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Association of a disintegrin and metalloproteinase 33 (ADAM33) gene polymorphisms with chronic obstructive pulmonary disease in the Chinese population: A meta-analysis

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ABSTRACT. Numerous studies have evaluated the association between polymorphisms of a disintegrin and metalloproteinase 33 (ADAM33) gene and chronic obstructive pulmonary disease (COPD) risk; however, the results remain conflicting. The aim of this study was to investigate whether ADAM33S2 and -T1 polymorphisms are associated with susceptibility to COPD risk in the Chinese population. Publications addressing the association between ADAM33S2 or T1 polymorphisms and COPD risk were selected from the PubMed, Cochrane Library, Embase, CNKI, and Wanfang databases. Two independent reviewers extracted data from the studies. Statistical analysis was performed

using the RevMan 5.0.25 and STATA 11.0 software. Six case-control studies were retrieved, including a total of 1201 COPD patients and 1203 controls. Meta-analysis results showed a significant association between the T1 polymorphism and COPD risk in both dominant model [odds ratio (OR) = 2.54, 95% confidence interval (CI) = 1.40-4.61, P = 0.002] and recessive model (OR = 3.50, 95%CI = 2.11-5.81, P < 0.00001) comparisons. For S2, no significant association was found in any genetic model. This suggests that the T1 polymorphism of ADAM33 would increase the risk of COPD in a Chinese individual, whereas the S2 polymorphism might not be a risk factor for COPD. To further evaluate the gene-to-gene and gene-to-environment interactions on ADAM33 genetic variations and COPD risk, more studies using large sample sizes of patients are needed.

Key words: COPD; ADAM33; Polymorphism; Meta-analysis

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), which is characterized as irreversible airflow obstruction, remains one of the leading causes of morbidity and mortality throughout the world. The most important risk factor for the development of COPD is cigarette smoking, which promotes chronic inflammatory processes in the airway, leading to increased numbers of goblet cells, airway remodeling, and tissue destruction. However, only 10 to 15% of smokers were shown to develop symptomatic COPD (Fletcher and Peto, 1977), suggesting that host genetic factors might play a crucial role in COPD susceptibility. Numerous family-based, case-control, and genome-wide association (GWA) studies have also demonstrated a hereditary contribution to the development of COPD (Sandford et al., 1997; Smolonska et al., 2009).

A disintegrin and metalloproteinase 33 (ADAM33), belonging to the disintegrin and metalloprotease family, plays a critical role in cell adhesion, proliferation, differentiation, signaling, apoptosis, and inflammatory responses (Sharma et al., 2011). van Eerdewegh et al. (2002) found an association between the ADAM33 gene with asthma and bronchial hyperresponsiveness. In the past ten years, an increasing number of studies have shown associations between ADAM33 polymorphisms and asthma susceptibility, as well as other pulmonary diseases in different populations (Holgate, 2010; Mocchegiani et al., 2011). van Diemen et al. (2005) reported, for the first time, that single nucleotide polymorphisms (SNPs) in ADAM33 were associated with accelerated lung function decline in the general population, and were also risk factors of COPD. Two important SNPs, S2 and T1, and their relationships with COPD risk have attracted widespread attention in recent years. Several eligible case-control studies on the association between the ADAM33 S2 and T1 polymorphisms and COPD have been extensively performed in China (Wang et al., 2009; Yin et al., 2010; Chi et al., 2011; Xiao et al., 2011; Qin et al., 2012; Zhou and Sun, 2012), but the results remain disputable, possibly due to the relatively small number of included populations, which compromised the power of the studies. Thus, in the present study, a meta-analysis was performed based on a total of six independent studies, which may clarify the evidence for an association of the ADAM33S2 and -T1 polymorphisms with COPD susceptibility in the Chinese population.

MATERIAL AND METHODS

Publication search

The electronic databases PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang were searched. The Mesh terms were as follows: "chronic obstructive pulmonary disease or COPD" in combination with "polymorphism or variant or mutation", "ADAM33", and "Chinese". The included articles were published from January 1980 to November 2012. If studies used partly overlapped subjects, the study with the 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) COPD demonstrated by a postbronchodilator FEV1%/FVC<70% normal predictive value, or as diagnosed by the Chronic Obstructive Lung Disease (GOLD) guidelines, and 3) evaluation of the ADAM33S2 or -T1 polymorphism and COPD in a Chinese population. Accordingly, the following exclusion criteria were used: 1) abstracts, reviews, and duplication of the literature, 2) non-case-control studies, 3) genotype frequency not reported, and 4) studies not consistent with Hardy-Weinberg equilibrium (HWE).

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 assessed these articles. The collected data included the first author's name, year of publication, country, ethnicity, genotyping methods, total number of cases and controls, and genotype distributions of cases and controls.

Statistical analysis

The association between ADAM33 gene polymorphisms and COPD risk was measured by the odds ratio (OR) with 95% confidence interval (CI). The significance of the pooled OR was determined by the Z test and $P < 0.05$ was considered to be statistically significant. The inter-study heterogeneity was calculated using the chi-squared-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-effects model was used to calculate the pooled OR; otherwise, the fixed-effects model was used. Four comparisons were performed: allelic contrast (G *vs* C in S2 and G *vs* A in T1), additive genetic model (GG *vs* CC in S2 and GG *vs* AA in T1), dominant genetic model (CG+GG *vs* CC in S2 and AG+GG *vs* AA in T1), and recessive genetic model (GG *vs* CG+CC in S2 and GG *vs* AG+AA in T1). Publication bias was tested with Begg's funnel plots. Funnel plot symmetry was further assessed using Egger's linear regression method (Egger et al., 1997) with significance set at $P < 0.05$. Sensitivity analysis was performed by sequentially excluding individual studies to evaluate the stability of the results (Zhang et al., 2011). HWE was tested using Pearson's c^2 test with significance set at $P < 0.05$. The Review

Manager software 5.0.24 (Cochrane Collaboration, Oxford, UK) and the STATA 11.0 software were used to perform all statistical analyses.

RESULTS

Eligible studies

A total of six case-control studies, including 1201 COPD patients and 1203 controls, met the inclusion criteria and were included in the meta-analysis. The study selection process is shown in Figure 1. Five studies examined the ADAM33S2 polymorphism, and three investigated the T1 polymorphism. The characteristics of each selected study are listed in Table 1.

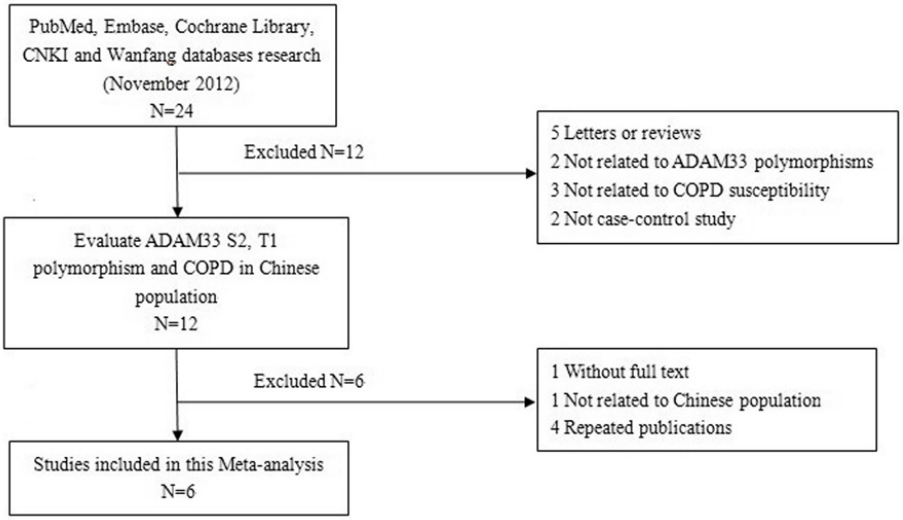

Figure 1. Flow chart of study selection procedure and specific reasons for exclusion from the meta-analysis.

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

SNP	First author	Year	Region	Genotyping method	COPD			Control			HWE
					CC	CG	GG	CC	CG	GG	
S2	Chi XY	2011	Shandong	Sequencing	61	39	12	73	28	4	0.530
	Qin RJ	2012	Shanxi	Sequencing	51	35	4	68	20	2	0.715
	Wang XY	2009	Heilongjiang	PCR-RFLP	30	121	161	23	105	191	0.702
	Xiao JL	2011	Tibet	PCR-RFLP	24	98	118	20	89	112	0.112
	Zhou JT	2012	Jiangsu	PCR-RFLP	57	24	3	47	43	6	0.348
					AA	AG	GG	AA	AG	GG	
T1	Wang XY	2009	Heilongjiang	PCR-RFLP	83	170	59	179	122	18	0.638
	Xiao JL	2011	Tibet	PCR-RFLP	200	36	4	208	13	0	0.652
	Yin YQ	2010	Shandong	PCR-RFLP	300	61	2	326	43	3	0.242

SNP = single nucleotide polymorphism; HWE = Hardy-Weinberg equilibrium. PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism.

Pooled analyses

Meta-analysis results showed no evidence of association between the S2 polymorphism and the risk of COPD in any genetic model (G *vs* C: OR = 1.11, 95%CI = 0.70-1.75, P = 0.67; GG *vs* CC: OR = 1.04, 95%CI = 0.54-2.01, P = 0.91; CG+GG *vs* CC: OR = 1.06, 95%CI = 0.59-1.92, P = 0.85; GG *vs* CG+CC: OR = 0.86, 95%CI = 0.69-1.08, P = 0.19). For the T1 polymorphism, however, significant associations were found in the dominant model (OR = 2.54, 95%CI = 1.40-4.61, P = 0.002) and the recessive model (OR = 3.50, 95%CI = 2.11-5.81, P < 0.00001), although similar associations were not observed when comparing other genetic models. The main results of the meta-analysis are summarized in Table 2.

Table 2. Meta-analysis of the association between ADAM33 polymorphism and COPD risk.

Analysis model	S2				T1			
	OR (95%CI)	P_h	I^2 (%)	P	OR (95%CI)	P_h	I^2 (%)	P
Allelic contrast	1.11 (0.70-1.75)	<0.00001	86	0.67	1.00 (0.10-10.04)	<0.00001	99	1.00
Additive model	1.04 (0.54-2.01)	0.06	56	0.91	3.62 (0.73-17.90)	0.06	65	0.11
Dominant model	1.06 (0.59-1.92)	0.0006	80	0.85	2.54 (1.40-4.61)	0.005	81	0.002
Recessive model	0.86 (0.69-1.08)	0.12	46	0.19	3.50 (2.11-5.81)	0.16	46	<0.00001

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

Publication bias

The publication bias of the studies was assessed with Begg's funnel plots and the Egger linear regression test. The Egger test was used to measure the asymmetry of the funnel plot. The results are shown in Table 3, and they indicated a lack of publication bias for all genetic models (all P values < 0.05) (Table 3).

Table 3. Evaluation of publication bias by the Egger and Begg tests.

Analysis model	S2		T1	
	Egger's test (t, p)	Begg's test (z, p)	Egger's test (t, p)	Begg's test (z, p)
Allelic contrast	1.07, 0.364	0.73, 0.462	0.02, 0.987	0.00, 1.000
Additive model	1.02, 0.382	0.73, 0.462	-0.64, 0.637	0.00, 1.000
Dominant model	0.01, 0.995	0.24, 0.806	-0.13, 0.920	0.00, 1.000
Recessive model	1.22, 0.309	0.73, 0.462	-0.41, 0.750	0.00, 1.000

Sensitivity analysis

Sensitivity analysis was performed to evaluate the influence of any single study on the overall OR of S2 by sequentially excluding each case-control study. The results showed that no individual study was qualitatively affecting the pooled OR, suggesting the stability of this meta-analysis.

DISCUSSION

COPD is one of the major causes of morbidity and mortality worldwide. It has been reported that heredity plays an important role in the etiology and pathogenesis of COPD. In recent

years, an increasing number of molecular genetic studies have focused on the relationship between ADAM33 variations and COPD risk; however, specific associations in the Chinese population remain controversial. As meta-analysis is an essential tool for accurately and reliably summarizing evidence, we performed the present meta-analysis to comprehensively assess these associations.

In the current study, we analyzed six case-control studies with a total of 1201 COPD cases and 1203 healthy controls. Two polymorphisms, S2 and T1, were examined in the studies with respect to COPD susceptibility. No significant association was found between S2 variation and the risk of COPD in any genetic model, suggesting that the S2 polymorphism might not be a risk factor for COPD in the Chinese population. There was a significant association between the T1 polymorphisms and COPD in the comparisons of AG+GG *vs* AA and GG *vs* AA+AG (OR = 2.54, 95%CI = 1.40-4.61, P = 0.002, OR = 3.50, 95%CI = 2.11-5.81, P < 0.00001, respectively), which indicated that G allele carriers may have a 154% higher risk of COPD than AA homozygotes, and GG homozygotes may have a 250% increased risk compared with A allele carriers.

Statistically significant inter-study heterogeneity was found in our study. There are several reasons that may explain it. First, northern and southern Chinese populations may have different genetic backgrounds, which could contribute to the observed genetic heterogeneity. Second, environmental factors that might affect genetic susceptibility were not investigated in most case-control studies. Thus, in the future, more studies should be performed to assess these results.

As in most meta-analyses, certain potential limitations exist in our study. First, only published studies were included in this meta-analysis, and unpublished data and ongoing studies were not sought, which may introduce some bias into our results. Second, the combined ORs were based on unadjusted data. Third, lack of the original data of the reviewed studies limited further investigations 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 (de Wit et al., 2011). Fourth, two studies included less than 100 cases in our meta-analysis (Qin et al., 2012; Zhou and Sun, 2012), which may have increased the chance of type 1 or type 2 errors, making the results potentially unreliable (Zhang et al., 2012). In addition, due to the limited number of studies included, we were unable to address the sources of heterogeneity existing among studies; for the same reason, sensitivity analysis was not performed for the T1 polymorphism. Therefore, the results of this meta-analysis should be interpreted with caution.

In conclusion, our meta-analysis suggested that the ADAM33T1 polymorphism might be associated with increased risk of COPD, while the S2 variant might not be a risk factor for COPD in the Chinese population. However, this association needs further investigation by performing more case-control studies in a larger group of populations.

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Conflicts of interest

The authors declare no conflict of interest.

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