

Association between *PTCH1* gene polymorphisms and chronic obstructive pulmonary disease susceptibility in a Chinese Han population: a case-control study

Xi Kang^{1,2,3}, Ting Guo^{1,2,3}, Lyu Liu^{1,2,3}, Shui-Zi Ding^{1,2,3}, Cheng Lei^{1,2,3}, Hong Luo^{1,2,3}

¹Department of Pulmonary and Critical Care Medicine, The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China;

²Research Unit of Respiratory Disease, Central South University, Changsha, Hunan 410011, China;

³Diagnosis and Treatment Center of Respiratory Disease, Central South University, Changsha, Hunan 410011, China.

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Genome-wide association studies in non-Asian population revealed a link between COPD and mutations in the *PTCH1* gene encoding Patched1, a receptor in the Hedgehog signaling pathway important for lung morphogenesis and pulmonary function. The aim of this study was to investigate the association between *PTCH1* polymorphisms and the COPD risk in the Chinese Han population.

Methods: We performed a case-control study including 296 patients with COPD and 300 healthy individuals. Single-nucleotide polymorphisms in the *PTCH1* gene were identified and genotyped based on the linkage disequilibrium analysis in all participants. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using logistic regression analysis after adjustment for age, gender, and smoking.

Results: In total, 28 single-nucleotide polymorphisms were identified in patients with COPD. Among them, “A” allele of rs28491365 (OR: 1.388, 95% CI: 1.055–1.827, $P = 0.018$), and “G” alleles of rs10512248 (OR: 1.299, 95% CI: 1.021–1.653, $P = 0.033$) and rs28705285 (OR: 1.359, 95% CI: 1.024–1.803, $P = 0.033$; respectively) were significantly associated with an increased COPD risk. Genetic model analysis revealed that the “T/T” genotype of rs34695652 was associated with a decreased COPD risk under the recessive model (OR: 0.490, 95% CI: 0.270–0.880, $P = 0.010$), whereas rs28504650/rs10512248 haplotype CG was significantly associated with an increased COPD risk after adjustment for age, gender, and smoking status (OR: 6.364, 95% CI: 1.220–33.292, $P = 0.028$).

Conclusions: The study provides a new insight into the role of *PTCH1* polymorphisms in the susceptibility to COPD in the Chinese Han population.

Keywords: *PTCH1*; Chronic obstructive pulmonary disease; Gene polymorphism; Case-control study; Single-nucleotide polymorphisms

Introduction

Chronic obstructive pulmonary disease (COPD) is a major chronic respiratory disease characterized by incompletely reversible airflow obstruction accompanied by airway mucus accumulation, chronic inflammation, and airway remodeling.^[1,2] According to the prediction of the Global Burden of Disease Study, COPD could be the fifth leading cause of morbidity and the third leading cause of mortality worldwide in the near future.^[3] Tobacco smoking is the primary risk factor for COPD in the general population and it is estimated that approximately 10% to 20% of smokers ultimately develop the disease^[4,5]; furthermore, long-term exposure to biomass fuel smoke is another

important cause of COPD in developing countries. However, individual variation in response to the same risk factor suggests a role of genetic predisposition in the development and progression of COPD; therefore, identification of the genetic factors associated with COPD could aid in its diagnosis and treatment.

The Hedgehog (Hh) signaling pathway plays an essential role in lung branching morphogenesis and embryonic development.^[6,7] Patched 1 (PTCH1) is a 12-pass transmembrane receptor for the Hh protein, and the binding of PTCH1 and Hh protein relieves the inhibition of Smoothened, resulting in the induction of the downstream signaling and transcriptional changes in the

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Correspondence to: Dr. Hong Luo, Department of Pulmonary and Critical Care Medicine, The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China
E-Mail: luohonghuxi@csu.edu.cn

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target genes. As a member of the Hh signaling pathway, *PTCH1* encoded by the *PTCH1* (OMIN 601, 309) which is located in chromosome 9q22, was shown to participate in multiple signaling mechanisms, including lung organogenesis and response to injury,^[8] and *PTCH1* mutations have been previously shown to be associated with the risk of COPD in the population of European descent.^[9] However, given the huge difference in the genetic background between European and Asian people, studies on *PTCH1* single-nucleotide polymorphisms (SNPs), which can influence gene expression and determine distinct phenotypic traits,^[10] should be also conducted in Asian countries.

In China, the association between *PTCH1* SNPs and COPD susceptibility has not been reported. Therefore, in this study, we aimed to investigate whether SNPs in the *PTCH1* gene were related to the development of COPD in a Chinese Han population.

Methods

Ethical approval

This study was conducted in accordance with the principles of *Declaration of Helsinki*. The study protocol was reviewed and approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, Changsha, China (No. NSFC: 2017-013). Written informed consent was provided by all participants in this study.

Study population

All participants in this study were of Han ethnicity and lived in Hunan Province, China. Patients diagnosed with stable COPD at the Second Xiangya Hospital of Central South University (Changsha, China) between May 2012 and May 2016 were consecutively recruited. Patients with a history of other respiratory diseases including bronchial asthma, pulmonary tuberculosis, interstitial lung disease, or lung cancer, and known Alpha-1-antitrypsin deficiency were excluded from this study. The control group consisted of healthy volunteers. Physical conditions of these participants were assessed by the same physicians, and we chose the controls with normal lung function, no lung-related diseases or chronic diseases. The diagnosis of COPD was confirmed according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease.^[11] All subjects were required to donate 4 mL peripheral blood. A questionnaire about demographic data, basic characteristics, and other information was collected from all subjects. Sample size was calculated based on type I error of 0.05 (α value), a power of 90% ($1 - \beta$ value) and a case-control ratio of 1:1 using PASS 11.0 software (NCSS LCC, Kaysville, UT, USA). Based on these assumptions, 251 cases and 251 controls enabled us to detect a minimum odds ratio of 2.0. Considering SNP minor allele frequency, this study finally recruited 296 cases and 300 control groups.

Selection and genotyping of tag SNPs

SNPs from the region of *PTCH1* were extracted from HapMap database with minor allele frequency of 5% or

above in Chinese Han population in Hunan. Genomic DNA samples from 30 controls were collected to select tag SNPs. The tag SNPs were identified using the tagger program in Haploview 4.2 (<https://www.broadinstitute.org/haploview/haploview>) based on the 1000 Genomes database (<http://www.internationalgenome.org/>) and linkage disequilibrium (LD) analysis.

Genomic DNA was extracted from peripheral blood of every participant using DNeasy blood and tissue kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions as we have described,^[12] and DNA concentration was measured using a NanoDrop 2000 (Thermo Scientific, Fitchburg, WI, USA). Tag SNPs were genotyped with the SNPseq assay, an efficient multiple gene region enrichment/next generation sequencing-based assay by Genesky Biotechnologies, Inc. (Shanghai, China). D' value was used to evaluate the LD for each pair of SNPs. D' value equaling to 0.8 or above indicated that the related tag SNPs formed one block.^[13,14]

Statistical analysis

SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Distribution of normality for the continuous variables was assessed by Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean \pm standard deviation and analyzed with Student's t test and those with non-normal distribution were expressed as median (interquartile range) and analyzed with Mann-Whitney U test. Categorical variables were expressed as counts (percentages) and compared using the Chi-squared test or Fisher's exact test as appropriate. Hardy-Weinberg equilibrium was tested for each of the SNPs. Odds ratios (ORs) and 95% confidence interval (95% CI) were calculated to assess the associations between *PTCH1* SNPs and COPD risk in the four models using logistic regression analysis. Genotypic model analysis (co-dominant, dominant recessive, and log-additive) was performed by SNPStats software (Catalan Institute of Oncology, Barcelona, Spain).^[15] LD, haplotype construction, and genetic associations at polymorphism loci were estimated using Haploview software version 4.2 (Dr Mark Daly's laboratory, Massachusetts Institute of Technology/Harvard Broad Institute, Cambridge, MA, USA) and SHEsis software platform (<http://www.nhgg.org/analysis/>).^[14] P values less than 0.05 were considered to indicate statistical significance.

Results

Study population characteristics

A total of 596 subjects from China were included in this study, including 296 cases (244 males) and 300 controls (251 males). Table 1 summarizes the basic clinical characteristics of the patients and healthy volunteers. There were no significant differences in the gender, body mass index, predicted percentage of forced expiratory volume in 1 s (FEV₁% predicted) and smoking status between the COPD and the control groups (all $P > 0.05$). However, patients with COPD were significantly older

Table 1: Characteristics of the COPD and control group.

Characteristics	Case (n = 296)	Control (n = 300)	Statistical values	P
Age (years)	67.1 ± 8.8	54.9 ± 9.6	3.215*	<0.001
Male	244 (82.4)	251 (83.6)	6.645†	0.688
BMI (kg/m ²)	23.4 ± 3.3	22.8 ± 3.2	5.424*	0.535
Smoking			3.122†	0.157
Yes	241 (81.4)	212 (70.7)		
No	55 (18.6)	88 (29.3)		
FEV ₁ % predicted (%)	53.1 ± 6.9	89.4 ± 8.8	4.231*	0.165

Data were presented as mean ± standard deviation or n (%). * *t* value. † χ^2 value. COPD: Chronic obstructive pulmonary disease; BMI: Body mass index; Smoking (Yes): Including current smokers and former smokers; Smoking (No): Including individuals who have never smoked regularly; FEV₁% predicted: Predicted percentage of forced expiratory volume in 1 s.

Table 2: Allele frequencies in cases and controls and their associations with COPD (positive loci).

SNP	Position	Locus	Alleles (A/B)	MAF		HWE <i>P</i> value	OR (95% CI)	<i>P</i>
				Case (n = 296)	Control (n = 300)			
rs10512248	98259703	9q22.3	T/G	0.364	0.306	0.521	1.299 (1.021–1.653)	0.033
rs28491365	98276374	9q22.3	T/A	0.251	0.195	0.556	1.388 (1.055–1.827)	0.018
rs28705285	98279801	9q22.3	T/G	0.229	0.180	0.846	1.359 (1.024–1.803)	0.033

COPD: Chronic obstructive pulmonary disease; SNP: Single-nucleotide polymorphism; Alleles (A/B): Minor/major alleles; MAF: Minor allele frequency; HWE: Hardy-Weinberg equilibrium; OR: Odds ratio; CI: Confidence interval.

than controls (67.1 ± 8.8 *vs.* 54.9 ± 9.6 years, *t* = 3.215, *P* < 0.001).

Allele analysis of COPD susceptibility

In total, we identified 28 SNPs in *PTCH1* genes of all subjects [Supplementary Table 1, <http://links.lww.com/CM9/A233>], but only three SNP variants, including the “A” allele of rs28491365 (OR: 1.388, 95% CI: 1.055–1.827, *P* = 0.018) and “G” alleles of rs10512248 (OR: 1.299, 95% CI: 1.021–1.653, *P* = 0.033) and rs28705285 (OR: 1.359, 95% CI: 1.024–1.803, *P* = 0.033) were found to be significantly associated with the risk of COPD development [Table 2]. All the 28 SNPs from controls were in Hardy-Weinberg equilibrium. The call rate of all SNPs was above 97%.

Genotypic model analysis of COPD susceptibility

In this study, we performed logistic regression analysis to analyze the associations between the 28 SNPs and COPD risk using four genetic models (co-dominant, dominant, recessive, and log-additive). Crude analysis revealed that the “T/T” genotype of rs34695652 was associated with a decreased COPD risk under the recessive model (OR: 0.550, 95% CI: 0.350–0.860, *P* < 0.001). After adjusting for age, gender, and smoking status, the “T/T” rs34695652 genotype was confirmed to significantly decrease the risk of COPD in the recessive model (OR: 0.490, 95% CI: 0.270–0.880, *P* = 0.010), indicating that the rs34695652 polymorphism may protect against COPD development. No associations between the other SNPs and COPD were revealed in the recessive model.

Crude analysis under the dominant model showed that T/G-G/G genotype of rs10512248 (OR: 1.450, 95% CI: 1.040–2.010, *P* = 0.020), T/A-A/A genotype of rs28491365 (OR: 1.470, 95% CI: 1.060–2.050, *P* = 0.020), A/C-C/C genotype of rs28469297 (OR: 1.400, 95% CI: 1.010–1.940, *P* = 0.040), and T/G-G/G genotype of rs28705285 (OR: 1.420, 95% CI: 1.020–1.990, *P* = 0.030) were significantly associated with an increased risk of COPD. Furthermore, rs10512248 (OR: 1.310, 95% CI: 1.020–1.670, *P* = 0.030), rs28491365 (OR: 1.380, 95% CI: 1.050–1.810, *P* = 0.021), and rs28705285 (OR: 1.350, 95% CI: 1.020–1.790, *P* = 0.030) were significantly associated with COPD under the log-additive model. However, after adjustment for age, gender, and smoking status, no correlations between these SNPs and COPD were revealed by logistic regression analysis [Table 3]. There were no statistically significant associations between the other 23 SNPs and COPD risk [Supplementary Table 2, <http://links.lww.com/CM9/A233>].

Haplotype and LD association analysis

As shown in Figure 1, seven LD blocks including 19 SNPs with *D'* = 1 were detected. Analysis of the association between haplotypes and COPD by Pearson's Chi-squared test revealed that two SNPs, rs28504650 and rs10512248, formed four haplotypes: CG, CT, TG, and TT. After adjustment for age, gender, and smoking status, only the CG haplotype was found to be related to an increased risk of COPD (OR: 6.364, 95% CI: 1.220–33.292, *P* = 0.028) [Table 4]. Furthermore, another pair of SNPs, rs113154802 and rs28705285, formed three haplotypes: CG, CT, and

Table 3: Genotypic model analysis of relationships between SNPs and COPD.

SNP	Model	Genotype	Case (n = 296)	Control (n = 300)	Unadjusted		Adjusted*	
					OR (95% CI)	P	OR (95% CI)	P
rs10512248	Co-dominant	T/T	115 (38.9)	144 (48.0)	1		1	
		T/G	146 (49.3)	128 (42.7)	1.428 (1.015–2.009)	0.040	1.403 (0.918–2.143)	0.110
		G/G	35 (11.8)	28 (9.3)	1.565 (0.899–2.724)	0.113	1.561 (0.768–3.169)	0.218
	Dominant	T/T	115 (38.9)	144 (48.0)	1		1	
		T/G–G/G	181 (61.1)	156 (52.0)	1.450 (1.040–2.010)	0.020	1.370 (0.900–2.080)	0.140
	Recessive	T/T–T/G	261 (88.2)	272 (90.7)	1		1	
		G/G	35 (11.8)	28 (9.3)	1.300 (0.770–2.200)	0.320	1.250 (0.630–2.500)	0.510
	Log-additive				1.310 (1.020–1.670)	0.030	1.260 (0.910–1.730)	0.150
rs28491365	Co-dominant	T/T	166 (56.1)	196 (65.3)	1		1	
		T/A	111 (37.5)	91 (30.3)	1.440 (1.019–2.035)	0.030	1.867 (0.745–4.677)	0.152
		A/A	19 (6.4)	13 (4.3)	1.726 (0.827–3.599)	0.145	1.367 (0.891–2.097)	0.182
	Dominant	T/T	166 (56.1)	196 (65.3)	1		1	
		T/A–A/A	130 (43.9)	104 (34.7)	1.470 (1.060–2.050)	0.020	1.360 (0.880–2.070)	0.150
	Recessive	T/T–T/A	277 (93.6)	287 (95.7)	1		1	
		A/A	19 (6.4)	13 (4.3)	1.510 (0.730–3.120)	0.260	1.650 (0.640–4.230)	0.290
	Log-additive				1.380 (1.050–1.810)	0.021	1.320 (0.930–1.870)	0.110
rs28469297	Co-dominant	A/A	156 (52.7)	183 (61.0)	1		1	
		A/C	121 (40.9)	100 (33.3)	1.419 (1.010–1.995)	0.040	1.461 (0.959–2.225)	0.760
		C/C	19 (6.4)	17 (5.7)	1.311 (0.658–2.610)	0.440	1.266 (0.485–3.298)	0.077
	Dominant	A/A	156 (52.7)	183 (61.0)	1		1	
		A/C–C/C	140 (47.3)	117 (39.0)	1.400 (1.010–1.940)	0.040	0.940 (0.610–1.450)	0.090
	Recessive	A/A–A/C	277 (93.6)	283 (94.3)	1		1	
		C/C	19 (6.4)	17 (5.7)	1.140 (0.580–2.240)	0.700	0.990 (0.405–2.419)	0.982
	Log-additive				1.270 (0.970–1.667)	0.070	1.271 (0.908–1.777)	0.180
rs28705285	Co-dominant	T/T	176 (59.5)	203 (67.7)	1		1	
		T/G	104 (35.1)	86 (28.7)	1.395 (0.983–1.979)	0.060	1.221 (0.780–1.911)	0.180
		G/G	16 (5.4)	11 (3.7)	1.678 (0.758–3.711)	0.201	2.333 (0.793–6.859)	0.181
	Dominant	T/T	176 (59.5)	203 (67.7)	1		1	
		T/G–G/G	120 (40.5)	97 (32.3)	1.420 (1.020–1.990)	0.030	1.310 (0.850–2.020)	0.210
	Recessive	T/T–T/G	280 (94.6)	289 (96.3)	1		1	
		G/G	16 (5.4)	11 (3.7)	1.500 (0.680–3.290)	0.310	2.180 (0.740–6.340)	0.150
	Log-additive				1.350 (1.020–1.790)	0.030	1.330 (0.920–1.920)	0.120
rs34695652	Co-dominant	G/G	105 (35.5)	111 (37.0)	1		1	
		G/T	155 (52.4)	129 (43.0)	1.270 (0.891–1.811)	0.180	1.136 (0.719–1.795)	0.073
		T/T	36 (12.2)	60 (20.0)	0.634 (0.387–1.037)	0.069	0.533 (0.281–1.900)	0.507
	Dominant	G/G	105 (35.5)	111 (37.0)	1		1	
		G/T–T/T	191 (64.5)	189 (63.0)	1.060 (0.760–1.490)	0.600	0.940 (0.610–1.450)	0.520
	Recessive	G/G–G/T	260 (87.8)	240 (80.0)	1		1	
		T/T	36 (12.2)	60 (20.0)	0.550 (0.350–0.860)	<0.001	0.490 (0.270–0.880)	0.010
	Log-additive				0.870 (0.690–1.100)	0.260	0.800 (0.590–1.080)	0.150

Data were presented as *n* (%). * Adjusted for age, gender, and smoking status. SNP: Single-nucleotide polymorphism; COPD: Chronic obstructive pulmonary disease; OR: Odds ratio; CI: Confidence interval.

TT; among them, the CG haplotype was found to be significantly associated with the COPD risk by crude analysis (OR: 1.335, 95% CI: 1.010–1.770, $P = 0.044$), but the association was not confirmed after adjustment for age, gender, and smoking status (OR: 1.354, 95% CI: 0.956–1.918, $P = 0.087$). Results of haplotype analysis for the other SNPs are shown in Supplementary Table 3, <http://links.lww.com/CM9/A233>.

Discussion

In this case-control study, we evaluated the associations between COPD and 28 selected SNPs of the *PTCH1* gene

in a Chinese Han population from Hunan province. The results indicated that three SNPs, rs10512248, rs28491365, and rs28705285, were associated with an increased risk of COPD, whereas one SNP, rs34695652 was correlated with a decreased risk of the disease.

Previous studies have shown that the Hh signaling pathway is involved in the origin of several pathological conditions such as cancer and Hirschsprung disease,^[6,7,16,17] and plays a key role in embryogenesis, including pulmonary branch formation and lung development.^[18–20] PTCH1 is a key signaling molecule in the Hh signaling pathway, which binds to Hh ligands, thus activating the Hh cascade. The Hh

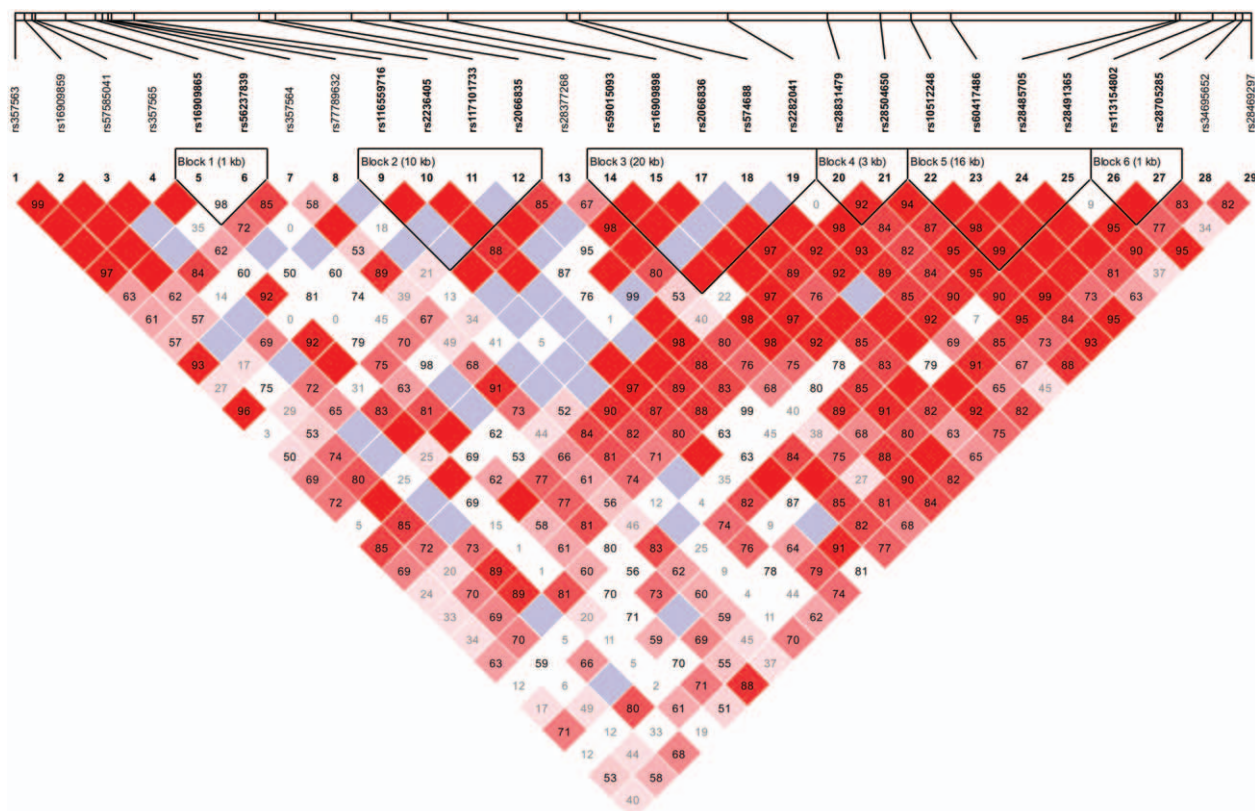


Figure 1: The haplotype block map constructed by candidate single-nucleotide polymorphisms in *PTCH1*.

Table 4: Haplotype frequencies of *PTCH1* gene polymorphisms and the associations with COPD risk.

SNP	Haplotype	Frequency		Unadjusted		Adjusted*	
		Case (n = 296)	Control (n = 300)	OR (95% CI)	P	OR (95% CI)	P
rs28504650/rs10512248	CT	0.615	0.668	1		1	
	CG	0.019	0.003	5.830 (1.280–26.580)	0.023	6.364 (1.220–33.292)	0.028
	TG	0.346	0.303	1.218 (0.951–1.560)	0.117	1.192 (0.872–1.630)	0.268
	TT	0.020	0.025	0.837 (0.395–1.773)	0.642	1.177 (0.439–3.151)	0.745
rs113154802/rs28705285	CT	0.650	0.722	1		1	
	CG	0.230	0.180	1.335 (1.010–1.770)	0.044	1.354 (0.956–1.918)	0.087
	TT	0.120	0.098	1.303 (0.889–1.910)	0.173	1.215 (0.753–1.959)	0.423

* Adjusted for age, gender, and smoking status. COPD: Chronic obstructive pulmonary disease; SNP: Single-nucleotide polymorphism; OR: Odds ratio; CI: Confidence interval.

signaling pathway is implicated in the COPD development, which is consistent with a genome-wide association studies showing that SNPs rs16909898, rs16909859, and rs10512249 in the *PTCH1* gene were significantly associated with pulmonary function in European population.^[21] Another study revealed that rs10512248 was correlated with FEV₁ and forced vital capacity.^[9] Furthermore, it was shown that *PTCH1* was a negative regulator of Hh pathway and the expression of the *PTCH1* protein was increased in the airway epithelium of patients with COPD.^[22] These findings together with our results suggest that *PTCH1* is related to COPD pathogenesis and may be a causal gene in the disease development.

SNP rs10512248 and rs28491365 identified in our study are located in intronic regions, which in most cases are not involved in protein synthesis and are considered as “junk DNA.” However, some studies indicate that introns can participate in gene expression at multiple levels in mammals; thus, regulatory elements in the intron region were shown to directly affect transcription.^[23,24] Therefore, we speculate that the SNP (rs10512248 and rs28491365) could be involved in the pathogenesis of COPD through regulation of *PTCH1* expression. The other identified SNPs rs28705285 and rs34695652 are located in 5' flanking region and our results indicate that they are significantly associated with an increased and decreased risk of COPD, respectively.

Thus, our study provides a new insight into the effect of common mutations in the *PTCH1* gene on the susceptibility to COPD in the Chinese Han population, presenting further evidence of *PTCH1* involvement in the disease pathogenesis. To the best of our knowledge, this is the first report about the association between *PTCH1* polymorphisms and the COPD risk in the Chinese population. However, the functional changes caused by *PTCH1* mutations are not fully understood and the obtained results need to be confirmed in future studies on the role of the *PTCH1* gene in COPD.

Our study had several intrinsic limitations. First, we could not confirm the interaction between genetic polymorphisms and environmental risk factors such as tobacco smoking which significantly increases the susceptibility to COPD, because our sample size was not sufficient. Studies involving a larger number of participants should be conducted in the future to explore the association between *PTCH1* polymorphisms and the smoking status of patients with COPD. Second, the molecular mechanism underlying the association of COPD with *PTCH1* polymorphisms was not clarified. After statistical adjustment, the significance of the association was not confirmed for some SNPs. Analysis of a higher number of loci is needed to verify the results of this study. In our study, the age difference was statistically significant between the two groups, however, we did not perform age-stratified analysis due to limited sample size.

In summary, we identified, for the first time, three loci (rs10512248, rs28491365, and rs28705285) positively associated and one locus (rs34695652) negatively associated with COPD susceptibility in a Chinese Han population. This information should contribute to understanding of the COPD pathogenesis and provide a foundation for further research into the correlation between the *PTCH1* gene and the COPD risk in different populations, thus promoting the development of new therapeutic strategies for this disease.

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Conflicts of interest

None.

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