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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 deceases 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; Danilko 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 ($P \geq 0.1$); 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 χ^2 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.

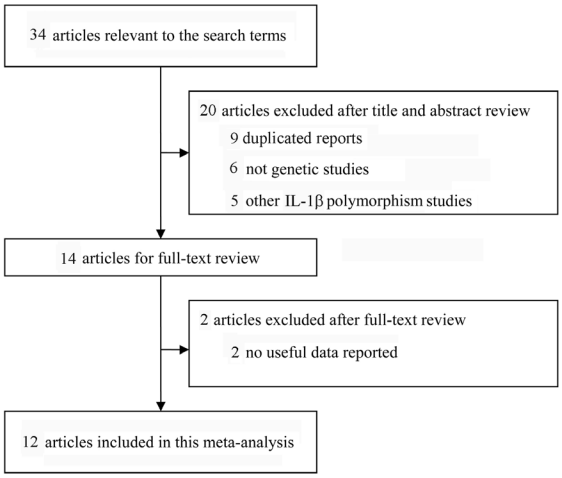

Figure 1. Flow diagram of search process.

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 (I^2 = 12%, P = 0.32). After stratification by ethnicity, no heterogeneity was observed among the studies in Asians (I^2 = 0%, P = 0.89) and Caucasians (I^2 = 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 (I^2 = 19%, P = 0.25).

Table 1. Main characteristics of studies included.

Reference	Country	Race	Genotyping	Source of Control	COPD				Control					Association (OR, 95%CI)
					Total	CC	CT	TT	Total	CC	CT	TT	HWE (P)	
Ishii et al., 2000	Japan	Asian	PCR+RFLP	Age and smoking history matched male smokers	53	14	29	10	65	16	27	22	0.4257	NS
Asada et al., 2005	Japan	Asian	PCR+RFLP	Healthy smokers	85	26	42	17	68	14	29	25	0.5922	0.43 (0.20-0.89) TT *vs* CT+CC
Hegab et al., 2005	Japan	Asian	PCR+RFLP	Age and smoking history matched population	88	20	52	16	60	21	31	8	0.8082	NS
Hegab et al., 2005	Egypt	Caucasian	PCR+RFLP	Age and smoking history matched population	105	49	45	11	71	26	29	16	0.3735	NS
Broekhuizen et al., 2005	Netherland	Caucasian	Double ARMS	Healthy population and renal and bone marrow donors	98	54	39	5	179	61	91	27	0.7641	Not described
Shi et al., 2006	China	Asian	PCR+RFLP	Healthy Smoker	88	14	48	26	96	36	44	16	0.9197	2.09 (1.03-4.24) for TT *vs* CC
Danilko et al., 2007	Russia	Caucasian	PCR+RFLP	Healthy Population	312	99	165	48	308	84	165	59	0.3868	NS
Lee et al., 2008	Korea	Asian	ABI Sequencer	Healthy Men	311	62	174	75	386	107	175	104	0.1869	1.67 (1.10-2.53) for CT *vs* CC
Trajkov et al., 2009	Macedonia	Caucasian	PCR+SSP	Healthy Population	60	30	25	5	301	143	118	40	0.1516	NS
Liu et al., 2012	China	Asian	PCR+RFLP	Healthy Population	162	32	102	28	162	36	99	27	0.0159	NS
Shukla et al., 2012	India	Caucasian	PCR+RFLP	Healthy Population	204	31	93	80	208	23	101	84	0.6658	NS
Sun et al., 2013	China	Asian	PCR+RFLP	Healthy Smokers	63	12	32	19	54	21	26	7	0.9721	4.75 (1.55-14.55) for TT *vs* CC
Issac et al., 2014	Egypt	Caucasian	PCR+RFLP	Healthy Population	63	9	35	19	51	13	26	12	0.9898	NS

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.

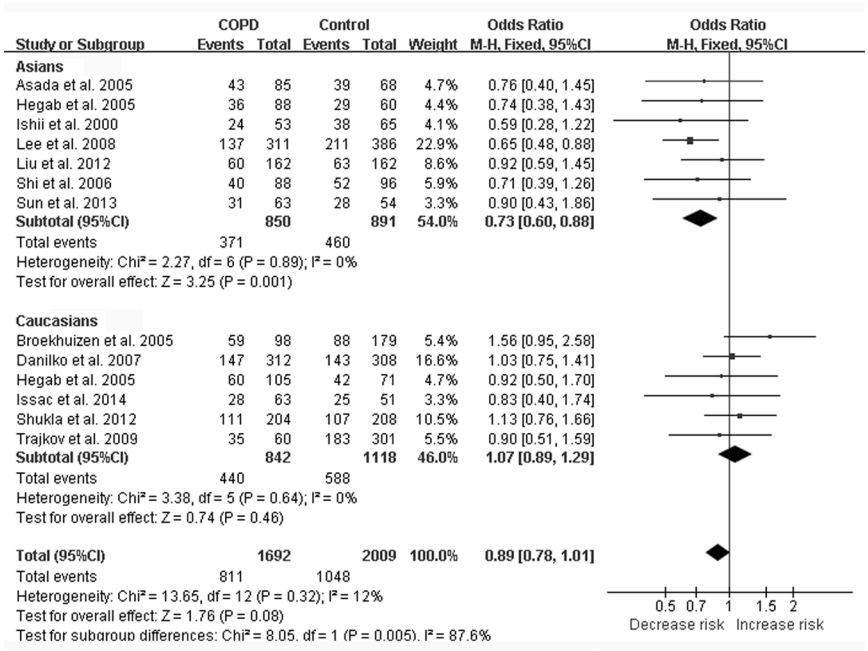

Figure 2. Forest plots of OR with 95%CI for the association of IL-1β -511 C/T and COPD risk subanalyzed by ethnicity in TT +CC *vs* CT.

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).

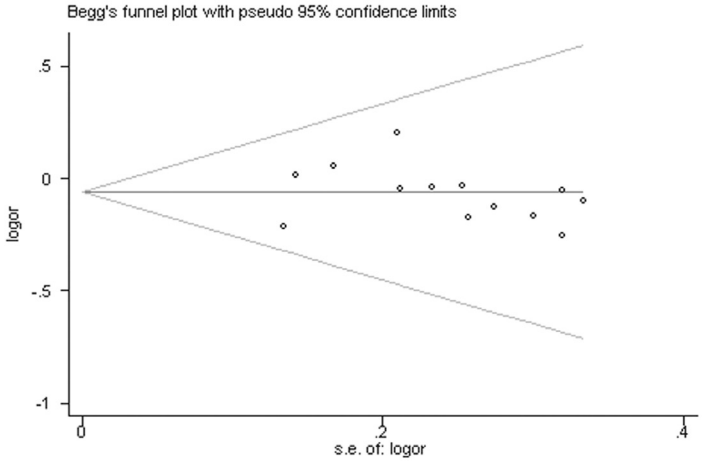

Figure 3. Begg's funnel plot for evaluation of publication bias in the included studies on the association of IL-1β -511 C/T with COPD risk.

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-β 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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