

## Original Article

# Associations between transforming growth factor- $\beta$ 1 gene -509C/T and +915G/C polymorphisms and pneumoconiosis: a meta-analysis

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**Abstract:** Transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) gene -509C/T and +915G/C polymorphisms has been reported to be associated with pneumoconiosis susceptibility. However, the relevant study results are still inconsistent. To further evaluate the impact of the TGF- $\beta$ 1 -509C/T and +915G/C polymorphisms on pneumoconiosis, we performed this meta-analysis. We performed a meta-analysis to analyze the association after searching the relevant studies through China National Knowledge Infrastructure (CNKI), PubMed and EMBASE databases. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the strength of the association. Totally, 10 studies involving 2,052 cases and 1,902 controls were retrieved in this meta-analysis. The results showed evidence for significant association between -509C/T, +915G/C polymorphisms and pneumoconiosis susceptibility. However, for -509C/T polymorphism, similar results were only found in coal workers' pneumoconiosis; +915G/C polymorphism merely increase the silicosis risk. This meta-analysis suggests that the TGF- $\beta$ 1 -509C/T and +915G/C polymorphisms are associated with pneumoconiosis. But they exerted different effects on different types of pneumoconiosis.

**Keywords:** Transforming growth factor- $\beta$ 1, -509C/T, +915G/C, meta-analysis, polymorphism

## Introduction

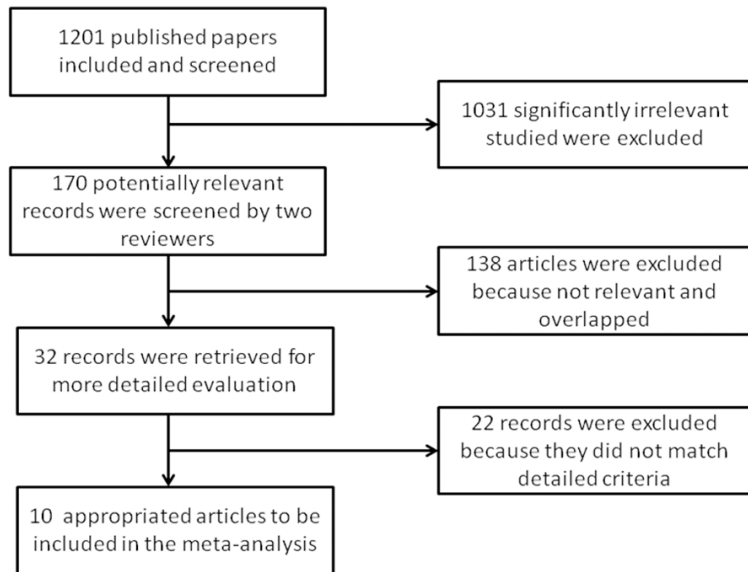
Pneumoconiosis is a fibrotic lung disease produced by the inhalation and deposition of microscopic crystalline silica particles and a variety of dust of other categories [1]. It is one of the most important occupational diseases worldwide, which is considered a major public health problem in some developing countries such as India, South African and China [2, 3]. China has the largest number of pneumoconiosis patients with more than 6000 deaths every year [4].

Although individuals may be exposed to similar levels of coal dust in the same time, only some of them develop lung fibrosis, suggesting that genetic predisposition may influence individual susceptibility to the development of lung fibrosis. Therefore, interindividual differences might play a crucial role in outcome and severity of pneumoconiosis.

The pathophysiology of pneumoconiosis has not been fully understood. Transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) plays an essential part in the disease process among several factors [5-7]. TGF- $\beta$ 1 is an important multifunctional cytokine that modulates myriad cellular and tissue processes, including cell growth, differentiation, apoptosis and inflammation [8]. TGF $\beta$ 1 is also known to promote the pathogenesis of lung fibrosis by suppressing the immune system and inducing extracellular matrix components; thus, overproduction of TGF- $\beta$ 1 contributes to the influx and activation of inflammatory cells, transdifferentiation of epithelium to mesenchyme, and influx of fibroblasts and their subsequent elaboration of extracellular matrix resulting in excessive deposition of scar tissue and fibrosis [9].

Until now, several locations have been studied to assess the association of TGF- $\beta$ 1 and pneumoconiosis in different populations [10-12].

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**Figure 1.** Study flow diagram of search strategy.

Among these polymorphisms, -509C/T (rs1800469) and +915G/C (rs1800872) polymorphisms were widely studied. However, the results were often controversial and ambiguous. Therefore, in order to summarize and clarify the published data, we designed this meta-analysis, using all eligible case-control studies to evaluate the genetic risk of TGF- $\beta$ 1 gene polymorphisms for pneumoconiosis. To our knowledge, this is the first meta-analysis evaluating the association between transforming growth factor- $\beta$ 1 gene -509C/T and +915G/C polymorphisms and pneumoconiosis.

### Materials and methods

#### Literature search

Relevant eligible studies were searched to investigate the association of -509C/T and +915G/C polymorphisms with the risk of pneumoconiosis. Two authors retrieved China National Knowledge Infrastructure (CNKI), PubMed and EMBASE databases independently to identify valuable papers published up to November 2015. The following key words and combinations of them were utilized: “transforming growth factor- $\beta$ 1”, “TGF- $\beta$ 1”, “-509C/T, 509”, “+915G/C, 915”, “rs1800469”, “rs1800471”, “polymorphism\*”, “variation, variant, mutation” “genetic\*”, “pneumoconiosis”, “silicosis”, “CWP”, “coal workers’ pneumoconiosis”. In addition to that, we also manually screened

the reference lists of all cited articles and relevant reviews and meta-analysis to confirm other potentially available studies.

#### Inclusion and exclusion criteria

For the meta-analysis, studies were included if they met the following criteria: (1) case-control studies that had original data to assess quantitatively the relationship between -509C/T and +915G/C polymorphisms and pneumoconiosis; (2) cases and controls were eligible regardless of country, ethnicity, types of pneumoconiosis and age; (3) providing sufficient data for calculation of odds ratio (OR) and 95% confidence interval (CI).

While for the exclusion criteria, we provided as follows: (1) not for -509C/T and +915G/C polymorphisms research; (2) studies containing overlapping data; (3) articles but not case-control study; (4) studies that investigated -509C/T and +915G/C variants as makers for response to therapy; (6) studies in which the number of genotypes or alleles were not offered.

#### Data extraction

Two investigators strictly extracted relevant information from all definite papers according to the inclusion and exclusion criteria. Discrepancy was resolved by consensus. The following parameters were extracted from each study: first author’s surname, year of publication, country, ethnicity, type of pneumoconiosis, the number of sample size and genotype distribution information. The accuracy of information was verified by comparing data drawn from papers. If different studies include the same population, we only included the most valuable study in this meta-analysis.

#### Statistical analysis

The data from these papers were used to investigate the association between -509C/T and +915G/C polymorphisms with the risk of pneu-

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**Table 1.** Characteristics of relevant studies included in meta-analysis

Position	First author	Year	Country	Ethnicity	type	Sample size	Genotype distribution (case/control)			P for HWE
							C/C	C/T	T/T	
-509C/T (rs1800469)	Yao [18]	2006	China	Han	CWP	220	20/52	56/40	34/18	0.714
	Fan [19]	2007	China	Han	Both	234	26/43	51/48	40/26	0.211
	Wu [20]	2008	China	Han	Silicosis	294	54/26	83/51	46/34	0.218
	Yucesoy [21]	2008	USA	Caucasian	CWP	608	143/170	109/121	31/34	0.145
	Li [22]	2009	China	Han	Silicosis	154	13/27	36/30	28/20	0.806
	Yang [24]	2010	China	Han	CWP	220	20/59	57/34	33/17	0.592
	Li [23]	2010	China	Han	CWP	80	12/16	15/18	13/6	0.115
	Qian [10]	2010	China	Han	CWP	1032	114/102	273/302	121/122	0.091
	Zhou [25]	2012	China	Zhuang	Silicosis	109	12/24	12/19	27/15	0.001
+915G/C (rs1800872)	Fan [19]	2007	China	Han	Both	234	83/97	34/20	0/0	0.066
	Wu [20]	2008	China	Han	Silicosis	294	181/111	2/0	0/0	0.941
	Li [22]	2009	China	Han	Silicosis	154	51/63	26/14	0/0	0.075
	Helmig [26]	2009	Germany	Caucasian	Silicosis	239	132/73	24/10	0/0	0.298
	Li [23]	2010	China	Han	CWP	80	32/34	8/6	0/0	0.482

HWE, Hardy-Weinberg equilibrium.

moconiosis. The strength of the association was evaluated by calculating the odds ratios (ORs) and 95% confidence intervals (CIs). The statistical significance of the pooled OR was evaluated by the Z test. Hardy-Weinberg equilibrium (HWE) in the control group for each included studies was estimated by a goodness of fit  $\chi^2$  test;  $P > 0.05$  was considered disequilibrium. We calculated the pooled ORs for allele comparison model (T vs. C; C vs. G), homozygote model (TT vs. CC; CC vs. GG), heterozygote model (CT vs. CC; GC vs. GG), dominant model [(CT+CC) vs. TT; (GC+GG) vs. CC] and recessive model [TT vs. (CC+CT); CC vs. (GG+GC)], respectively. Heterogeneity was evaluated with the chi-square-based Q test. In addition to that, heterogeneity was also assessed by the  $I^2$  statistic ( $I^2=0-25\%$ : no heterogeneity;  $I^2=25-50\%$ : moderate heterogeneity;  $I^2=50-75\%$ : large heterogeneity;  $I^2=75-100\%$ : extreme heterogeneity) [13]. When the heterogeneity was obvious, we will use the random-effect model to calculate the pooled OR [14], otherwise the fix-effect model was used [15]. Moreover, we also performed the stratified analysis by types of pneumoconiosis. In order to assess the stability of the results, sensitivity analyses were performed by deleting one study successively at a time to evaluate it. We performed funnel plots to assess the potential publication bias. And the publication bias was also explored using Begg's [16] and Egger's [17] tests ( $P < 0.01$  indi-

cates a significant publication bias). All analyses for this meta-analysis were performed with STATA Version 12.0 (Stata Corporation, College Station, TX).

### Results

#### *Characteristics of included studies*

The detailed selection process of this literature is given in **Figure 1**. According to our strategy, 1201 published papers were included and screened. Of these, 1191 articles were excluded based on our detailed criteria. Eventually, a total of 10 eligible studies met the inclusion criteria including 2,052 cases and 1,902 controls [10, 18-26]. Of the 10 papers, there were 9 studies investigated the association between TGF-β1 gene -509C/T polymorphism and pneumoconiosis and 5 papers involved TGF-β1 gene +915G/C polymorphism. For -509C/T polymorphism, 5 studies performed in coal workers' pneumoconiosis and 3 in silicosis population. For +915G/C polymorphism, 1 research recruited coal workers and 3 recruited silicosis population. The characteristics of the selected studies in the current meta-analysis are summarized in **Table 1**.

#### *Quantitative synthesis*

For TGF-β1 gene -509C/T polymorphism, 9 papers were combined [10, 18-25]. There was

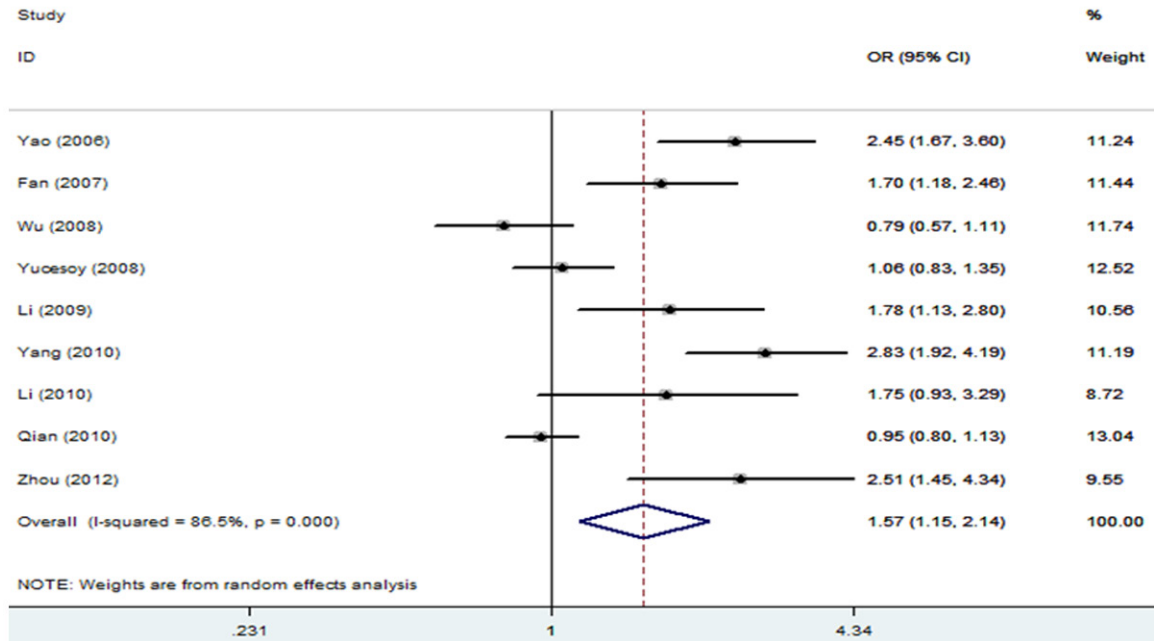
## Associations between TGF-β1 polymorphisms and pneumoconiosis

**Table 2.** Overall and subgroup meta-analysis of the association between -509C/T and +915G/C polymorphisms and pneumoconiosis under genetic models

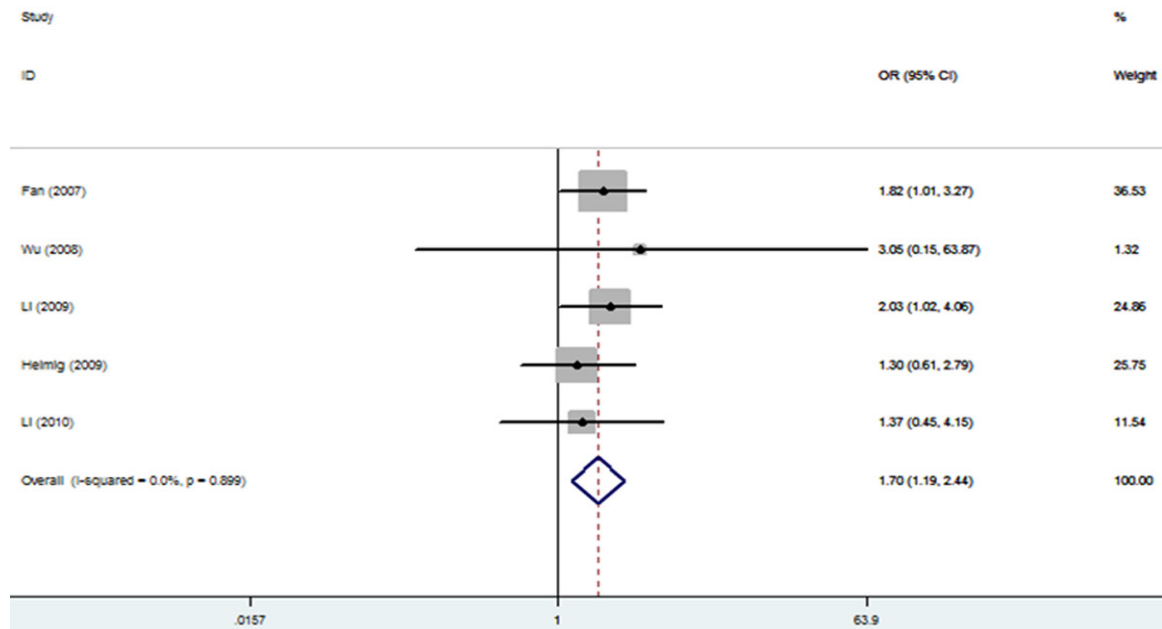
Groups	N	Allelic		Homozygout		Heterozygous		Dominant		Recessive	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
rs1800469	9	1.57 (1.15, 2.14)	0.000	2.11 (1.23, 3.63)	0.000	1.17 (0.97, 1.42)	0.484	1.55 (1.13, 2.13)	0.006	1.80 (1.13, 2.86)	0.000
CWP	5	1.61 (1.03, 2.51)	0.000	2.26 (1.01, 5.06)	0.000	1.15 (0.91, 1.44)	0.677	1.55 (1.02, 2.36)	0.029	1.91 (0.95, 3.81)	0.000
Silicosis	3	1.49 (0.73, 3.02)	0.000	1.82 (0.58, 5.75)	0.003	1.28 (0.66, 2.48)	0.095	1.52 (0.66, 3.49)	0.009	1.58 (0.65, 3.85)	0.008
rs1800872	5	1.70 (1.19, 2.44)	0.899	NA	NA	NA	NA	NA	NA	1.82 (1.24, 2.68)	0.853
CWP	1	1.37 (0.45, 4.15)	NA	NA	NA	NA	NA	NA	NA	1.42 (0.44, 4.53)	NA
Silicosis	3	1.69 (1.02, 2.81)	0.647	NA	NA	NA	NA	NA	NA	1.81 (1.06, 3.09)	0.579

N: total number of studies involved in the analysis; NA: the data were not available.

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**Figure 2.** Forest plots for TGF-β1 gene -509C/T polymorphism and pneumoconiosis susceptibility in allelic model.

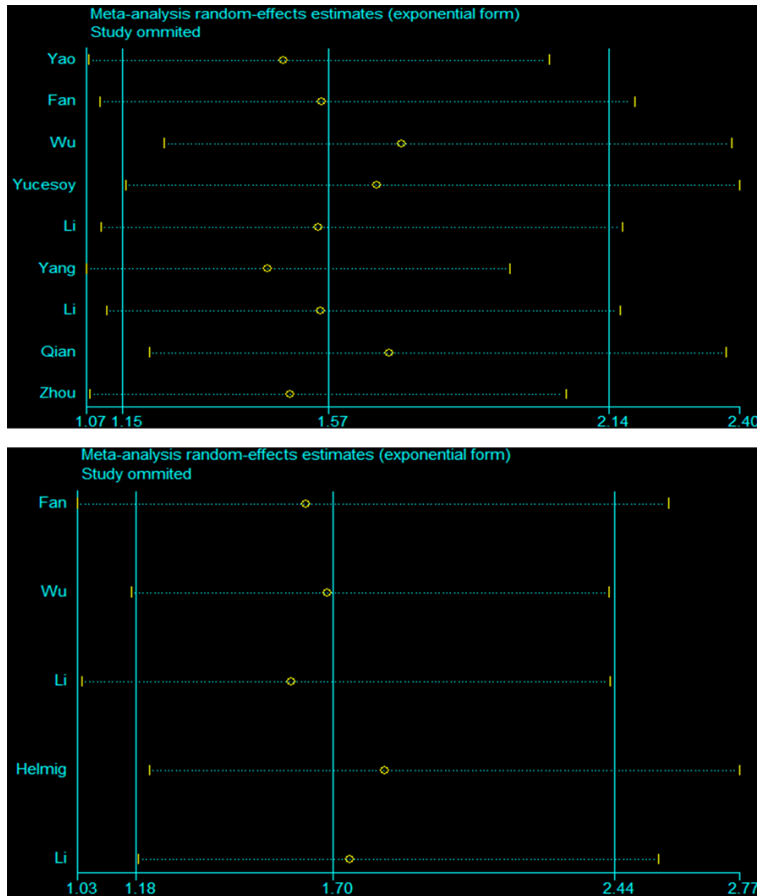


**Figure 3.** Forest plots for TGF-β1 gene +915G/C polymorphism and pneumoconiosis susceptibility in allelic model.

significant association existed between this polymorphism and pneumoconiosis susceptibility in allele model, homozygote model and dominant model (for T vs. C: OR=1.57, 95% CI=1.15-2.14, P=0.000; for TT vs. CC: OR=2.11, 95% CI=1.23-3.63, P=0.000 ; for (CT+CC) vs. TT: OR=1.55, 95% CI=1.13-2.13, P=0.006) but

not in heterozygote model and recessive model (for CT vs. CC: OR=1.17, 95% CI=0.97-1.42, P=0.484; for TT vs. (CC+CT): OR=1.80, 95% CI=1.13-2.86, P=0.000). In the subgroup analysis based on types of pneumoconiosis, similar result was found in coal workers' pneumoconiosis. However, we did not find any association

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**Figure 4.** The results of one-way sensitivity analysis for -509C/T and +915G/C polymorphisms.

between -509C/T polymorphism and silicosis. The main results are shown in **Table 2** and **Figure 2**, respectively.

For TGF-β1 gene +915G/C polymorphism, 5 studies were combined [19, 20, 22, 23, 26]. Significantly increased risk for +915G/C polymorphism and pneumoconiosis was found in allele model and recessive model (for C vs. G: OR=1.70, 95% CI=1.19-2.44,  $P=0.899$ ; CC vs. (GG+GC): OR=1.82, 95% CI=1.24-2.68,  $P=0.853$ ). In subgroup analysis based on pneumoconiosis types, the results showed evidence for significant association among silicosis population but not in coal workers' pneumoconiosis. The main results are shown in **Table 2** and **Figure 3**, respectively.

### Sensitivity analysis and publication bias

In order to evaluate the stability of the pooled results, we further conducted sensitivity analy-

sis by sequentially excluding individual studies. For TGF-β1 gene -509C/T and +915G/C polymorphisms, the pooled ORs were not altered significantly, suggesting that our statistical results are robust (**Figure 4**).

Both Begg's and Egger's test were performed to assess the publication bias of the literatures. The shape of funnel plots did not show any obvious asymmetry ( $P>0.01$ ). Our statistical data indicated similar results: (-509C/T: Egger's test  $P=0.024$ ; Begg's test  $P=0.175$ ; +915G/C: Egger's test  $P=0.938$ ; Begg's test  $P=1.000$ ) (**Figure 5**).

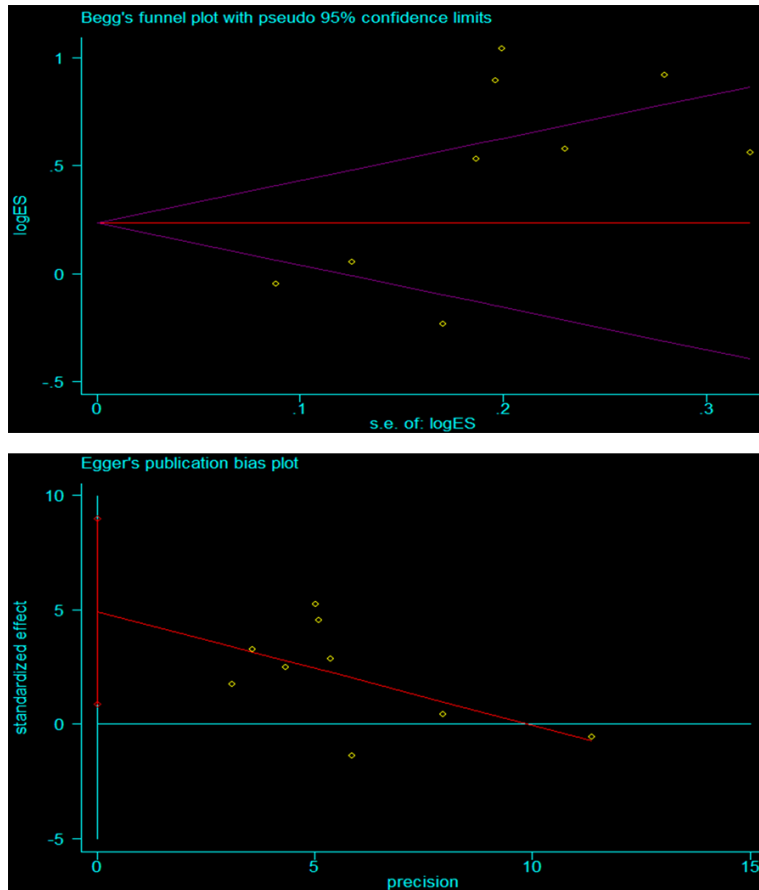
### Discussion

Pneumoconiosis continues to be a common occupational disease, despite being preventable by dust control measures. Identification of new risk factors for pneumoconiosis other than the known environmental factors would improve recognition of pati-

ents at risk and could help to determine an effective prophylaxis. In recent years, an increasing number of molecular genetic studies have focused on the association between TGF-β1 gene -509C/T (rs1800469) and +915G/C (rs1800872) polymorphisms and pneumoconiosis risk, but the results are still controversial.

Several other studies demonstrated that TGF-β1 gene -509C/T and +915G/C were associated with an increased risk of pneumoconiosis [18, 19, 22, 24, 25]; However Wu and Li found that TGF-β1 gene -509C/T and +915G/C polymorphisms were not risk factors for pneumoconiosis [20, 23]. Moreover, the sample size in each of the published studies is usually small and underpowered and thus unable to provide a definite answer even in the case where a true association exists. Therefore, we designed this meta-analysis to derive a more precise association between TGF-β1 gene -509 and +915

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**Figure 5.** Begg's and Egger's test was held to detect potential publication bias for -509C/T and +915G/C polymorphisms.

alleles and pneumoconiosis risk by collecting and sorting the previous published studies.

TGF- $\beta$ 1 has been found to play a key role in the regulation of proliferation and differentiation of various cell types. It plays an important role in the development of lung fibrosis, and increased expression of TGF- $\beta$ 1 occurred in lung tissue in patients with lung fibrosis and animal models of pulmonary fibrosis [27-29]. Several functional polymorphisms have been described in the TGF- $\beta$ 1 gene that may control the level of TGF- $\beta$ 1 in the serum. The plasma concentrations of TGF- $\beta$ 1 were about twice as high in homozygous individuals of the T allele compared with the concentration for homozygous individual for C allele at position -509C/T in the TGF- $\beta$ 1 promoter region [30]. In the signaling sequence of TGF- $\beta$ 1 gene, +915G/C in the first exon has been described with a polymorphism results in an amino acid substitution from arginine to proline at codon 25. Alteration within the signaling

sequence may affect the production or secretion of the protein or may cause an altered intracellular transport of the protein. Award et al. reported that individuals homozygous for Arg(GG) at codon 25 produced significantly more total TGF- $\beta$ 1 in vitro than heterozygous Arg-25Pro(GC) subjects [31].

Grainger DJ [30] noted the potential role of TGF- $\beta$ 1 genetic variants in the pathogenesis of pneumoconiosis by demonstrating that the TGF- $\beta$ 1 gene -509 and +915 sites polymorphism influenced the concentration of TGF- $\beta$ 1 in serum, but was not different among stages and exposure period of pneumoconiosis. In contrast, Wu et al [20] did not find an association between the TGF- $\beta$ 1 gene polymorphisms at positions -509C/T (rs1800469) and +915G/C (rs1800471) and pneumoconiosis risk in Chinese iron miners.

On the whole, the current meta-analysis suggests a significant relationship between TGF- $\beta$ 1 gene rs1800469 polymorphisms and pneumoconiosis risk under the allele model, homozygote model and dominant model (for T vs. C: OR=1.57, 95% CI=1.15-2.14, P=0.000; for TT vs. CC: OR=2.11, 95% CI=1.23-3.63, P=0.000; for (CT+CC) vs. TT: OR=1.55, 95% CI=1.13-2.13, P=0.006) but not in heterozygote model and recessive model (for CT vs. CC: OR=1.17, 95% CI=0.97-1.42, P=0.484; for TT vs. (CC+CT): OR=1.80, 95% CI=1.13-2.86, P=0.000). In the subgroup analysis based on types of pneumoconiosis, similar result was found in coal workers' pneumoconiosis. However, we did not find any association between -509C/T polymorphism and silicosis. For rs1800471, significantly increased risk for +915G/C polymorphism and pneumoconiosis was found in allele model and recessive model (for C vs. G: OR=1.70, 95% CI=1.19-2.44, P=0.899; CC vs. (GG+GC): OR=1.82, 95% CI=1.24-2.68, P=0.853). In sub-

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group analysis based on pneumoconiosis types, the results showed evidence for significant association among silicosis population but not in coal workers' pneumoconiosis. Thereby, the current study indicates TGF- $\beta$ 1 gene rs1800469 and rs1800471 polymorphisms might increase pneumoconiosis risk.

We must admit that some limitations should be taken into account when interpreting our research, although meta-analyses have been made to resolve the matter. First, the sample size of the published studies was not enough to confirm an adequate large-scale research on the relationship between -509C/T (rs1800469) and +915G/C (rs1800471) polymorphisms and pneumoconiosis. Second, most data of included papers were from Chinese population. There was only two from Caucasian and none from other population like Africans so that we cannot make some relative precise conclusions and this may increase the risk of false-negative findings in all population levels. Third, some studies were excluded from our research since not providing the original data, which may result in selection bias. Fourth, our result was based on unadjusted estimates, while a more precise analysis should be conducted adjusted by risk factors related to pneumoconiosis. In addition, papers included in our articles only were written in English and Chinese, and therefore some qualified studies written in other languages were not included in our study. Therefore, we are not sure whether there has significantly association between -509C/T (rs1800469) and +915G/C (rs1800471) polymorphisms and pneumoconiosis in the whole population.

In conclusion, the results of our meta-analysis indicate that the rs1800469 and rs1800471 polymorphisms may exert a role in the risk of pneumoconiosis. However, for Asians, there existed some diversity, especially in Chinese population. Hence, we cannot predict the risk of them just by the research of only two genes but to comprehensively analyze all kinds of factors including environment, ethnicity, region and different genes. It is necessary to carry out further researches with a larger number of worldwide studies in standardized and unbiased ways to confirm our findings.

### Disclosure of conflict of interest

None.

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