]} The relation between IL-6–174G/C and risk of obesity is not conclusive. In this study, we investigated
whether the IL-6-174G>C polymorphism is associated with the risk of obesity.

2. Methods

2.1. Literature search

Study data were extracted by an electronic search from online databases (PubMed and Embase) and a manual search of references of relative articles using the search terms “IL-6,” “polymorphism(s),” and “obesity.” The search had no limitations, and the last search was conducted on February 20, 2018.

2.2. Inclusion and exclusion criteria

Studies were selected according to the following inclusion criteria: case-control studies or cohort studies; studies investigating the associations between IL-6 polymorphisms and obesity susceptibility; studies providing detailed genotype distribution data, or data for calculating genotype; the standard of obesity was defined according to body mass index (BMI) > 25 or waist-hip ratio (WHR) > 0.85; and participants in studies were not limited by age. The exclusion criteria were as follows: articles that did not present detailed genotype frequencies; review articles; articles that did not address obesity susceptibility; and articles that were not in Hardy–Weinberg equilibrium (HWE) according to an exact test.

2.3. Data extraction

Two reviewers (Yu and Luo) extracted eligible studies independently according to the inclusion criteria. Disagreements between the 2 reviewers were discussed with another reviewer (Zhang) until a consensus was reached. We extracted the following data from the original publications: name of first author; year of publication; country of the study; ethnicity; obesity definition; the age group of the population; and genotype frequency in cases and controls.

2.4. Statistical analysis

The association strength between the IL-6–174G>C polymorphism and obesity risk was measured by the odds ratio (OR) with a 95% confidence interval (95% CI). The estimates of the pooled ORs were achieved by calculating the weighted average of the OR from each study. A 95% CI was used for the statistical significance test and a 95% CI without 1 for the OR, indicating a significant increased or decreased cancer risk. The pooled ORs were calculated for an allelic comparison (C vs G), homozygote comparison (CC vs GG), heterozygote comparison (GC vs GG), dominant model (CC/GC vs GG), and recessive model (CC vs GG/GC). C was the variant allele. G was the wild-type allele. The heterogeneity assumption was validated using Chi-squared based on the $Q$ and $I^2$ test. An $I^2$ value of > 50% signified a “substantial heterogeneity.” A random-effects model was used to account for possible heterogeneities between studies. Funnel plots and the Egger linear regression test were used to diagnose potential publication bias ($P < .05$) as indicated statistically (significant publication bias). The statistical analysis was calculated using the STATA 12.0 (StataCorp, College Station, Texas). All $P$ values were 2-sided.

2.5. Ethical approval

All analyses of this meta-analysis were based on previous published studies, and this meta-analysis did not have original...
3. Results

3.1. Characteristics of eligible studies

In our study, 124 articles were identified after the first screening according to the inclusion and exclusion criteria. The detailed screening process is shown in Fig. 1. Here, 39 articles were retained after the full-text articles were reviewed. Among these articles, 26 studies were excluded because the genotype frequencies in the case and control groups were not provided. Three studies that were not in the HWE were also excluded. Seven of the studies consisted of Caucasian populations. Three studies were of children or adolescents. The obesity cases were diagnosed by the BMI or WHR in all studies. The polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay was used for genotyping in nine studies, and a chip-based matrix-assisted laser-desorption/ionization time-of-flight (MALDI-TOF) genotyping assay was performed in 1 study.[13] Blood samples were used for genotyping in all studies. The HWE of genotype distribution in the controls was tested in all the studies and was 10, consistent with the HWE. Further, 3 additional studies that were not consistent with the HWE were excluded. Overall, 10 studies satisfied the meta-analysis criteria.[11–22] The details of the studies are summarized in Table 1.

3.2. Quantitative synthesis

The pooled results from the assessment of the association between the IL-6–174G/C polymorphism and obesity susceptibility in 4 genotypes (dominant model: GC/CC vs GG; recessive model: CC vs GC/CC; homozygote: CC vs GG; and heterozygote model: GC/CC) are summarized in Table 2. We observed a significantly increased risk of obesity susceptibility, which was consistent with the study by Grallert et al.[23] This occurred in the dominant model (GC/CC vs GG: OR = 1.58, 95% CI: 1.09–2.28, P < .01, Fig. 2) and homozygote comparison (CC vs GC: OR = 1.61, 95% CI: 1.13–2.29, P < .01, Fig. 3) when all eligible studies were pooled. Moreover, we conducted the subgroup studies using the confounded factors. We found increased risks between the IL-6–174G/C polymorphism and the control source under the heterozygote model (CC vs GG). The result is shown in Fig. 4.

3.3. Sensitivity analysis and publication bias

We performed a sensitivity analysis to assess the stability of the results by sequentially removing each eligible study. Because no substantial change was found, the sensitivity analysis showed that no individual study affected the pooled results. The potential publication bias was assessed by Begg funnel plot (Fig. 5) and Egger test. The funnel plots did not indicate evidence of obvious asymmetry. In addition, the Egger test did not demonstrate...
significant publication bias (C vs G: \( P = .442 \); CC vs GG: \( P = .782 \); CG vs GG: \( P = .148 \); CG+CC vs GG: \( P = .180 \); CC vs GC+GG: \( P = .483 \)).

4. Discussion

Obesity has become a worldwide health problem because it is associated with a number of diseases, including heart disease, insulin resistance, hypertension, and atherosclerosis, which reduce life expectancy and contribute to higher medical expenses. The unbalanced production of inflammatory factors can contribute to the pathogenesis of obesity-linked diseases.[9] IL-6 inhibits the action of Treg cells and is involved in metabolic processes.[24] The adipose tissue is a major source of circulating IL-6, and the excessive secretion of IL-6 appears to be directly related to obesity.[24] In addition, IL-6 can affect metabolism directly or indirectly by its action on skeletal muscle cells.[25]

Recently, numerous studies suggested that SNPs in the promoter region of the \( IL-6 \) gene might be risk factors for the development of diabetes.[26] A number of studies indicated that the \( IL-6-174G/C \) polymorphism was highly associated with obesity, fatty liver, insulin resistance, and the metabolic syndrome.[27,28] Meanwhile, many studies found that the \( IL-6-174G/C \) polymorphism was significantly associated with susceptibility to obesity.[13,20] However, some studies have reported no significant associations between adiposity and the \( IL-6-174G/C \) genotypes.[12,29]

Circulating IL-6 is derived from different cells in tissues, such as the adipose tissue, muscles, and hypothalamus, all of which contribute to controlling the energy balance.[30] Further, IL-6 gene expression is tightly regulated by hormones, cytokines, and their transcription factors. Therefore, the differences in study findings may relate to environmental factors, such as dietary intake. Indeed, several studies have reported the relationship between \( IL-6-174G>C \) and diet. Corpeleijn et al[31] reported that the ability to increase fat oxidation after a high-fat load was increased in obese European Caucasians with the \( IL-174C \) allele. Further, diet can affect an individual’s genes and can, in turn, affect the response to supplementation.[32] Meanwhile, a study reported that the \( IL-6-174G>C \) polymorphism has been associated with exercise-related phenotypes.[33] With the combination of the reported studies, we hypothesized that environmental factors and lifestyle could affect the IL-6 polymorphism, and the \( IL-6-174G>C \) polymorphism, in turn, could affect the balance of energy intake and energy expenditure. However, whether the \( IL-6-174G>C \) polymorphism is related to obesity susceptibility remains controversial. To resolve this
conflicting theory, we conducted a meta-analysis that included 10 studies.

Overall, we observed that the IL6–174G>C polymorphism was associated with a statistically increased risk of obesity in all genetic models. The results are consistent with the study by Yu et al.[34] who performed an analysis of 3 studies, whereas 1 of the studies was not consistent with the HWE due to confounding factors, such as race, age, and the control source. Therefore, we conducted subgroup studies by these factors. We found an increased risk between the IL-6–174G/C polymorphisms and the control source in the genotype of the homozygote model (CC vs GG), and the association between -174G/C and obesity susceptibility was increased in the community-based control.

In this meta-analysis, 10 eligible studies, including 4291 cases and 2919 controls, were identified and analyzed to provide sufficient statistical power and strengthen the reliability of our results. In addition, the limitation of language did not exist when searching, thus the chance of selection bias was low. Compared with the previous meta-analysis,[3,34] our study included more studies, and all of the studies were consistent with the HWE, which increased the statistical power and provided stable results. However, some limitations of our meta-analysis still exist. First, because the selected studies were limited to inclusion and exclusion criteria, heterogeneity in the studies was difficult to avoid due to confounding factors in these criteria. Meanwhile, the selection bias was increased because of limited inclusion and exclusion criteria. Second, we only screened articles published electronically in 2 large-scale databases (PubMed and Embase), which contributed to selection bias. Third, because the meta-analysis was based on published literature, we had no access to the individual data and could not adjust and evaluate the effect of confounding factors, such as smoking, age, and family history, which could affect the final results. Fourth, we have no access to relevant data to assess the potential of gene–gene and gene–environment interactions. Thus, all data of this meta-analysis were interpreted cautiously. As such, we performed Egger test and Begg funnel plot to detect publication bias, used Q test and I² statistics to evaluate the heterogeneity in studies, and conducted subgroup analysis carefully in order to reduce the effect of confounding factors.

In summary, in this meta-analysis, we found that the IL-6–174G/C polymorphism was associated with the risk of obesity. Considering the variety of interference factors, larger studies related to the gene–environment interactions should be performed in the future to clarify the association between the IL-6–174G/C polymorphism and obesity susceptibility.
Figure 4. Subgroup results distinguished by control source in homozygote genotype (CC vs GG).

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| CB       |             |          |
| Joffe, Y. T. | 1.66 (0.65, 4.27) | 8.55 |
| Gupta, A. | 2.47 (1.38, 4.40) | 13.85 |
| Ibrahim, O. M. | (Excluded) | 0.00 |
| Subtotal (I-squared = 0.0%, p = 0.487) | 2.21 (1.35, 3.63) | 22.40 |
| HB       |             |          |
| Suazo, J. | 1.27 (0.36, 4.46) | 5.82 |
| Bouhaha et al. | 1.60 (0.46, 5.57) | 5.86 |
| Hamid, Y. H. | 2.26 (0.98, 5.21) | 9.86 |
| Wernstedt et al. | 1.10 (0.92, 1.30) | 21.08 |
| Subtotal (I-squared = 45.3%, p = 0.120) | 2.13 (1.20, 3.77) | 13.97 |
| Not mention | 1.50 (1.01, 2.22) | 56.69 |

NOTE: Weights are from random effects analysis.

Figure 5. Begg funnel plot of the association between the IL-6-174G>C polymorphism and obesity risk under the dominant model (GC/CC vs GG).
Author contributions

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