

Role of Genetic Polymorphisms in *IL12Rβ2* in Chronic Obstructive Pulmonary Disease

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Background: Chronic obstructive pulmonary disease (COPD) is the most common chronic inflammatory airway disease. *IL-12Rβ2* (*IL-12Rβ2*) is important for the production of pathogenic Th1 cells. We aimed to explore the association between *IL-12Rβ2* genetic variants and COPD risk among southern Chinese Han population.

Methods: We recruited 996 participants to perform an association analysis through SNPStats online software. We used false-positive report probability analysis to detect whether the positive findings were noteworthy. Haploview 4.2 software and SNPStats were used to conduct the haplotype analysis and linkage disequilibrium. Finally, the interaction of SNP-SNP in COPD risk was evaluated by multi-factor dimensionality reduction.

Results: The study found evidence that genetic loci in *IL-12Rβ2* (rs2201584, rs1874791, rs6679356, and rs3790567) were potentially associated with the COPD susceptibility. In particular, *IL-12Rβ2*-rs2201584 and -rs1874791 showed close associations with COPD risk in both overall and several stratified analyses. Overall analysis or several stratified analyses indicated that allele A or homozygous genotype AA of *IL-12Rβ2*-rs2201584 were risk factors for COPD (Allele A: OR (95% CI) = 1.23 (1.02–1.48), $p = 0.033$; genotype AA: OR (95% CI) = 1.76 (1.15–2.69), $p = 0.009$). The allele A or homozygous genotype AA of *IL-12Rβ2*-rs1874791 were also risk factors for COPD (Allele A: OR (95% CI) = 1.36 (1.10–1.68), $p = 0.004$; genotype AA: OR (95% CI) = 2.17 (1.18–3.99), $p = 0.013$).

Conclusion: Intronic variants in *IL-12Rβ2* (rs2201584, rs1874791, rs6679356, and rs3790567) were associated with the COPD susceptibility. In particular, there were sufficient evidences that *IL-12Rβ2*-rs2201584 and -rs1874791 were associated with the increasing risk of COPD.

Keywords: chronic obstructive pulmonary disease, *IL-12Rβ2*, genetic variants, Chinese Han population

Introduction

Chronic obstructive pulmonary disease (COPD) is a common and frequently-occurring disease of respiratory system. It is a preventable and treatable chronic airway inflammatory disease.^{1,2} For a long time, exploring the potential mechanism related to the occurrence and development of COPD has been a research hotspot. At present, it is widely accepted that airway remodeling in COPD is closely related to repeated inflammatory stimulation and abnormal inflammatory response induced by harmful particles such as cigarette smoke and gas stimulation. Although smoking is an important factor affecting the development of COPD,^{3,4} many studies have reported the importance of genetic factors in the development of COPD in recent years.^{5–7}

Airway inflammation is mediated by the expression of inflammatory genes.^{8–10} Chemokines and cytokines are the most important inflammatory mediators of chronic obstructive pulmonary airway inflammation, such as IL-17,¹¹ IL-4, IL-12¹² and IL-5,¹³ etc. Interleukin-12 receptor (IL-12R), mainly expressed in Th1 cells and natural killer cells (NK cells) producing interferon- γ (IFN- γ), is a heterodimer composed of two different subunits *IL-12Rβ1* and *IL-12Rβ2*.¹⁴ *IL-12/IL-12Rβ2* pathway is a key mediator in Th1 differentiation.¹⁴ More importantly, COPD is related to a series of Th cell-mediated biological processes.^{15,16} Based on the above evidence, we believe that *IL-12β2* is potentially associated

with the development of COPD. Up to now, we have found that many researchers have carried out studies on the association between *IL-12Rβ2* gene polymorphism and pulmonary tuberculosis susceptibility in a variety of populations.^{17–19} However, the association between *IL-12Rβ2* and the occurrence and development of COPD has not been reported.

Therefore, this study intends to conduct a case-control study in southern Chinese Han population. To investigate the association between *IL-12Rβ2* genetic polymorphism and COPD susceptibility. We also conducted a stratified analysis based on some potential risk factors for COPD (age, gender, smoking, drinking, etc.). The association between *IL-12Rβ2* genetic polymorphism and these influencing factors was also evaluated. This study laid a foundation for the study of the mechanism of *IL-12Rβ2* in the occurrence and development of COPD, and provided new ideas for the individualized prevention and treatment of COPD in southern Chinese Han population.

Materials and Methods

Sample Source

We recruited 498 patients with COPD and 498 healthy individuals for this case-control study. The 996 participants were recruited in the same hospital (Hainan General Hospital). We continuously recruited 498 COPD patients in the outpatient or inpatient department of respiratory medicine. These patients were all newly diagnosed. Patients met the clear and diagnostic criteria of the World Health Organization (WHO) on COPD. Incomplete reversibility of airflow restriction is a prerequisite for COPD diagnosis. The main basis was FEV1/FVC <70% and FEV1 <80% predicted value of lung function after inhaling bronchodilators. A few patients without common cough, expectoration, shortness of breath and other clinical symptoms were diagnosed with COPD only after FEV1/FVC <70% and FEV1 ≥80% were tested for lung function, excluding other diseases. Exclusion criteria: (1) Patients with pneumonia, bronchial asthma, bronchiectasis, pulmonary tuberculosis, lung cancer, silicosis, interstitial pneumonia and other lung diseases; (2) Patients with serious diseases of heart, liver, kidney and endocrine organs. Patients treated with antibiotics, bronchodilators, and glucocorticoids due to recent severe lung infections. During the same period, 498 healthy individuals were recruited in the health examination center as the control group in this study. We obtained the demographic information and basic epidemiological information of the participants by consulting medical records or professional questionnaire survey. After obtaining the informed consent of all participants, we collected their blood samples for further study. This study has been approved by the ethics committee of the Hainan General Hospital before the beginning.

Selection of SNPs

As shown in Figure 1, the selection process of candidate SNPs is as follows: first, we found that the physical position of the *IL-12Rβ2* was on the Chromosome 1: 67307364–67398724 through the e!GRCh37 database (http://asia.ensembl.org/Homo_sapiens/Info/Index). Then, we use the online converter window (VCF to PED: http://grch37.ensembl.org/Homo_sapiens/Tools/VcftoPed) to download the related files of *IL-12Rβ2* genetic variants. For the population, we chose CHB and CHS. Finally, after setting specific conditions, six candidate *IL-12Rβ2* SNPs (rs2201584, rs10489626, rs6659932, rs1874791, rs6679356, and rs3790567) were selected using Haploview software. These special conditions are as follows: Tagger $r^2 > 0.8$, Min Genotype > 75%, MAF > 0.05 and HWE > 0.01.

DNA Extraction and Genotyping

In this study, we chose the kit (GoldMag Co. Ltd. Xi'an, China) to complete the extraction and purification of genomic DNA, and the specific experimental steps were carried out according to the instructions. According to the DNA sequence of *IL-12Rβ2*, we designed specific amplification primers and extension primers for candidate genetic loci by MassARRAY Assay Design software. Genotyping was performed by the MassARRAY® -IPLEX SNP genotyping technology.

At the same time, we randomly selected 5% DNA samples for repeated experiments. The repetition rate of the results should reach >99% to ensure the reliability and repeatability of the experimental results.

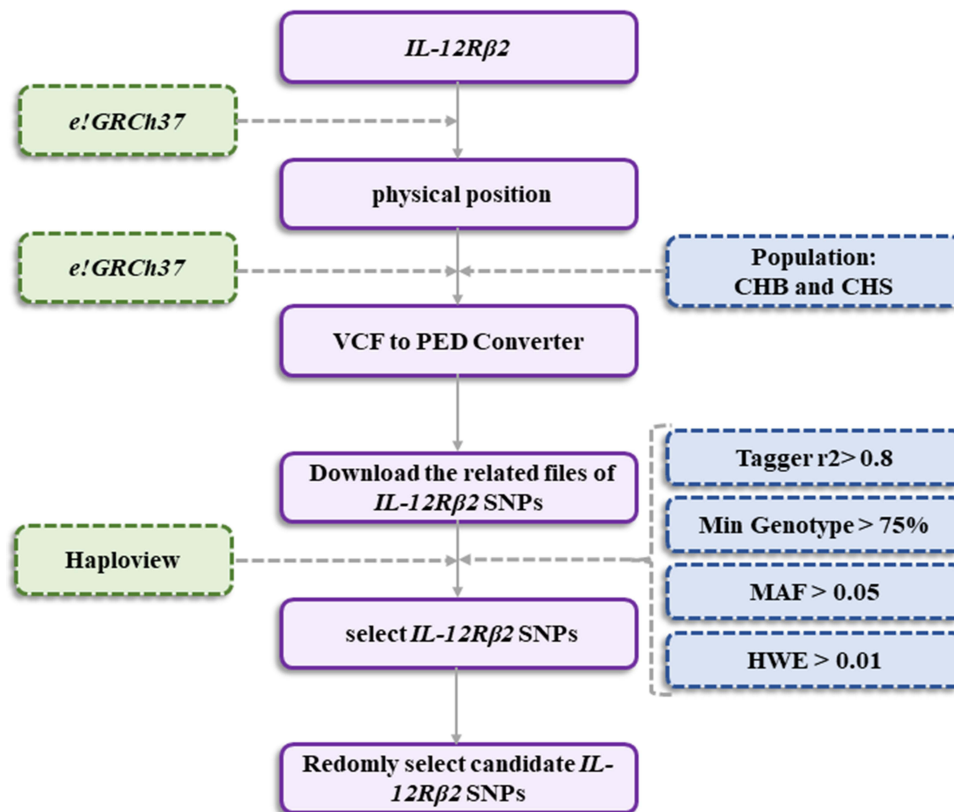


Figure 1 Flowchart for screening candidate SNPs.

Abbreviations: CHB, Han Chinese population in Beijing, China; CHS, Han Chinese population in Shanghai, China.

Data Analysis

We used online software (HaploReg v4.1: <https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>) to predict the potential function of candidate SNPs. In this study, continuous variables such as age, forced vital capacity (FVC), and forced the first second of expiratory volume (FEV1) were expressed as “mean ± standard deviation”. Categorical variables such as sex, smoking or alcohol status were expressed as frequency. The p value of continuous variables was calculated by t -test, and the p value of categorical variables was calculated by Chi-square test. The statistical analysis of this study was mainly completed by SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). In this study, the association between COPD risk and candidate genetic polymorphism under multiple genetic models was completed by SNPStats online software (<https://www.snpstats.net/start.htm?q=snpstats/start.htm>). We mainly evaluated the impact of candidate SNPs on the risk of COPD through the Odds ratios (OR) and 95% confidence intervals (CI). In order to avoid the influence of confounding factors on the results, all the results were adjusted by the confounding factors, such as age, gender, smoking or drinking. In addition, we also used false-positive report probability (FPRP) analysis to detect whether all positive results are noteworthy at a prior probability level of 0.25 and FPRP threshold of 0.2. Haploview 4.2 software and SNPStats online software were used to perform the haplotype analysis of candidate SNPs and evaluation of linkage disequilibrium (LD). Finally, the interaction of candidate SNPs in COPD risk was evaluated by multi-factor dimensionality reduction (MDR). The $p < 0.05$ indicated statistically significant.

Results

There were 996 participants in the case group (498) and the control group (498) enrolled in this study. The average ages of the case and control groups were 70.89 ± 10.19 years and 65.86 ± 5.56 years (Table 1). The number of males and females in the case group were 328 (65.9%) and 170 (34.1%), and in the control group were 322 (64.7%) and 176 (35.3%), respectively. The basic information of the participants can be found in Table 1.

Table 1 Characteristics of Patients with COPD and Healthy Individuals

Characteristics		Cases	Control	p
		n = 498	n = 498	
Age (years)	Mean ± SD	70.89 ± 10.19	65.86 ± 5.56	<0.0001 ^a
	>68	311 (62.4%)	126 (25.3%)	
	≤68	187 (37.6%)	372 (74.7%)	
Gender	Male	328 (65.9%)	322 (64.7%)	0.690 ^b
	Female	170 (34.1%)	176 (35.3%)	
Smoking status	Yes	218 (43.8%)	221 (44.4%)	0.898 ^b
	No	280 (56.2%)	277 (55.6%)	
Drinking status	Yes	251 (50.4%)	255 (51.2%)	0.800 ^b
	No	247 (49.6%)	243 (48.8%)	
FVC (L)		2.10 ± 0.62		
FEV1 (L)		1.12 ± 0.39		
FEV1/FVC		0.57 ± 0.23		

Notes: ^aRepresents the p value calculated by the t-test; ^brepresents the p value calculated by the chi-square test.

Abbreviations: COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV1, forced the first second of expiratory volume.

Genotyping and Information About Candidate SNPs

Six *IL-12Rβ2* candidate genetic loci (rs2201584, rs10489626, rs6659932, rs1874791, rs6679356, and rs3790567) have been successfully genotyped. These genetic variants are all intronic variants in *IL-12Rβ2*. After testing, the distribution of all candidate genetic loci is in accordance with Hardy-Weinberg equilibrium (HWE $p > 5\%$). HaploReg online software was used to predict the potential functions of candidate genetic loci and found that the six SNPs may be regulated by a variety of factors (Table 2).

Association Analysis Between *IL-12Rβ2* SNPs and COPD Risk (Overall Analysis)

The association analysis between candidate SNPs and the COPD risk showed that *IL-12Rβ2*-rs2201584 and rs1874791 were significantly associated with the susceptibility of COPD among participants (Table 3). Specifically, compared with the allele 'G' or homozygous genotype 'GG', 'A' and 'AA' of *IL-12Rβ2*-rs2201584 were risk factors for COPD (A vs G: OR (95% CI) = 1.23 (1.02–1.48), $p = 0.033$; AA vs GG: OR (95% CI) = 1.76 (1.15–2.69), $p = 0.009$). *IL-*

Table 2 The Basic Information and HWE About the Candidate SNPs of *IL-12Rβ2*

SNP ID	Function	Chr: Position	Alleles (A/B)	MAF		HWE (P value)	Haploreg 4.1
				Cases	Controls		
rs2201584	Intronic	1: 67322032	A/G	0.353	0.308	0.461	Motifs changed; GRASP eQTL hits; Selected eQTL hits
rs10489626	Intronic	1: 67327488	G/C	0.044	0.052	1.000	Motifs changed; Selected eQTL hits
rs6659932	Intronic	1: 67336688	A/C	0.040	0.049	0.334	Promoter histone marks; Enhancer histone marks; DNase; Motifs changed; Selected eQTL hits
rs1874791	Intronic	1: 67340749	A/G	0.257	0.203	0.782	Promoter histone marks; Enhancer histone marks; DNase; Motifs changed; Selected eQTL hits
rs6679356	Intronic	1: 67354511	C/T	0.043	0.050	0.354	Motifs changed; GRASP eQTL hits; Selected eQTL hits
rs3790567	Intronic	1: 67356694	A/G	0.291	0.262	0.562	Promoter histone marks; Enhancer histone marks; DNase; Motifs changed; NHGRI/EBI GWAS hits; GRASP eQTL hits; Selected eQTL hits

Note: $P > 0.05$ indicates that the genotypes were in Hardy-Weinberg Equilibrium.

Abbreviations: A, minor allele; B, wild-type allele; HWE, Hardy-Weinberg equilibrium; SNP, single nucleotide polymorphisms; MAF, minor allele frequency.

Table 3 Intronic Variants in *IL-12Rβ2* Associated with Susceptibility of COPD

SNP ID	Model	Genotype	Control	Case	OR (95% CI)	p-value
rs2201584	Allele	G	686 (69.15%)	644 (64.46%)	1	
		A	306 (30.85%)	352 (35.34%)	1.23 (1.02–1.48)	0.033
	Codominant	GG	241 (48.6%)	218 (43.8%)	1	
		AA	204 (41.1%)	208 (41.8%)	1.76 (1.15–2.69)	0.009
		GA	51 (10.3%)	72 (14.5%)	1.05 (0.80–1.39)	0.715
	Dominant	GG	241 (48.6%)	218 (43.8%)	1	
		GA-AA	255 (51.4%)	280 (56.2%)	1.19 (0.91–1.54)	0.200
	Recessive	GG-GA	445 (89.7%)	426 (85.5%)	1	
		AA	51 (10.3%)	72 (14.5%)	1.72 (1.15–2.57)	0.008
	Overdominant	GG-AA	292 (58.9%)	290 (58.2%)	1	
GA		204 (41.1%)	208 (41.8%)	0.94 (0.72–1.22)	0.640	
	Log-additive	-	-	-	1.24 (1.02–1.50)	0.028
rs1874791	Allele	G	786 (79.72%)	740 (74.30%)	1	
		A	200 (20.28%)	256 (25.70%)	1.36 (1.10–1.68)	0.004
	Codominant	GG	312 (63.3%)	279 (56%)	1	
		AA	162 (32.9%)	182 (36.5%)	2.17 (1.18–3.99)	0.013
		GA	19 (3.8%)	37 (7.4%)	1.26 (0.95–1.66)	0.105
	Dominant	GG	312 (63.3%)	279 (56%)	1	
		GA-AA	181 (36.7%)	219 (44%)	1.36 (1.04–1.77)	0.025
	Recessive	GG-GA	474 (96.2%)	461 (92.6%)	1	
		AA	19 (3.8%)	37 (7.4%)	1.99 (1.09–3.64)	0.022
	Overdominant	GG-AA	331 (67.1%)	316 (63.5%)	1	
GA		162 (32.9%)	182 (36.5%)	1.19 (0.90–1.56)	0.220	
	Log-additive	-	-	-	1.35 (1.09–1.69)	0.007

Notes: “-” indicates log-additive model. *p*-value < 0.05 and bold text represent statistical significance.

Abbreviations: COPD, chronic obstructive pulmonary disease; SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

IL12Rβ2-rs2201584 can significantly increase the COPD risk under recessive (AA vs GG-GA, OR (95% CI) = 1.72 (1.15–2.57), *p* = 0.008) and log-additive genetic models (OR (95% CI) = 1.24 (1.02–1.50), *p* = 0.028).

In addition, compared with the allele ‘G’ or homozygous genotype ‘GG’, ‘A’ and ‘AA’ of *IL-12Rβ2*-rs1874791 were risk factors for COPD (A vs G: OR (95% CI) = 1.36 (1.10–1.68), *p* = 0.004; AA vs GG: OR (95% CI) = 2.17 (1.18–3.99), *p* = 0.013). *IL-12Rβ2*-rs1874791 can significantly increase the COPD risk under dominant (GA-AA vs GG, OR (95% CI) = 1.36 (1.04–1.77), *p* = 0.025), recessive (AA vs GG-GA, OR (95% CI) = 1.99 (1.09–3.64), *p* = 0.022) and log-additive genetic models (OR (95% CI) = 1.35 (1.09–1.69), *p* = 0.007).

We found that other intronic variants in *IL-12Rβ2* were not associated with the COPD risk in overall analysis.

Association Analysis Between *IL-12Rβ2* SNPS and COPD Risk (Stratified Analysis)

In order to further avoid the influence of other factors on the reliability of the association analysis results, we divided the participants according to different influencing factors and carried out stratified analyses (age, gender, smoking, drinking).

Age (≤68 Years Old)

The analysis showed (Table 4) that the *IL-12Rβ2*-rs2201584 has a significant association with COPD risk among participants ≤68 years old under recessive genetic model (AA vs GG-GA, OR (95% CI) = 1.74 (1.06–2.84), *p* = 0.029). Heterozygous genotype ‘GA’ of -rs1874791 is a risk factor for COPD AA (GA vs GG: OR (95% CI) = 1.48 (1.00–2.18), *p* = 0.048). And *IL-12Rβ2*-rs1874791 can significantly increase the COPD risk under dominant (GA-AA vs GG, OR (95% CI) = 1.49 (1.04–2.13), *p* = 0.029) and log-additive genetic models (OR (95% CI) = 1.38 (1.02–1.85), *p* = 0.035). We also found evidence that *IL-12Rβ2*-rs6679356 was associated with COPD risk under multiple genetic models (Allele: OR (95% CI) = 0.57 (0.42–0.79), *p* = 0.001; dominant: OR (95% CI) = 0.49 (0.23–1.04), *p* = 0.048; log-additive: OR (95% CI) = 0.49 (0.23–1.02), *p* = 0.042).

Table 4 Intronic Variants in *IL-12Rβ2* Associated with Susceptibility of COPD in the Subgroup Analysis (Age and Gender)

SNP ID	Model	Genotype	≤68 Years Old		>68 Years Old		Female		Male	
			OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
rs2201584	Allele	G								
		A	0.94 (0.66–1.34)	0.740	1.34 (0.97–1.84)	0.075	1.47 (1.06–2.02)	0.019	1.12 (0.88–1.41)	0.357
	Codominant	GG								
		AA	1.61 (0.93–2.79)	0.086	1.96 (0.86–4.47)	0.111	2.57 (1.25–5.29)	0.010	1.43 (0.84–2.42)	0.190
	Dominant	GA	1.01 (0.68–1.51)	0.948	1.10 (0.69–1.75)	0.690	1.26 (0.79–2.00)	0.330	0.94 (0.66–1.33)	0.712
		GG								
	Recessive	GA-AA	1.16 (0.81–1.65)	0.410	1.37 (0.90–2.08)	0.140	1.37 (0.86–2.19)	0.180	1.01 (0.73–1.41)	0.930
		GG-GA								
	Overdominant	AA	1.74 (1.06–2.84)	0.029	1.87 (0.87–4.00)	0.092	2.33 (1.11–4.89)	0.021	1.48 (0.89–2.46)	0.130
		GG-AA								
Log-additive	GA	0.88 (0.61–1.26)	0.470	1.10 (0.73–1.68)	0.640	0.96 (0.60–1.53)	0.860	0.85 (0.61–1.20)	0.350	
	-	1.24 (0.96–1.58)	0.096	1.36 (0.98–1.88)	0.060	1.43 (1.02–2.01)	0.038	1.10 (0.86–1.40)	0.430	
rs1874791	Allele	G								
		A	1.01 (0.48–1.37)	0.423	1.32 (0.93–1.88)	0.125	1.29 (0.91–1.83)	0.156	1.40 (1.08–1.82)	0.012
	Codominant	GG								
		AA	1.34 (0.58–3.09)	0.496	3.33 (0.93–11.95)	0.065	1.79 (0.67–4.80)	0.245	2.56 (1.17–5.6)	0.018
	Dominant	GA	1.48 (1.00–2.18)	0.048	0.99 (0.62–1.58)	0.954	1.16 (0.73–1.83)	0.532	1.32 (0.93–1.88)	0.123
		GG								
	Recessive	GA-AA	1.49 (1.04–2.13)	0.029	1.19 (0.78–1.83)	0.410	1.28 (0.80–2.05)	0.300	1.45 (1.03–2.04)	0.032
		GG-GA								
	Overdominant	AA	1.39 (0.63–3.07)	0.420	3.89 (1.15–13.17)	0.051	1.61 (0.57–4.56)	0.360	2.20 (1.02–4.75)	0.039
		GG-AA								
Log-additive	GA	1.42 (0.99–2.05)	0.061	0.92 (0.59–1.42)	0.700	1.17 (0.72–1.90)	0.530	1.25 (0.88–1.77)	0.220	
	-	1.38 (1.02–1.85)	0.035	1.33 (0.93–1.89)	0.110	1.27 (0.86–1.87)	0.230	1.44 (1.08–1.91)	0.011	
rs6679356	Allele	T								
		C	0.57 (0.42–0.79)	0.001	0.98 (0.52–1.87)	0.958	0.87 (0.39–1.97)	0.742	0.84 (0.51–1.36)	0.469
	Codominant	TT	/	/	/	/	/	/	/	/
		CC	/	/	/	/	/	/	/	/
	Dominant	TC	0.56 (0.26–1.20)	0.134	1.22 (0.58–2.57)	0.596	/	/	0.79 (0.46–1.36)	0.393
		TT								
	Recessive	TC-CC	0.49 (0.23–1.04)	0.048	1.00 (0.51–1.97)	1.000	/	/	0.74 (0.43–1.28)	0.280
		TT-TC	/	/	/	/	/	/	/	/
	Overdominant	CC	/	/	/	/	/	/	/	/
		TT-CC								
Log-additive	TC	0.50 (0.24–1.07)	0.060	1.09 (0.54–2.20)	0.800	/	/	0.80 (0.46–1.39)	0.430	
	-	0.49 (0.23–1.02)	0.042	0.92 (0.48–1.76)	0.800	/	/	0.70 (0.42–1.18)	0.180	

Notes: “-” indicates Log-additive model; “/” indicates that the data is missing. p-value <0.05’ and bold text represent statistical significance.
Abbreviations: SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

In addition, there are no intronic variants in *IL-12RB2* associated with the COPD risk among participants >68 years old.

Gender (Female)

Among female participants, only *IL-12Rβ2*-rs2201584 was associated with COPD risk. Specifically, compared with the homozygous genotype 'GG', 'AA' of *IL-12Rβ2*-rs2201584 were risk factors for COPD (OR (95% CI) = 2.57 (1.25–5.29), $p = 0.010$). And *IL-12Rβ2*-rs2201584 was significantly associated with increasing risk of COPD under multiple genetic models (recessive: OR (95% CI) = 2.33 (1.11–4.89), $p = 0.021$); (log-additive: OR (95% CI) = 1.43 (1.02–2.01), $p = 0.038$).

Gender (Male)

Among male participants, only *IL-12Rβ2*-rs1874791 was associated with COPD risk. Specifically, compared with the allele 'G' or homozygous genotype 'GG', 'A' and 'AA' of *IL-12Rβ2*-rs1874791 were risk factors for COPD (A vs G: OR (95% CI) = 1.40 (1.08–1.82), $p = 0.012$; AA vs GG: OR (95% CI) = 2.56 (1.17–5.6), $p = 0.018$). *IL-12Rβ2*-rs1874791 can significantly increase the COPD risk under dominant (GA-AA vs GG, OR (95% CI) = 1.45 (1.03–2.04), $p = 0.032$), recessive (AA vs GG-GA, OR (95% CI) = 2.20 (1.02–4.75), $p = 0.039$) and log-additive genetic models (OR (95% CI) = 1.44 (1.08–1.91), $p = 0.011$).

Smoking (Yes)

Among smoking participants, we only found that *IL-12Rβ2*-rs1874791 was associated with COPD risk under allele (A vs G: OR (95% CI) = 1.40 (1.08–1.82), $p = 0.012$) and log-additive genetic models (OR (95% CI) = 1.43 (1.01–2.03), $p = 0.041$).

In addition, there are no intronic variants in *IL-12Rβ2* associated with the COPD risk among non-smoking participants.

Drinking (Yes)

Among drinking participants, homozygous genotype 'AA' of *IL-12Rβ2*-rs2201584 was a risk factor for COPD (AA vs GG: OR (95% CI) = 2.00 (1.09–3.67), $p = 0.025$). -rs2201584 also associated with increasing risk of COPD under recessive genetic models (AA vs GG-GA, OR (95% CI) = 2.11 (1.18–3.76), $p = 0.010$). Similarly, homozygous genotype 'AA' of *IL-12Rβ2*-rs1874791 was a risk factor for COPD (AA vs GG: OR (95% CI) = 3.77 (1.45–9.80), $p = 0.007$). -rs1874791 also associated with increasing risk of COPD under recessive (AA vs GG-GA, OR (95% CI) = 3.66 (1.42–9.43), $p = 0.004$) and log-additive genetic models (OR (95% CI) = 1.41 (1.03–1.93), $p = 0.030$). In addition, we have found evidence that *IL-12Rβ2*-rs3790567 have certain association with COPD risk (homozygous genotype 'AA': OR (95% CI) = 2.68 (1.18–6.09), $p = 0.019$; recessive genetic model: AA Vs GG-GA, OR (95% CI) = 2.92 (1.31–6.53), $p = 0.006$) (Table 5).

In addition, there are no intronic variants in *IL-12Rβ2* associated with the COPD risk among non-drinking participants.

FPRP Analysis

The results of FPRP analysis showed that a very few positive results may be accidental, and most of them were noteworthy findings at the prior probability level of 0.25 and FPRP threshold of 0.2 (Supplemental Table 1).

IL-12Rβ2-rs6679356 may be associated with the COPD risk among participants ≤68 years (dominant: prior probability (0.25) = 0.284; log-additive: prior probability (0.25) = 0.262). *IL-12Rβ2*-rs1874791 may be associated with the COPD risk among participants >68 years (genotype AA (0.25): prior probability = 0.204) or male participants (recessive: prior probability (0.25) = 0.249). The above positive results may not be worth noting. The remaining positive results were all noteworthy findings. In particular, it is a noteworthy finding that the allele 'A' of *IL-12Rβ2*-rs2201584 (allele A (overall analysis): prior probability = 0.078, statistical power = 100%) was risk factor for COPD. Similarly, it is also noteworthy that allele 'A' is a risk factor for COPD (allele A (overall analysis): prior probability = 0.013, statistical power = 100%).

Table 5 Intronic Variants in *IL-12Rβ2* Associated with Susceptibility of COPD in the Subgroup Analysis (Drinking and Smoking)

SNP ID	Model	Genotype	Smoking				Drinking			
			Yes		No		Yes		No	
			OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
rs2201584	Allele	G	1		1		1		1	
		A	1.12 (0.88–1.41)	0.357	1.25 (0.98–1.61)	0.078	1.26 (0.97–1.63)	0.087	1.26 (0.97–1.63)	0.087
	Codominant	GG	1		1		1		1	
		AA	1.27 (0.65–2.48)	0.481	2.12 (1.18–3.78)	0.011	2.00 (1.09–3.67)	0.025	1.53 (0.84–2.79)	0.167
		GA	1.00 (0.64–1.56)	0.998	1.01 (0.69–1.47)	0.976	0.89 (0.60–1.33)	0.573	1.24 (0.83–1.84)	0.292
	Dominant	GG	1		1		1		1	
		GA-AA	1.06 (0.70–1.60)	0.790	1.20 (0.84–1.70)	0.320	1.08 (0.74–1.56)	0.700	1.29 (0.89–1.88)	0.180
	Recessive	GG-GA	1		1		1		1	
		AA	1.27 (0.67–2.39)	0.470	2.11 (1.22–3.67)	0.007	2.11 (1.18–3.76)	0.010	1.38 (0.78–2.43)	0.270
	Overdominant	GG-AA	1	0.830	1	0.430	1	0.190	1	0.530
GA		0.95 (0.63–1.45)		0.86 (0.60–1.24)		0.78 (0.53–1.13)		1.13 (0.77–1.64)		
Log-additive	-	1.09 (0.80–1.47)	0.590	1.30 (1.01–1.69)	0.045	1.23 (0.94–1.60)	0.130	1.23 (0.94–1.62)	0.130	
rs1874791	Allele	G	1		1		1		1	
		A	1.40 (1.08–1.82)	0.012	1.41 (1.07–1.88)	0.016	1.32 (0.98–1.76)	0.064	1.32 (0.98–1.76)	0.064
	Codominant	GG	1		1		1		1	
		AA	2.08 (0.84–5.14)	0.114	2.19 (0.93–5.20)	0.074	3.77 (1.45–9.80)	0.007	1.3 (0.56–3.04)	0.540
		GA	1.39 (0.89–2.17)	0.152	1.23 (0.85–1.79)	0.274	1.09 (0.73–1.62)	0.663	1.44 (0.97–2.14)	0.070
	Dominant	GG	1		1		1		1	
		GA-AA	1.50 (0.98–2.30)	0.064	1.32 (0.92–1.89)	0.130	1.29 (0.88–1.89)	0.190	1.44 (0.98–2.10)	0.061
	Recessive	GG-GA	1		1		1		1	
		AA	1.87 (0.77–4.58)	0.160	2.02 (0.86–4.74)	0.097	3.66 (1.42–9.43)	0.004	1.16 (0.50–2.67)	0.740
	Overdominant	GG-AA	1	0.230	1	0.430	1	0.980	1	0.078
GA		1.31 (0.84–2.04)		1.16 (0.80–1.68)		0.99 (0.67–1.47)		1.42 (0.96–2.10)		
Log-additive	-	1.43 (1.01–2.03)	0.041	1.33 (0.98–1.80)	0.063	1.41 (1.03–1.93)	0.030	1.31 (0.95–1.80)	0.093	
rs3790567	Allele	G	1		1		1		1	
		A	1.21 (0.95–1.55)	0.120	1.17 (0.9–1.52)	0.245	1.15 (0.88–1.51)	0.306	1.15 (0.88–1.51)	0.306
	Codominant	GG	1		1		1		1	
		AA	1.73 (0.79–3.78)	0.172	1.48 (0.73–3.01)	0.278	2.68 (1.18–6.09)	0.019	1.07 (0.53–2.14)	0.850
		AG	1.07 (0.69–1.66)	0.752	0.96 (0.66–1.39)	0.821	0.81 (0.55–1.19)	0.287	1.19 (0.81–1.76)	0.380
	Dominant	GG	1		1		1		1	
		AG-AA	1.18 (0.78–1.80)	0.430	1.02 (0.72–1.45)	0.910	0.97 (0.67–1.40)	0.860	1.18 (0.81–1.71)	0.390
	Recessive	GG-AG	1		1		1		1	
		AA	1.70 (0.79–3.66)	0.170	1.51 (0.76–3.01)	0.240	2.92 (1.31–6.53)	0.006	1.00 (0.51–1.96)	0.990
	Overdominant	GG-AA	1	0.980	1	0.610	1	0.110	1	0.380
AG		1.01 (0.66–1.54)		0.91 (0.64–1.31)		0.73 (0.50–1.07)		1.19 (0.81–1.73)		
Log-additive	-	1.22 (0.88–1.69)	0.230	1.09 (0.82–1.44)	0.570	1.16 (0.86–1.56)	0.330	1.10 (0.83–1.48)	0.500	

Notes: "-" indicates log-additive model. p-value <0.05' and bold text represent statistical significance.

Abbreviations: SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

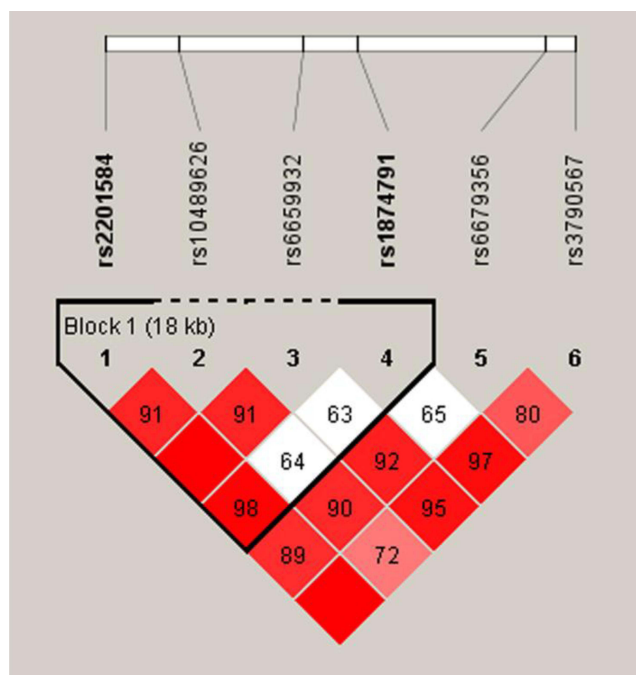


Figure 2 One linkage disequilibrium block composed by the *IL-12Rβ2* genetic loci (rs2201584 and rs1874791). The numbers inside the diamonds indicate The D' for pairwise analyses.

Haplotype Analysis

The result of linkage disequilibrium showed that (Figure 2) the two candidate *IL-12Rβ2* SNPs (rs2201584, rs1874791) composed one LD block ($D' = 0.968$, $R^2 = 0.108$). Haplotype analysis showed that the haplotype ‘ $A_{rs2201584}G_{rs1874791}$ ’ (OR (95% CI) = 1.46 (1.19–1.80), $p = 0.0004$) and ‘ $A_{rs2201584}A_{rs1874791}$ ’ (OR (95% CI) = 1.61 (1.26–2.05), $p = 0.0001$) were associated with increasing risk of COPD (Table 6).

MDR Analysis

As is shown in Figure 3, the dendrogram has described the interaction between the six candidate SNPs. The color of the lines in the dendrogram represents the level of redundancy or synergy. The closer to the red, the stronger the synergy, and the closer to the blue, the stronger the redundancy. The MDR results showed that the three loci model (rs2201584, rs1874791, rs3790567) has the highest test accuracy (Table 7). Therefore, the three loci model composed of rs2201584, rs1874791, and rs3790567 was chosen as the best model for predicting COPD risk ($p < 0.0001$), with a test accuracy of 0.551 and a perfect CVC = 10/10.

Table 6 Haplotype Analysis About *IL-12Rβ2* Genetic Polymorphisms with COPD Risk

SNP	Haplotype	Freq (Case)	Freq (Control)	Crude Analysis		Adjusted by Gender, Age, Smoking and Drinking	
				OR (95% CI)	p	OR (95% CI)	p
rs2201584 rs1874791	GG	0.390	0.490	1			
rs2201584 rs1874791	AG	0.353	0.307	1.43 (1.17–1.74)	0.0005	1.46 (1.19–1.80)	0.0004
rs2201584 rs1874791	AA	0.257	0.201	1.59 (1.27–2.00)	0.0001	1.61 (1.26–2.05)	0.0001

Note: $p < 0.05$ and bold text represent statistical significance.

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

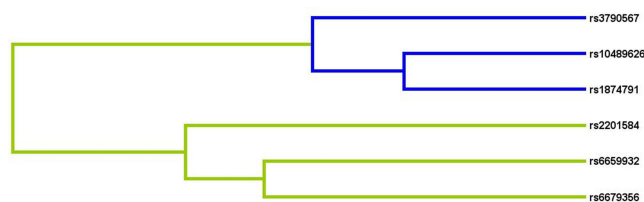


Figure 3 Multifactor dimensionality reduction (MDR) analysis of interaction between the candidate genetic loci of *IL-12R β 2* (rs2201584, rs10489626, rs6659932, rs1874791, rs6679356, and rs3790567). SNP-SNP Interaction Dendrogram: the color represents the degree of redundancy or synergy between SNP-SNP; the closer the color is to red, the more synergy, and the closer to blue, the more redundancy.

Discussion

Smoking has long been considered a major environmental risk factor for COPD, but only a small number of smokers develop airway obstruction.²⁰ It has been reported that it may be due to the genetic factors that play an indispensable role in the occurrence and development of COPD.²¹ With the development of molecular biology, many genetic polymorphisms associated with lung function have been reported, such as HLA-DQB1-rs9273410,²² TNF-A gene-308 G/A polymorphism,²³ ADRB2-rs12654778²⁴ and SREK1-rs74794265.²⁵ However, limited by race and sample size, only a small proportion of the population's susceptibility to COPD can be explained.

The association between *IL-12R β 2* genetic polymorphism and COPD susceptibility was studied in a case-control study involving 998 participants. Combined with association analysis and FPRP results, four genetic loci in *IL-12R β 2* (rs2201584, rs1874791, rs6679356, and rs3790567) were found to be associated with COPD risk in southern Chinese Han population. *IL-12R β 2*-rs2201584 and -rs1874791 are not only significantly associated with COPD risk in the overall analysis, but also in multiple stratified analysis. To our knowledge, this study is the first to report that *IL-12R β 2* genetic polymorphisms are associated with COPD risk in southern Chinese Han population.

Overall analysis showed that the presence of allele 'A' or genotype 'AA' of *IL-12R β 2*-rs2201584 or -rs1874791 was significantly associated with increased risk of COPD. In addition, in order to eliminate the influence of confounding factors on the reliability of this study, we have conducted stratified analyses according to potential risk factors of COPD. *IL-12R β 2*-rs2201584 was significantly associated with an increased risk of COPD among participants younger than 68 years of age, women or drinkers. *IL-12R β 2*-rs1874791 was significantly associated with increased COPD risk among participants younger than 68 years of age, men, drinking or smoking participants. It is worth noting that no candidate genetic polymorphism in this study was associated with the COPD risk of participants older than 68 years old. We analyzed that *IL-12R β 2*-rs2201584 and -rs1874791 were associated with an increased risk of COPD, which may not be affected by aging, although age growth has been reported as a potential risk factor for COPD.²⁶ COPD is considered to be a disease of older men. However, more and more studies have shown that women are increasingly burdened with COPD.^{27,28} According to the gender-specific prevalence rate of COPD, it is necessary to prevent and treat COPD for different genders. Combined with the results of this study, *IL-12R β 2*-rs2201584 and -

Table 7 *IL-12R β 2* SNP-SNP Interaction Models Analyzed by the MDR Method

Model	Training Bal. Acc	Testing Bal. Acc	OR (95% CI)	p value	CVC
rs1874791	0.538	0.538	1.37 (1.07–1.77)	0.014	10/10
rs2201584, rs1874791	0.562	0.549	1.64 (1.28–2.10)	0.0001	10/10
rs2201584, rs1874791, rs3790567	0.572	0.551	2.18 (1.62–2.93)	<0.0001	10/10
rs2201584, rs10489626, rs1874791, rs3790567	0.577	0.533	2.24 (1.67–3.00)	<0.0001	5/10
rs2201584, rs10489626, rs1874791, rs6679356, rs3790567	0.580	0.536	2.35 (1.75–3.16)	<0.0001	9/10
rs2201584, rs10489626, rs6659932, rs1874791, rs6679356, rs3790567	0.581	0.535	2.38 (1.77–3.21)	<0.0001	10/10

Note: p values were calculated using χ^2 tests; p-value <0.05 and bold text represent statistical significance.

Abbreviations: MDR, multifactor dimensionality reduction; Bal. Acc., balanced accuracy; CVC, cross-validation consistency; OR, odds ratio; 95% CI, 95% confidence interval.

rs1874791 may be expected to become new targets for the prevention and treatment of COPD in female and male Han populations in southern China, respectively. Similarly, *IL-12Rβ2*-rs2201584 (associated with increased risk of COPD in drinking participants) and -rs1874791 (associated with increased risk of COPD in smoking participants) are also expected to become new targets for individualized prevention and treatment of COPD in southern Chinese Han population. Combined with the FPRP analysis, the above new findings are worth noting.

The up-regulation of *IL-12Rβ2* can promote the differentiation of cells into Th1 cells. Th1 cells are closely related to the occurrence and development of COPD: Th1 cells cause inflammatory infiltration and pathological changes by secreting pro-inflammatory factors (IL-12, TNF-α and IFN-γ).²⁹ Combined with the results of this study, we speculated that *IL-12Rβ2*-rs2201584 and -rs1874791 may cause the up-regulation of *IL-12Rβ2* expression to promote cell differentiation into Th1 cells, thereby secreting proinflammatory cytokines, and ultimately increasing the risk of COPD. The above is only speculation, and further molecular mechanism studies are necessary to explore how *IL-12Rβ2*-rs2201584 and -rs1874791 affect COPD susceptibility in southern Chinese Han population by affecting *IL-12Rβ2* expression.

In addition, we also found evidence that *IL-12Rβ2*-rs6679356 was associated with COPD susceptibility. *IL-12Rβ2*-rs6679356 has been reported to be associated with a variety of inflammatory diseases, such as primary biliary cholangitis³⁰ and allergic rhinitis.³¹ However, *IL-12Rβ2*-rs6679356 was only associated with COPD risk in participants younger than 68 years old in our study. *IL-12Rβ2*-rs3790567 has also been reported to be associated with the occurrence and development of systemic lupus erythematosus,³² allergic rhinitis³¹ and other diseases. But we only found *IL-12Rβ2*-rs3790567 was associated with COPD risk in female participants. Therefore, the evidence that *IL-12Rβ2*-rs6679356 and -rs3790567 are identified as susceptibility loci of COPD in Han population from southern China is insufficient, and further validation experiments are necessary.

In any case, this study has laid a reliable theoretical foundation for the study on mechanism of *IL-12Rβ2* in the development of COPD. At the same time, it provides a new idea for the risk assessment and clinical individualized prevention and treatment of COPD in southern Chinese Han population. There are still some limitations in this study: on the one hand, in order to ensure the reliability and repeatability of the results, a large sample size verification study is necessary; on the other hand, necessary functional tests should be added in subsequent studies to further understand the molecular mechanism of *IL-12Rβ2* in the occurrence and development of COPD. In any case, this study is the first to explore the association between the genetic polymorphisms of *IL-12Rβ2* and the susceptibility to COPD in Han population from southern China and found noteworthy positive results.

Conclusion

Genetic polymorphisms in *IL-12Rβ2* (rs2201584, rs1874791, rs6679356, and rs3790567) were associated with the COPD susceptibility. In particular, there were sufficient evidences that *IL-12Rβ2*-rs2201584 and -rs1874791 were associated with the increasing risk of COPD. This study has laid a theoretical foundation for clinical COPD risk assessment and individualized treatment.

Data Sharing Statement

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted under the standard approved by the ethics committee of Hainan General Hospital. And conformed to the ethical principles for medical research involving humans of the World Medical Association Declaration of Helsinki. All participants signed informed consent forms before participating in this study.

Consent to Publication

All authors agreed to publish the manuscript.

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Disclosure

The authors declare that they have no conflicts of interest in relation to this work.

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