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# TRPV1 genetic polymorphisms and risk of COPD or COPD combined with PH in the Han Chinese population

Mingmei Xiong[a*], Meihua Guo[b*], Dongjian Huang[a], Jing Li[a], and Yan Zhou[a]

[a]Department of Critical Care Medicine, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [b]Department of Respiration, Guangzhou Chest Hospital, Guangzhou, China

**ABSTRACT**

COPD is a common chronic disease with genetic predisposition. TRPV1 is mainly expressed in peripheral neuron which widely exists in entire respiratory tract. In present study, we aimed to study the relationship between single nucleotide polymorphisms (SNPs) of transient receptor potential vanilloid-1 (TRPV1) and the risk of chronic obstructive pulmonary disease (COPD) or COPD combined with pulmonary hypertension (PH) in Chinese Han population. A total of 1019 individuals, including 506 healthy volunteers and 513 COPD patients (150 patients combined with PH among them) were recruited in this study. Genomic DNA were extracted and sequenced. Genotype and allele frequencies of the TRPV1 SNPs among COPD, COPD combined with PH and control groups were compared. Then, the association of TRPV1 SNPs and smoking status were analyzed. Genotype frequencies of SNP rs3744683 had a significant difference in COPD patients with PH patients compared with control ($p$ = 0.006) or COPD patients without PH patients ($p$ = 0.016). Likewise, SNP rs3744683 was remarkedly associated with the risk of COPD ($p$ = 0.004) in current-smoker groups which phenomenon was not observed in nonsmoker or former-smoker groups. Compared with the control group, there was a significant difference for the distribution of SNP rs4790521 alleles in the COPD group ($p$ = 0.041). For further, logical regression analysis showed that SNP rs3744683 genotype of "TC" was a protective factor for PH in COPD patients compared with the genotype of "TT" (OR = 0.364, 95%CI = 0.159–0.829, $p$ = 0.016). Our findings firstly revealed the relevance between TRPV1 SNPs and the risk for COPD/COPD combined with PH.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by persistent respiratory tract symptoms and incomplete reversible airflow limitation, which has currently become the third leading cause of death worldwide [1]. In general, COPD is aggravated and associated with chronic inflammatory response of the airway and the lung when exposed to respirable noxious gas or particles [2]. The pathogenic factors for COPD are various and complex, including genetic factors, protease/anti-protease imbalances, environmental noxious gas or particles, and inflammation [3]. Although tobacco smoking is considered to be the primary environmental factor for COPD [4], several genome-wide association (GWA) studies and the phenomenon of familial aggregation in COPD patients reflect that genetic factors may play a critical role in COPD development as well [5–8].

In general, pulmonary hypertension (PH) is defined as over 25 mmHg of the mean pulmonary arterial blood pressure in a resting state, which is a common complication in chronic respiratory disease [9]. In COPD patients, the occurrence of PH is associated with aggravated condition and increased mortality [10]. Meanwhile, level of pulmonary arterial pressure is also a critical indicator for COPD prognosis [11].

Transient receptor potential vanilloid-1 (TRPV1) belongs to the transient receptor potential (TRP) family of ion channels, involving in multiple cellular progress[12]. As a transmembrane ion-channel-protein, TRPV1 is mainly expressed in peripheral neuron to function as a cellular sensor [13]. It can be activated or

**CONTACT** Mingmei Xiong mmx_xiong@sina.com
*These authors contributed equally to this work.

modulated by various stimulating factors, such as heat, capsaicin, acidic pH, endocannabinoid anandamide, and ethanol [14–17]. Since the important sensory transducer function of TRPs, many researchers have devoted to study the functional and pathogenic characterization of these TRPs channels. Study in Spanish children by Gerard. C et al. have reported that TRPV1 SNP (single nucleotide polymorphism) rs8065080 is relevant for asthma by means of reducing channel activity in response to heat and capsaicin [18]. In our previous study, we have investigated the association between transient receptor potential cation channel subfamily M member 8 (TRPM8, another TRP family member) gene SNPs and COPD/COPD combined with PH [19]. In present study, we aim to explore the relationship between TRPV1 gene SNPs and COPD/COPD combined with PH in Chinese Han population.

## Materials and methods

### Study population

A total of 1,019 Chinese Han individuals, including 506 COPD patients and 513 healthy persons, were recruited in this study. Demographic and clinical information (gender, age, ethnicity, smoking status/index, and BMI et al.) were collected from all individuals. COPD was diagnosed according to the criteria of the WHO Global initiative for chronic Obstructive Lung Disease (GOLD) or National Heart, Lung and Blood Institute (NHLBI) [20]. PH in present study was confirmed by transthoracic Doppler echocardiography. The inclusion/exclusion criteria for patients with COPD/COPD combined with PH were described in our previous study [19]. 432 males and 81 females were included in the COPD group, with an average age of 68.02 ± 11.21(mean ± SD). 414 males and 92 females were included in the control group (healthy individuals), with an average age of 56.49 ± 9.43 (mean ± SD). 5 mL peripheral blood was drawn from each enrolled person. Written informed consents were obtained from all recruited individuals before the study. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University.

### Spirometry and TTE

Based on the GOLD guideline, patients with post-bronchodilator (BD) $FEV_1$/FVC (forced expiratory volume in 1 sec/forced vital capacity) ratio < 0.7 and age ≥ 40 years were regarded as COPD cases. $FEV_1$% was presented as the percentage of $FEV_1$ in predicted $FEV_1$ for men/women. According to the Morris's predictive equations, predicted $FEV_1$ for men/women was calculated as following: predicted $FEV_1$ for men = 0.092× height (in inches) − 0.032 × age −1.26; predicted $FEV_1$ for women = 0.089 × height (in inches) − 0.025 × age −1.932.

PH in the study was determined by TTE. In detail, TTE was used to evaluate the right ventricular systolic pressure (RVSP), which value was equal to the systolic pulmonary arterial pressure. RVSP could be calculated by the simplified Bernoulli equation: RVSP = $4v^2$ + RAP (right atrial pressure), $v$ (m/s) = the peak velocity of the TR jet. Pulmonary artery systolic pressure (PASP) was equal to RVSP when without the existence of pulmonic stenosis or right ventricular outflow obstruction. In present study, COPD patients with the peak velocity of the TR jet ≥ 2.8 m/s and PASP ≥ 40 mmHg were considered as COPD combined with PH cases.

### Sequencing and TRPV1 SNPs selection

The procedures for DNA sequencing were similar with the descriptions in our earlier study [19]. Briefly, genomic DNA was extracted from 5 mL blood sample by using a QIAamp DNA Blood Mini Kit (QIAGEN Co. Ltd., Germany). Quantified the concentration of extracted DNA using a Nano Drop 2000 ultraviolet spectrophotometer (Thermo Scientific, USA). Amplified the DNA fragments by using an EasyTarget™ Amplification Kit (Genesky Biotechnologies, Inc., China). Sequenced the DNA by using a HiSeq 2000 Sequencer (Illumina, Inc., USA). Then, mapped the sequences against reference genome using Burrows-Wheeler Aligner software (BWA, v0.7.5a). *TRPV1* SNPs (rs465563, rs3744683, rs224495, and rs4790521, respectively) discovery and genotyping were performed using the Genome Analysis Toolkit (GATK). SNP annotation was performed using the Annovar program.

### Statistical analysis

An exact test was performed to access Hardy–Weinberg equilibrium (HWE) for SNP genotypes in enrolled population [21]. Data in the study were presented as mean ± SD. Comparison between quantitative data was performed with one-way analysis of variance (one-way ANOVA), and comparison between qualitative data were performed with Fisher's exact test or $\chi^2$ test. The association between genetic polymorphisms and COPD/COPD combined with PH were analyzed by establishing multivariate logistic regression models. Assuming one homozygosity as the reference, odds ratios (ORs) and 95% confidence intervals (95% CI) of the other genotypes were calculated. Analyses were also adjusted with age, sex, and smoking status. Analyses in present study were performed by using MedCalc Statistical Software version 15.2.2 (MedCalc Software bvba, Ostend, Belgium). $P < 0.05$ was regarded as significant statistical difference.

## Results

The general and clinical information of the enrolled population are shown in Table 1. 506 healthy volunteers were in the control group, and 513 COPD patients were in the COPD group, of which 150 cases were combined with PH. Patients with COPD were divided into COPD with PH group and COPD without PH group according to their PASP. There was no significant difference in aspects of gender, smoking status and BMI between the control and COPD without/with PH groups. However, the average age of the control group was significantly lower than either the COPD without PH group (56.49 ± 9.43 *vs.* 67.19 ± 10.60, $p < 0.05$) or the COPD with PH group (56.49 ± 9.43 *vs.* 70.03 ± 12.37, $p < 0.05$). Meanwhile, compared with the control group, the smoking index (SI, product of smoking amounts every day and smoking year) of the COPD group was significant higher, which indicated that COPD patients have longer exposure to cigarette smoking than healthy people (42.68 ± 27.9 *vs.* 38.97 ± 25.18, $p < 0.05$). Similarly, the pulmonary function of COPD patients was much worse than that in the control group, in aspects of $FEV_1$% (predicted, $p < 0.001$) and $FEV_1$/FVC % ($p < 0.001$). The percentage of $FEV_1$/FVC in COPD patients with PH was also significantly lower than that in COPD patients without PH (0.43 ± 0.15 *vs.* 0.45 ± 0.26, $p < 0.05$). There was a significant difference in aspect of PASP between COPD patients with PH and COPD patients without PH (25.37 ± 5.73 *vs.* 49.64 ± 14.25, $p < 0.05$).

### Association between TRPV1 SNPs and the risk for COPD/COPD combined with PH

The genotypes and allele frequencies of the 4 types of *TRPV1* SNPs (rs465563, rs3744683, rs224495 and rs4790521) in control, COPD, and COPD with PH groups are presented in Table 2. $\chi^2$ test showed that the distribution of SNP rs3744683 genotypes and alleles in the COPD with PH group had a significant difference compared with

**Table 1.** General and clinical information of the population recruited in the study.

| | | COPD | |
|---|---|---|---|
| Characteristics | Control | Without PH | With PH |
| Case number | 506 | 363 | 150 |
| Gender (male/female) | 414/92 | 306/57 | 126/24 |
| Age (years) | 56.49 ± 9.43 | 67.19 ± 10.60 # | 70.03 ± 12.37 # |
| Smoking (no/yes) | 121/385 | 91/271 | 35/116 |
| Smoking index (pack-year) | 38.97 ± 25.18 | 42.68 ± 27.9 # | 44.16 ± 26.67 # |
| BMI (kg/m$^2$) | 24.18 ± 2.48 | 23.57 ± 2.69 | 24.16 ± 2.27 |
| $FEV_{1\%}$ (predicted) | 95.77 ± 12.98 | 37.23 ± 18.64 # | 35.67 ± 16.10 # |
| $FEV_1$/FVC % | 0.81 ± 0.96 | 0.45 ± 0.26 # | 0.43 ± 0.15 # * |
| PASP (mmHg) | | 25.37 ± 5.73 | 49.64 ± 14.25 * |

Notes: # $p < 0.05$ represents significant difference, compared with control. * $p < 0.05$ represents significant difference, compared with COPD without PH.

Abbreviations: BMI, body mass index; COPD, Chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in one second; FVC, forced vital capacity; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension.

**Table 2.** Genotype and allele frequencies of the SNPs in different population groups.

| SNPs | Genotypes | Control (n = 506) | COPD (n = 513) | $P^a$ | COPD with PH (n = 150) | $P^b$ |
|---|---|---|---|---|---|---|
| rs465563 | G/G | 43 (8.5) | 47 (9.11) | 0.854 | 13 (8.67) | 0.91 |
| | A/A | 242 (47.83) | 245 (47.48) | | 73 (48.67) | |
| | G/A | 209 (41.3) | 202 (39.15) | | 58 (38.67) | |
| | G:A | 295:693 | 296:692 | 1 | 84:204 | 0.879 |
| rs3744683 | T/T | 438 (86.56) | 454 (87.98) | 0.118 | 141 (94) | 0.006 |
| | C/C | 0 | 2 (0.39) | | 1 (0.67) | |
| | T/C | 67 (13.24) | 50 (9.69) | | 7 (4.67) | |
| | T:C | 943:67 | 958:54 | 0.256 | 289:9 | 0.028 |
| rs224495 | G/G | 313 (61.86) | 305 (59.11) | 0.704 | 85 (56.67) | 0.297 |
| | A/A | 18 (3.56) | 22 (3.93) | | 9 (6) | |
| | G/A | 172 (33.99) | 179 (34.69) | | 55 (36.67) | |
| | G:A | 798:208 | 789:223 | 0.49 | 225:73 | 0.184 |
| rs4790521 | T/T | 293 (57.91) | 270 (52.33) | 0.11 | 80 (53.33) | 0.353 |
| | C/C | 21 (4.15) | 31 (6) | | 10 (6.67) | |
| | T/C | 160 (31.62) | 184 (35.66) | | 50 (33.33) | |
| | T:C | 746:202 | 724:246 | 0.041 | 210:70 | 0.221 |

Notes: [a] *P*-value were calculated by $\chi^2$ test, COPD group compared with control. [b] *P*-value were calculated by $\chi^2$ test, COPD combined with PH group compared with control. The ratio of alleles(A:B) were calculated as: AB+2*AA: AB+2*BB.
Abbreviations: SNP, single nucleotide polymorphism; COPD, Chronic obstructive pulmonary disease; PH, pulmonary hypertension.

the control group ($p = 0.03$, and $p = 0.028$, respectively), indicating that the major allele "T" in SNP rs3744683 was related to the risk of COPD combined with PH. Meanwhile, compared with the control group, there was a significant difference for the distribution of SNP rs4790521 alleles in the COPD group ($p = 0.041$).

The association analysis of the *TRPV1* SNPs (rs3744683 and rs4790521) gene models and the risk of COPD are shown in Table 3. There was no significant difference in the alternation of COPD risk under different SNP rs3744683 gene models. However, it's noteworthy that the SNP rs4790521gene model of "TC+CC" can slightly increase the risk of COPD ($p = 0.062$; OR = 1.289; 95%CI = 1–1.668) compared with gene model of "TT", but adjusting for sex, age, and smoking status fade this influence. For further, we investigated the relationship of *TRPV1* SNPs and risk of PH in COPD patients (Table 4). The results revealed that the genotype "TC" of SNP rs4790521 was significantly associated with a decreased risk of PH in COPD under the codominant model ($p = 0.033$, OR = 0.37, 95%

**Table 3.** Analysis of the association between genotypes of *TRPV1* SNP rs3744683 and rs4790521 and the COPD risk.

| | | | | | Without adjustment | | With adjustment | |
|---|---|---|---|---|---|---|---|---|
| SNPs | Model | Genotypes | Control (n = 506) | COPD (n = 513) | OR (95% CI) | $P^a$ | OR (95% CI) | $P^b$ |
| rs3744683 | Codominant | TT | 438 (86.56) | 454 (87.98) | 1 | | 1 | |
| | | TC | 67 (13.24) | 50 (9.69) | 0.72 (0.488–1.062) | 0.118 | 0.787(0.51–1.214) | 0.278 |
| | | CC | 0 | 2 (0.39) | 4.82 (0.231–100.8) | 0.5 | - | - |
| | Dominant | TT | 438 (86.56) | 454 (87.98) | 1 | | 1 | |
| | | TC-CC | 67 (13.24) | 52 (10.08) | 0.749 (0.509–1.1) | 0.141 | 0.841(0.547–1.292) | 0.429 |
| | Recessive | CC | 0 | 2 (0.39) | 1 | | | |
| | | TC-TT | 505 (99.8) | 504 (97.67) | 5 (0.24–104.6) | 0.5 | - | - |
| | Over-dominant | TT-CC | 438 (86.56) | 456 (88.37) | 1 | | 1 | |
| | | TC | 67 (13.24) | 50 (9.69) | 0.717 (0.486–1.06) | 0.093 | 0.78(0.506–1.203) | 0.26 |
| rs4790521 | Codominant | CC | 21 (4.15) | 31 (6) | 1 | | 1 | |
| | | TC | 160 (31.62) | 184 (35.66) | 0.779 (0.431–1.41) | 0.409 | 0.841(0.437–1.616) | 0.603 |
| | | TT | 293 (57.91) | 270 (52.33) | 0.624 (0.35–1.113) | 0.11 | 0.715(0.378–1.352) | 0.301 |
| | Dominant | CC | 21 (4.15) | 31 (6) | 1 | | 1 | |
| | | TC-TT | 453 (89.53) | 454 (87.98) | 0.679 (0.384–1.2) | 0.182 | 0.76(0.406–1.423) | 0.392 |
| | Recessive | TT | 293 (57.91) | 270 (52.33) | 1 | | 1 | |
| | | TC-CC | 181 (35.77) | 215 (41.67) | 1.289 (1–1.668) | 0.062 | 1.203(0.945–1.6) | 0.204 |
| | Over-dominant | TT-CC | 314 (62.06) | 301 (58.33) | 1 | | 1 | |
| | | TC | 160 (31.62) | 184 (35.66) | 1.2 (0.921–1.563) | 0.179 | 1.144(0.853–1.532) | 0.369 |

Notes: $p < 0.05$ represents significant difference. [a] *P*-value were analyzed by $\chi^2$ test or Fisher's exact tests. [b] *P*-value were analyzed by logical regression adjusted for age and smoking status. $p < 0.05$ represents significant difference.
Abbreviations: SNP, single nucleotide polymorphism; COPD, Chronic obstructive pulmonary disease; CI, confidence interval; OR, odds ratio.

**Table 4.** Analysis of the association between genotypes of *TRPV1* SNP rs3744683 and rs4790521 and the risk of COPD combined with PH.

| SNPs | Model | Genotypes | COPD without PH (n = 363) | COPD with PH (n = 150) | Without adjustment | | With adjustment | |
|---|---|---|---|---|---|---|---|---|
| | | | | | OR (95% CI) | *P* [a] | OR (95% CI) | *P* [b] |
| rs3744683 | Codominant | TT | 313 (90.9) | 141 (94) | 1 | | 1 | |
| | | TC | 43 (11.85) | 7 (4.67) | 0.37 (0.162–0.844) | 0.033 | 0.364 (0.159–0.829) | 0.016 |
| | | CC | 1 (0.28) | 1 (0.67) | 2.22 (0.138–35.745) | 0.574 | 3.255 (0.196–54.041) | 0.41 |
| | Dominant | TT | 313 (90.9) | 141 (94) | 1 | | 1 | |
| | | TC-CC | 44 (12.12) | 8 (5.33) | 0.404 (0.185–0.88) | 0.029 | 0.411 (0.188–0.897) | 0.026 |
| | Recessive | CC | 1 (0.28) | 1 (0.67) | 1 | | 1 | |
| | | TC-TT | 356 (98.07) | 148 (98.67) | 0.416 (0.026–6.691) | 0.503 | 0.282 (0.017–4.484) | 0.378 |
| | Over-dominant | TT-CC | 314 (86.5) | 142 (94.67) | 1 | | 1 | |
| | | TC | 43 (11.85) | 7 (4.67) | 0.36 (0.158–0.82) | 0.018 | 0.362 (0.159–0.825) | 0.016 |
| rs4790521 | Codominant | CC | 21 (5.79) | 10 (6.67) | 1 | | | |
| | | TC | 134 (36.91) | 51 (34) | 0.784 (0.345–1.779) | 0.56 | 0.814 (0.357–1.852) | 0.623 |
| | | TT | 190 (52.34) | 80 (53.33) | 0.884 (0.399–1.962) | 0.765 | 0.923 (0.415–2.054) | 0.844 |
| | Dominant | CC | 21 (5.79) | 10 (6.67) | 1 | | 1 | |
| | | TC-TT | 324 (89.26) | 131 (87.33) | 0.843 (0.386–1.838) | 0.67 | 0.877 (0.401–1.919) | 0.743 |
| | Recessive | TT | 190 (52.34) | 80 (53.33) | 1 | | 1 | |
| | | TC-CC | 155 (42.7) | 61 (40.67) | 0.919 (0.619–1.366) | 0.678 | 0.91 (0.611–1.354) | 0.614 |
| | Over-dominant | TT-CC | 211 (58.13) | 90 (60) | 1 | | 1 | |
| | | TC | 134 (36.91) | 51 (34) | 0.875 (0.582–1.315) | 0.52 | 0.874 (0.581–1.361) | 0.519 |

Notes: [a] *P*-value were analyzed by $\chi^2$ test or Fisher's exact tests. [b] *P*-value were analyzed by logical regression adjusted for age and smoking status. $p < 0.05$ represents significant difference.

Abbreviations: SNP, single nucleotide polymorphism; PH, pulmonary hypertension; COPD, Chronic obstructive pulmonary disease; CI, confidence interval; OR, odds ratio.

CI = 0.162–0.844), and over-dominant model ($p$ = 0.018, OR = 0.36 95%CI = 0.158–0.82). After adjusting for age, sex and smoking status, the influence of SNP rs479052 gene models on the risk of PH in COPD patients still existed. No significant difference was observed in the distribution of SNP rs3744683 gene models between COPD without PH and COPD with PH groups.

### Association between TRPV1 SNPs and smoking status in patients with COPD

A stratification analysis was performed to investigate the genotypes and allele frequencies of the 4 *TRPV1* SNPs (rs465563, rs3744683, rs224495 and rs4790521) in control and COPD groups with different smoking status (Table 5). No significant difference was observed in the distribution of genotypes and alleles of *TRPV1* SNPs in

**Table 5.** Stratified analysis of association between *TRPV1* SNPs (rs465563, rs3744683, rs224495 and rs4790521) and smoking status.

| SNPs | Genotypes | Nonsmokers (n = 247) | | | Former-smokers (n = 454) | | | Current-smokers (n = 318) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Control (n = 121) | COPD (n = 126) | *P* | Control (n = 240) | COPD (n = 214) | *P* | Control (n = 145) | COPD (n = 173) | *P* |
| rs465563 | G/G | 11 (9.09) | 8 (6.35) | | 21 (8.75) | 23 (10.75) | | 11 (7.59) | 16 (9.25) | |
| | A/A | 61 (50.41) | 69 (54.76) | 0.779 | 109 (45.42) | 90 (42.06) | 0.119 | 72 (49.66) | 86 (49.71) | 0.58 |
| | G/A | 45 (37.19) | 43 (34.13) | 0.87 | 105 (43.75) | 92 (43) | 0.2 | 59 (40.69) | 67 (38.73) | 0.576 |
| | G:A | 67:167 | 59:181 | 0.372 | 147:323 | 138:272 | 0.471 | 81:203 | 99:239 | 0.859 |
| rs3744683 | T/T | 107 (88.43) | 111 (88.1) | | 207 (86.25) | 181 (84.58) | | 124 (85.52) | 162 (93.64) | |
| | C/C | 0 | 1 (0.79) | 0.993 | 0 | 1 (0.47) | 0.993 | 0 | 0 | - |
| | T/C | 14 (11.57) | 11 (8.73) | 0.43 | 33 (13.75) | 28 (13.08) | 0.442 | 20 (13.79) | 11 (6.36) | 0.031 |
| | T:C | 228:14 | 233:13 | 0.845 | 447:33 | 390:30 | 0.896 | 268:20 | 335:11 | 0.04 |
| rs224495 | G/G | 74 (61.16) | 85 (67.46) | | 143 (59.58) | 117 (54.67) | | 96 (66.21) | 103 (59.54) | |
| | A/A | 3 (2.48) | 3 (2.38) | 0.982 | 10 (4.17) | 8 (3.74) | 0.933 | 5 (3.45) | 11 (6.36) | 0.127 |
| | G/A | 43 (35.54) | 35 (27.78) | 0.399 | 86 (35.83) | 85 (39.72) | 0.276 | 43 (29.66) | 59 (34.1) | 0.274 |
| | G:A | 191:49 | 205:41 | 0.296 | 368:106 | 319:101 | 0.579 | 235:53 | 265:81 | 0.143 |
| rs4790521 | T/T | 71 (58.68) | 63 (50) | | 140 (58.33) | 113 (52.8) | | 82 (57.75) | 94 (54.34) | |
| | C/C | 4 (3.31) | 5 (3.97) | 0.845 | 8 (3.33) | 13 (6.07) | 0.281 | 9 (6.21) | 13 (7.51) | 0.773 |
| | T/C | 35 (28.93) | 48 (38.1) | 0.183 | 77 (32.08) | 75 (35.05) | 0.605 | 48 (33.1) | 61 (35.26) | 0.85 |
| | T:C | 177:43 | 174:58 | 0.176 | 357:93 | 301:101 | 0.141 | 212:66 | 249:87 | 0.574 |

Notes: $p < 0.05$ represents significant difference. P-values for genotypes were calculated by logistic regression adjusted for age and sex. P-values for allele were calculated by $\chi 2$ test or Fisher's exact tests.

Abbreviations: SNP, single nucleotide polymorphism; COPD, Chronic obstructive pulmonary disease.

nonsmokers and former-smokers. However, in current smokers, a significant difference in the distribution of *TRPV1* SNP rs3744683 alleles was observed between control and COPD groups ($p$ = 0.04), indicating that the genotype "TC" could be a protective factor for COPD in current smokers.

## Discussion

COPD is a common chronic disease with genetic predisposition. In present study, we explored the relationship between TRPV1 gene SNPs and COPD/COPD combined with PH in Chinese Han population. The results suggest that compared with healthy volunteers or COPD without PH patients, the genotypes frequencies of SNP rs3744683 have a significant difference in COPD patients with PH patients. Likewise, SNP rs3744683 was remarkedly associated with the risk of COPD in current smokers, but the same phenomenon was not observed neither in nonsmokers or former smokers.

Environmental noxious gas or particles and genetic factors are the predominant pathogenesis for COPD [3]. It has reported that TRP channels superfamily proteins are expressed in neurons and other cell types to participate in respiratory diseases [22,23]. TRPV1 is mainly expressed in peripheral neuron, which widely exists in entire respiratory tract, including nose, larynx, trachea, smooth muscle, blood vessels and lung. As a sensor for multiple chemical or physical stimuli, TRPV1 acts a key role in the nociception and transmission of pain [24,25]. In patients with respiratory diseases, the expression of TRPV1 in airway nerve and smooth muscle is elevated compared with healthy person [26]. Likewise, either activation or block of TRPV1 lead to an alternation of respiratory response induced by some stimulus. In rat model, the increase of vascular permeability induced by tobacco smoke can be restrained by TRPV1 agonists capsaicin pre-treatment [27]. In TRPV1 knock-out mice, intranasal LPS administration induced airway inflammation and bronchial hyperreactivity are enhanced [28]. It has also been reported that TRPV1 antagonists can restrain the tobacco smoke-induced cough response [29]. Study in Spanish children revealed that TRPV1 SNP rs8065080 is associated with the risk of asthma by means of reducing channel activity in response to heat and capsaicin [18]. In adults, four SNPs of TRPV1 can increase the risk of cough symptoms from irritant exposures in a Europe's population [30]. All these studies suggest a close connection between TRPV1 activity and respiratory diseases. In present study, we found that TRPV1 SNP rs3744683 allele "T" has a significant association with the risk of COPD in current smokers, and TRPV1 SNP rs4790521 allele "C" has a significant association with the risk of COPD in all smoking groups. Hence, we suppose that SNPs of rs3744683 and rs4790521 may regulate the activity of TRPV1 to affect the occurrence of COPD.

PH, as a common complication for COPD, is an important indicator in the prognostic evaluation of COPD patients. The expression of TRPV1 in pulmonary artery smooth muscle cells (PASMC) is involved in the remodeling of pulmonary artery. In rat PASMC, membrane translocation of TRPV1 and activation of the Ca (2+)/calcineurin/NFAT pathway were observed under hypoxic conditions, suggesting that the TRPV1 channel may be associated with signal transduction in the PH pathophysiology [31]. In present study, we found that the genotype and allele frequencies of TRPV1SNP rs3744683 in patients with COPD combined with PH has a significant difference compared with healthy volunteers or COPD patients without PH. We suggest that TRPV1 SNP rs3744683 may act as an independent factor to participate in the occurrence of PH through its particular function in PASMC.

However, there are some limitations in our study. First, further investigation about the expression or activity of TPRV1 protein in COPD patients with different TPRV1 SNPs genotypes is needed to state the underlying mechanism. Second, the size of the investigated population should be greater to get a better study of the association between TPRV1 SNPs and the risk of COPD or PH. Third, in present study, the percentage of rs3744683 genotype "CC" in the investigated population is only 0.2% for which the reason is unclear. We hypothesis this genotype is harmful to the individual survival and development.

In conclusion, we firstly investigate the relationship of TPRV1 SNPs and the risk of COPD or PH in Chinese Han population. We identified that SNP rs3744683 is an independent-related factor for the risk of PH in COPD patients, meanwhile, it promotes the risk of COPD in current smokers. These results might provide us important points to explore the pathogenesis and therapeutic target for COPD or PH.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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