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ORIGINAL ARTICLE

Gln223Arg polymorphism in the Caucasian population and Pro1019Pro polymorphism in the Chinese population are risk factors for OSAS: An updated meta-analysis of 1159 subjects

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Abstract
Background: We conducted a meta-analysis of published literature to identify the correlation between leptin receptor gene polymorphisms and the risk of obstructive sleep apnea syndrome (OSAS).
Methods: Five different single nucleotide polymorphisms (SNPs) were studied. Only Gln223Arg and Pro1019Pro had multiple studies. Nine studies focused on the correlation between Gln223Arg and Pro1019Pro polymorphisms and OSAS risk. Fixed-effects model or random-effects model was used to calculate the pooled odds ratio (ORs) and its corresponding 95% confidence interval (95% CI). The Begg's, Egger's, Perter's and Harbord tests were used to measure publication bias. Sensitivity analysis was also performed to ensure the robustness of the findings.
Results: Six studies on Gln223Arg polymorphisms (661 cases and 498 controls) and three studies on Pro1019Pro polymorphisms (561 cases and 561 controls) were extracted. There was no correlation between the leptin receptor Gln223Arg polymorphism and the risk of OSAS (odd ratio = 0.86, 95% CI = 0.68–1.10, $P = 0.23$). However, Caucasian OSAS patients had a higher Arg allele frequency; whereas Chinese population with G genotype were more susceptible to OSAS (odd ratio = 1.28, 95% CI = 1.04–1.57, $P = 0.02$) in the studies on Pro1019Pro polymorphisms.

Abbreviations: ACC, acetyl-CoA carboxylase; AMPK, 5′ adenosine monophosphate-activated protein kinase; CI, confidence intervals; CNKI, Chinese National Knowledge Infrastructure; Grb2, growth factor receptor-bound protein 2; HWE, Hardy–Weinberg equilibrium; IRS, insulin receptor substrate; JAK2, Janus kinase 2; MAPK, mitogen-activated protein kinase; OR, odds ratios; OSAS, obstructive sleep apnea syndrome; PDE3B, phosphodiesterase 3B; PI3K, phosphatidylinositol 3 kinase; SHP2, SH2-containing protein tyrosine phosphatase 2; SNPs, single nucleotide polymorphisms; SOCS3, suppressor of cytokine signaling 3; STAT3, signal transducer and activator of transcription 3.

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Conclusion: The Gln223Arg polymorphisms in the Caucasian population and the Pro1019Pro polymorphisms in the Chinese population are risk factors for OSAS.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a prevalent sleep disorder characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep, resulting in oxygen desaturation and sleep fragmentation. A report from the World Health Organization estimates that OSAS affects 5–20 million people in Europe.[1] However, the etiology of OSAS is unclear. Previous studies indicate that leptin receptor may play an important role in the pathogenesis of OSAS.

Obesity is an important risk factor of OSAS.[2,3] Leptin and leptin receptors contribute significantly to obesity.[2–6] Plasma leptin levels are usually higher in patients with obesity. Leptin is a protein hormone secreted by adipose cells, especially white adipose cells. It can suppress appetite, reduce energy intake, increase energy expenditure and inhibit fat synthesis. Normally, a high level of leptin causes weight loss in healthy controls, but leptin does not work on obese people. This phenomenon is termed ''leptin resistance''.[4] In animal studies, genetically mutated mice lack functional leptin receptors are obese, although they have a higher level of plasma leptin.[5,6] The results from animal studies imply that the leptin resistance caused by leptin receptor mutation may also exist in humans.

The plasma leptin binds to the homodimeric leptin receptors. The extracellular domain of leptin receptor contains 816 amino acid residues. The leptin-bond leptin receptor recruits Janus kinase 2 (JAK2) in its intracellular domain. The complex is activated by the phosphorylation of JAK2, Tyr985, Tyr1077, and Tyr1138. Phosphor-Tyr985 is recruited to SH2-containing protein tyrosine phosphatase 2 (SHP2), then binds to the adaptor protein growth factor receptor-bound protein 2 (Grb2). The mitogen-activated protein kinase (MAPK) is activated to initiate the signaling cascade. Leptin regulates metabolism through Janus kinase 2 (AMPK) and acetyl-CoA carboxylase (ACC) in hypothalamus and peripheral organs. At the same time, leptin receptor-JAK2 complex also activates phosphatidylinositol 3 kinase (PI3K) pathways. In this signaling pathway, insulin receptor substrate (IRS) is phosphorylated first, leading to PI3K activation. Phosphodiesterase 3B (PDE3B) is an important downstream target of PI3 K in the leptin signaling pathway.[7]

Signal transducer and activator of transcription 3 (STAT3) and STAT5 bind to phospho-Tyr1138 and phospho-Tyr1077, respectively. The active STAT3 and STAT5 recruit another STAT3 and STAT5. The dimers are transported into the nucleus and begin the transcription of target genes. The anorexigenic effect is activated by this signaling pathway. Suppressor of cytokine signaling 3 (SOCS3), a target gene of STAT3, inhibits the JAK2/STAT3 pathway by interacting with phospho-Tyr985 or JAK2 and acting as a feedback inhibitor of leptin signaling pathway. The signaling pathway of leptin receptor is shown in Fig. 1.[7]

Previous studies show that there is a positive correlation between the serum leptin levels and obesity.[8] Furthermore, the mutations in leptin receptor gene cause severe obesity in humans[9] and the OSAS patients have a higher plasma leptin level.[10] Therefore, the evidence may imply that the leptin receptor mutations may be associated with the risk of OSAS.

OSAS is a familial disease and is caused by the interaction between environmental and genetic factors.[11] The leptin receptor gene is located on chromosome 1p31, and contains 20 exons and 19 introns. The total length of the leptin receptor gene is ~70 kb and is composed of 1165 amino acid. From a public health perspective, the current challenge is to identify the susceptibility gene and ascertain the cause of OSAS. Previous studies show that the mutation of melanocortin-4 receptor gene induces deficits in leptin-melanocortin pathway, which represents the genetic basis of obesity and OSAS. Other leptin receptor genes may also play important roles in the pathogenesis of this disorder. It is important to understand the association between leptin receptor polymorphisms and OSAS risk; therefore, individuals with higher genetic risk can be identified and receive targeted preventive therapy. We have conducted a systematic review of published literature on this topic and analyzed the correlations between leptin receptor polymorphisms and OSAS risk.

Materials and methods

Literature review

The Excerpt Medica Database, Web of science, Pubmed, Springer Link, Chinese National Knowledge Infrastructure, EBSCO and Science Direct databases were searched to find the literatures that reported the relationship between the leptin receptor polymorphisms and risk for OSAS from December 1971 to October, 2014. The keywords used were 'leptin receptor, obstructive sleep apnea, single nucleotide polymorphisms (SNPs)', 'leptin receptor, obstructive sleep apnea, polymorphism', 'leptin receptor, obstructive sleep apnea, allele', 'leptin receptor, OSAS, SNP', 'leptin receptor, OSAS, polymorphism', 'leptin receptor, OSAS, allele', 'lepr, obstructive sleep apnea, polymorphism', 'lepr, obstructive sleep apnea, allele', 'lepr, OSAS, SNP', 'lepr, OSAS, polymorphism', 'lepr, OSAS, allele'. Only the articles in English or Chinese with an English abstract were selected. After excluding duplicates, titles and abstracts were reviewed. The articles were included if they: (1) were case–control studies (compare the difference between patients and health controls); (2) had genotype polymorphisms in both cases and controls. The articles were excluded if they were: (1) review articles; (2) not related to

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