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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-

00genomes.org/). The *IL6* 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 x^2 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 I^2 statistics. A $P < 0.05$ for Q test or I^2 values ≥ 50% indicates substantial heterogeneity [20]. Funnel plots, as well as Begg's rank correlation test and Egger's

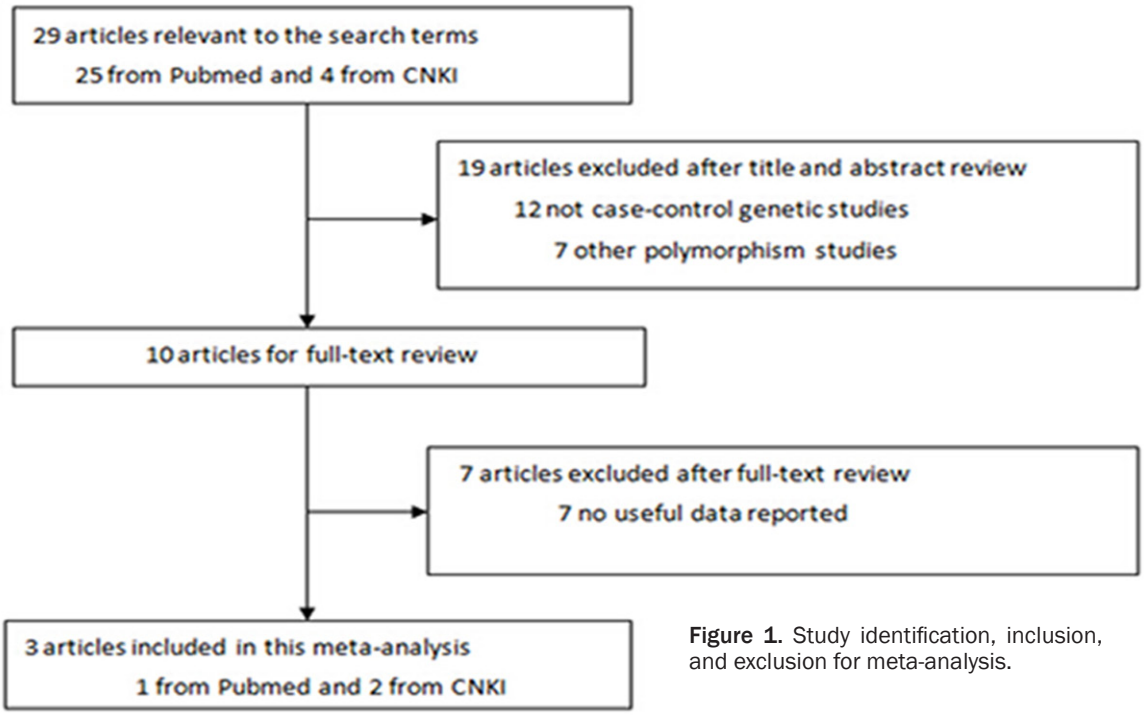

Figure 1. Study identification, inclusion, and exclusion for meta-analysis.

Table 1. Main characteristics of included studies

Ref.	Country	Race	Genotyping	Source of controls	COPD				Controls				
					Total	CC	CG	GG	Total	CC	CG	GG	HWE (p)
[24]	China	Asian	PCR-RFLP	Healthy population	192	108	60	24	195	147	42	6	0.1745
[25]	China	Asian	PCR-RFLP	Healthy population	30	23	2	5	30	29	1	0	0.9260
[23]	Spain	European	PCR-RFLP	Healthy population	191	1	18	172	371	1	65	305	0.2006

Abbreviations: HWE, Hardy-Weinberg equilibrium; PCR, polymerase chain reaction; RFLP-restriction fragment length polymorphism.

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

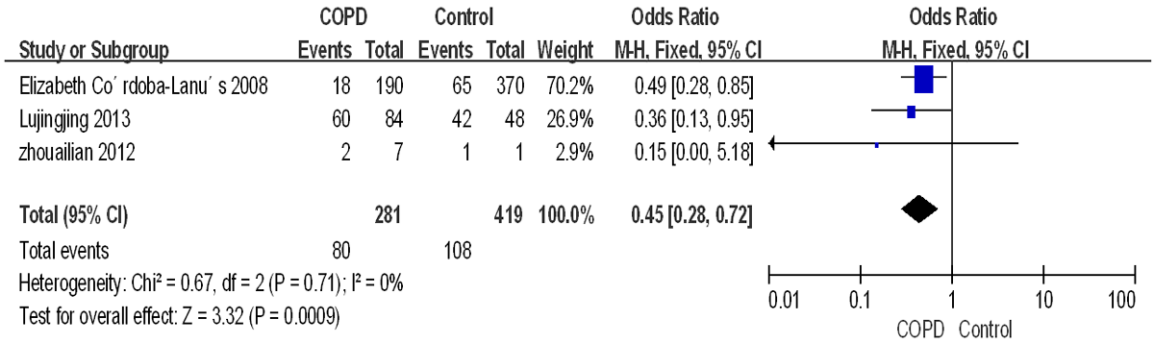

Figure 2. Forest plots of OR with 95% CI for the association of the *IL6* rs1800796 and COPD risk (GC vs. GG).

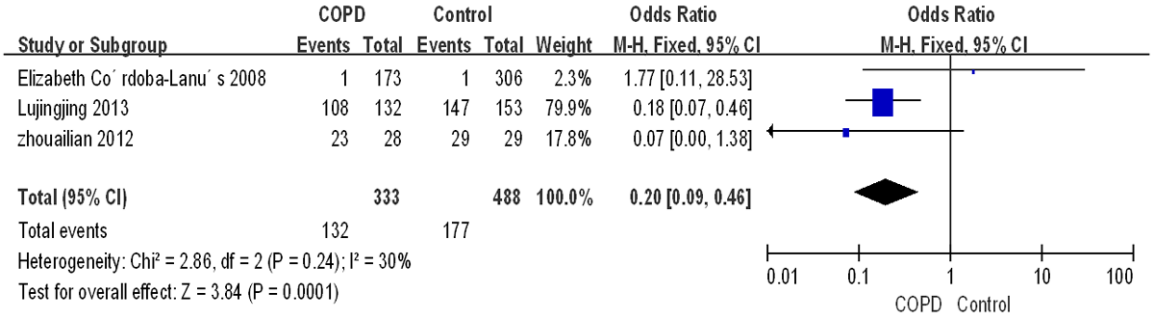

Figure 3. Forest plots of OR with 95% CI for the association of the *IL6* rs1800796 and COPD risk (CC vs. GG).

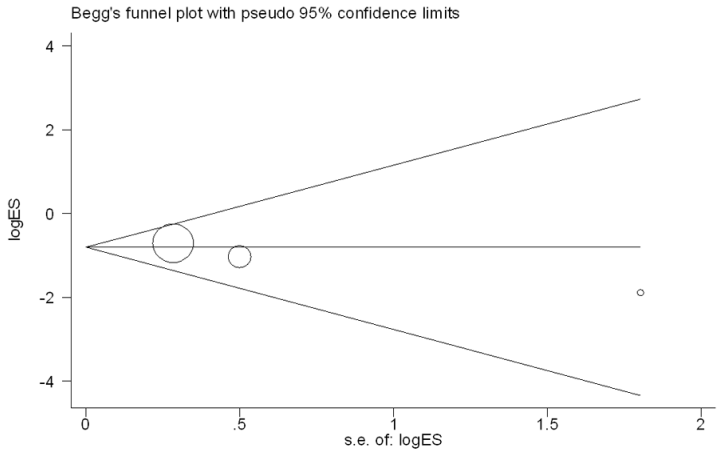

Figure 4. Begg's funnel plot for evaluation of publication bias in the included studies on the associations of the *IL6* rs1800796 with COPD risk (GC vs GG).

were employed. Significant heterogeneity was not revealed between all studies in GC vs GG and CC vs GG comparisons (codominant model) for the rs800796 polymorphism (I^2 = 0%, P = 0.71; I^2 = 30%, P = 0.24, respectively). Thus, the fixed model was utilized to synthesize the data for this analysis.

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-

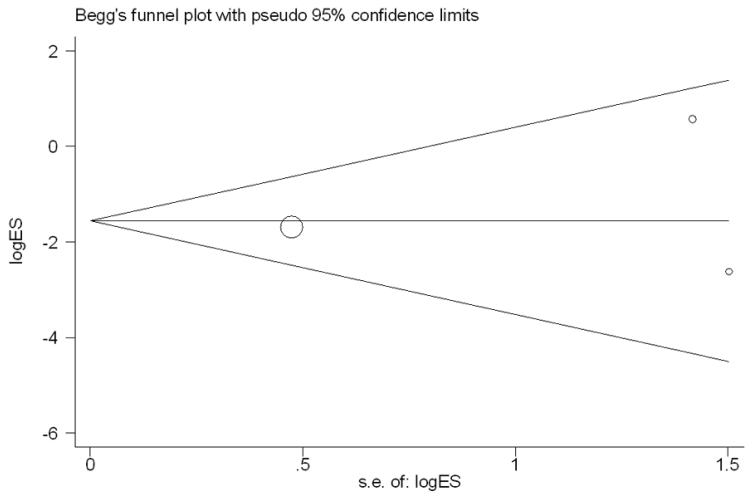

Figure 5. Begg's funnel plot for evaluation of publication bias in the included studies on the associations of the *IL6* rs1800796 COPD risk (CC vs GG).

ance within the protease-antiprotease system, and overloads the detoxification system [25]. Even though smoking is the most important risk factor for COPD, only a small proportion of smokers develop this disease. Therefore, additional factors such as environmental, genetic and epigenetic components, are thought to play important roles in the development of COPD [3]. The combination of these risk factors alters lung development and immunity and results in the predisposition for COPD. While environmental factors play crucial roles in the etiology of COPD, genetic factors also seem to have important effects in disease susceptibility and severity [26]. However, the fundamental molecular mechanisms that result in COPD development are not fully understood. Some studies have established that inflammatory cytokines play an important role in the pathogenesis of COPD and its progress [3]. In addition, many genetic factors were identified to play important roles in the etiology of COPD and its progression. Therefore, genetic marker-based risk assessment might offer new preventative and therapeutic strategies.

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-

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.

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Disclosure of conflict of interest

None.

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