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Interaction study of the effects of environmental exposure and gene polymorphisms of inflammatory and immune-active factors on chronic obstructive pulmonary disease

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease, influenced by both environmental and genetic factors. Single nucleotide polymorphism (SNP) in the human genome may influence the risk of developing COPD and the response to treatment. We assessed the effects of gene polymorphism of inflammatory and immune-active factors and gene-environment interaction on risk of COPD in middle-aged and older Chinese individuals.

Methods In this community-based case–control study, 471 patients with COPD and 485 controls aged 40–76 years in Heilongjiang Province, China were included. Face-to-face interviews, lung function tests, and multiplex polymerase chain reaction were used to obtain data. Logistic regression model, generalized multifactor dimensionality reduction and crossover analysis were used to analyse the effects of SNPs, gene–gene interactions, and gene-environment interactions on COPD.

Results CRP gene[rs1130864-A allele (OR, 1.77; 95% CI 1.11–2.81); G/A + A/A genotype (OR, 1.75; 95% CI 1.07–2.84)], FCAR gene[rs4806606-G (OR, 0.72; 95% CI 0.53–0.98); rs8112766-G (OR, 0.79; 95% CI 0.64–0.98)] and FCGR2A gene[rs4656308-C (OR, 0.74; 95% CI 0.55–1.00); rs4656309-T (OR, 0.81; 95% CI 0.66–0.99)] are independent influential factors for COPD. Rs1205 [RERI: 0.15 (0.07–1.00)] and rs1130864 [RERI: 2.45 (0.73–4.18)] of CRP gene, rs11084376 [OR: 0.54 (0.29–0.97)] of FCAR gene, rs844 of FCGR2B [SI: 0.30 (0.11–0.77); OR: 0.46 (0.24–0.90)] gene, rs4656308-rs4656309-rs2165088 haplotype [SI: 0.48 (0.26–0.89)] of FCGR2A gene and exposure to smoking index > 200, indoor coal/wood/straw use, and outdoor straw burning play synergistic or antagonistic roles in the development of COPD.

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Conclusions Alleles and genotypes of the CRP/FCAR/FCGR2A gene can increase the susceptibility to COPD in the northern Chinese population. For the first time, environmental exposure to the CRP/FCAR/FCGR2A/FCGR2B genes has been shown to have synergistic or antagonistic effects on COPD susceptibility on genotypes or haplotypes.

Keywords Chronic obstructive pulmonary disease, Environmental exposure, Single nucleotide polymorphism, Haplotype, Interactions

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a pulmonary or systemic inflammatory disease caused by harmful gases or particles and is characterized by progressive and irreversible airflow restriction, which is preventable and treatable [1]. Environmental exposure, represented by smoking, is considered to be the most common risk factor for COPD, and biofuels are an important cause of COPD in developing countries [2]. Our research group previously identified the smoking index, outdoor straw burning, and indoor use of coal/wood/straw/mixed fuel as risk factors for COPD in Heilongjiang Province, China [3]. However, not all smokers and individuals with a history of air pollution exposure develop COPD. Studies have shown that individuals with a family history of COPD, particularly those with parents who have the disease, are at an increased risk of developing COPD. Alpha one-antitrypsin deficiency has been identified as a genetic factor that contributes to COPD [4]. With the development of molecular biology and GWAS technology, genetic factors have gained increasing attention, although research on other genetic factors related to COPD still yields inconsistent results.

At present, studies have revealed that single nucleotide polymorphisms (SNPs) in the human genome play crucial roles in the occurrence of various diseases, clinical manifestations, and response to drug treatment. COPD is a heterogeneous disease influenced by both environmental and genetic factors. Extensive research has been conducted on the pathogenic mechanisms of COPD-related genes. In recent years, domestic and international scholars have discovered new susceptibility genes related to COPD through genetic polymorphism association analysis, whole-genome scanning, and other methods. Several studies have revealed significant associations between SNP sites such as serine peptidase inhibitor 2 (SERPINE2), hedgehog interacting protein (HHIP), β2-adrenergic receptor (ADRB2), vascular endothelial growth factor (VEGFA), vitamin D binding protein (VDBP), heat shock protein 70 (Hsp70), serine and arginine-rich with an additional glutamic acid-lysine-rich 1 (SREK1), Toll-like receptor (TLR), and human leukocyte antigen (HLA) [5–11], and COPD in different regions and ethnic groups. However, there are inconsistencies and even contradictions in the association studies of these candidate genes with COPD.

The main feature of COPD is chronic, progressive inflammation of the lung tissue. However, systemic immune and inflammatory responses are also important features of COPD. Our research group revealed that elevated C-reactive protein (CRP) levels are a risk factor for COPD; thus, it is necessary to conduct in-depth research on the associations between CRP expression-related genes and COPD. Fadi G HAge et al. reported that serum CRP levels are influenced by genetic factors. In family and twin studies, the heritability of elevated CRP ranges from 39 to 52% [12]. Wener MH et al. reported that the CRP levels of African descendants in the United States were higher than those of European descent. Aroon D Hingorani et al. reported that certain subtle changes in the CRP gene sequence, mainly SNPs, can affect blood CRP levels. By exploring the function of SNPs in the CRP gene in vitro, Carlson CS et al. reported that a variety of SNPs and haploids constructed in the CRP promoter region are closely related to the CRP level [13].

Our research group also reported that immunoglobulin G (IgG) and immunoglobulin A (IgA) are associated with the development of COPD. Both the Fc fragment of the IgG receptor (FCGR) and the Fc fragment of the IgA receptor (FCAR) genes are members of the immunoglobulin gene superfamily and are associated with the Fc receptors for IgA and IgE, which are also the Fc receptors for CRP [14]. The Fc fragment of IgG receptor IIa (FCGR2A) and the Fc fragment of IgG receptor IIb (FCGR2B) are expressed on the surface of monocytes, neutrophils, eosinophils, dendritic cells and macrophages and are the two receptors that cover most white blood cells. FCGR2B transmits inhibitory signals to play an anti-inflammatory role, while all other receptors trigger cell activation to play a proinflammatory role, and the combination of IgG and FCGR can play both proinflammatory and anti-inflammatory roles. Previous studies have shown that the genetic polymorphism of FCGR in IgG is associated with the risk and disease progression of systemic lupus erythematosus [15]. Through competitive binding and mutation analysis, the FCAR, the main receptor of IgA, was determined to be the receptor of pentraxin. The binding site of the FCAR identified by

CRP is different from that identified by IgA. Therefore, CRP and IgA do not compete with each other for binding sites and receptors. Moreover, CRP promotes the ability of IgA to recognize the FCAR [16]. Simultaneous recognition of different FCAR regions by CRP and IgA can increase FCAR activation, improving the effect of the FCAR on the innate immune response.

Previous studies have shown that SNPs in the CRP gene are closely related to the occurrence of a variety of diseases, including cardiovascular diseases, autoimmune diseases and tumors. Immunoglobulin-related gene SNPs are also closely related to the occurrence of many diseases, including autoimmune diseases, infectious diseases and tumors. However, it is not clear whether CRP, IgG and IgA gene-associated SNPs are related to the development of COPD. Moreover, there is a lack of relevant studies on the impact of environmental factors and interactions between gene SNPs or gene haplotypes on COPD. Therefore, the effects of alleles, genotypes, haplotypes, gene–gene interactions and environment–gene interactions of CRP/FCAR/FCGR2A/FCGR2B polymorphic sites on COPD development need to be further studied.

Material and methods

Selection of cases and controls

The selection of study subjects, questionnaire surveys, physical examinations, serological testing and diagnostic criteria for COPD are consistent with the findings of a previously published study by our group on the effects of environmental, immune, and inflammatory risk factors on COPD [3]. The baseline survey for this prospective cohort study was conducted from November 2018 to September 2019, and the study subjects were selected from the community population in Mingshui County, Suihua, Heilongjiang Province, China. The study included 471 cases and 485 cases in the control group, with a total of 956 participants ranging in age from 40 to 76 years. Patients with chronic obstructive pulmonary disease were defined as individuals with a forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of less than 70% ($FEV_1/FVC < 70\%$) to represent the definition of an epidemiological case; the remaining patients were included as eligible controls according to the inclusion and exclusion criteria. The investigation was conducted with the approval of the Ethics Committee of the Center for Endemic Disease Control of the Chinese Center for Disease Control and Prevention. All participants signed written informed consent.

Questionnaires and genotyping

The data collected through the questionnaire survey regarding demographics, disease history, smoking status, indoor fuel use, and outdoor straw burning information and the classification of the study subjects were in line with previously published research [3]. By referencing the 1000 Genomes Project data (https://www.internationalgenome.org) and using Haploview software (version 4.2), we employed a criterion of minor allele frequency (MAF) ≥ 5% for screening target gene SNPs and a linkage disequilibrium (LD) threshold of $r^2 \geq 0.8$ for the haplotypes in the Chinese population. Additionally, we referred to previous relevant studies to select SNP loci associated with inflammation and immune-related diseases. Genomic DNA (Deoxyribonucleic acid) was extracted from the blood via a DNA extraction kit (MagPure Blood DNA KF Kit), and the DNA concentration was quantified via a NanoDrop One microspectrophotometer. Genotype sequencing of DNA samples whose concentrations were above 20 μg/ml was completed in the laboratory of Genesky Biotechnologies (Shanghai, China), and SNP genotyping was performed via multiplex polymerase chain reaction (PCR).

Statistical analyses

All the data were gathered via dedicated software and analysed via the SAS statistical analysis system (ver 9.1.4), R software (ver 3.6.3) and Excel software. First, univariate analysis, including the Wilcoxon rank sum test or t test for continuous data and the chi-square test for classification variables, was performed to identify factors significantly associated with COPD. The chi-square test was used to assess the Hardy–Weinberg equilibrium (HWE) of SNPs in control participants. The chi-square test and Fisher's exact test were applied to analyse the differences in allele frequency and genotype frequency in SNPs of each target gene. SNPStats software was used to adjust for the influence of confounding factors such as age, body mass index (BMI) and education level and analyse the genetic model of the gene SNPs associated with the risk of COPD. A logistic regression model was used to analyse the haplotypes associated with the risk of COPD after adjusting for confounding factors such as age, BMI and education level. Haploview software (version 4.2) was used to construct LD and haplotypes, and the differences in haplotype frequency distributions between groups were compared. Generalized multifactor dimensionality reducation (GMDR) software (ver 0.9) was used to analyse the higher-order interactions between the SNPs and the haploids.

We evaluated the impact of gene–environment interactions on COPD by using odds ratios (ORs). In addition, the relative excess risk due to interaction (RERI) and synergy index (SI) were applied to evaluate the additive interaction effect between candidate gene SNPs and environmental exposure on COPD. The evaluation criteria

were as follows: (1) if the RERI values and the upper and lower limits of the 95% CI are both greater than 0, a positive additive interaction exists; if both the RERI value and the upper and lower limits of the 95% CI are less than 0, then a negative additive interaction exists; otherwise, no additive interaction exists. (2) If the SI value and the upper and lower limits of the 95% CI are both greater than 1, then there is a positive additive interaction; if the SI value and the upper and lower limits of the 95% CI are both less than 1, then there is a negative additive interaction; otherwise, there is no additive interaction. A two-sided probability test with $P<0.05$ was considered statistically significant.

Results

Study population characteristics and major risk factors

In our previous study [3], we compared the characteristics of 471 cases and 485 controls with respect to the main demographic characteristics, disease history, environmental exposure, lifestyle, dietary habits and disease history. Statistical differences were found in age, income, education, BMI, smoking, indoor fuel use (no fuel/natural gas/electricity vs. coal/wood/straw), outdoor straw burning, history of respiratory disease (RD), history of coronary heart disease and congestive heart failure (CHD/CHF) and history of cerebrovascular disease (CVD) between the two groups ($P<0.05$) [3]. The correlations between genetics or the genetic or genetic-environmental factors and COPD were analysed after adjustment for the above covariates in the present study.

A HWE test of the SNP loci of the candidate genes

A chi-square test (Table S1 in the Supplementary Appendix) revealed that five SNPs (rs1341665, rs1865096, rs438228, rs56159502 and rs1771576) failed the HWE test ($P<0.05$) in the controls and were excluded from the analysis. rs1800947 and rs16986050 were also excluded because the MAF was < 5% in the study population. Eventually, 18 SNPs, including rs1130864, rs1205, rs2808630, rs4806606, rs4806608, rs62123424, rs7259090, rs8112766, rs11084376, rs1865097, rs2304225, rs4656308, rs4656309, rs4657040, rs1801274, rs2165088, rs844 and rs16827592, were included in the subsequent analysis.

Association analysis of SNP genotypes

There were significant differences in the compositions of alleles and genotypes between the case and control groups (Table 1 and Figure S1 in the Supplementary Appendix). The rs1130864-A allele in the CRP gene was positively associated with susceptibility to COPD (OR, 1.77; 95% CI 1.11–2.81); the rs4806606-G and rs8112766-G alleles in the FCAR gene and the rs4656308-C and rs4656309-T alleles in the FCGR2A gene were negatively associated with susceptibility to COPD [OR, 0.72; 95% CI 0.53–0.98; OR, 0.79; 95% CI 0.64–0.98; OR, 0.74; 95% CI 0.55–1.00; OR, 0.81; 95% CI 0.66–0.99].

Remarkable differences were found in the compositions of the rs1130864 genotypes in the CRP gene between the case and control groups (Table S2 in the Supplementary Appendix). In the dominant model, individuals with at least one mutation allele (G/A + A/A genotypes) had a greater risk of COPD than did wild-type homozygotes (G/G genotype) (OR, 1.75; 95% CI 1.07–2.84).

Owing to the limited frequency observed in the case and control groups, specifically with a count of three in each for the A/A genotype of the CRP gene in the codominant, recessive, and log-additive models, the reliability of the results may be compromised. Therefore, it is advisable to exclude these three models from consideration (Tables S3-S6 in the Supplementary Appendix).

Association analysis of haplotypes

Linkage disequilibrium (LD) analysis and haplotype construction were performed for each SNP site, and $D'>0.8$ was used as the criterion for meeting the strong linkage relationship. The following haplotypes were constructed: strong linkage disequilibrium was detected between rs2808630 and rs1205 ($r^2=0.264$, $D'>0.8$), and the haplotype block rs2808630-rs1205 in the CRP gene was constructed. Three haplotypes were identified. A second strong linkage disequilibrium was detected among rs2304225, rs11084376 and rs8112766 in the FCAR gene, and four haplotypes were identified. In addition, strong LD was found for rs1865097 and rs62123424 in the FCAR gene, and three haplotypes were identified. Additionally, a fourth strong linkage disequilibrium was constructed among rs4656308, rs4656309 and rs2165088 in the FCGR2A gene, and five haplotypes were identified. Nonetheless, no strong linkage disequilibrium was found between rs1801274 and rs16827592 in the FCGR2B gene (Fig. 1).

The results revealed that none of the haplotypes were associated with COPD susceptibility ($P>0.05$) (Table S7 in the Supplementary Appendix).

Association analysis of GMDR

The GMDR results for the gene SNP–gene SNP interaction models revealed that the three-locus model (rs1205, rs8112766, and rs844) had the highest test accuracy (Table S8 in the Supplementary Appendix and Fig. 2). Therefore, the three-locus model composed of rs1205, rs8112766 and rs844 was chosen as the best model for predicting COPD risk, with a test accuracy of 0.5147 and a perfect CVC = 6/10.

Table 1 Allele frequencies in COPD and control subjects for SNPs

SNP (Gene)	Genotype	Control n (%)	Case n (%)	OR (95%CI)	*P*-value
rs1130864	G	**896 (95.7)**	**853 (92.9)**	**Ref**	**0.02**
(CRP)	A	**40 (4.3)**	**65 (7.1)**	**1.77 (1.11–2.81)**	
rs2808630	T	800 (85.5)	787 (85.7)	Ref	0.93
(CRP)	C	136 (14.5)	131 (14.3)	0.99 (0.74–1.32)	
rs1205	T	589 (62.9)	543 (59.2)	Ref	0.22
(CRP)	C	347 (37.1)	375(41.9)	1.14 (0.93–1.40)	
rs4806606	A	**810 (86.5)**	**813 (88.6)**	**Ref**	**0.04**
(FCAR)	G	**126 (13.5)**	**105 (11.4)**	**0.72 (0.53–0.98)**	
rs8112766	A	**592 (63.3)**	**624 (68.0)**	**Ref**	**0.03**
(FCAR)	G	**344 (36.8)**	**294 (32.0)**	**0.79 (0.64–0.98)**	
rs4806608	A	814 (87.0)	824 (89.8)	Ref	0.06
(FCAR)	G	122 (13.0)	94 (10.2)	0.73 (0.53–1.01)	
rs62123424	C	605 (64.6)	588 (64.1)	Ref	0.55
(FCAR)	T	331 (35.4)	330 (36.0)	0.94 (0.76–1.16)	
rs7259090	G	830 (88.7)	834 (90.9)	Ref	0.13
(FCAR)	A	106 (11.3)	84 (9.2)	0.77(0.55–1.08)	
rs11084376	C	657 (70.2)	670 (73.0)	Ref	0.18
(FCAR)	G	279 (29.8)	248 (27.0)	0.86 (0.68–1.07)	
rs1865097	G	611 (65.3)	594 (64.7)	Ref	0.59
(FCAR)	A	325 (34.7)	324 (35.3)	0.94 (0.76–1.17)	
rs2304225	C	812 (86.8)	794 (86.5)	Ref	0.98
(FCAR)	G	124 (13.3)	124 (13.5)	1.00 (0.74–1.35)	
rs4656308	T	**796 (85.0)**	**791 (86.2)**	**Ref**	**0.04**
(FCGR2A)	C	**140 (15.0)**	**127 (13.8)**	**0.74 (0.55–1.00)**	
rs4656309	C	**469 (50.1)**	**474 (51.6)**	**Ref**	**0.05***
(FCGR2A)	T	**467 (49.9)**	**444 (48.4)**	**0.81 (0.66–0.99)**	
rs1801274	A	613 (65.5)	604 (65.8)	Ref	0.55
(FCGR2A)	G	323 (34.5)	314 (34.2)	0.94 (0.76–1.16)	
rs2165088	G	795 (84.9)	780 (85.0)	Ref	0.82
(FCGR2A)	A	141 (15.1)	138 (15.0)	0.97 (0.73–1.29)	
rs4657040	T	794 (84.8)	778 (84.8)	Ref	0.44
(FCGR2A)	C	142 (15.2)	140 (15.3)	0.89 (0.67–1.19)	
rs844	G	671 (71.7)	702 (76.5)	Ref	0.11
(FCGR2B)	A	265 (28.3)	216 (23.5)	0.83 (0.65–1.04)	
rs16827592	T	761 (81.5)	730 (79.9)	Ref	0.48
(FCGR2B)	G	173 (18.5)	184 (20.1)	1.10 (0.85–1.42)	

Adjusted for age, Income, BMI, Education, History of RD, History of CVD, Smoking, Indoor fuel use, History of CHD/CHF, Straw burning outdoor

The bolded content represents the distribution of each group, statistical results, and *P*-values of the statistically significant indicators

"* indicates $P<0.05$

The GMDR results for haplotype–haplotype interaction models for COPD indicated that the three loci model (rs2808630–rs1205, rs2304225–rs11084376–rs8112766, and rs1865097–rs62123424) has the highest test accuracy (Table S9 in the Supplementary Appendix and Fig. 2). Thus, the three loci model composed of rs2808630-rs1205, rs2304225-rs11084376-rs8112766 and rs1865097-rs62123424 was identified as the best model for predicting COPD risk, with a test accuracy of 0.5315 and a perfect CVC = 5/10.

However, high-order interactions with significant differences between gene SNPs and haplotypes associated with COPD were not detected ($P > 0.05$).

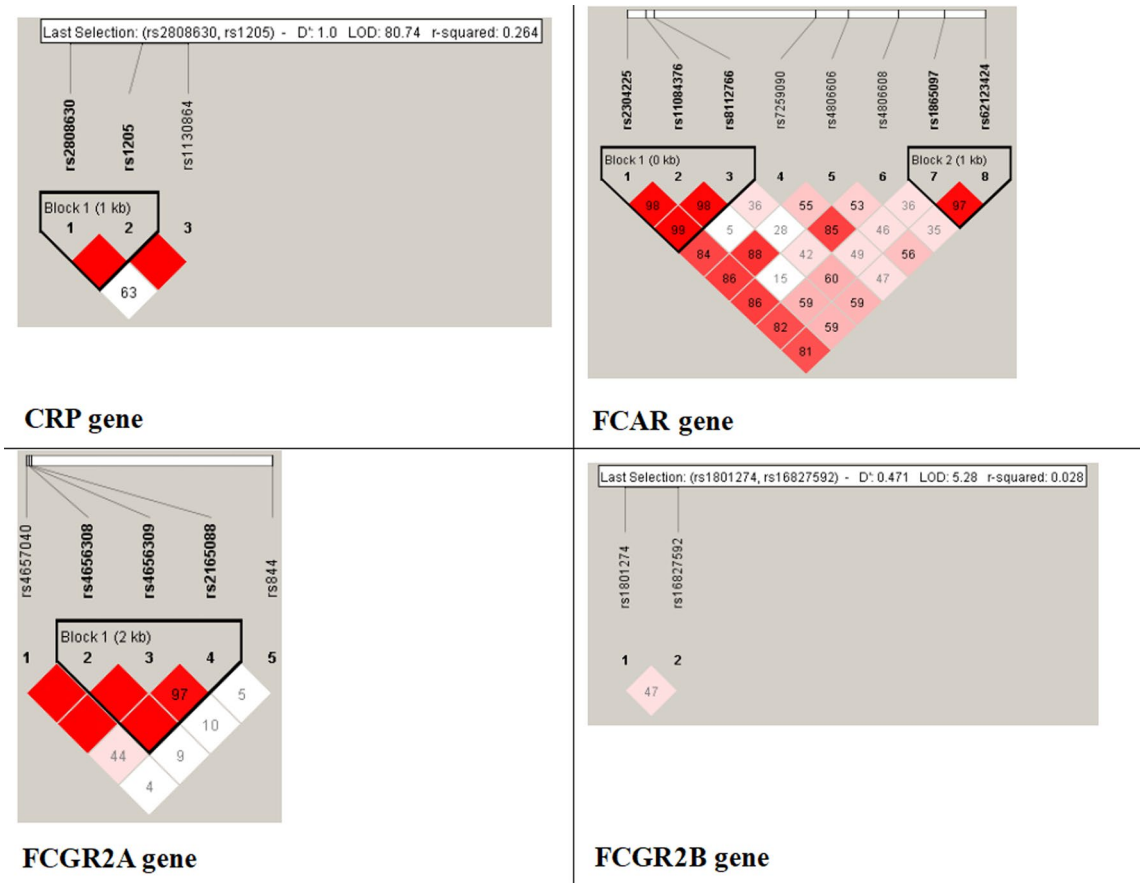

Fig. 1 Linkage disequilibrium plot for SNPs of genes. (Shades in bright red indicate LOD ≥ 2 and *D'* = 1. Shades in white indicate LOD < 2 and *D'* < 1. The number in the block represents the value of *D'*)

Association analysis of the interaction between the environment and the genes

We identified four SNPs that interact with the investigated environmental exposures in COPD.

Two SNPs in the CRP gene significantly interact with the effects of environmental exposure on COPD. Logistic regression analysis and crossover analysis revealed that the RERI (95% CI) value of the interaction between exposure to a smoking index > 200 and the C/T + C/C genotype at the rs1205 locus in the CRP gene was 0.15 (0.07–1.00), and coexposure had positive and additive effects on COPD. The prevalence of COPD was significantly increased in people with a smoking index > 200 and C/T + C/C genotypes due to synergistic effects [OR: 1.81, 95% CI (1.183–2.79)] (Tables 2 and 3 and Figure S2 in the Supplementary Appendix). In addition, the RERI (95% CI) value of the interaction between exposure to indoor use of coal/wood/straw and the G/A + A/A genotypes at the rs1130864 locus in the CRP gene was 2.45 (0.73–4.18), and coexposure presented positive and additive interactions with COPD. The prevalence of COPD was significantly increased in people exposed to indoor use of the coal/wood/straw and G/A + A/A genotypes because of synergistic effects [OR: 3.01, 95% CI (1.39–6.75)] (Tables 3 and 4 and Figure S3 in the Supplementary Appendix).

The other two SNPs were located in the FCAR gene and FCGR2B gene. The OR (95% CI) value of the interaction between exposure to a smoking index > 200 and the C/G + G/G genotypes at the rs11084376 locus in the FCAR gene was 0.54 (0.29–0.97), and coexposure had negative and multiplicative effects on COPD. It can be inferred that when individuals are exposed to a smoking index > 200 alone, their susceptibility to COPD is significantly increased [OR: 1.89, 95% CI (1.25–2.88)], whereas when the C/G + G/G genotype is carried at the same time, the antagonistic effect of copresence leads to no difference in susceptibility to COPD. Additionally, the SI (95% CI) value of the interaction between exposure to straw burning outdoors and the A/G + A/A genotype at the rs844 locus in the FCGR2B gene was 0.295 (0.11–0.77), the OR (95% CI) value of the interaction was 0.463

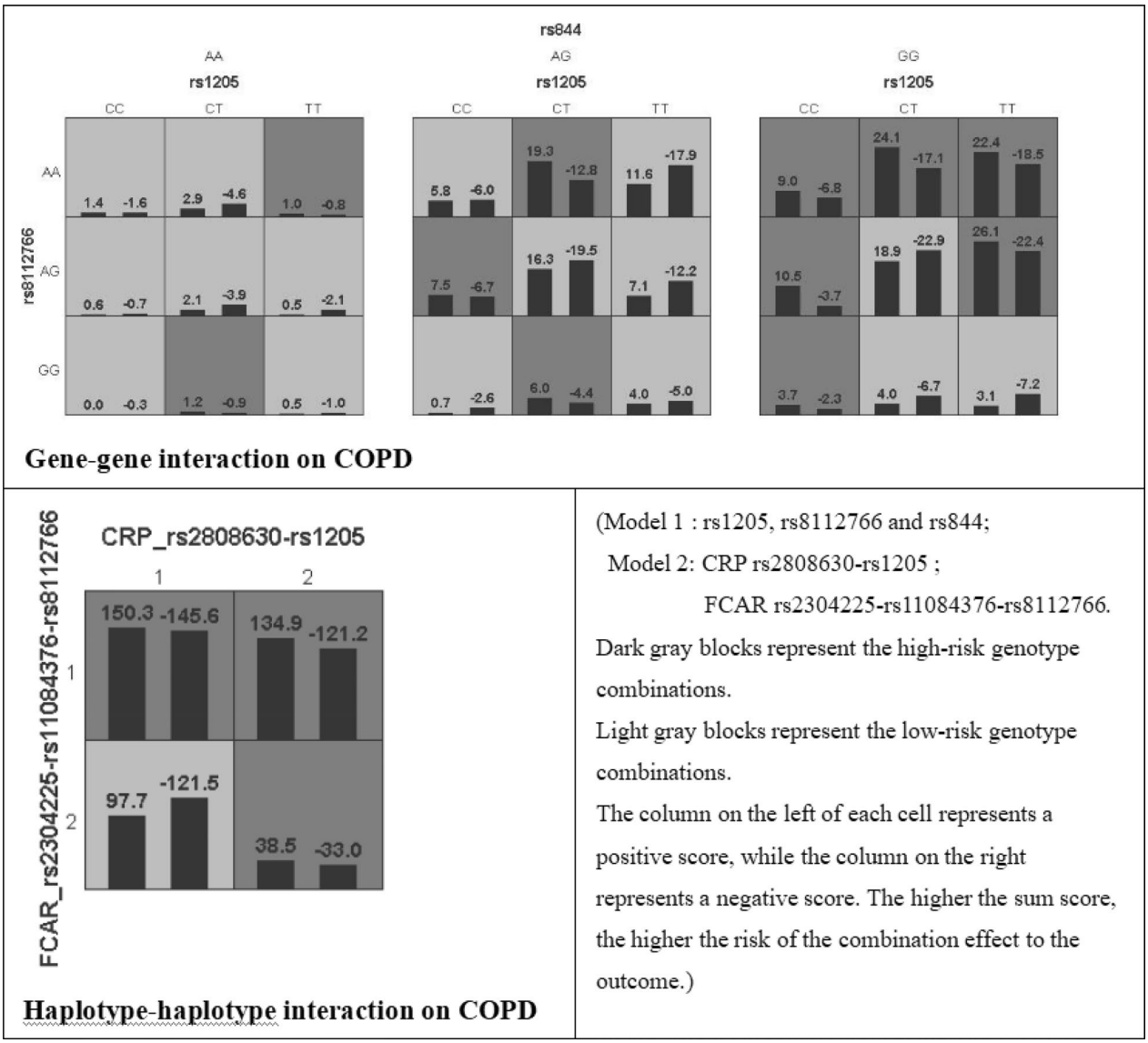

Fig. 2 Optimum model of the GMDR analysis results

(0.24–0.90), and coexposure had a negative multiplicative or additive interaction on COPD. It was suggested that when exposed to straw burning outdoors alone, the susceptibility to COPD is highly increased [OR: 2.18, 95% CI (1.39–3.46)], whereas when the A/G + A/A genotype is carried simultaneously, the effect of coexposure is not significant for susceptibility to COPD (Tables 3, 5 and Figure S4 in the Supplementary Appendix).

Association analysis of the interactions between the environment and the haplotypes

We identified only one haplotype block in the FCGR2A gene that interacted with the investigated environmental exposures to COPD (Tables 6 and 7). The SI (95% CI) value of the interaction between exposure to straw burning outdoors and the CTG + TCA + TTA + TTG haplotype in the FCGR2A gene was 0.48 (0.26–0.89), and coexposure had negative and additive effects on COPD. When exposed to straw burning outdoors alone, susceptibility to COPD is significantly increased [OR: 1.93, 95% CI (1.36–2.76)]; however, when the CTG + TCA + TTA + TTG haplotype is carried simultaneously, the antagonistic effect of coexposure causes a lower risk of COPD in the population [OR: 1.55, 95% CI (1.11–2.19).

Table 2 Interaction between smoking exposure and SNPs on COPD

SNP (Gene)	Genotype	RERI (95%CI)	SI (95%CI)	OR (95%CI)*	*P-value*
rs1205 (CRP)	C/T + C/C vs T/T	**0.15 (0.07–1.00)**	1.23 (0.35–4.28)	1.03 (0.56–1.89)	0.93
rs1130864 (CRP)	G/A + A/A vs G/G	− 1.29 (− 3.32–0.75)	0.36 (0.06–2.17)	0.46 (0.17–1.21)	0.11
rs2808630 (CRP)	C/T + C/C vs T/T	0.19 (− 0.72–1.10)	1.50 (0.20–11.39)	1.13 (0.57–2.25)	0.72
rs11084376 (FCAR)	CG + GG vs C/C	− 0.88 (− 1.79–0.04)	0.12 (0.00–6.54)	**0.54 (0.29–0.97)**	**0.04**
rs4806606 (FCAR)	A/G + G/G vs A/A	− 0.11 (− 0.82–0.61)	0.13 ($9.09e^{-6}$–$1.93e^{13}$)	1.01 (0.50–2.05)	0.98
rs4806608 (FCAR)	A/G + G/G vs A/A	− 0.13 (− 0.88–0.62)	0.31 ($2.12e^{-5}$–$4.39e^{3}$)	0.97 (0.47–1.99)	0.93
rs62123424 (FCAR)	T/C + T/T vs C/C	0.32 (− 0.38–1.03)	2.80 (0.05–149.49)	1.28 (0.70–2.35)	0.42
rs7259090 (FCAR)	A/G + A/A vs G/G	− 0.25 (− 1.05–0.55)	0.15 ($4.14e^{-7}$–$5.52e^{4}$)	0.86 (0.40–1.82)	0.69
rs8112766 (FCAR)	A/G + G/G vs A/A	− 0.45 (− 1.26–0.36)	0.13 (0.00–59.83)	0.74 (0.41–1.35)	0.33
rs1865097 (FCAR)	A/G + A/A vs G/G	0.20 (− 0.54–0.94)	0.65 (0.17–16.35)	1.15 (0.63–2.11)	0.65
rs2304225 (FCAR)	CG + GG vs C/C	− 0.82 (− 1.79–0.14)	0.21 (0.01–3.44)	0.53 (0.27–1.6)	0.07
rs4656308 (FCGR2A)	C/T + C/C vs T/T	0.22 (− 0.48–0.92)	− 2.21 (Na-Na)	1.40 (0.71–2.81)	0.34
rs4656309 (FCGR2A)	T/C + T/T vs C/C	0.00 (− 0.81–0.81)	1.00 ($7.95e^{-5}$–$1.25e^{4}$)	1.08 (0.54–2.17)	0.82
rs4657040 (FCGR2A)	T/C + C/C vs T/T	− 0.17 (− 0.95–0.61)	0.54 (0.03–10.67)	0.91 (0.47–1.76)	0.77
rs1801274 (FCGR2A)	A/G + G/G vs A/A	− 0.00 (− 0.74–0.73)	0.99 (0.06–15.29)	1.04 (0.56–1.90)	0.91
rs2165088 (FCGR2A)	G/A + A/A vs G/G	− 0.48 (− 1.38–0.42)	0.37 (0.04–3.29)	0.69 (0.35–1.34)	0.27
rs844 (FCGR2B)	A/G + A/A vs G/G	− 0.25 (− 1.00–0.49)	0.39 (0.02–6.85)	0.86 (0.47–1.56)	0.61
rs16827592 (FCGR2B)	T/G + G/G vs T/T	0.07 (− 0.83–0.97)	1.10 (0.29–4.27)	0.99 (0.53–1.84)	0.97

The smoking exposure is classified into Smoking index > 200 vs Smoking index ≤ 200; Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Indoor fuel use, Straw burning outdoor

* Multiplication interaction; *P-value* for Multiplication interaction

The bolded content represents the statistically significant indicators and their statistical results and *P*-values

Table 3 Interaction between smoking and SNPs on COPD

SNP (Gene)	Genotype	Environmental exposure	OR (95%CI)	*P*-value
rs1205* (CRP)	T/T	Smoking index ≤ 200	Ref	
	C/T + C/C	Smoking index ≤ 200	1.27 (0.87–1.86)	0.22
	T/T	Smoking index > 200	1.39 (0.86–2.25)	0.18
	C/T + C/C	Smoking index > 200	**1.81 (1.18–2.79)**	**0.01**
rs1130864 @ (CRP)	G/G	No fuel/Natural gas/Electricity	Ref	
	G/A + A/A	No fuel/Natural gas/Electricity	$1.39e^{-6}$ (NA-$1.28e^{11}$)	0.97
	G/G	Coal/Wood/Straw	1.56 (0.83–3.04)	0.18
	G/A + A/A	Coal/Wood/Straw	**3.01 (1.39–6.745)**	**0.01**
rs11084376* (FCAR)	C/C	Smoking index ≤ 200	Ref	
	C/G + G/G	Smoking index ≤ 200	1.09 (0.75–1.59)	0.64
	C/C	Smoking index > 200	**1.89 (1.25–2.88)**	**<0.01**
	C/G + G/G	Smoking index > 200	1.11 (0.72–1.77)	0.65
rs844# (FCGR2B)	G/G	No straw burning outdoor	Ref	
	A/G + A/A	No straw burning outdoor	1.47 (0.84–2.60)	0.18
	G/G	Straw burning outdoor	**2.18 (1.39–3.46)**	**<0.01**
	A/G + A/A	Straw burning outdoor	1.49 (0.94–2.37)	0.09

* Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Straw burning outdoor, Indoor fuel use

@Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Smoking, Straw burning outdoor

Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Smoking, Indoor fuel use

The bolded content represents the statistically significant indicators and their statistical results and *P*-values

Table 4 Interaction between indoor fuel use and SNPs on COPD

SNP (Gene)	Genotype	RERI (95%CI)	SI (95%CI)	OR (95%CI)*	*P-value*
rs1205 (CRP)	C/T + C/C vs T/T	0.41 (-0.73–1.56)	1.56 (0.17–13.94)	1.20 (0.33–4.18)	0.78
rs1130864 (CRP)	G/A + A/A vs G/G	**2.45 (0.73–4.18)**	– 4.57 (Na-Na)	1.39e^{6} (1.61e-^{11}-Na)	0.97
rs2808630 (CRP)	C/T + C/C vs T/T	0.45 (– 0.63–1.53)	2.31 (0.04–140.48)	1.56 (0.41–6.85)	0.53
rs11084376 (FCAR)	CG + GG vs C/C	0.24 (– 0.69–1.16)	2.34 (0.00–4808.09)	1.54 (0.44–5.96)	0.51
rs4806606 (FCAR)	A/G + G/G vs A/A	0.25 (– 0.58–1.08)	– 1.17 (Na-Na)	2.01 (0.50–10.35)	0.35
rs4806608 (FCAR)	A/G + G/G vs A/A	– 0.17 (– 1.47–1.12)	0.68 (0.09–5.53)	1.02 (0.27–4.46)	0.97
rs62123424 (FCAR)	T/C + T/T vs C/C	0.62 (– 0.05–1.29)	– 1.51 (Na-Na)	2.15 (0.63–7.60)	0.22
rs7259090 (FCAR)	A/G + A/A vs G/G	– 0.45 (– 2.05–1.15)	0.53 (0.11–2.45)	0.77 (0.21–3.05)	0.70
rs8112766 (FCAR)	A/G + G/G vs A/A	– 0.37 (– 1.91–1.16)	0.60 (0.19–1.84)	0.85 (0.24–2.93)	0.80
rs1865097 (FCAR)	A/G + A/A vs G/G	0.63 (– 0.04–1.30)	– 1.54 (Na-Na)	2.17 (0.63–7.65)	0.22
rs2304225 (FCAR)	CG + GG vs C/C	0.37 (– 0.97–1.72)	1.69 (0.10–27.64)	1.37 (0.31–7.45)	0.69
rs4656308 (FCGR2A)	C/T + C/C vs T/T	– 0.71 (– 2.49–1.07)	0.38 (0.08–1.81)	0.64 (0.17–2.56)	0.51
rs4656309 (FCGR2A)	T/C + T/T vs C/C	0.39 (– 0.48–1.25)	0.27 (0.00–16.78)	2.00 (0.46–8.43)	0.34
rs4657040 (FCGR2A)	T/C + C/C vs T/T	– 0.09 (– 1.44–1.26)	0.87 (0.14–5.52)	1.02 (0.28–4.40)	0.98
rs1801274 (FCGR2A)	A/G + G/G vs A/A	0.46 (– 0.25–1.17)	– 0.66 (Na-Na)	2.05 (0.60–7.26)	0.26
rs2165088 (FCGR2A)	G/A + A/A vs G/G	0.21 (– 1.04–1.46)	1.36 (0.13–14.07)	1.22 (0.33–5.29)	0.77
rs844 (FCGR2B)	A/G + A/A vs G/G	– 0.37 (– 1.90–1.17)	0.65 (0.22–1.98)	0.82 (0.24–2.79)	0.74
rs16827592 (FCGR2B)	T/G + G/G vs T/T	0.02 (– 1.76–1.80)	1.02 (0.23–4.50)	0.89 (0.23–3.69)	0.87

The indoor fuel use exposure is classified into Coal/Wood/Straw vs No fuel/Natural gas/Electricity; Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Smoking, Straw burning outdoor

*: Multiplication interaction; *P-value* for Multiplication interaction

The bolded content represents the statistically significant indicators and their statistical results and *P*-values

Table 5 Interaction between Straw burning outdoor exposure and SNPs on COPD

SNP (Gene)	Genotype	RERI (95%CI)	SI (95%CI)	OR (95%CI)*	*P-value*
rs1205 (CRP)	C/T + C/C vs T/T	0.38 (– 0.34–1.11)	1.86 (0.26–13.33)	1.24 (0.63–2.42)	0.54
rs1130864 (CRP)	G/A + A/A vs G/G	0.77 (– 1.27–2.81)	1.82 (0.29–11.29)	1.25 (0.39–4.13)	0.71
rs2808630 (CRP)	C/T + C/C vs T/T	0.11 (– 0.78–1.00)	1.22 (0.23–6.50)	1.07 (0.50–2.29)	0.86
rs11084376 (FCAR)	CG + GG vs C/C	– 0.09 (– 0.83–0.64)	0.77 (0.14–4.39)	0.98 (0.51–1.90)	0.96
rs4806606 (FCAR)	A/G + G/G vs A/A	– 0.48 (– 1.36–0.39)	0.17 (0.00–16.51)	0.72 (0.33–1.58)	0.41
rs4806608 (FCAR)	A/G + G/G vs A/A	– 0.07 (– 0.84–0.70)	0.73 (0.03–18.33)	1.07 (0.47–2.49)	0.87
rs62123424 (FCAR)	T/C + T/T vs C/C	– 0.36 (– 1.36–0.63)	0.69 (0.31–1.53)	0.74 (0.38–1.44)	0.38
rs7259090 (FCAR)	A/G + A/A vs G/G	– 0.48 (– 1.46–0.51)	0.29 (0.02–4.24)	0.71 (0.31–1.67)	0.43
rs8112766 (FCAR)	A/G + G/G vs A/A	– 0.53 (– 1.47–0.41)	0.37 (0.10–1.31)	0.72 (0.37–1.39)	0.33
rs1865097 (FCAR)	A/G + A/A vs G/G	– 0.51 (– 1.57–0.55)	0.62 (0.30–1.31)	0.67 (0.34–1.30)	0.24
rs2304225 (FCAR)	CG + GG vs C/C	0.15 (– 0.75–1.05)	1.28 (0.25–6.68)	1.09 (0.52–2.31)	0.83
rs4656308 (FCGR2A)	C/T + C/C vs T/T	– 0.43 (– 1.31–0.45)	0.23 (0.01–7.34)	0.76 (0.34–1.71)	0.50
rs4656309 (FCGR2A)	T/C + T/T vs C/C	– 0.62 (– 1.82–0.57)	0.40 (0.14–1.12)	0.69 (0.33–1.45)	0.33
rs4657040 (FCGR2A)	T/C + C/C vs T/T	– 0.38 (– 1.29–0.53)	0.47 (0.10–2.25)	0.76 (0.37–1.58)	0.46
rs1801274 (FCGR2A)	A/G + G/G vs A/A	– 0.27 (– 1.14–0.60)	0.62 (0.20–1.91)	0.84 (0.43–1.64)	0.60
rs2165088 (FCGR2A)	G/A + A/A vs G/G	– 0.83 (– 2.05–0.38)	0.41 (0.14–1.22)	0.55 (0.26–1.13)	0.10
rs844 (FCGR2B)	A/G + A/A vs G/G	– 1.17 (– 2.38–0.05)	**0.30 (0.11–0.77)**	**0.46 (0.24–0.90)**	**0.02**
rs16827592 (FCGR2B)	T/G + G/G vs T/T	0.47 (– 0.30–1.23)	2.38 (0.22–25.45)	1.37 (0.69–2.73)	0.37

The straw burning outdoor exposure is classified into Straw burning outdoor vs No Straw burning outdoor; Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Indoor fuel use, Smoking

*: Multiplication interaction; *P-value* for Multiplication interaction

The bolded content represents the statistically significant indicators and their statistical results and *P*-values

Table 6 Interaction between environmental exposure and haplotypes on COPD

Haplotype block(Gene)	Environment	Haplotypes	Environmental classification	RERI (95%CI)	SI (95%CI)	OR (95%CI)*	*P*-value
rs2808630-rs1205 (CRP)	Smoking*	TC + CC vs TT	Smoking index > 200 vs Smoking index ≤ 200	0.15 (– 0.40–0.69)	1.29 (0.44–3.79)	1.17 (0.72–1.88)	0.53
rs2808630-rs1205 (CRP)	Indoor fuel use@	TC + CC vs TT	Coal/Wood/Straw vs No fuel/Natural gas/Electricity	0.47 (– 0.32–1.25)	1.86 (0.28–12.44)	1.36 (0.57–3.37)	0.50
rs2808630-rs1205 (CRP)	Straw burning outdoor#	TC + CC vs TT	Yes vs No	0.29 (– 0.28–0.85)	1.56 (0.51–4.80)	1.17 (0.72–1.88)	0.53
rs2304225-rs11084376-rs8112766 (FCAR)	Smoking*	CCG + CGG + GGG vs CCA	Smoking index > 200 vs Smoking index ≤ 200	– 0.50 (– 1.04–0.05)	0.06 ($1.81e^{-6}$–$2.03e^{3}$)	0.69 (0.44–1.08)	0.11
rs2304225-rs11084376-rs8112766 (FCAR)	Indoor fuel use@	CCG + CGG + GGG vs CCA	Coal/Wood/Straw vs No fuel/Natural gas/Electricity	0,10 (– 0.63–0.83)	1.35 (0.07–26.20)	1.35 (0.54–3.55)	0.53
rs2304225-rs11084376-rs8112766 (FCAR)	Straw burning outdoor#	CCG + CGG + GGG vs CCA	Yes vs No	– 0.15 (– 0.68–0.39)	0.63 (0.16–2.54)	0.96 (0.58–1.57)	0.85
rs1865097-rs62123424 (FCAR)	Smoking*	AT + GT + AC vs CC	Smoking index > 200 vs Smoking index ≤ 200	– 0.05 (– 0.60–0.50)	0.88 (0.22–3.57)	0.97 (0.63–1.50)	0.89
rs1865097-rs62123424 (FCAR)	Indoor fuel use@	AT + GT + AC vs CC	Coal/Wood/Straw vs No fuel/Natural gas/Electricity	0,10 (– 0.63–0.83)	1.35 (0.07–26.20)	2.45 (0.95–6.98)	0.08
rs1865097-rs62123424 (FCAR)	Straw burning outdoor#	AT + GT + AC vs CC	Yes vs No	– 0.14 (– 0.73–0.45)	0.79 (0.31–1.98)	0.90 (0.56–1.46)	0.67
rs4656308-rs4656309-rs2165088 (FCGR2A)	Smoking*	CTG + TCA + TTA + TTG vs TCG	Smoking index > 200 vs Smoking index ≤ 200	– 0.08 (– 0.61–0.46)	0.78 (0.15–3.93)	0.97 (0.63–1.50)	0.90
rs4656308-rs4656309-rs2165088 (FCGR2A)	Indoor fuel use@	CTG + TCA + TTA + TTG vs TCG	Coal/Wood/Straw vs No fuel/Natural gas/Electricity	0,10 (– 0.63–0.83)	1.35 (0.07–26.20)	1.47 (0.61–3.56)	0.39
rs4656308-rs4656309-rs2165088 (FCGR2A)	Straw burning outdoor#	CTG + TCA + TTA + TTG vs TCG	Yes vs No	– 0.59 (– 1.31–0.13)	0.48 (0.26–0.89)	0.67 (0.42–1.06)	0.09

* : Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Straw burning outdoor, Indoor fuel use

@: Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Smoking, Straw burning outdoor

: Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Smoking, Indoor fuel use

Discussion

In our previous study, several environmental exposure factors associated with COPD were identified. Considering the important role of genetic factors, the present study focused on the effects of the genotypes, alleles and haplotypes of the CRP/FCAR/FCGR2A/FCGR2B genes on COPD, and the environment–gene interactions were explored.

The CRP gene is located at the 1q23.2 position. Rs1130864 (G > A) is a mutation located in the 3 ′UTR (untranslated region) of the CRP gene. CRP is an important cytokine involved in the inflammatory process of COPD. This study revealed that the rs1130864 (G > A) allele and dominant model in the CRP gene are associated with COPD; that is, rs1130864-A allele, G/A and A/A genotype carriers have increased COPD susceptibility. The concentration of CRP in the airway and blood is often elevated [3]. An increasing number of studies have confirmed that the rs1130864-A allele in the CRP gene is associated with an increase in CRP; these studies

Table 7 Interaction between straw burning outdoors and the FCGR2A rs4656308-rs4656309-rs2165088 haplotypes on COPD

Genotype	Straw burning outdoor	OR (95%CI)	*P*-value
TCG	No	Ref	
CTG + TCA + TTA + TTG	No	1.21 (0.81–1.80)	0.36
TCG	Yes	**1.93 (1.36–2.76)**	**0.00**
CTG + TCA + TTA + TTG	Yes	**1.55 (1.11–2.19)**	**0.01**

Adjusted for Age, Education, Income, BMI, History of RD, History of CHD/CHF, History of CVD, Indoor fuel use, Smoking

* Multiplication interaction

The bolded content represents the statistically significant indicators and their statistical results and *P*-values

were conducted in Shanghai and Europe [17, 18]. Navarro P et al. reported that the rs1130864 genotype in the CRP gene was associated with high CRP levels through a cohort study in Spain. However, some of the findings are inconsistent with this study. Bolton CE et al. conducted a study on British men and reported that serum CRP was associated with decreased lung function, whereas the rs1130864 genotype was not associated with decreased lung function [19]. A clinical study conducted by Guo et al. in Shanghai in a Han population revealed that the rs1130864 locus was not correlated with COPD [20]. The reason for these inconsistent results may be that the populations selected for this study differed. This study chose people in cold rural areas in northern China. Therefore, this study highlights the influence of genetic differences between southern and northern Chinese people on COPD. Guo J et al. reported that rs1130864 was an independent predictor of the prognosis of ischemic stroke patients in the Chinese Han population [21]. A European study by Nimptsch K et al. revealed that the A allele at rs1130864 was associated with elevated CRP and colorectal cancer risk [22]. Our group previously demonstrated that serum CRP is a risk factor for COPD, and we speculated that the variable sequence of the rs1130864 locus in the untranslated region of the CRP gene may regulate the inflammatory response of the body and exacerbate airflow restriction by affecting posttranscriptional regulation and translation.

Rs1205 (T > C) is a mutation located in the untranslated 3 'UTR of the CRP gene. Rs2808630 (T > C) is a mutation located downstream of the CRP gene. In this study, no significant associations were found between the rs1205 or rs2808630 genotype or haplotype and COPD. However, a clinical study conducted by Yi Guo et al. in Shanghai in a Han population revealed that the CRP gene rs1205-T allele was a protective factor for COPD, and the TT haplotype frequency of rs1205 and rs2808630 was significantly greater than that of the control group [22]. The reason for these different results may be genetic differences between the northern and southern populations in China.

The FCAR gene is located at the 19q13.42 position. The eight loci included in this study are all mutation sites located in the introns of the FCAR gene. FCAR genes mediate a variety of immune system functions, including degranulation, endocytosis, phagocytosis, cytokine synthesis, and cytokine release. There are no studies on the associations of SNPs in the FCAR gene with COPD, and some evidence has revealed that these SNPs contribute to the pathogenesis of other inflammation-related diseases. The FCAR gene can increase the proinflammatory activity of IgA in serum [23] and thus affect many diseases, such as dermatitis herpetiformis, celiac disease, periodontal disease and IgA nephropathy [24]. Wu J et al. reported that the rs16986050 locus in the FCAR gene is involved in the production of proinflammatory cytokines and the release of IL-6 cytokines from neutrophils in vitro, which plays an important role in the regulation of the immune response in systemic lupus erythematosus [24]. In the present study, the rs4806606-G and rs8112766-G alleles were found to reduce susceptibility to COPD. Since these genes are located in introns of the FCAR gene, we hypothesized that they regulate gene expression through initiation and selective splicing, enhancing the anti-inflammatory effect mediated by the FCAR gene.

Both the FCGR2A gene and FCGR2B gene are located at the 1q23.3 position. Among the five FCGR2A gene loci included in this study, only rs1801274 was the mutation site of the FCGR2A gene exon, and the other four were located in introns. Among the two FCGR2B gene loci included in the study, rs844 is a mutation site located in the 3 'UTR (nontranslated region) of the FCGR2B gene, and rs16827592 is in an intergenic mutation site. At present, no studies have investigated the associations between SNPs in the FCGR2A and FCGR2B genes and COPD. Some studies have reported that FCGR2A and FCGR2B play roles in the pathogenesis of other immune-related diseases. FCGR2A is a susceptibility gene for several autoimmune diseases, such as systemic lupus erythematosus (SLE) [25], rheumatoid arthritis [26], multiple sclerosis [27], type 1 diabetes [28], and ulcerative colitis [28, 29]. The homozygous C/C at rs1801274 in the FCGR2A gene reduces susceptibility to ulcerative colitis in the Chinese population, whereas the TC haplotype consisting of the rs1801274 and rs511278 loci in the FCGR2A gene increases the risk of ulcerative colitis in the Chinese population [30]. The rs2099684 locus in the FCGR2A gene is a genetic risk factor for arteritis in the Chinese Han population [31]. The FCGR2A gene was

found to be strongly associated with giant cell arteritis in Spain [32]. SNPs of the FCGR2B gene inhibit binding to its ligands IgG1, IgG2, and IgG3. The alleles rs4656308-C and rs4656309-T in the FCGR2A gene are located in introns, and our results revealed that both can reduce the susceptibility of the population to COPD. Therefore, we speculated that the regulation of gene expression through initiation and selective splicing involves FCGR2A receptors on the surface of monocytes, macrophages, neutrophils, natural killer cells, T lymphocytes and B lymphocytes and subsequently enhances the phagocytosis of FCGR2A-mediated immune complexes and the anti-inflammatory effect of B cells on antibody production.

This study revealed that a smoking index > 200 had a positive additive interaction with the rs1205 locus in the CRP gene and a multiplicative interaction with the rs11084376 locus in the FCAR gene in COPD patients. However, no independent role of the rs1205 locus or the rs11084376 locus in COPD pathogenesis was found, suggesting that susceptibility to COPD is significantly increased when individuals carry the C/T + C/C genotype at the rs1205 locus or the C/G + G/G genotype at the rs11084376 locus accompanied by a smoking index > 200. No previous study has explored the association of the rs1205 locus with COPD, and it was found to be involved in the pathogenesis of other inflammation-related diseases. A European population study by Nimptsch K et al. revealed that the rs1205-T allele was associated with reduced CRP and a lower risk of colorectal cancer [33]. Todendi PF et al. reported that in overweight and obese people, the CRP level was lower than that in those who carried the rs1205-T allele in the CRP gene [34]. A Chinese population study conducted by Tian Yaping revealed that the C/C genotype frequency at the rs1205 locus in the CRP gene in a healthy Han population was lower than that in T2DM patients [35]. Previous studies have suggested that the rs1205-C allele may promote the development of inflammatory diseases. Our results suggested that the C/T + C/C genotype at the rs1205 locus has no significant effect on COPD compared with the T/T genotype, with a synergistic effect between the C/T + C/C genotype and a smoking index > 200. The effects of the rs1205 locus and smoking alone can be amplified by additive interactions, increasing the risk of COPD.

Both exposure to coal/wood/straw and the rs1130864 locus in the CRP gene are independent risk factors for COPD, and the interaction is also a risk factor, suggesting that susceptibility to COPD increases through synergistic effects when coexposure to straw burning outdoors and that the rs844 locus in the FCGR2B gene has negative additive and multiplicative interactions with COPD. No significant effect of the rs844 locus in the FCGR2B gene was found on COPD, whereas straw burning outdoors was found to be an independent risk factor, and the interaction between the two factors was a protective factor against COPD. Previous studies on the rs844 locus and disease are lacking, but studies on the mechanism of the FCGR2B gene are lacking. The FCGR2B gene functions to produce inhibitory signals in cells and is highly expressed on B cells to inhibit the activation signals induced by immunoglobulin on the surface of the B-cell membrane. It is also expressed in monocytes, macrophages and dendritic cells to inhibit prophagocytosis signals [36–38]. Rs844 is a mutation site in the 3 'UTR untranslated region of the FCGR2B gene. Our results suggested that the rs844-G allele in the FCGR2B gene may promote the occurrence of inflammation by influencing posttranscriptional regulation and translation, inhibiting the activation signal induced by immunoglobulin on the surface of the B-cell membrane or inhibiting the phagocytosis signal from monocytes, macrophages and dendritic cells. However, the mutated rs844-A allele can change the function of inhibitory signals, influence the immune response, enhance immunity, inhibit inflammation, and have a weak effect on COPD alone. The smoke produced by outdoor straw burning may contain some chemical components, which can multiply the effect of the rs844 locus after it enters the body. When the two factors coexist, they exhibit antagonistic effects, which can reduce susceptibility to COPD.

Exposure to straw burning outdoors had a negative additive interaction with haplotypes at rs4656308-rs4656309-rs2165088 in the FCGR2A gene on COPD. Previous studies on the rs4656308, rs4656309, and rs2165088 loci and diseases have not been reported. The FCGR2A gene is widely expressed in monocytes, macrophages, dendritic cells, neutrophils and platelets and can induce cellular defense mechanisms [39]. This study revealed that straw burning outdoors was a risk factor for COPD. Both the rs4656308 and rs4656309 loci are protective factors for COPD. However, no effect of this haplotype on the occurrence of COPD was found. Rs4656308, rs4656309 and rs2165088 are located in introns of the FCGR2A gene. Compared with the TCG haplotype at rs4656308-rs4656309-rs2165088, the susceptibility of the population with the CTG + TCA + TTA + TTG haplotypes to COPD was significantly lower in those exposed to straw burning outdoors. This haplotype gene mutation may regulate changes in gene expression through initiation and selective splicing and enhance the phagocytosis of the FCGR2A-mediated immune complex and the immune and anti-inflammatory effects of B cells on antibody production, thus increasing the susceptibility of this population to COPD.

Admittedly, there are still limitations in this study. First, the inclusion of environmental exposure factors and genetic polymorphic loci in this study is limited, and the possibility of interactions between other environmental risk factors and genes cannot be ruled out. Second, in the genetic model construction and stratified analysis of this study, the mutation rates of some genes in the investigated population may have been lower, and the sample size after classification may have been affected to some extent. Although the sample size is sufficient, the results of this study need to be further verified in different areas and ethnicities.

Conclusions

Overall, the present study revealed that alleles and genotypes of the CRP, FCAR and FCGR2A genes can increase susceptibility to COPD in the northern Chinese population. In addition, exposure to a smoking index > 200, indoor coal/wood/straw use, and outdoor straw burning were found to have synergistic or antagonistic effects on the genotypes or haplotypes of the CRP/FCAR/FCGR2A/FCGR2B genes. The above findings can provide new ideas and references for personalized and COPD research.

Abbreviations

BMI	Body mass index
CHD	Coronary heart disease
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary diseases
CRP	C-reactive protein
CVD	Cerebrovascular disease
DNA	Deoxyribonucleic acid
FCAR	Fc fragment of IgA receptor
FCGR	Fc fragment of IgG receptor
FCGR2A	Fc fragment of IgG receptor IIa
FCGR2B	Fc fragment of IgG receptor IIb
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GMDR	Generalized multifactor dimensionality reducation
HWE	Hardy–weinberg equilibrium
IgA	Immunoglobulin A
IgG	Immunoglobulin G
LD	Linkage disequilibrium
PCR	Polymerase chain reaction
RD	Respiratory disease
RERI	Relative excess risk of interaction
SI	The synergy index
SNP	Single nucleotide polyorphism

Supplementary Information

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Supplementary material 1.

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Author contributions

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Availability of data and materials

The data are available upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved in June 2018 by Harbin Medical University (research project: hrbmuecdc20180601). All participants provided informed consent prior to starting the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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