Original Article

Association between the IL-6 rs1800796 (-572C/G) polymorphism and chronic obstructive pulmonary disease risk: a meta-analysis

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Abstract: Interleukin-6 (IL-6), a pleiotropic proinflammatory and immunomodulatory cytokine, is highly involved in the pathogenesis of chronic obstructive pulmonary disease (COPD). Thus we conducted a meta-analysis to investigate the relationship between the IL-6 rs1800796 (-572C/G) polymorphism and COPD risk. We conducted a literature search up to April 20, 2015, using the PubMed, Embase and Chinese National Knowledge Infrastructure (CNKI) databases. Studies published in languages other than English or Chinese were excluded. A total of 413 COPD cases and 596 controls in 3 case-control studies were included in this study. The results of our meta-analysis suggested that the IL-6 rs1800796 (-572C/G) was significantly associated with COPD in a codominant genetic model (GC vs. GG, OR: 0.45, 95% CI: 0.28-0.72; CC vs. GG, OR: 0.20, 95% CI: 0.09-0.46). Moreover, no publication bias was detected in this study.

Keywords: Chronic obstructive pulmonary disease, interleukin-6, meta-analysis, polymorphism, susceptibility

Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem characterized by progressive airflow limitation that is not fully reversible. Chronic inflammation of the airways and pulmonary parenchyma results in partially reversible but progressive obstruction of the peripheral airways [1]. Numerous risk factors are related to COPD and its progression, but cigarette smoking is by far the most important of cigarette smokers develop COPD [2, 3]. Although the causal mechanisms underlying COPD are still not fully understood, a genetic susceptibility to COPD has been strongly suggested.

Inflammatory cytokines are one of the predominant underlying mechanisms in COPD [4]. Cytokines play important roles in inflammatory responses and are also critical in the regulation of progression of inflammation diseases [5]. Cytokines are central to the pathogenesis of COPD, as they play important roles in many pathophysiological processes such as the chronic inflammatory process and emphysema [4].

Interleukin-6 (IL-6), a pleiotropic pro-inflammatory and immunomodulatory cytokine, secreted by airway epithelial cells, has been identified as a candidate gene for COPD [6]. An important role of IL-6 is to act as a mediator of the acute phase response and the highly variable levels of acute and chronic inflammation attributed to this cytokine are thought to play a leading role in disease progression [6].

The IL-6 gene, located on chromosome 7p21 in humans, is composed of 5 exons, 4 introns, and a promoter region [7]. In the field of non-pulmonary diseases, the IL6 promoter polymorphisms have been widely studied. The IL6 rs1800796 (also called -572C/G) is in the promoter of the IL6 gene. The minor allele is C in most populations but G is the minor allele in Chinese, Japanese and Vietnamese populations (1000 Genomes project: http://www.10-
The IL-6 rs1800796 G allele was significantly associated with the susceptibility to Enterovirus 71 encephalitis in Chinese Han patients [8]. The IL6 rs1800795 (-174G/C) polymorphism was strongly related to coronary artery disease [9]. In addition, IL6 promoter polymorphisms have been associated with higher risk of multiple sclerosis severity [10] and rheumatic heart disease [11].

In pulmonary diseases, several studies revealed that IL-6 is associated with skeletal muscle weakness in COPD [12] as well as with exacerbations pulmonary infections in COPD patients [13]. Moreover, in the murine lung, overexpression of IL-6 resulted in airway inflammation and emphysema-like airspace enlargement [14]. Furthermore, IL-6, at the transcriptional level, can up-regulate C-reactive protein, an important mediator of the acute phase reactant [15]. C-reactive protein has been related to lung function decline in smoking-induced COPD and lung function levels in healthy individuals [16].

Over the past few years, the association of gene polymorphisms with COPD risk has been well studied, including the rs1800796 polymorphism in the IL-6 gene. However, consistent results have not been provided in those studies and our meta-analysis was performed to investigate the association of the IL-6 rs1800796 with risk of COPD. A meta-analysis can be used as a powerful tool to draw conclusions from pooled data. It utilizes quantitative methods to pool the data from individual studies where individual sample sizes are small [17].

Material and methods

Search strategy

Our team conducted the literature search by using PubMed, Embase and Chinese National Knowledge Infrastructure (CNKI) databases, including all studies up to April 20, 2015. We limited the analysis to studies published in English or Chinese. We used following search terms: interleukin 6 or IL-6, and polymorphism or variant or SNP (single nucleotide polymorphism) or genotype, and chronic obstructive pulmonary disease or COPD.

Data extraction

With the inclusion and exclusion criteria, two individuals of our team collected the data. The studies included in this meta-analysis were required to meet the following criteria: (1) case-control study in design; (2) evaluation of the IL6 rs1800796 polymorphism and COPD susceptibility; (3) genotype frequencies in both cases and controls were available. Criteria for exclusion in the meta-analysis were: (1) IL6 polymorphisms other than rs1800796; (2) duplicated reports; (3) languages other than English or Chinese. We did not consider unpublished data. We selected the study with the higher sample size, when the same group using overlapping sets of cases and published more than one article. We would solve disagreement by discussion before reaching a consensus.

Statistical analysis

We presented the data as odds ratio (OR) with 95% confidence interval (CI). GG, GC and CC are the genotypes of the IL6 rs1800796 polymorphism. OR1, OR2 and OR3 were calculated as follows: OR1 = CC vs. GG; OR2 = GC vs. GG; OR3 = CC vs. GC. Pairs of differences (OR1, OR2 and OR3) were used to calculate the most appropriate genetic model as follows: if OR1 = OR2 ≠ 1 and OR3 = 1, then it suggests a dominant model; if OR1 = OR3 ≠ 1 and OR2 = 1, then it suggests a recessive model; if OR2 = 1/OR3 ≠ 1 and OR1 = 1, then it suggests a overdominant model; if OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), then it suggests a codominant model [18].

Once the most appropriate genetic model was determined, this model was used to divide the three genotypes into two groups (except a codominant model) and to pool the results again. If the calculation indicated P < 0.05, we considered it statistically significant. Heterogeneity was checked by the Q test [19]. When there was no heterogeneity (P > 0.1), the fixed-effects model was used in the meta-analysis but otherwise, the random-effects model was used [19]. Pearson’s x² test was utilized to determine whether the calculated frequencies of genotypes in the controls accorded with the Hardy-Weinberg equilibrium (HWE). In order to check the consistency of the overall effect size was conducted when studies with control population departing from HWE (P < 0.5). Heterogeneity was evaluated with Chi-square statistics based on the Q-test and I² statistics. A P < 0.05 for Q test or I² values ≥ 50% indicates substantial heterogeneity [20]. Funnel plots, as well as Begg’s rank correlation test and Egger’s
linear regression test, were utilized to check for potential publication bias, and $P < 0.05$ was considered significant publication bias [21]. All analyses were conducted using Revman 5.3 and Stata 13.1.

**Results**

Studies included in the meta-analysis

Twenty-nine studies were related to the search terms. After scrutinizing the titles, abstracts and articles, 26 studies were excluded, because they were case reports, included other polymorphisms of IL-6, or contained insufficient data. Thus 3 articles [22-24] with 3 case-control studies for the IL6 rs1800796 matched the inclusion criteria (Figure 1). The three included studies were hospital-based and used the polymerase chain reaction restriction fragment length polymorphism genotyping method. Of the 3 included articles, 1 was published in English, and 2 were published in Chinese (Table 1).

**Quantitative synthesis**

For the purpose of selecting the most appropriate genetic model, OR1, OR2 and OR3 were calculated. Results revealed OR1 = 0.201, OR2 = 0.445 and OR3 = 0.535 for rs1800796, suggesting a codominant genetic model (GC vs. GG; CC vs. GG). The pooled effect size showed that there was a significant association of IL6 rs800796 with the risk of COPD (GC vs. GG OR: 0.45, 95% CI: 0.28-0.72, $P = 0.001$, fixed model; CC vs. GG OR: 0.20, 95% CI: 0.09-0.46, $P = 0.00001$) (Figures 2, 3).

**Test of heterogeneity**

In order to detect heterogeneity among the included studies, the Q-test and $I^2$ statistics

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**Table 1.** Main characteristics of included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>Race</th>
<th>Genotyping</th>
<th>Source of controls</th>
<th>COPD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>CC</td>
</tr>
<tr>
<td>[24]</td>
<td>China</td>
<td>Asian</td>
<td>PCR-RFLP</td>
<td>Healthy population</td>
<td>192</td>
<td>108</td>
</tr>
<tr>
<td>[25]</td>
<td>China</td>
<td>Asian</td>
<td>PCR-RFLP</td>
<td>Healthy population</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>[23]</td>
<td>Spain</td>
<td>European</td>
<td>PCR-RFLP</td>
<td>Healthy population</td>
<td>191</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: HWE, Hardy-Weinberg equilibrium; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.
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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>COPD</th>
<th>Control</th>
<th>Odds Ratio M-H. Fixed, 95% CI</th>
<th>COPD</th>
<th>Control</th>
<th>Odds Ratio M-H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elizabeth Co rdoba-Lanu’s 2008</td>
<td>18</td>
<td>190</td>
<td>0.49 [0.28, 0.85]</td>
<td>18</td>
<td>190</td>
<td>0.49 [0.28, 0.85]</td>
</tr>
<tr>
<td>Luojingjing 2013</td>
<td>60</td>
<td>84</td>
<td>0.36 [0.13, 0.95]</td>
<td>60</td>
<td>84</td>
<td>0.36 [0.13, 0.95]</td>
</tr>
<tr>
<td>Zhouqian 2012</td>
<td>2</td>
<td>7</td>
<td>0.15 [0.00, 5.18]</td>
<td>2</td>
<td>7</td>
<td>0.15 [0.00, 5.18]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>281</td>
<td>419</td>
<td>0.45 [0.28, 0.72]</td>
<td>281</td>
<td>419</td>
<td>0.45 [0.28, 0.72]</td>
</tr>
<tr>
<td>Total events</td>
<td>80</td>
<td>108</td>
<td></td>
<td>80</td>
<td>108</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Ch^2 = 0.67, df = 2 (P = 0.71); P = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)

Publication bias

We utilized Begg’s funnel plot and Egger’s test to test publication bias among the selected publications. The funnel plots of this study showed no significant asymmetry in this meta-analysis (Figures 4, 5). Moreover, publication bias was not observed by Begg's rank correlation test (GC vs. GG: P = 0.296; CC vs. GG: P = 1) or Egger’s linear regression test (GC vs. GG: P = 0.195; CC vs. GG: P = 0.770).

Discussion

It has long been known that smoking is the principal risk factor for COPD development. Exposure to cigarette smoke causes an imbal-
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As mentioned above, IL6, a well-characterized pleiotropic proinflammatory and immunomodulatory cytokine, possibly plays a role in chronic inflammation as well as COPD. The rs1800796 polymorphism is located in the promoter region of IL6 and therefore could affect IL6 gene transcription and protein expression both in vivo and in vitro [27]. Although several studies showed an association between COPD and IL6 polymorphisms, the results were inconclusive and contradictory. Córdoba-Lanús [22] demonstrated that the C allele of rs1800796 may confer a diminished risk of developing COPD. Zhou [24] reported that the rs1800796 G allele may confer a increase risk of developing COPD. Similarly, Lu [23] showed that the rs1800796 G allele may confer a increase risk of developing COPD. Because the three included studies were conducted in two different races, there was the expected difference in MAF between the studies. This difference may be one of reasons why some of the OR estimates vary between studies.

Individual studies with a small sample size might have not sufficient statistical power to detect a risk factor of small effect. Loannidis JP have suggested that pooled ORs generated from large sample sizes have the ability to increase the statistical power of the results and that combining data from multifarious studies has the advantage of decreased random errors [28]. Thus, for the purpose of gaining more precise results, we conduct a meta-analysis to evaluate whether a correlation exists between the IL6 rs1800796 polymorphism and risk of developing COPD.

This meta-analysis is the first study to summarize the correlation between the rs18000796 polymorphism and COPD risk. To identify genetic variants associated with this illness, much effort has been expanded to explore the association between them via case-control study or cohort studies. After statistical analysis, the pooled effect size showed that the IL6 rs1800796 was significantly associated with COPD susceptibility in a codominant genetic model, indicating that allele C had a decreased risk for COPD compared with allele G. We did not observe any significant heterogeneity between all studies in the GC vs. GG and CC vs. GG comparisons for rs1800796. However, complex genetic diseases differ from simple Mendelian diseases and since COPD is poly-

![Figure 5. Begg's funnel plot for evaluation of publication bias in the included studies on the associations of the IL6 rs1800796 COPD risk (CC vs GG).](image-url)
genic, a single genetic variant is always inadequate to predict the risk of this common disease. Publication bias was not suggested in the meta-analysis, possibly due to the deliberate and circumspect search strategy and data extraction. In our meta-analysis we did not perform sensitive analysis on account of the lack of sufficient original studies.

In summary, our meta analysis suggests that the IL6 rs1800796 C allele confers protection against COPD. Further studies with larger sample sizes, well phenotyped COPD cases and matched controls, as well as more extensive data on individual and environmental factors are warranted.

Acknowledgements

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Disclosure of conflict of interest

None.

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References

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