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Original Article

Association of the FAM13A rs7671167 polymorphism with COPD risk: a meta-analysis

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Abstract: Background: It has been reported that FAM13A rs7671167 polymorphism might be associated with the risk of chronic obstructive pulmonary disease (COPD). Due to inconclusive results, we conducted this meta-analysis to clarify the effect of rs7671167 polymorphism on COPD susceptibility. Material/Methods: A systematic literature search was performed to find relevant studies. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Publication bias, heterogeneity and sensitivity analysis were also assessed. Results: A total of 7 eligible studies with 2841 COPD cases and 3843 controls were retrieved in the analysis. The pooled results indicated a significant association between FAM13A rs7671167 polymorphism and COPD risk under all of the genetic models (T versus C: OR = 1.283, 95% CI = 1.093-1.506, *P* = 0.002; TT versus CC: OR = 1.616, 95% CI = 1.183-2.208, *P* = 0.003; TC versus CC: OR = 1.337, 95% CI = 1.098-1.679, *P* = 0.005; TT+TC versus CC: OR = 1.449, 95% CI = 1.133-1.854, *P* = 0.003; TT versus TC+CC: OR = 1.314, 95% CI = 1.092-1.580, *P* = 0.004). Subgroup analysis showed the similar results in Caucasians (T versus C: OR = 1.429, 95% CI = 1.080-1.890, *P* = 0.012) and Asians (T versus C: OR = 1.232, 95% CI = 1.007-1.506, *P* = 0.043). Conclusions: The results of this meta-analysis suggest that T allele of the FAM13A rs7671167 polymorphism might act as a significant risk factor for the development of COPD. Further large-scale and well-designed studies with different populations are still required to validate our findings.

Keywords: COPD, FAM13A, polymorphism, genetic, meta-analysis

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent progressive airflow limitation resulting from enhanced chronic inflammation in the airways in response to noxious particles or gases [1]. Although cigarette smoking is the first major environmental risk factor, only 10-20% of smokers will ever develop clinically significant disease [2]. In addition, the decline of lung function highly varies between those exposed to similar levels of cigarette smoke [3]. These observations suggest that genetic background is an important determinant of susceptibility to COPD. Generally, COPD is the result of a complex interaction between environmental exposure and genetic factor [4, 5]. Several genomic-wide association studies (GWAS) have revealed some genomic regions associated with COPD, including the gene FAM13A (family with sequence similarity 13, member A) [5, 6].

Human FAM13A gene is located on chromosome 4q22 and encodes FAM13A protein. The N-terminal extension of FAM13A protein contains the Rho (Ras homologous)-GAP (GT-Pase-activating protein) domain, which leads to the inhibition of RhoA by enhancing intrinsic GTPase activity [7-9]. Based on the presence of this domain, a putative Rho-GAP function suggests the anti-inflammatory and tumor suppressive activity of FAM13A [10]. Rho-GTPases has been shown to be dysregulated in COPD, and subsequent, activation of RhoA/Rho-kinase has been implicated in causing impairment of endothelium-dependent relaxation [11-13]. Therefore, the variants of this gene may affect Rho-GTPases activity and associated cellular pathways in COPD. The single-nucleotide polymorphism (SNP) of FAM13A rs7671167 was identified as a significant location that influences COPD in GWAS [5]. Several studies have demonstrated the association between the SNP

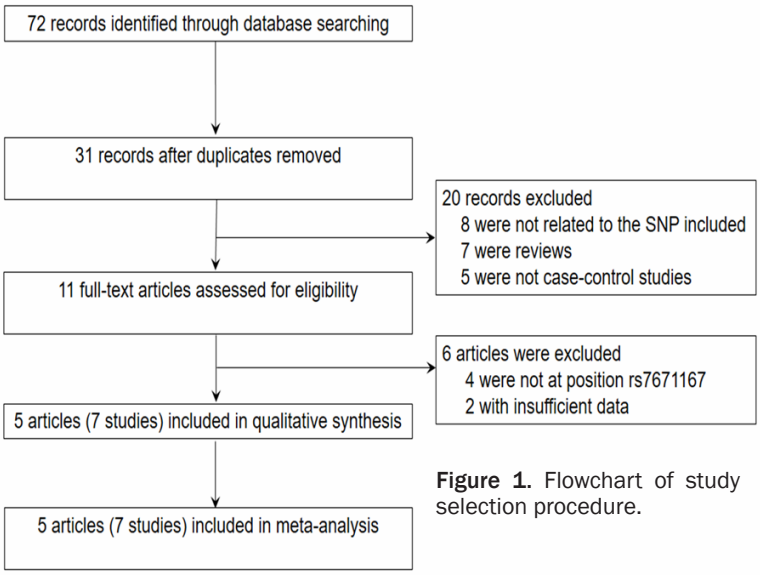

Figure 1. Flowchart of study selection procedure.

and COPD risk in different ethnicities. Two studies demonstrated that the C allele of rs7671167 is associated with a reduced risk of COPD [10, 14]. However, another study in Poland demonstrated that no significant association between the SNP and COPD [15]. Considering of the controversial and inconclusive results, we conducted this meta-analysis to clarify the role of FAM13A rs7671167 polymorphism in COPD.

Materials and methods

Literature search strategy

We performed a comprehensive electronic search in PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI) and Wanfang Database for potentially relevant studies from inception to October 2015. The following key words were used: ("FAM13A" or "the family with sequence similarity 13 member A") and ("polymorphism" or "variant" or "variation" or "mutation") and ("COPD" or "Chronic Obstructive Pulmonary Disease" or "Chronic obstructive airway disease" or "chronic airflow obstructive"). No restrictions were applied for language.

Inclusion and exclusion criteria

Two reviewers (Shaojun Li and Fangwei Li) independently reviewed the studies according to the following inclusion criteria: (1) studies with case-control design; (2) studies evaluating the association of FAM13A rs7671167 polymorphism with COPD risk; (3) studies providing sufficient genotype data in both case and control groups to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). When overlapping data existed, the one with the largest sample size or the more reliability was included. The major exclusion criteria were as follows: (1) studies that did not meet these inclusion criteria; (2) case reports, letters, reviews, abstracts, meta-analyses and editorials; (3) duplication publications. Studies without sufficient data were excluded after failing to extract data from the original paper or contact with the authors.

Data extraction

Two reviewers (Shaojun Li and Yang Song) independently extracted the following data from each individual study: first author, year of publication, country, ethnicity, number of cases and controls and phenotypic distribution in both groups, Hardy-Weinberg equilibrium (HWE) evidence in the controls. Different ethnic descents were categorized as Caucasian and Asian. Disagreements were resolved after discussion with a third reviewer (Wei Feng), and consensus was achieved on each item.

Quality assessment

Two reviewers (Xiaofan Su and Lan Yang) evaluated quality of studies independently using the Newcastle-Ottawa Scale (NOS) criteria (www.ohri.ca/programs/clinical epidemiology/oxford.asp). Quality score was calculated based on the following three aspects: (1) subject selection: 0*4; (2) comparability of subject: 0*2; (3) clinical outcome: 0*3. The total NOS scores range from 0 (lowest) to 9 (highest). According to the NOS scores, the included studies were classified into two levels: low quality (0-6), and high quality (7-9), respectively. Any discrepancies between the two reviewers on NOS scores of the enrolled articles were resolved by discussion and consultation with a third reviewer (Wei Feng).

Table 1. Characteristics of all eligible studies evaluating FAM13A rs7671167 polymorphism and COPD

Study	Year	Country	Ethnicity	Source of controls	Genotyping method	Case (n)	Control (n)	Quality score
Young	2011	NewZealand	Caucasian	PB	TaqMan	458	485	8
Wang	2013	China	Asian	PB	Sequencing	679	687	8
Ding	2015	China	Asian	HB	Sequencing	231	238	7
Xie-1	2015	China	Asian	PB	TaqMan	1324	1549	7
Xie-2	2015	China	Asian	PB	TaqMan	409	611	8
Xie-3	2015	China	Asian	PB	TaqMan	541	377	8
Suchanek	2015	Poland	Caucasian	HB	TaqMan	374	560	7

Abbreviations: HB, hospital-based; PB, population-based.

Table 2. Genotypic distribution of the FAM13A rs7671167 polymorphisms in cases and controls

Study	Case			Control			*P* for HWE
	TT	TC	CC	TT	TC	CC	
Young	117	234	107	100	240	145	0.969
Wang	163	317	199	177	333	177	0.423
Ding	43	120	68	41	110	87	0.539
Xie-1	132	189	88	143	268	200	0.004
Xie-2	156	272	113	87	170	120	0.076
Xie-3	121	188	65	149	277	134	0.712
Suchanek	57	70	22	126	262	136	0.993

Abbreviations: HWE, Hardy-Weinberg equilibrium.

Statistical analysis

The STATA12.0 software (Stata Corporation, College Station, TX, USA) was applied in this analysis. Hardy-Weinberg equilibrium (HWE) in the control was tested for each study by using the chi-square test, and P value < 0.05 was considered out of HWE. Heterogeneity was assessed by the Chi-square-based Q testing and I^2 statistics [16]. A random-effects model (the DerSimonian and Laird method) was adopted If there was a significant heterogeneity (P < 0.10) [17]. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used [18]. The pooled OR with corresponding 95% CIs were calculated in allele model (T versus C), homozygote comparison (TT versus CC) and heterozygous model (TC versus CC), dominant model (TT+TC versus CC), recessive model (TT versus TC+CC), respectively. Publication bias was assessed with Begg's test [19] and Egger's test [20]. The P value < 0.05 for Begg's test or Egger's test indicated significant publication bias.

Results

Study characteristics

A total of 72 articles were identified through the initial search of databases. The flow chart of the study selection process was shown in **Figure 1**. After screening, 5 case-control studies [10, 14, 21-23] fulfilled the inclusion criteria. In one study [22], genotype frequencies of FAM13A rs7671167 was presented in 3 replicate studies, thus 7 included references containing 2841 cases and 3843 controls for FAM13A rs7671167 were finally analyzed in our meta-analysis. Two references [10, 14] were carried out among Caucasian, and another 5 references [21-23] among Asians. The genotyping distribution was in agreement with HWE in all studies except for one reference in Xie's research [22]. The main characteristics of the eligible studies are presented in **Table 1**. The detailed genotype and allele frequencies and HWE examination are listed in **Table 2**.

Meta-analysis and subgroup analysis

The main results of the relationship between FAM13A rs7671167 polymorphism and COPD risk are listed in **Table 3**. The random-effects model was selected since statistically heterogeneity existed ($P_{Q\text{-test}}$ < 0.1, I^2 > 50%). Overall, results of our meta-analysis showed that there was a strong association of FAM13A rs7671167 with the risk of COPD in all the genetic models (T versus C: OR = 1.283, 95% CI = 1.093-1.506, P = 0.002; TT versus CC: OR = 1.616, 95% CI = 1.183-2.208, P = 0.003; TC versus CC: OR = 1.337, 95% CI = 1.098-1.679, P = 0.005; TT+TC versus CC: OR = 1.449, 95% CI = 1.133-1.854, P = 0.003; TT versus TC+CC: OR = 1.314, 95%

Table 3. Meta-analysis of FAM13A rs7671167 polymorphism and COPD risk

Subgroup	Genotype/Allele	No.of study	Test of association		Test of heterogeneity	
			OR (95% CI)	*P*	*P* (Q-test)	I^2
Asian	T vs. C	5	1.232 (1.007, 1.506)	0.043	0.000	82.7%
	TT vs.CC		1.485 (1.008, 2.186)	0.046	0.004	81.5%
	TC vs. CC		1.337 (1.005, 1.778)	0.045	0.000	74.3%
	TT+TC vs. CC		1.393 (1.011, 1.919)	0.043	0.000	82.1%
	TT vs. TC+CC		1.229 (0.998, 1.514)	0.052	0.019	57.2%
Caucasian	T vs. C	2	1.429 (1.080, 1.890)	0.012	0.078	67.8%
	TT vs. CC		2.027 (1.168, 3.517)	0.012	0.091	64.9%
	TC vs. CC		1.404 (1.078, 1.829)	0.012	0.470	0.0%
	TT+TC vs. CC		1.553 (1.211, 1.992)	0.001	0.206	37.6%
	TT vs. TC+CC		1.578 (1.075, 2.316)	0.020	0.117	59.3%
Overall	T vs. C	7	1.283 (1.093, 1.506)	0.002	0.000	79.1%
	TT vs. CC		1.616 (1.183, 2.208)	0.003	0.000	77.8%
	TC vs. CC		1.337 (1.098, 1.679)	0.005	0.012	63.5%
	TT+TC vs. CC		1.449 (1.133, 1.854)	0.003	0.000	76.0%
	TT vs. TC+CC		1.314 (1.092, 1.580)	0.004	0.010	58.8%

Abbreviations: OR, odds ratio; CI, confidence interval; *P*, *P*-value of pooled effect. Significant results ($P < 0.05$) for overall effect were marked in bold characters.

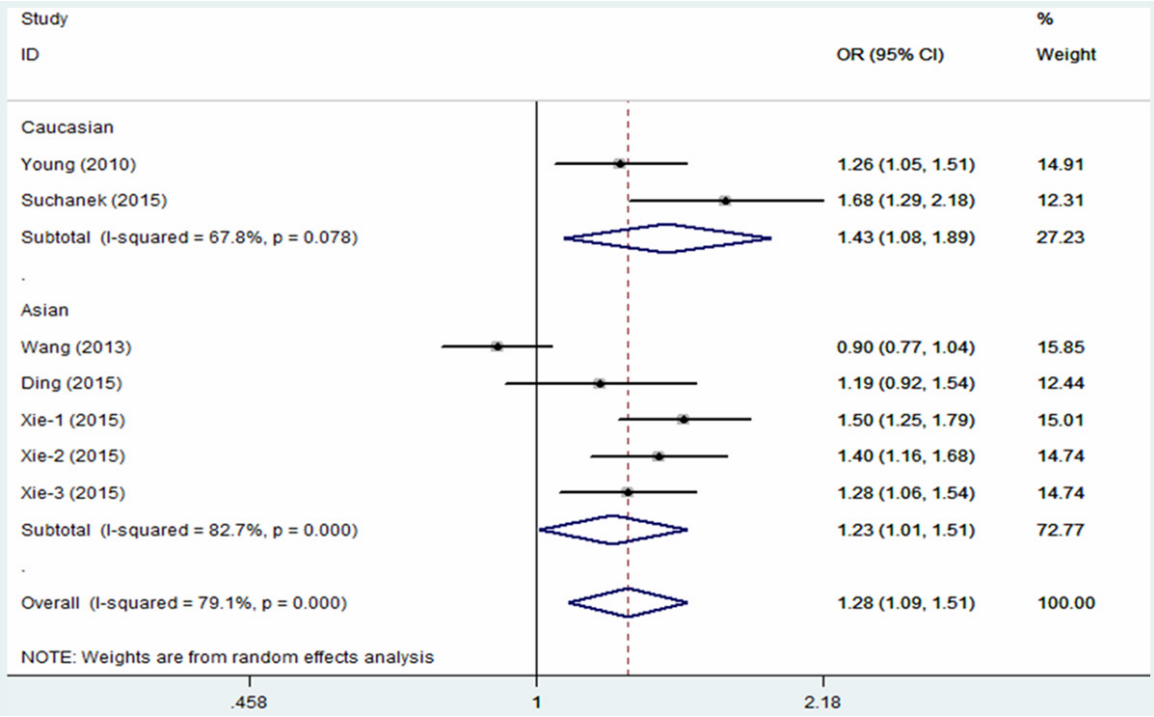

Figure 2. Forest plot of the association between FAM13A rs7671167 polymorphism and COPD risk under the allele model (T vs. C).

CI = 1.092-1.580, *P* = 0.004) (**Figures 2-6**), indicating that the T allele of the SNP might act as an important risk factor for the development of COPD.

Next, subgroup analysis was conducted according to ethnicity. In Caucasians, no significant statistical heterogeneity was identified in the dominant and heterozygous models so that

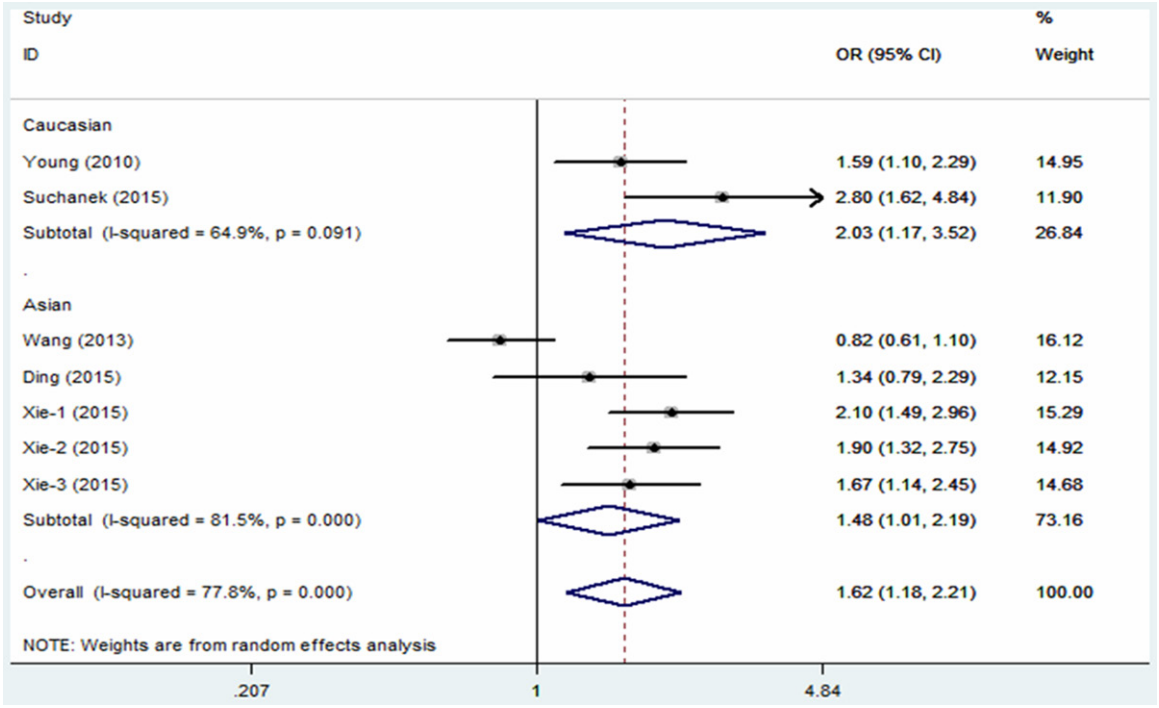

Figure 3. Forest plot of the association between FAM13A rs7671167 polymorphism and COPD risk under the homozygote model (TT vs. CC).

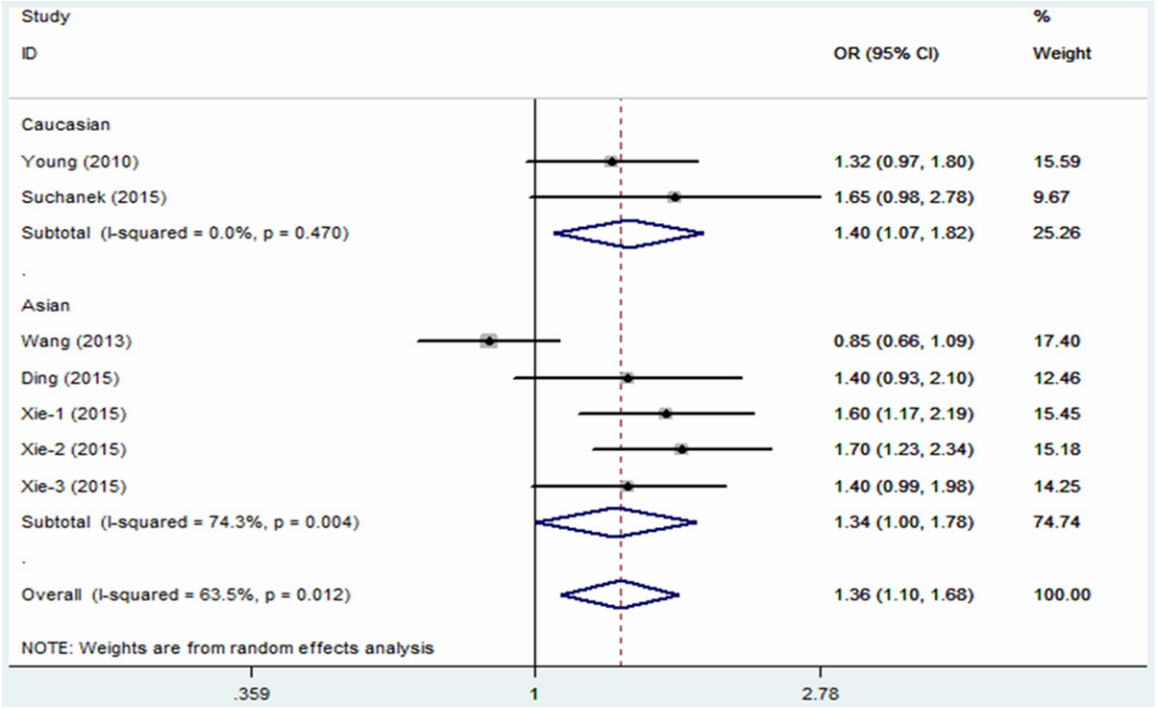

Figure 4. Forest plot of the association between FAM13A rs7671167 polymorphism and COPD risk under the heterozygote model (TC vs. CC).

fixed-effects model was used. The random-effects model was used in other three genetic models. Results demonstrated positive correlation between the genetic variants in rs7671167

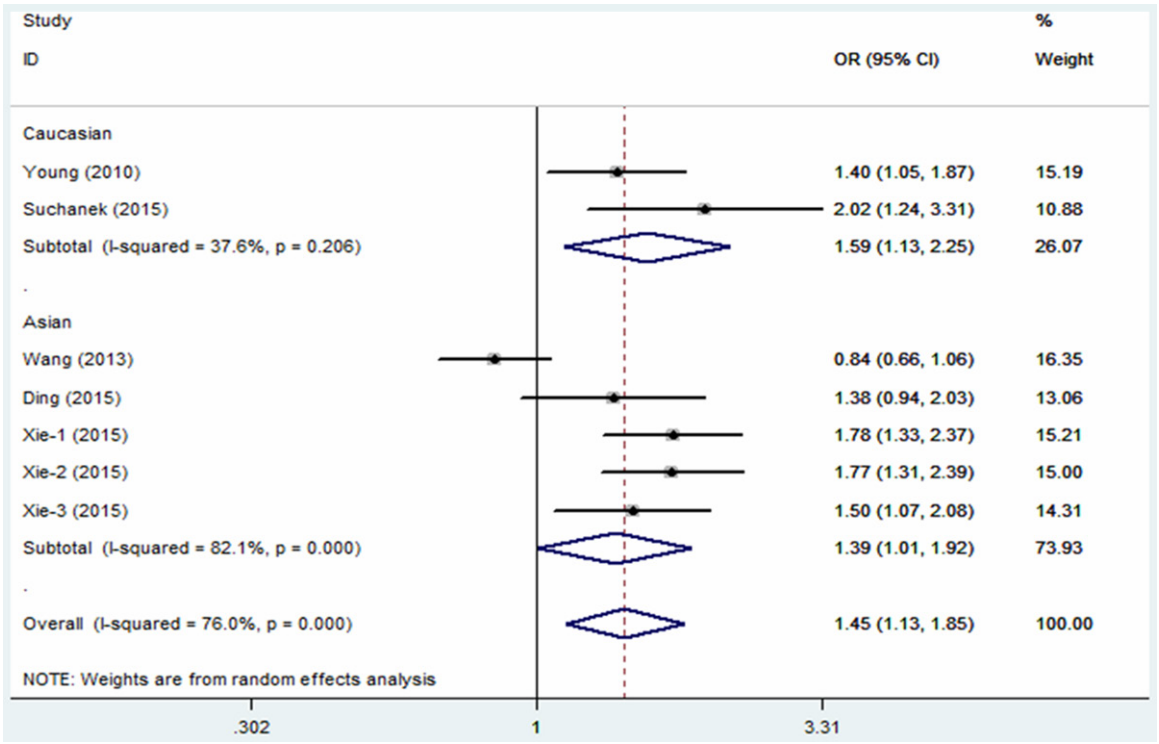

Figure 5. Forest plot of the association between FAM13A rs7671167 polymorphism and COPD risk under the dominant model (TT+TC vs. CC).

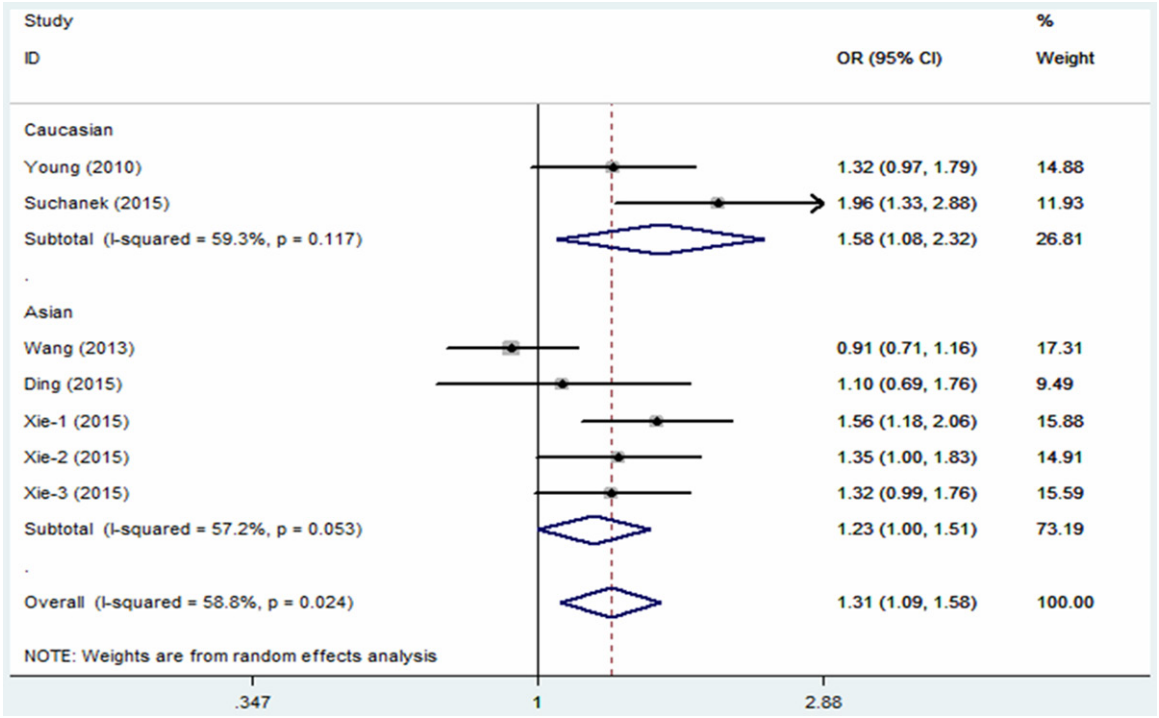

Figure 6. Forest plot of the association between FAM13A rs7671167 polymorphism and COPD risk under the recessive model (TT vs. TC+CC).

with risk of COPD among Caucasians under all of the genetic models (all $P < 0.05$, **Table 3**). In Asians, heterogeneity existed in all of the five genetic models, thus the random-effects model

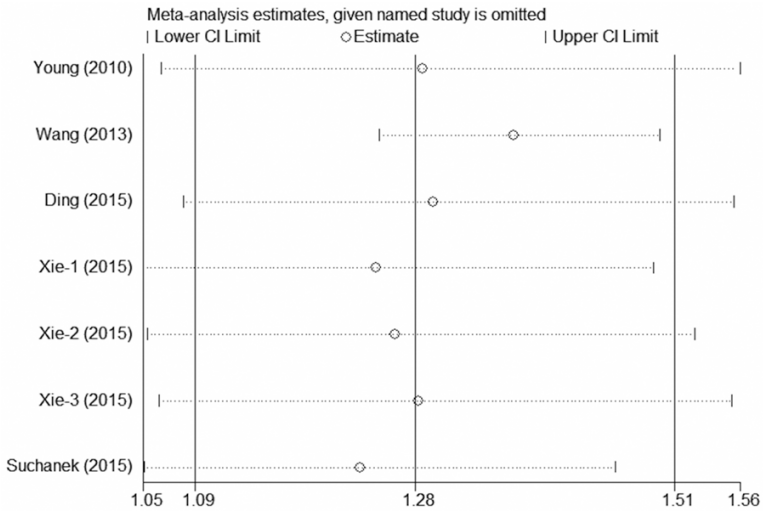

Figure 7. One-way sensitivity analysis for the FAM13A rs7671167 polymorphism and COPD risk under the allele model (T vs. C).

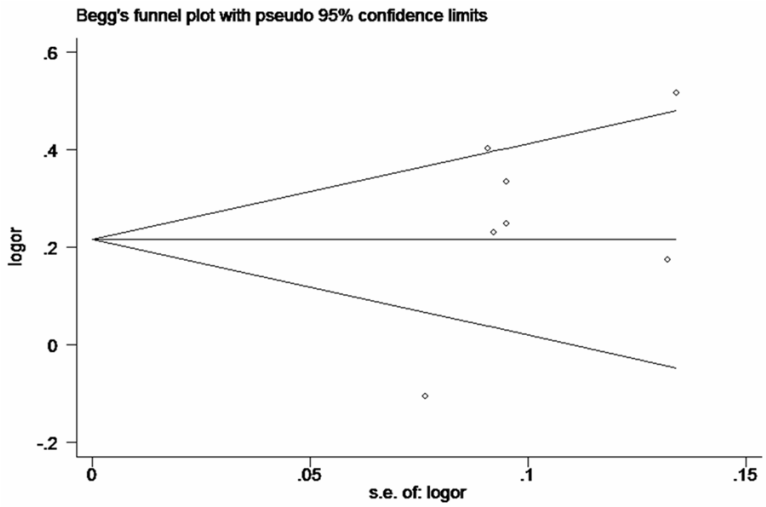

Figure 8. Begg's funnel plot test of publication bias for the association between the FAM13A rs7671167 polymorphism and COPD risk under the allele model (T vs. C).

was employed. Significant association was also found in all genetic models (all $P < 0.05$, **Table 3**).

Sensitivity analysis

We conducted sensitivity analysis to explore the potential influence of each individual study on the pooled ORs for FAM13A rs7671167 by deleting one study each time in every genetic model. Consistently, the results showed no individual study could affect the pooled OR, indicating that our results of the meta-analysis were robust (**Figure 7**).

Publication bias

No significant publication bias for the association between FAM13A rs7671167 and COPD susceptibility was detected by Begg's funnel plot ($P = 0.293$, T versus C, **Figure 8**) or Egger's regression test ($P = 0.170$, T versus C) (**Table 4**).

Discussion

COPD is a common complex disease resulting from cumulative effect of different environmental exposures and genetic susceptibility [24]. Human Genomic Project and HapMap offer an opportunity to study the genetic architecture of COPD from the genomic level. Recent GWASs have discovered several candidate genes that are involved in COPD, including FAM13A, HHIP (hedgehog-interacting protein) [25-27], IREB2 (iron regulatory binding protein 2) [25, 28-31], CHRNA3/5 (cholinergic nicotine receptor alpha 3/5) [15, 26, 32-34] and AGER (advanced glycosylation end product-specific receptor) [15]. They have been replicated in multiple populations. Recently, SNPs at FAM13A region have been shown significant associations with COPD and COPD-related phenotypes by GWAS and integrative genomic approaches in Asian and Caucasian populations.

FAM13A, also known as FAM13A1, is localized on chromosome 4q22. There were two splice variants in humans, named FAM13A isoform 1 (long variant) and isoform 2 (short variant), respectively. FAM13A isoform 1 (NM_014883.3), used as the reference transcript, encodes a protein of 117 kDa that has a Rho-GAP domain which suggests its involvement in Rho-GTPase signaling pathways [8]. Northern blot data have shown high expression of

Table 4. Results of publication bias test

Polymorphism	Genotype/ Allele	Begg's test		Egger's test	
		z value	*P* value	t value	*P* value
FAM13A rs7671167	T vs. C	1.05	0.293	1.60	0.170
	TT vs. CC	0.75	0.453	1.49	0.196
	TC vs. CC	1.05	0.293	1.69	0.152
	TT+TC vs. CC	0.15	0.881	1.80	0.132
	TT vs. TC+CC	0.15	0.881	0.98	0.373

FAM13A in the kidney, pancreas, liver, lung and thymus [9]. In COPD, the activation of RhoA/Rho-kinase has been found to contribute to the pathogenesis caused by agents such as inflammatory cytokines and cigarette smoke [11, 12, 35]. Based on the presence of this domain, a putative Rho-GAP function of FAM13A suggests its role in modulating Rho-GTPases activity and associated endothelial barrier function in COPD. Increased expression of FAM13A has been observed in response to hypoxia in cell lines from several tissues [36]. Furthermore, differences in respiratory epithelial cell expression of FAM13A have been noted during differentiation into pulmonary type 2 cells in vitro [37]. Also, analysis of lung expression QTL (eQTL) with 409 lung/blood samples supports FAM13A as a causal COPD gene [38]. In COPD patients, a strong association has also been shown between the SNP and lung volume and emphysema assessed by chest CT scans [39]. In addition, Kim et al has demonstrated that expression of FAM13A is significantly higher in the lung tissue of individuals with COPD compared to controls [40], which suggests that FAM13A may act as a novel COPD susceptibility gene.

As mentioned above, the genetic variants in FAM13A gene may determine susceptibility to COPD. Cho et al first detected FAM13A rs7671167 and demonstrated that the C allele of rs7671167 is associated with a reduced risk of COPD in Caucasians [5]. The association with COPD susceptibility in pulmonary function has been replicated in several studies with independent cohorts in different ethnicities [21-23, 41, 42], suggesting a real contribution to the lung phenotype. Meanwhile, another study in Poland demonstrated that no significant association between the SNP and COPD [15]. The results of the relationship between FAM13A rs7671167 T/C polymorphism and COPD risk are inconsistent. Therefore, it is critical to systematically evaluate all studies from different groups and to quantify the overall association between the gene polymorphism and the risk of COPD.

In this meta-analysis, a total of seven eligible case-control studies including 2841 COPD cases and 3843 controls for FAM13A rs7671167 were analyzed. This meta-analysis indicated that FAM13A rs7671167 polymorphism was significantly associated to the occurrence of COPD, indicating that rs7671167 polymorphism might act as a causative factor for the progression and development of COPD, both in Caucasian and Asian population.

Furthermore, T allele in FAM13A rs7671167 might act as a risk factor in the development of COPD under all of the inheritance models according to ethnicity, which were in the same direction as previously reported among the two populations. It is suggested that further well-designed studies with larger sample size on different ethnicities are still needed to conform the relationship between FAM13A gene polymorphism and COPD risk.

The heterogeneity needs to be mentioned when interprets the meta-analysis results. Significant heterogeneity was found for the stable results of rs7671167 T/C polymorphism in the two genetic models (dominant model and heterozygous model). After stratifying by ethnicity, there was no relatively significant heterogeneity in Caucasians, which suggests that ethnicity, to some extent, contribute to the source of heterogeneity. As for another three models, though heterogeneity existed, our results remained stable, and the results became more significant in Caucasians.

Some limitations should be pointed out in this meta-analysis. Firstly, the limited number of included studies for FAM13A rs7671167 polymorphism may lead to a relatively insufficient power. Secondly, one study for FAM13A rs7671167 did not conform to Hardy-Weinberg equilibrium expectations. However, when restricted to those who were in Hardy-Weinberg equilibrium, the pooled estimate of the association between FAM13A rs7671167 polymorphism and susceptibility of COPD remained significant. Thirdly, heterogeneity was not resolved after ethnicity stratified, suggesting that other

factors such as age, gender or smoking history may influence the heterogeneity. At last, only published studies with sufficient information were included and the inevitable publication bias may exist even though the results of Begg's test or Egger's test did not detect. Considering these limitations, the results of this meta-analysis should be interpreted with caution. Further larger well-designed case-control studies among different populations are still required to confirm these results.

Conclusion

In conclusion, the current meta-analysis suggests that the T allele of FAM13A rs7671167 polymorphism might act as a significant risk factor for the development of COPD. Further larger and well-designed case-control studies based on different populations are still needed to validate our results.

Acknowledgements

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Disclosure of conflict of interest

None.

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