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Original Article

IL-1RA +2018 polymorphism and the susceptivity to pneumoconiosis: a Meta-analysis

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Abstract: Background and objectives: It has been reported that host genetic factors may play a crucial role in pneumoconiosis susceptibility. The present study aimed to study the association between IL-1RA +2018 polymorphism and pneumoconiosis by Meta-analysis. Materials and methods: Literatures addressing the association between *IL-1RA* gene polymorphisms and pneumoconiosis were selected from the PubMed, Cochrane Library, EMBASE, CNKI and Wanfang databases. Statistical analyses were performed by Review Manager Software 5.0.24 and STATA 11.0 software. Results: 5 case-control studies with a total of 609 pneumoconiosis patients and 579 controls were retrieved. Meta-analysis results showed significant association between *IL-1RA* +2018 polymorphism and pneumoconiosis risk. The C allele carriers have increased risk compared with the T allele carriers (*OR*=1.68, 95% *CI*: 1.25-2.27, *P*=0.0007). Individuals who carry TC or CC genotype have higher risk than those with TT homozygote (*OR*=1.79, 95% *CI*: 1.18, 2.71, *P*=0.006). In subgroup analysis by pneumoconiosis type, a significant association between *IL-1RA* +2018 polymorphism and pneumoconiosis risk were found in silicosis (C *vs* T: *OR*=2.12, 95% *CI*: 1.63-2.76, *P*=0.000; TC+CC *vs* TT: *OR*=1.79, 95% *CI*: 1.18-2.71, *P*=0.006) but not in coal workers' pneumoconiosis. Conclusion: This Meta-analysis suggests that *IL-1RA* +2018 polymorphism might be risk factors for pneumoconiosis, especially in silicosis.

Keywords: Pneumoconiosis, *IL-1RA*, polymorphism, Meta-analysis

Introduction

Pneumoconiosis, an interstitial lung disease prevalent among miners, is characterized by lung chronic inflammation that usually leads to pulmonary fibrotic changes and the prevalence of pneumoconiosis among examined miners with 15 or more years of coal-mining tenure has increased markedly since 2000 [1, 2]. Early pneumoconiosis can be asymptomatic, but advanced disease often leads to disability and premature death [3]. There are many reasons contributing to the pathogenesis of pneumoconiosis, including the workplace characteristics, host immune response and gene environment interactions [4, 5]. It is reported that not all the individuals who had a similar exposure history developed lung fibrosis, suggesting that host genetic factors may play a crucial role in pneumoconiosis susceptibility [6, 7].

In humans, the interleukin-1 (IL-1) family consists of three genes located on the long arm of chromosome 2 that code for IL-1a, IL-1b, and the IL-1 receptor antagonist (*IL-1RA*). Each of these genes possesses exonic SNPs that affect their expression, by increasing either message stability or the rate of mRNA synthesis. *IL-1RA*, an important anti-inflammatory cytokine, blocks the inflammatory effects of IL-1 by inhibiting the binding of IL-1 to IL-1 receptor, and is now shown to be involved in many human inflammatory diseases [8, 9]. In recent years, several eligible case-control studies were performed to identify the association of *IL-1RA* +2018 polymorphism with pneumoconiosis risk [10-14]. However, the results remain inconclusive and disputable because of the relatively small included populations, which compromised the power of the studies. Meta-analysis is a powerful tool for analyzing cumulative data from studies where individual sample sizes are small and the statistical power is low [15]. Thus, a Meta-analysis based on a total of five independent studies was performed, which may provide a holistic and comprehensive understanding of the rela-

Table 1. Characteristics of studies included in the Meta-analysis

First author	Year	Country	Pneumoconiosis type	Controls	Case			Control			HWE
					TT	TC	CC	TT	TC	CC	
Berran Y [8]	2001	America	Silicosis	Healthy coal workers	149	102	23	113	38	6	0.229
Fan XY [9]	2006	China	CWP	Healthy coal workers	57	38	30	60	43	22	0.007
Ilker A [10]	2011	Turkey	CWP	Healthy coal workers	25	29	13	35	46	11	0.484
Wang DJ [11]	2006	China	Silicosis	Healthy coal workers	38	32	5	100	33	4	0.531
Wang YW [12]	2012	China	Silicosis	Healthy coal workers	35	29	4	52	15	1	0.945

Abbreviations: CWP=coal workers' pneumoconiosis; HWE=Hardy-Weinberg equilibrium.

tionship between *IL-1RA* +2018 polymorphism and the risk of pneumoconiosis.

Materials and methods

Publication search

The electronic databases PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI) and Wanfang database were searched. The Mesh terms were as follows: "pneumoconiosis or silicosis or asbestosis or lung fibrosis" in combination with "polymorphism or variant or mutation" and in combination with "interleukin-1 or IL-1". The included articles were published from January 1980 to January 2013. If studies had partly overlapped subjects, the one with a larger sample size was selected. The languages were limited to English and Chinese.

Inclusion and exclusion criteria

The studies included had to be in accordance with the following major criteria: 1) Case-control studies, 2) including only cases with definitive diagnosis of pneumoconiosis, and 3) evaluating *IL-1RA* +2018 polymorphism and pneumoconiosis. Accordingly, the following exclusion criteria were used: 1) abstracts, reviews and duplication of literatures; 2) non-case-control studies; 3) genotype frequency not reported.

Data extraction

Two reviewers extracted all data independently according to the inclusion and exclusion criteria, and reached a consensus on all items. In case of disagreement, a third author would assess these articles. The collected data included the first author's name, year of publication, country, ethnicity, genotyping methods, total number of cases and controls, genotype distributions in cases and controls.

Statistical analysis

The association between *IL-1RA* +2018 polymorphism and pneumoconiosis risk was measured by the odds ratio (*OR*) with 95% confidence interval (*CI*). The significance of the pooled *OR* was determined by a Z test and $P < 0.05$ was considered as statistically significant. The inter-study heterogeneity was calculated by the Chi-square-based Q-test and the inconsistency index I^2. When a significant Q-test ($P < 0.1$ or $I^2 > 50\%$) indicated heterogeneity among studies, the random-effect model was used to calculate the pooled *OR*; otherwise, the fixed-effect model was used. Two comparisons were performed: allelic contrast (C *vs* T), and dominant genetic model (TC+CC *vs* TT). The publication bias was tested by Begg's funnel plots. Funnel plot symmetry was further assessed by using Egger's linear regression method [16] and the significance was set at $P < 0.05$. Pearson χ^2 test was used to test whether genotype frequencies in control groups were in Hardy-Weinberg equilibrium (HWE). Review Manager Software 5.0.24 (Cochrane Collaboration, Oxford, UK) and STATA 11.0 software were used to perform all statistical analyses.

Results

Eligible studies

5 case-control studies published between with met the inclusion criteria. Among them, three studies originated from China [11, 13, 14], one from America [10] and one from Turkey [12]. A total of 609 pneumoconiosis patients and 579 controls were included in the Meta-analysis. Genotype distributions in the control groups in one study [11] did not conform to the HWE (P=0.007), which indicated the presence of genotyping errors and/or population stratification. The characteristics of each selected study were listed in **Table 1**.

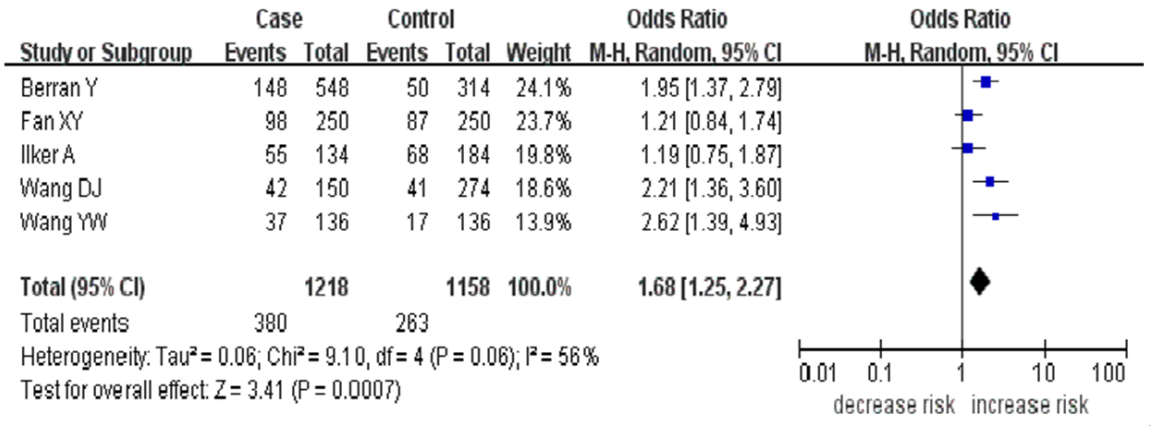

Figure 1. Meta-analysis of the association between IL-1RA +2018 polymorphism and pneumoconiosis susceptibility (C *vs* T).

Table 2. Meta-analysis of the association between *IL-1RA* +2018 polymorphism and pneumoconiosis risk

Comparison	N	Method	OR(95%CI)	P_h	I^2 (%)	P
C vs. T						
Total	5	Random	1.68 (1.25, 2.27)	0.06	56	0.0007
Silicosis	3	Fixed	2.12 (1.63-2.76)	0.72	0	0.000
CWP	2	Fixed	1.20 (0.90-1.59)	0.95	0	0.21
TC+CC vs. TT						
Total	5	Random	1.79 (1.18, 2.71)	0.03	63	0.006
Silicosis	3	Fixed	2.42 (1.77-3.30)	0.68	0	0.000
CWP	2	Fixed	1.07 (0.72-1.60)	0.88	0	0.72

Abbreviations: 95% CI=95% confidence interval; P_h=*P* value of the Q-test for heterogeneity test.

Pooled analyses

Meta-analysis results showed significant association between *IL-1RA* +2018 polymorphism and the risk of pneumoconiosis in terms of the frequency of allele comparison (C *vs* T: *OR*=1.68, 95% *CI*: 1.25-2.27, *P*=0.0007) (**Figure 1**). Similarly, analysis of the dominant model also indicate a significant association (TC+CC *vs* TT: *OR*=1.79, 95% *CI*: 1.18-2.71, *P*=0.006) (**Figure 2**). In the subgroup study by the type of pneumoconiosis, the significant association was found between *IL-1RA* +2018 polymorphism and increased silicosis risk (C *vs* T: *OR*=2.12, 95% *CI*: 1.63-2.76, *P*=0.000; TC+CC *vs* TT: *OR*=2.42, 95% *CI*: 1.77-3.30, *P*=0.000), while no association was observed between *IL-1RA* +2018 polymorphism and the risk of coal workers' pneumoconiosis (C *vs* T: *OR*=1.20, 95% *CI*: 0.90-1.59, *P*=0.21; TC+CC *vs* TT: *OR*=1.07, 95% *CI*: 0.72-1.60, *P*=0.72). A summary of main results of the Meta-analysis is shown in **Table 2**.

Publication bias

The publication bias of the studies was assessed by Begg's funnel plots and Egger's linear regression test. The shapes of the funnel plots didn't reveal asymmetry. No statistically significant difference was shown in the Egger's test, which indicated a lack of publication bias for both genetic models (all *P* values < 0.05).

Sensitivity analysis

Sensitivity analysis was performed to evaluate the influence of any single study on the overall *OR* by sequentially excluding each case-control study. The results showed that there was no individual study qualitatively affecting the pooled *OR*, suggesting the stability of this meta-analysis.

Discussion

Pneumoconiosis is one of the most common occupational diseases worldwide and the prevalence of pneumoconiosis has increased markedly since 2000 [2]. It has been reported that heredity plays an important role in the etiology and pathogenesis of pneumoconiosis. In recent years, an increasing number of molecular genetic studies have focused on the association between *IL-1RA* +2018 polymorphism and

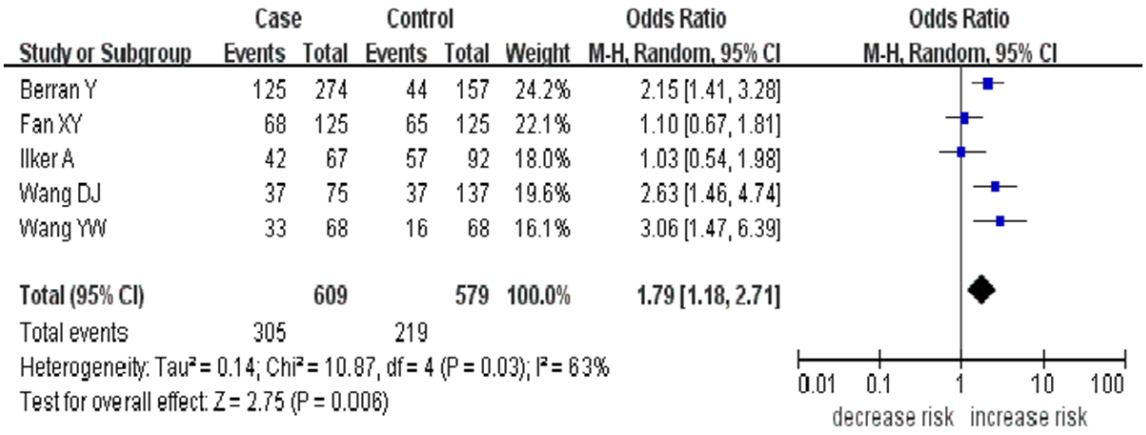

Figure 2. Meta-analysis of the association between IL-1RA +2018 polymorphism and pneumoconiosis susceptibility (TC+CC *vs* TT).

pneumoconiosis risk, but the results are still controversial. As Meta-analysis is an essential tool for accurately and reliably summarizing evidence, we performed this Meta-analysis to comprehensively assess these associations.

In the current study, we analyzed five case-control studies with a total of 609 pneumoconiosis patients and 579 controls. Significant association was found between *IL-1RA* +2018 polymorphism and the risk of pneumoconiosis (C *vs* T: *OR*=1.68, 95% *CI*: 1.25-2.27, *P*=0.0007; TC+CC *vs* TT: *OR*=1.79, 95% *CI*: 1.18-2.71, *P*=0.006), suggesting that the C allele carriers may have 68% higher risk of pneumoconiosis than those with T allele, while individuals who carry TC or CC genotype may have a 79% increased risk compared with the TT homozygote carriers. In the subgroup analysis by the type of pneumoconiosis, significant associations were only found in silicosis population but not in coal workers' pneumoconiosis. The heterogeneity of disease might account for these differences in genetic susceptibility. However, further studies on coal workers' pneumoconiosis and other types of pneumoconiosis are needed to validate our results.

Statistically significant inter-study heterogeneity was found in our study. There are several reasons that may explain it. First, different populations may have different genetic backgrounds, which contribute to genetic heterogeneity. Secondly, the environmental factors, which might affect the genetic susceptibility, were not investigated in most case-control studies. Thirdly, homogeneity in either the case and control groups was uncertain. Ideally, all cases and controls in this Meta-analysis should be matched for age, sex and environmental exposures. However, these issues could not all be explained precisely because of insufficient clinical information for individual person. Thus, in the future, more studies should be performed to assess these results.

As most Meta-analyses, certain potential limitations exist in our study. First, only published studies were included in this Meta-analysis, unpublished data and ongoing studies were not sought, which may bring some bias into our results, although our statistical tests did not show this. Secondly, lack of the original data of the reviewed studies limited our further investigation of potential gene-gene and gene-environment interactions, because the expression of one gene may be enhanced or hindered by another gene or environmental factors [17]. In addition, to keep higher statistical power, we did not do subgroup analyses to address the sources of heterogeneity existing among studies because of the limited numbers of the studies included. A single study might have low power to detect the overall effects.

Despite these limitations, our study is the first comprehensive Meta-analysis to date to have assessed the relationship between *IL-1RA* +2018 polymorphism and pneumoconiosis risk. Our findings suggest that variants in *IL-1RA* may be important for susceptibility to pneumoconiosis. These results might be helpful for pre-

employment medical examination, screening of susceptible populations and improving quality of working life in the future.

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Disclosure of conflict of interest

None of the authors has conflicts of interest to report with regard to this manuscript.

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