Association of interleukin-1β -511C/T promoter polymorphism with COPD risk: a meta-analysis

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ABSTRACT. Studies examining the role of interleukin (IL)-1β -511C/T promoter polymorphism in the pathogenesis of chronic obstructive pulmonary disease (COPD) have shown inconsistent results. This meta-analysis was performed to assess the association between the IL-1β -511C/T promoter polymorphism and COPD susceptibility. Published case-control, cross-sectional, and cohort studies from Pubmed, Embase, and China National Knowledge Infrastructure databases were retrieved. Data were extracted and pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Twelve studies with 1692 cases and 2009 controls were included in this meta-analysis. Pooled effect size showed an overall but not significantly decreased risk of IL-1β -511 C/T with COPD susceptibility (OR = 0.89, 95%CI = 0.78-1.01) in a complete overdominant genetic model (TT+CC vs CT), indicating that homozygous individuals (CC and TT) have a decreased risk for COPD compared with heterozygotes.
(CT). In subgroup analysis by ethnicity, IL-1β -511C/T was significantly correlated with a decreased risk of COPD in Asians (OR = 0.73, 95% CI = 0.60-0.88, P = 0.001), but not in Caucasians (OR = 1.02, 95% CI = 0.83-1.24, P = 0.46), confirming a protective role of IL-1β -511C/T in COPD in Asians. Moreover, after excluding studies that included populations not in Hardy-Weinberg equilibrium, the pooled results were robust and no publication bias was observed. This meta-analysis suggests that the IL-1β -511C/T promoter polymorphism decreases the risk of COPD in Asians.

**Key words:** Chronic obstructive pulmonary disease; Interleukin-1β; Polymorphism

**INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is a worldwide disease characterized by persistent airflow limitation that is progressive and associated with an enhanced inflammatory response in the airways and lungs. Although the underlying mechanisms of COPD have not been fully elucidated, a previous study found that genetic predisposition strongly influences COPD development (Vestbo et al., 2013).

Interleukin (IL)-1β, a proinflammatory cytokine encoded by the IL1B gene on chromosome 2q14, plays an important role in COPD (Chung and Adcock, 2008). However, the IL1B gene was not found to be a candidate gene for COPD in recent genome-wide association studies (GWAS) (Soler Artigas et al., 2012). This may be because the most recent GWAS were performed in Northern European populations (Todd et al., 2011); some single-nucleotide polymorphisms may have been significant but did not reach the genome-wide significant level for the GWAS (Haq et al., 2010). Thus, the lack of GWAS results may not rule out the involvement of polymorphisms in the IL1B gene with COPD.

In the past decade, the relationship between polymorphisms in the IL1B gene and COPD risk has been well studied, particularly the -511 C/T promoter polymorphism in the IL1B gene, which may alter transcriptional activity (Wen et al., 2006). However, inconsistent results have been reported (Ishii et al., 2000; Asada et al., 2005; Hegab et al., 2005; Broekhuizen et al., 2005; Shi et al., 2006; Daniiko et al., 2007; Lee et al., 2008; Trajkov et al., 2009; Liu et al., 2012; Shukla et al., 2012; Sun et al., 2013; Issac et al., 2014), which may be because of differences in ethnicity and sample size between studies, resulting in lower statistical power. Meta-analysis may be useful for pooling independent statistical powers and thus achieving a quantitative understanding of the associations. Two meta-analyses examining the -511 C/T promoter polymorphism and COPD risk were conducted previously (Smolonska et al., 2009; Mei et al., 2013); however, different conclusions were reached, likely because of the different studies included and different genetic models used. In the present study, we conducted a meta-analysis including more studies with larger sample sizes and using the most appropriate genetic model for examining the relationship between IL-1β -511C/T promoter polymorphisms and COPD risk.

**MATERIAL AND METHODS**

**Search strategy**

A literature search was conducted of the Pubmed, Embase, and China National Knowl-
edge Infrastructure (http://www.cnki.net/) databases. The languages were limited to English and Chinese. The following search terms were utilized: interleukin 1beta or interleukin 1b or IL1beta or IL1b, and polymorphism or variant or single-nucleotide polymorphism or genotype or rs16944, and chronic obstructive pulmonary disease or COPD or emphysema.

Data extraction

Two independent reviewers collected the data according to inclusion and exclusion criteria. For inclusion in the meta-analysis, retrieved articles had to provide the number of cases and controls and number of individual genotypes in the cases and controls. Exclusion criteria in the meta-analysis were: 1) not a genetic study, 2) duplicated report, 3) no useful data reported, and 4) analysis of IL-1β polymorphisms other than -511C/T. Unpublished data were not considered. Disagreement was resolved by discussion before reaching a consensus. If more than 1 article was published by the same group using the same cases, the study with higher sample size was selected.

Statistical analyses

Categorical variables were analyzed based on the odds ratio (OR) with the 95% confidence interval (CI). CC, CT, and TT are the genotypes of IL-1β -511C/T. OR1, OR2, and OR3 were calculated as follows: OR1: TT vs CC; OR2: CT vs CC; OR3: TT vs CT. These pairwise differences (OR1, OR2, and OR3) were used to indicate the most appropriate genetic model as follows: if OR1 = OR2 ≠ 1 and OR3 = 1, a dominant model was suggested; if OR1 = OR3 ≠ 1 and OR2 = 1, a recessive model was suggested; if OR2 = 1/OR3 ≠ 1 and OR1 = 1, a complete overdominant model was suggested; if OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), a codominant model was suggested. Once the best genetic model was identified, this model was used to combine the 3 genotypes into 2 groups (except a codominant model) and to pool the results (Chen et al., 2013). Pooled ORs with 95% CIs were calculated and P < 0.05 considered to indicate statistical significance. Heterogeneity was evaluated using the Q test. Meta-analysis was conducted with the fixed-effects model when there was no heterogeneity (P ≥ 0.1); otherwise, the random-effects model was used. Subgroup analysis was performed by ethnicity to assess the effect of possible clinical heterogeneity on the summary ORs. Pearson’s χ² test was used to determine whether the observed frequencies of genotypes in controls conformed to Hardy-Weinberg equilibrium (HWE). Studies with controls that departed from HWE (P < 0.05) were subjected to sensitivity analysis in order to evaluate the consistency of the overall effect size. Funnel plots, as well as the Begg’s rank correlation test and Egger’s linear regression test, were used to determine potential publication bias, and P < 0.05 was considered significant publication bias. All analyses were conducted using Revman 5.0 (Oxford, UK) and Stata 11.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Studies included in the meta-analysis

Thirty-four studies were identified to be relevant to the search terms. After reviewing the titles, abstracts, and articles, 22 studies were excluded, and 12 articles with 13 case-control...
studies for -511C/T matched the inclusion criteria (Figure 1). Of the 10 articles included, 8 were published in English and 2 were published in Chinese. These studies were carried out in China, Japan, Korea, India, Egypt, Macedonia, Russia, and the Netherlands. The main features of the studies included in this meta-analysis are presented in Table 1.

**Quantitative synthesis**

To identify the most appropriate genetic model, OR1, OR2, and OR3 were calculated. The results were OR1 = 0.94, OR2 = 1.13, and OR3 = 0.83 for -511C/T, suggesting a complete overdominant genetic model (TT+CC vs CT). Pooled effect size showed an overall decrease, but not significant risk of -511 C/T with COPD susceptibility (OR = 0.89, 95%CI = 0.78-1.01, P = 0.08, fixed model, Figure 2). In subgroup analysis by ethnicity, the results indicated that IL-1β -511C/T was significantly correlated with COPD susceptibility in Asians (OR = 0.73, 95%CI = 0.60-0.88, P = 0.001, fixed model, Figure 2), but a weak positive correlation was observed in Caucasians (OR = 1.02, 95%CI = 0.83-1.24, P = 0.46, fixed model, Figure 2).

**Test of heterogeneity**

Significant heterogeneity was not observed among all studies for the TT+CC vs CT comparison for -511C/T (I² = 12%, P = 0.32). After stratification by ethnicity, no heterogeneity was observed among the studies in Asians (I² = 0%, P = 0.89) and Caucasians (I² = 0%, P = 0.64).

**Sensitivity analyses**

In the present meta-analysis, only 1 study (Liu et al., 2012) was not in HWE, which may have influenced the robustness of the present meta-analysis. After exclusion of this study, the pattern of the pooled effect size persisted, while overall heterogeneity was not significantly altered for -511C/T (I² = 19%, P = 0.25).

Figure 1. Flow diagram of search process.
Table 1. Main characteristics of studies included.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Race</th>
<th>Genotyping</th>
<th>Source of Control</th>
<th>COPD Total</th>
<th>Control Total</th>
<th>HWE (P)</th>
<th>Association (OR, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishii et al., 2000</td>
<td>Japan</td>
<td>Asian</td>
<td>PCR+RFLP</td>
<td>Age and smoking history matched male smokers</td>
<td>53 CC</td>
<td>14 CT</td>
<td>10 TT</td>
<td>0.42 (0.26-0.70)</td>
</tr>
<tr>
<td>Asada et al., 2005</td>
<td>Japan</td>
<td>Asian</td>
<td>PCR+RFLP</td>
<td>Healthy smokers</td>
<td>85 CC</td>
<td>26 CT</td>
<td>17 TT</td>
<td>0.59 (0.20-0.89)</td>
</tr>
<tr>
<td>Hegab et al., 2005</td>
<td>Japan</td>
<td>Asian</td>
<td>PCR+RFLP</td>
<td>Age and smoking history matched population</td>
<td>88 CC</td>
<td>20 CT</td>
<td>16 TT</td>
<td>0.80 (0.39-1.65)</td>
</tr>
<tr>
<td>Hegab et al., 2005</td>
<td>Egypt</td>
<td>Caucasian</td>
<td>PCR+RFLP</td>
<td>Age and smoking history matched population</td>
<td>105 CC</td>
<td>49 CT</td>
<td>45 TT</td>
<td>0.37 (0.21-0.65)</td>
</tr>
<tr>
<td>Broekhuizen et al., 2005</td>
<td>Netherlands</td>
<td>Caucasian</td>
<td>Double ARMS</td>
<td>Healthy population and renal and bone marrow donors</td>
<td>98 CC</td>
<td>54 CT</td>
<td>39 TT</td>
<td>0.76 (0.40-1.46)</td>
</tr>
<tr>
<td>Shi et al., 2006</td>
<td>China</td>
<td>Asian</td>
<td>PCR+RFLP</td>
<td>Healthy Smoker</td>
<td>88 CC</td>
<td>14 CT</td>
<td>48 TT</td>
<td>0.91 (0.57-1.44)</td>
</tr>
<tr>
<td>Danilko et al., 2007</td>
<td>Russia</td>
<td>Caucasian</td>
<td>PCR+RFLP</td>
<td>Healthy Population</td>
<td>312 CC</td>
<td>99 CT</td>
<td>165 TT</td>
<td>0.38 (0.20-0.73)</td>
</tr>
<tr>
<td>Lee et al., 2008</td>
<td>Korea</td>
<td>Asian</td>
<td>ABI Sequencer</td>
<td>Healthy Men</td>
<td>311 CC</td>
<td>62 CT</td>
<td>174 TT</td>
<td>0.17 (0.10-0.29)</td>
</tr>
<tr>
<td>Trajkov et al., 2009</td>
<td>Macedonia</td>
<td>Caucasian</td>
<td>PCR+SSP</td>
<td>Healthy Population</td>
<td>60 CC</td>
<td>30 CT</td>
<td>5 TT</td>
<td>0.15 (0.05-0.44)</td>
</tr>
<tr>
<td>Liu et al., 2012</td>
<td>China</td>
<td>Asian</td>
<td>PCR+RFLP</td>
<td>Healthy Population</td>
<td>162 CC</td>
<td>32 CT</td>
<td>28 TT</td>
<td>0.01 (0.00-0.17)</td>
</tr>
<tr>
<td>Shukla et al., 2012</td>
<td>India</td>
<td>Caucasian</td>
<td>PCR+RFLP</td>
<td>Healthy Population</td>
<td>204 CC</td>
<td>31 CT</td>
<td>93 TT</td>
<td>0.66 (0.42-1.04)</td>
</tr>
<tr>
<td>Sun et al., 2013</td>
<td>China</td>
<td>Asian</td>
<td>PCR+RFLP</td>
<td>Healthy Smokers</td>
<td>63 CC</td>
<td>12 CT</td>
<td>32 TT</td>
<td>0.97 (0.35-2.65)</td>
</tr>
<tr>
<td>Issac et al., 2014</td>
<td>Egypt</td>
<td>Caucasian</td>
<td>PCR+RFLP</td>
<td>Healthy Population</td>
<td>63 CC</td>
<td>9 CT</td>
<td>35 TT</td>
<td>0.99 (0.31-3.23)</td>
</tr>
</tbody>
</table>

ARMS = amplification refractory mutation system; HWE = Hardy-Weinberg equilibrium; NS = not significant; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; SSP = sequence-specific priming.
Publication bias

The funnel plots showed no significant asymmetry in this meta-analysis (Figure 3). Moreover, publication bias was not suggested by Begg’s rank correlation test (P = 0.200) and Egger’s linear regression test (P = 0.756).

Figure 2. Forest plots of OR with 95%CI for the association of IL-1β -511 C/T and COPD risk subanalyzed by ethnicity in TT +CC vs CT.

Figure 3. Begg’s funnel plot for evaluation of publication bias in the included studies on the association of IL-1β -511 C/T with COPD risk.
DISCUSSION

IL-1β, a proinflammatory cytokine, contributes to the pathogenesis of COPD. Recently, the association between the IL-1β -511 C/T promoter polymorphism and COPD risk has received increasing attention, but studies have shown inconsistent results. In the present study, the pooled effect size showed an overall, but not significant, decreased risk of -511 C/T with COPD susceptibility in a complete overdominant genetic model with no heterogeneity between studies, indicating that homozygous individuals have a decreased risk of COPD compared to heterozygotes. In subgroup analysis by ethnicity, IL-1β -511C/T was significantly correlated with a decreased risk of COPD in Asians, which is consistent with the results of Asada et al. (2005) in a Japanese population (OR = 0.58 for T vs C), although no significant association between the distribution of -511C/T alleles and genotypes with COPD and decrease in lung function (Joos et al., 2001) was reported in most previous studies. However, 3 studies from Korea and China suggested a positive role of the -511C/T T allele in COPD, but the positive association reported by Lee et al. (2008) did not persist in the subgroup of mild COPD (OR = 1 for TT vs CC); the relatively small sample size in the 2 Chinese studies had positive outcomes (Shi et al., 2006; Sun et al., 2013). Moreover, a weak positive association between -511C/T and COPD risk in Caucasians was observed in the present study, which was not as significant as that reported in the recent meta-analysis by Mei et al. (2013) (OR = 1.76, 95%CI = 1.22-2.54) based on only 2 individual studies (Hegab et al., 2005; Broekhuizen et al., 2005). Additional studies including larger Caucasian sample sizes in the present study with stronger statistical power may account for these different views.

Polymorphisms in the IL-1β gene may alter transcriptional activity as well as IL-1β protein level. However, although the contribution of the IL-1β -511C/T polymorphism to the IL-1β protein level has been observed in various diseases (Al-Tahhan et al., 2011; Olsson et al., 2012), there are no data regarding the correlation of genotypes of IL-1β -511C/T and IL-1β protein level in COPD. The haplotype of the IL-1β gene may have larger effects on IL-1β protein expression than does a single polymorphism (Chakravorty et al., 2006), but only 3 included studies conducted haplotype analysis of the IL-1β gene (Hegab et al., 2005; Lee et al., 2008; Trajkov et al., 2009), limiting further analysis.

Furthermore, after excluding the study by Liu et al. (2012) that was not in HWE, the pattern of the pooled effect size persisted, while the overall heterogeneity was not significantly altered. Publication bias was not observed in the present study, possibly because of the deliberate search strategy and data extraction methods used.

However, there were some limitations to this meta-analysis. First, large sample size studies were lacking (cases or controls in 8 included studies were lower than 100). Second, the pooled estimates were not adjusted by confounding factors (age, gender, smoking history, etc.). Third, haplotype data were unavailable and therefore we could not further analyze the relationship between haplotype and COPD risk.

In conclusion, although the pooled estimates should be interpreted with caution, our meta-analysis suggests that the IL-1β -511 C/T promoter polymorphism confers protection against COPD in Asians. However, larger sample size studies including more detailed data are warranted.

Conflicts of interest

The authors declare no conflict of interest.
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