Original Article

Polymorphisms in the *FCER2* gene have associations with asthma and chronic obstructive pulmonary disease

Zhoude Zheng[1#], Jia Li[1#], Yi Liu[2]^, Lun Li[3], Tingting Huang[1], Yilin Huang[1], Siyao Song[2], Jinming Gao[1]

[1]Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China; [2]Department of Respiratory Medicine, Civil Aviation General Hospital, Beijing, China; [3]Department of Allergy, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China

Contributions: (I) Conception and design: Z Zheng, J Li, Y Liu, J Gao; (II) Administrative support: Y Liu, J Gao; (III) Provision of study materials or patients: Y Liu, L Li; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yi Liu. Department of Respiratory Medicine, Civil Aviation General Hospital, Beijing, China. Email: cassieliu@126.com; Jinming Gao. Peking Union Medical College Hospital (Dongdan Campus), No. 1 Shuaifuyuan Wangfujing Dongcheng District, Beijing, China. Email: gao.jin.ming@hotmail.com.

Background: Asthma and chronic obstructive pulmonary disease (COPD) are heterogenetic diseases and exhibit many similarities. Dutch hypothesis proposed that these two diseases may have common genetic origins. This study aims to investigate whether asthma and COPD share a common genetic background in Chinese patients.

Methods: In this case-control study, single nucleotide polymorphisms (SNPs) were genotyped using SNaPshot. Haplotype disease analysis and haplotype phenotype analysis were applied to assess the relationship between three polymorphisms of the *FCER2* gene and the risk of COPD/asthma. Additionally, associations between polymorphisms of the *FCER2* gene and phenotypes were analyzed.

Results: We detected ten SNPs of seven genes (*FCER1A*, *FCGR2A*, *FCGR2B*, *CHI3L1*, *ADRB2*, *STAT6*, and *FCER2*) expressed by airway epithelial cells. We detected genotypes and allele distributions in 251 COPD patients, 597 asthma patients, and 632 healthy controls. A significant difference was found in the *FCER2* gene (rs28364072) between COPD patients and controls (P=0.009). Significant differences were observed in the genotype and allele distributions of rs1801274 (*FCGR2A*), rs12368672 (*STAT6*), and rs2228137 (*FCER2*) between asthma patients and controls (P=0.004, 0.007 and 0.010, respectively). Notably, polymorphisms of *FCER2* gene were associated with the risk of both COPD (P=0.009 for rs28364072) and asthma (P=0.01 for rs2228137). Haplotype analysis revealed that haplotype T-G-T (alleles of rs28364072, rs2228137, and rs3760687, respectively) was significantly associated with a higher risk of asthma [odds ratios (OR) =2.25, 95% confidence interval (CI): 1.26–4.01, P=0.006]. Further analysis showed that the C-A-C haplotype and C-G-T haplotype were associated with increased blood eosinophils in either COPD or asthma patients (P=0.034, and P<0.001, respectively). Moreover, haplotypes C-A-C, C-G-C, and T-G-C showed significant associations with serum IgE levels in asthma patients (P=0.002, 0.041, and 0.004, respectively).

Conclusions: Our data suggest that the *FCER2* gene might associate with predisposition to asthma and COPD, while *FCER2* haplotypes were associated with pulmonary function measurements and blood eosinophils counts in both diseases. Our findings support the common genetic basis for asthma and COPD, suggesting a potential therapeutic target for the two diseases.

Keywords: Asthma; chronic obstructive pulmonary disease (COPD); FCER2; single nucleotide polymorphisms (SNPs)

^ ORCID: 0000-0003-1044-5284.

Submitted Jun 13, 2022. Accepted for publication Jan 13, 2023. Published online Feb 06, 2023.
doi: 10.21037/jtd-22-820
View this article at: https://dx.doi.org/10.21037/jtd-22-820

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the major health problems worldwide (1,2). Airway obstruction occurs in both diseases with asthma showing reversible and COPD being irreversible. However, persistent airflow limitation could present in severe asthma and partially reversible airflow obstruction may occur in COPD (3). Despite the differences in pathogenic factors and endotypes (4,5), the two diseases showed many phenotypic similarities. Typically, chronic inflammation in asthmatic airways is featured by infiltration of CD4 (+) lymphocytes and eosinophils, while CD8 (+) lymphocytes, macrophages, and neutrophils are elevated in COPD airways (6). However, the endotypes of chronic inflammation could be represented by neutrophilia in asthma (7) and eosinophilia in COPD (8). A recent study reported that the Th2 inflammation-related genetic signature, a typical feature in asthma, co-occurred in COPD (9).

"Dutch hypothesis" was proposed by Orie and colleagues that asthma and COPD are two different manifestations of one disease entity called "chronic non-specific lung disease" (CNSLD), which resulted from the interactions between genetic predisposition and exposure to similar environmental factors, further leading to the clinical presentations of the disease (10,11). By contrast, the "British hypothesis" stated that asthma and COPD are two distinct disease entities with different clinical syndromes, inflammatory processes, therapy responses, genetic substrate, and atopy status (4).

In recent years, growing evidence supported the Dutch hypothesis by showing the commonalities between asthma and COPD (12-14). Both diseases have common environmental risk exposure, such as maternal smoking during pregnancy, environmental tobacco exposure, and air pollution (14). Airway hyperresponsiveness (AHR) and atopy defined by IgE level are two important characteristics of asthma (15). Previous studies have reported that AHR led to chronic COPD-associated respiratory symptoms and worse lung function in COPD (15,16), while IgE correlated with development, exacerbations, and lung function decline (17,18). Importantly, several single nucleotide polymorphisms (SNPs) of specific genes were reported to be associated with both asthma and COPD, including *CHI3L1*, *CHIT1*, *IL-13*, *ADAM33*, *MMP12*, and others (19-25). Besides, Hayden and colleagues suggested that childhood asthma was associated with a higher risk for COPD, while the known childhood asthma loci like *IL1RL1*, *IL13*, and *GSDMB*, correlated with COPD (26). However, a genome-wide association study (GWAS) suggested that no common genetic component was found in asthma and COPD (27). So far, a consensus on the origins of these two disorders has not been reached (28).

The present study aims to investigate whether asthma and COPD share the possible common genetic susceptibility in Chinese patients by selecting 10 SNPs within 7 candidate genes (*FCER1A*, *FCGR2A*, *FCGR2B*, *CHI3L1*, *ADRB2*, *STAT6*, and *FCER2*), that are mainly expressed in airway epithelial cells. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-820/rc).

Highlight box

Key findings

- Polymorphisms of the *FCER2* gene (encoding low-affinity receptor for IgE) demonstrated positive association with the susceptibility to both COPD and asthma in Chinese population.

What is known and what is new?

- Asthma and COPD are heterogeneous airway diseases and exhibit many similarities. It is suggested by Dutch hypothesis that these two diseases may share common genetic origins.
- Polymorphisms of the *FCER2* gene were genetically associated with predisposition to COPD and asthma. Moreover, the haplotypes of *FCER2* gene were in association with pulmonary function measurements and blood eosinophils counts in both diseases.

What is the implication, and what should change now?

- Our findings suggest a possible implication that anti-IgE biologic, widely accepted as an asthma treatment, might be beneficial for the specific subtype of COPD.

Methods

Study participants

This case-control study included 848 patients, 251 with COPD and 597 with asthma, and 632 healthy controls, who were recruited from August 2017 to September 2019 from two medical centers, Peking Union Medical College Hospital and Beijing Aviation General Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research protocol was reviewed and approved by the Ethics Committee for Human Research of Peking Union Medical College Hospital (S-767) and Beijing Aviation General Hospital (MHZYY 2014-05-01) and informed written consent was obtained from all participants.

Inclusion and exclusion criteria

All participants were aged 18 years or older. Asthma was diagnosed based on Global Initiative for Asthma (GINA) criteria (29): (I) history of variable respiratory symptoms; (II) variable expiratory airflow limitation, e.g., increase in forced expiratory volume in the first second (FEV_1) of >12% and >200 mL after salbutamol (albuterol) inhalation; (III) effective of medications for asthma. COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (30): FEV_1 to forced vital capacity (FVC) of <0.7 after salbutamol (albuterol) inhalation. COPD patients with asthma were excluded from our study.

Healthy controls were eligible for this study according to the following criteria: (I) without a diagnosis of COPD, asthma, or any other respiratory diseases; (II) no history of respiratory allergic diseases or any other respiratory symptom, like wheezing, shortness of breath; (III) no use of medications for asthma and COPD. Spirometry without bronchodilation was performed for all healthy controls.

Individuals were excluded from the study if they (I) were diagnosed with asthma-COPD overlap syndrome; (II) had a suspected acute inflammatory or infectious disease; (III) had a history of stroke or acute coronary syndrome; (IV) experienced venous thromboembolism; (V) received anticoagulant therapy; (VI) were diagnosed with cancer within the last 5 years; (VII) were pregnant or under hormone-replacement therapy.

Demographic and clinical measurements

We collected the following variables: age, gender, and smoking status. Fasting venous blood samples were drawn into tubes and transported to the laboratory within 4 hours to test blood eosinophil and serum IgE levels. The missing data were less than 5% and replaced using linear interpolation.

According to the GINA, participants were stratified into three groups based on age: (I) age between 18 and 40 years; (II) age between 40 and 65 years; (III) and age ≥65 years.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes by standard protocols. After a comprehensive literature search and consultation with a respiratory established geneticist, a total of 10 SNPs of interest within 7 genes which are mainly expressed in airway epithelial cells were selected, including *FCER1A* (rs2427837), *FCGR2A* (rs1801274), *FCGR2B* (rs1050501), *CHI3L1* (rs4950928), *ADRB2* (rs1042713 and rs1042714), *STAT6* (rs12368672) and *FCER2* (rs28364072, rs2228137, and rs3760687). These SNPs were to some extent the most frequently reported candidates in the two diseases according to our literature review. Genotyping was done using SNaPshot as previously described (31). The PCR products were sequenced and analyzed using ABI 3730XL DNA Analyzer (Applied Biosystems) and GeneMapper 4 software, respectively. Hardy-Weinberg equilibrium was tested as shown in Table S1 (P cutoff-value =0.05).

Statistical analysis

The baseline characteristics of the participants were compared using a chi-square test (discrete variables) and Student's *t*-test (continuous variables). The odds ratio (OR) and 95% confidence interval (CI) were calculated for evaluating differences in genotype distributions and haplotype disease analysis by binary logistic regression with adjusting for age and sex. SNK-q test and Student's *t*-test were used to assess the associations between polymorphisms and phenotypes. Results were expressed as mean ± SD. Multiple factors analysis of variance (ANOVA) was used to evaluate the relationship between each haplotype and phenotypes. We used multiple-factor analysis such as binary logistic regression and multiple factors ANOVA to control the population stratification as a confounder. A P<0.05 was considered statistically significant. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Table 1 Baseline characteristics of all participants involved in the study

Variables	Controls (n=632)	COPD		Asthma	
		n=251	P*	n=597	P*
Age (years), n (%) or mean ± SD	37.9±11.7	68.9±10.1	<0.001	43.9±13.07	<0.001
≥18, <40	390 (61.7)	1 (0.4)	<0.001	218 (36.5)	<0.001
≥40, <65	215 (34.0)	88 (35.1)	0.769	233 (39.0)	0.068
≥65	27 (4.3)	162 (64.5)	<0.001	146 (24.5)	<0.001
Gender (male), n (%)	284 (42.5)	212 (84.5)	<0.001	214 (35.8)	0.606
Smoking status, n (%)					
Non-smokers	N/A	72 (28.7)	N/A	520 (87.1)	N/A
Ex-smokers	N/A	53 (21.1)	N/A	24 (4.0)	N/A
Current smokers	N/A	126 (50.2)	N/A	53 (8.9)	N/A
Blood Eso (%), mean ± SD	2.28±1.45	2.24±1.99	0.78	5.72±4.54	<0.001
Serum IgE (U/L), mean ± SD	48.33±56.12	132±152.52	<0.001	275±385.90	<0.001
FEV_1/FVC (%), mean ± SD	84.9±8.54	49.64±15.28	<0.001	65.59±14.17	<0.001
FEV_1%pred, mean ± SD	102.97±13.40	52.01±17.79	<0.001	70.55 ± 23.63	<0.001
≥18, <40	101.6±13.4	65.6	N/A	77.6±22.4	<0.001
≥40, <65	107.3±124	51.6±17.8	<0.001	65.2±23.4	<0.001
≥65	N/A	52.2±17.7	N/A	65.0±20.7	N/A
The severity of airflow limitation, n (%)					
GOLD 1	N/A	73 (29.1)	N/A	N/A	N/A
GOLD 2	N/A	99 (39.4)	N/A	N/A	N/A
GOLD 3	N/A	65 (25.9)	N/A	N/A	N/A
GOLD 4	N/A	14 (5.6)	N/A	N/A	N/A

*, relative to controls. COPD, chronic obstructive pulmonary disease; Eos, eosinophil; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; pred, predicted; N/A, not applicable; GOLD, The Global Initiative for Chronic Obstructive Lung Disease.

Results

Baseline characteristics of the study population

Baseline characteristics were presented in *Table 1*. The average age of participants with COPD and asthma was significantly higher than those of healthy controls (both P<0.001). Compared with the controls, the percentage of male participants was significantly higher in the COPD group (P<0.001), while no significant differences were found between asthma groups (P=0.78). The percentage of total smokers (ex-smokers and current smokers) in COPD patients was 71.3%, higher than those in asthma patients (12.9%). There was a higher percentage of blood eosinophil in asthma but not in COPD as compared to those in controls. Additionally, patients with COPD/asthma displayed significantly higher levels of serum IgE than those of the controls (both P<0.001). Moreover, we found significantly higher levels of blood eosinophil in asthma patients than those in controls (P<0.001). As expected, the two key spirometry indices FEV_1% predicted and FEV_1/FVC were significantly lower in the patients with COPD or asthma than those in controls (both P<0.001).

Genotype analysis and single-locus analysis

Table 2 showed the genotype distributions of selected polymorphisms between asthma/COPD patients and controls. Genotype analyses showed that, of 10 variants

Table 2 Distribution of alleles and genotypes of genes in COPD and asthma patients and controls

Gene	Marker	Ref./Alt.*	Alt. frequency analysis							Genotype analysis***					
			Controls	COPD			Asthma			Controls	COPD		Asthma		
				Case	OR (95% CI)	P value**	Case	OR (95% CI)	P value**		Case	P value**	Case	P value**	
FCER1A	rs2427837	G/A	0.04	0.044	0.987 (0.596–1.635)	0.96	0.044	1.000 (0.681–1.469)	0.999	576/54/1	229/22/0	0.959 (0.888)	545/51/1	0.999 (0.929)	
FCGR2A	rs1801274	T/C	0.3	0.309	1.045 (0.835–1.307)	0.703	0.357	1.302 (1.100–1.541)	0.002#	307/270/54	114/119/18	0.696 (0.093)	240/287/70	0.002 (0.004)#	
FCGR2B	rs1050501	T/C	0.21	0.217	1.071 (0.832–1.378)	0.594	0.188	0.892 (0.731–1.088)	0.26	372/260/0	144/105/2	0.538 (0.139)	374/222/1	0.196 (0.474)	
CHI3L1	rs4950928	C/G	0.14	0.126	0.864 (0.635–1.175)	0.352	0.16	1.147 (0.919–1.430)	0.224	460/164/8	193/53/5	0.344 (0.637)	421/161/15	0.217 (0.524)	
ADRB2	rs1042713	A/G	0.39	0.356	0.867 (0.700–1.076)	0.195	0.352	0.852 (0.723–1.003)	0.055	227/318/87	90/142/18	0.171 (0.342)	250/274/73	0.051 (0.161)	
ADRB2	rs1042714	C/G	0.1	0.096	0.911 (0.643–1.290)	0.598	0.096	0.907 (0.696–1.181)	0.468	505/122/5	203/46/1	0.591 (0.212)	487/104/5	0.464 (0.768)	
STAT6	rs12368672	C/G	0.2	0.173	0.863 (0.659–1.130)	0.285	0.237	1.276 (1.052–1.547)	0.013#	416/185/31	171/73/7	0.296 (0.789)	348/214/34	0.015 (0.007)#	
FCER2	rs28364072	A/G	0.3	0.323	1.113 (0.890–1.390)	0.347	0.324	1.120 (0.944–1.328)	0.194	297/291/44	107/126/18	0.319 (0.009)#	260/287/50	0.172 (0.663)	
FCER2	rs2228137	C/T	0.07	0.08	1.153 (0.782–1.701)	0.473	0.101	1.502 (1.127–2.001)	0.005#	543/86/1	211/40/0	0.459 (0.331)	484/105/8	0.006 (0.010)#	
FCER2	rs3760687	C/T	0.2	0.193	0.986 (0.759–1.281)	0.917	0.209	1.085 (0.891–1.321)	0.418	401/215/16	162/81/8	0.914 (0.588)	365/215/17	0.397 (0.292)	

*, Ref./Alt.: Reference/Alternative. **, P value adjusted for gender and age with binary logistic regression. ***, the three values represent the number of individuals carrying major allele homozygote, heterozygote, and mutant allele homozygote. #, represents significant value. COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

within 7 genes, only one SNP rs28364072 (*FCER2*) was significantly different between COPD patients and controls (P=0.009), while 3 SNPs (rs1801274 in *FCGR2A*, rs12368672 in *STAT6*, rs2228137 in *FCER2*) differed significantly between asthma and controls (P=0.004, 0.007 and 0.01, respectively). Additionally, single-locus analysis showed that polymorphisms of rs1801274 (*FCGR2A*), rs12368672 (*STAT6*) and rs2228137 (*FCER2*) were significantly associated with asthma (OR =1.302, P=0.004; OR =1.276, P=0.007; and OR =1.502, P=0.010, respectively). No SNP was found to be associated with COPD. Our results suggested that the *FCER2* gene was a common hereditary factor in COPD or asthma.

Polymorphism-phenotype analysis

Since only polymorphisms of the *FCER2* gene were found to be associated with asthma and COPD, three included SNPs (rs28364072, rs2228137, and rs3760687) in the *FCER2* gene were selected for further analysis. *Table 3* showed the associations between polymorphisms of the *FCER2* gene and blood eosinophil and serum IgE levels in COPD/asthma patients. We observed that asthma patients carrying homozygote CC genotype of rs2228137 had a lower level of blood eosinophils counts than those carrying heterozygote CT (5.4%±4.3% *vs.* 7.0%±4.7%, P=0.034). Additionally, asthma patients carrying homozygote CC genotype of rs3760687 had a significantly higher level of serum IgE than those with homozygote TT (391.0±655.9 *vs.* 184.3±169.1 U/L, P=0.009). However, no significant difference was observed between the three SNPs and COPD.

Haplotype-disease analysis

To identify the combined effects of these three polymorphisms of the *FCER2* gene on the risk of COPD or asthma, we performed haplotype analysis. As shown in *Table 4*, we focused only on the haplotypes related to the target SNPs detected at frequencies ≥3%. Using haplotype C-A-C (allele of rs28364072, rs2228137, and rs4950928, respectively) as a reference and adjusting for age and gender, only haplotypes T-G-T were found to be significantly associated with a higher risk of asthma (OR =2.25, 95% CI: 1.26–4.01, P=0.006).

Haplotype-phenotype analysis

The associations of phenotypes with *FCER2* haplotypes

Table 3 Association between polymorphisms of FCER2 and blood eosinophil and serum IgE in COPD and asthma patients

Marker	Genotype	COPD						Asthma					
		Eos			IgE			Eos			IgE		
		N	Mean ± SD	P value	N	Mean ± SD	P value	N	Mean ± SD	P value	N	Mean ± SD	P value
rs28364072	AA	99	1.9±1.7	0.141	17	20.4±16.8	0.633	125	5.6±4.4	0.980	173	368.1±585.5	0.993
	GA	117	2.4±2.1		43	250.3±435.8		147	5.8±4.4		198	353.7±550.7	
	GG	14	2.4±1.3		6	112.4±112.9		10	6.3±4.3		31	457.4±909.8	
rs2228137	CC	195	2.1±2.0	0.791	55	211.3±388.1	0.602	233	5.4±4.3	0.034#	322	372.9±599.5	0.977
	CT	35	2.4±1.2		11	47.6±42.7		49	7.0±4.7		78	344.5±612.6	
	TT	0	N/A		0	N/A		0	N/A		2	474.0±343.0	
rs3760687	CC	152	2.1±1.8	0.788	41	112.8±100.7	0.744	168	5.4±4.7	0.314	240	391.0±655.9	0.009#
	CT	72	2.4±2.0		24	252.3±464.4		107	6.3±3.9		149	346.7±524.9	
	TT	6	1.3±1.2		1	48.4		7	3.4±2.2		13	184.3±169.1	

#, represents significant value. COPD, chronic obstructive pulmonary disease; Eos, eosinophil; N, number; SD, standard deviation; NA, not applicable.

Table 4 Distributions of haplotypes (frequency >3%) in the three SNPs in FCER2 between patients and healthy controls

Haplotype (%)*	Controls	COPD				Asthma			
		Patients	OR (95% CI)	P value	P value**	Patients	OR (95% CI)	P value	P value**
C-A-C	28.41	27.49	1			26.63	1		
C-G-C	24.92	25.90	1.07 (0.72–1.60)	0.727	0.258	22.61	0.97 (0.71–1.33)	0.839	0.607
C-G-T	9.52	11.16	1.21 (0.71–2.05)	0.477	0.187	11.89	1.33 (0.89–2.00)	0.164	0.224
T-A-C	17.46	15.14	0.90 (0.57–1.42)	0.642	0.248	16.58	1.01 (0.71–1.42)	0.966	0.914
T-G-C	15.40	15.54	1.04 (0.66–1.66)	0.859	0.175	15.24	1.06 (0.74–1.51)	0.764	0.770
T-G-T	3.17	4.78	1.56 (0.72–3.35)	0.256	0.493	6.70	2.25 (1.26–4.01)	0.005#	0.006#

*, alleles in each haplotype were appointed in the order of rs28364072, rs2228137, and rs3760687, respectively. **, P value adjusted for age and gender with binary logistic regression. #, represents significant value. SNPs, single nucleotide polymorphisms; COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

in COPD and asthma patients were presented in *Table 5*. We found C-A-C was associated with FEV_1/FVC, blood eosinophil, and serum IgE levels in asthma patients (P=0.033, <0.001, and 0.002, respectively), while it was related with blood eosinophils in COPD patients (P=0.034). In addition, C-G-C was associated with blood eosinophils and serum IgE levels in asthma patients (P<0.001 and P=0.041, respectively). Moreover, C-G-T was related to blood eosinophils both in COPD and asthma patients (P=0.040 and 0.049, respectively). T-A-C was associated with FEV_1/FVC and blood eosinophils in asthma patients (P<0.001 and P=0.005, respectively), whereas it correlated with FEV_1% predicted in COPD patients (P=0.003). Meanwhile, T-G-C was associated with FEV_1% predicted, blood eosinophil, and serum IgE levels in asthma patients (P=0.029, 0.004, and 0.004, respectively), and it was also associated with FEV_1/FVC in COPD patients (P=0.004).

Overall, FECR2 was associated with blood eosinophils, FEV1/FVC, FEV1% predicted, and serum IgE levels in asthma patients, while FECR2 was associated with blood eosinophils, FEV1/FVC, and FEV1% predicted in COPD patients.

Table 5 Association of phenotype with haplotypes (frequency >3%) in COPD and asthma patients

Haplotype*	COPD**				Asthma**			
	FEV_1/FVC	FEV_1% pred	Eos	IgE	FEV_1/FVC (P**)	FEV_1% pred	Eos	IgE
C-A-C	0.879	0.645	0.034#	0.900	0.033	0.089	<0.001#	0.002#
C-G-C	0.163	0.070	0.323	0.972	0.419	0.433	<0.001#	0.041#
C-G-T	0.079	0.124	0.040#	0.683	0.897	0.672	0.049#	0.907
T-A-C	0.178	0.003#	0.607	0.431	<0.001#	0.155	0.005#	0.244
T-G-C	0.004#	0.184	0.973	0.990	0.198	0.029#	0.004#	0.004#
T-G-T	0.201	0.411	0.446	0.826	0.372	0.310	0.136	0.995

*, alleles in each haplotype were appointed in the order of rs28364072, rs2228137, and rs3760687, respectively. **, relative to controls, P value adjusted for age and gender with multiple factors ANOVA. #, represents significant value. COPD, chronic obstructive pulmonary disease; Eos, eosinophil; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; pred: predicted.

Discussion

Although many SNPs of genes are associated with both asthma and COPD, to the best of our knowledge, no study has so far demonstrated associations between *FCER2* polymorphisms and COPD. The present study suggested that rs28364072 (*FCER2*) was a risk factor in COPD predisposition, while rs2228137 (*FCER2*) conferred asthma susceptibility. Haplotype analyses suggested that *FCER2* haplotypes C-A-C and C-G-T were associated with blood eosinophils in both diseases, while a haplotype T-A-C correlated with FEV_1% predicted in COPD and FEV_1/FVC ratio in asthma, haplotype T-G-C correlated with FEV_1/FVC ratio in COPD and FEV_1% predicted in asthma. Our results suggested that *FCER2* polymorphisms may genetically play a role in both overall asthma and COPD susceptibility, partly supporting the Dutch hypothesis that asthma and COPD share common genetic backgrounds.

FCER2 gene is an 11-exon gene located at chromosome 19p13.3, encoding the low-affinity receptor for IgE (CD23) (32). CD23 interacts with IgE with low affinity, playing a dual role in regulating IgE synthesis in activated B lymphocytes and facilitating allergen-specific activation in T lymphocytes (33,34). Previous studies have demonstrated the role of *FCER2*/CD23 polymorphisms in exacerbations, lung function, regulation of IgE synthesis, and immunotherapy in asthma (35-37). The rs28364072, rs2228137 and rs3760687, are the three most frequently reported SNPs in FCER2 (38). The rs2228137, encoding a nonsynonymous amino acid change (R62W), produced increased IgE binding and Egr-1 expression in human B cells, which may responsible for the atopic phenotypes (39).

Consistently, our results suggested that a SNP rs2228137 in *FCER2* was associated with higher blood eosinophils in asthma patients, while several *FCER2* haplotypes were associated with declines in FEV_1/FVC and FEV_1% predicted, elevated eosinophils, and serum IgE levels. Interestingly, we found that serum IgE levels in asthma patients carrying allele T were significantly lower than those carrying homozygote CC, suggesting that rs3760687 might be involved in the regulation of serum IgE. In contrast to our results, rs3760687 was reported to be associated with increased total serum IgE in the randomly selected population (40). However, no significant association was observed between IgE levels and rs3760687 in asthmatics (40). Functionally, the marker rs3760687, a promoter SNP in the *FCER2* gene, was reported to alter transcriptional activity by binding transcription factors Sp1 and Sp3, leading to the regulation of CD23 expression (38).

The rs28364072, also known as the FCER2 T2206C variant, was associated with asthma severity (37,41). A previous study found that the percentage of rs28364072 of FCER2 was significantly higher in patients with controlled asthma than those in patients with uncontrolled asthma (40). However, no prior studies correlated FCER2 with COPD. In the present study, we first reported that rs28364072 (*FCER2*) was associated with COPD susceptibility after adjusting for age and sex. Although no association between *FCER2* polymorphisms and COPD susceptibility was demonstrated previously, the rs28364072 has been well demonstrated to be genetically linked to asthma. Positive associations between rs28364072 and lower levels of fractional exhaled nitric oxide (FENO) and poor responsiveness to inhaled corticosteroids (ICS) were presented in asthmatic children (35,37,42,43).

Recent evidence has indicated that atopy is also a feature of COPD (18,44). 25–47.3% of COPD patients had atopy, as defined by elevated specific IgE for any inhaled antigen (3,45). Additionally, COPD patients with higher serum total IgE levels showed worse clinical symptoms (17,46). Therefore, it is hypothesized that *FCER2* polymorphisms may involve COPD pathogenesis. Consistently, we found that serum IgE levels in COPD patients carrying alternative variants of *FCER2* polymorphisms (rs28364072 and rs3760687) were slightly higher than those with corresponding reference homozygote genotype, although statistical significance was not reached. Our results suggested that the *FCER2* gene was the common genetic factor shared by asthma and COPD, indicating that CD23 could be a therapeutic target in allergic diseases and COPD. A recent cohort study found that increased plasma IgE correlated with a higher risk of severe exacerbation and all-cause mortality in COPD patients after adjusting for blood eosinophils, suggesting that anti-IgE antibody, such as a famous commercial drugs omalizumab, may be effective for patients with COPD (47,48).

Genotype analysis showed significant associations between *FCER2* polymorphisms and blood eosinophils or serum IgE levels in COPD. However, haplotype analyses in association with phenotypes suggested that certain haplotypes were involved in FEV_1/FVC, FEV_1% predicted, and the percentage of eosinophils in COPD. The interactions among different polymorphisms may regulate FCER2/CD23 expression at different levels and in interacting manners (38).

FCGR2A gene encodes low-affinity IgG Fc receptors, which play critical roles in immune processes (49). *STAT6* gene is an important factor in Th2 response and allergic inflammation. Previous studies have indicated that genetic variants in the *STAT6* gene were associated with serum IgE levels and asthma (50,51). In line with previous studies (49,50), we found that rs1801274 (*FCGR2A*) was linked to asthma. Previous studies showed that rs2427837 (*FCER1A*) and rs1050501 (*FCGR2B*) are associated with asthma (49,52), while *CHI3L1* polymorphism (rs4950928) *ADRB2* polymorphisms (rs1042713 and rs1042714) correlated with both asthma and COPD susceptibility (20,53). However, no statistically significant associations were found in patients with asthma and COPD in this study. The reasons for the inconsistencies may be due to different environmental exposure, ethnic differences, and the sample size of the population studied.

Notably, the present study showed that the *FCER2* gene was genetically associated with asthma and COPD, providing evidence for the common genetic origins of the two diseases. Although the mechanisms remain unclear, our results suggested that *FCER2* SNPs might be involved in regulating pulmonary function and blood eosinophils in COPD.

There are several limitations to this study. First, as a case-control study, the causality could not be determined between *FCER2* variants and COPD. Second, only 1 to 3 SNPs of 7 genes were evaluated in our study, which may underestimate potential common genes associated with asthma and COPD. More variants and candidate genes are warranted in future studies to justify the Dutch hypothesis. Third, the sample size of some groups with homozygote alternative variants was small (less than 10), leading to potential biases, studies with larger populations are needed to identify more common genes between asthma and COPD. Fourth, because this study was a case-control investigation aiming to compare the similarities and differences in the genetic background of two common airway diseases, we didn't include data regarding the allergic status, antigen exposure, therapy intensification, and adherence to therapy, when recruitment. Future studies focusing on how the environmental factors interacting with genes influence disease expression are needed. Fifth, we did not adjust for the smoking status in the logistic regression because of lacking related information on the control subjects. However, we found that several manuscripts similar to our study did not adjust for smoking status (20,54), indicating that adjusting for smoking status may have a limited influence on the conclusion. Last, our sample compromised exclusively on northern Chinese. The generalization of the findings to other populations with different demographics should be cautious.

Conclusions

In conclusion, the current study suggested that the *FCER2* gene was a potential candidate gene for asthma and COPD susceptibility, and haplotypes in the *FCER2* gene were associated with pulmonary function and blood eosinophils in both diseases. Our findings may provide evidence for further studies to demonstrate the mechanisms and causality of the *FCER2* gene in asthma and COPD.

Acknowledgments

Funding: This work was supported by the National

Natural Science Foundation of China (No. 81970025, No. 81470229, and No. 81170040).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-820/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-820/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-820/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-820/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research protocol was reviewed and approved by the Ethics Committee for Human Research of Peking Union Medical College Hospital (S-767) and Beijing Aviation General Hospital (MHZYY 2014-05-01) and informed written consent was obtained from all participants.

References

1. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med 2020;8:585-96.
2. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204-22.
3. Suzuki M, Makita H, Konno S, et al. Asthma-like Features and Clinical Course of Chronic Obstructive Pulmonary Disease. An Analysis from the Hokkaido COPD Cohort Study. Am J Respir Crit Care Med 2016;194:1358-65.
4. Barnes PJ. Against the Dutch hypothesis: asthma and chronic obstructive pulmonary disease are distinct diseases. Am J Respir Crit Care Med 2006;174:240-3; discussion 243-4.
5. Suzuki M, Cole JJ, Konno S, et al. Large-scale plasma proteomics can reveal distinct endotypes in chronic obstructive pulmonary disease and severe asthma. Clin Transl Allergy 2021;11:e12091.
6. Leung JM, Sin DD. Asthma-COPD overlap syndrome: pathogenesis, clinical features, and therapeutic targets. BMJ 2017;358:j3772.
7. Kurche JS, Schwartz DA. Deciphering the Genetics of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2019;199:4-5.
8. Annangi S, Nutalapati S, Sturgill J, et al. Eosinophilia and fractional exhaled nitric oxide levels in chronic obstructive lung disease. Thorax 2022;77:351-6.
9. Christenson SA, Steiling K, van den Berge M, et al. Asthma-COPD overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2015;191:758-66.
10. Sluiter HJ, Koëter GH, de Monchy JG, et al. The Dutch hypothesis (chronic non-specific lung disease) revisited. Eur Respir J 1991;4:479-89.
11. Kreukniet J, Orie NG. Chronic bronchitis, bronchial asthma, a host factor in patients with pulmonary tuberculosis. Allerg Asthma (Leipz) 1961;7:220-30.
12. Ruse CE, Parker SG. Genetics and the Dutch Hypothesis. Chron Respir Dis 2004;1:105-13.
13. Postma DS, Weiss ST, van den Berge M, et al. Revisiting the Dutch hypothesis. J Allergy Clin Immunol 2015;136:521-9.
14. Postma DS, Kerkhof M, Boezen HM, et al. Asthma and chronic obstructive pulmonary disease: common genes, common environments? Am J Respir Crit Care Med 2011;183:1588-94.
15. Postma DS, Boezen HM. Rationale for the Dutch hypothesis. Allergy and airway hyperresponsiveness as genetic factors and their interaction with environment

in the development of asthma and COPD. Chest 2004;126:96S-104S; discussion 159S-161S.
16. Kraft M. Asthma and chronic obstructive pulmonary disease exhibit common origins in any country! Am J Respir Crit Care Med 2006;174:238-40; discussion 243-4.
17. Lommatzsch M, Speer T, Herr C, et al. IgE is associated with exacerbations and lung function decline in COPD. Respir Res 2022;23:1.
18. Karakioulaki M, Papakonstantinou E, Goulas A, et al. The Role of Atopy in COPD and Asthma. Front Med (Lausanne) 2021;8:674742.
19. Sahu A, Swaroop S, Kant S, et al. Signatures for chronic obstructive pulmonary disease (COPD) and asthma: a comparative genetic analysis. Br J Biomed Sci 2021;78:177-83.
20. Yu T, Niu W, Niu H, et al. Chitinase 3-like 1 polymorphisms and risk of chronic obstructive pulmonary disease and asthma in a Chinese population. J Gene Med 2020;22:e3208.
21. Li XX, Peng T, Gao J, et al. Allele-specific expression identified rs2509956 as a novel long-distance cis-regulatory SNP for SCGB1A1, an important gene for multiple pulmonary diseases. Am J Physiol Lung Cell Mol Physiol 2019;317:L456-63.
22. James AJ, Reinius LE, Verhoek M, et al. Increased YKL-40 and Chitotriosidase in Asthma and Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2016;193:131-42.
23. Beghé B, Hall IP, Parker SG, et al. Polymorphisms in IL13 pathway genes in asthma and chronic obstructive pulmonary disease. Allergy 2010;65:474-81.
24. Hunninghake GM, Cho MH, Tesfaigzi Y, et al. MMP12, lung function, and COPD in high-risk populations. N Engl J Med 2009;361:2599-608.
25. Fakih D, Akiki Z, Junker K, et al. Surfactant protein D multimerization and gene polymorphism in COPD and asthma. Respirology 2018;23:298-305.
26. Hayden LP, Cho MH, Raby BA, et al. Childhood asthma is associated with COPD and known asthma variants in COPDGene: a genome-wide association study. Respir Res 2018;19:209.
27. Smolonska J, Koppelman GH, Wijmenga C, et al. Common genes underlying asthma and COPD? Genome-wide analysis on the Dutch hypothesis. Eur Respir J 2014;44:860-72.
28. Ghebre MA, Bafadhel M, Desai D, et al. Biological clustering supports both "Dutch" and "British" hypotheses of asthma and chronic obstructive pulmonary disease. J Allergy Clin Immunol 2015;135:63-72.
29. The Global Initiative for Asthma. global strategy for asthma management and prevention, 2020.
30. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med 2017;195:557-82.
31. Li L, Liu Y, Chiu C, et al. A Regulatory Role of Chemokine Receptor CXCR3 in the Pathogenesis of Chronic Obstructive Pulmonary Disease and Emphysema. Inflammation 2021;44:985-98.
32. Acharya M, Borland G, Edkins AL, et al. CD23/FcεRII: molecular multi-tasking. Clin Exp Immunol 2010;162:12-23.
33. Selb R, Eckl-Dorna J, Neunkirchner A, et al. CD23 surface density on B cells is associated with IgE levels and determines IgE-facilitated allergen uptake, as well as activation of allergen-specific T cells. J Allergy Clin Immunol 2017;139:290-299.e4.
34. Colas L, Magnan A, Brouard S. Immunoglobulin E response in health and disease beyond allergic disorders. Allergy 2022;77:1700-18.
35. Tantisira KG, Silverman ES, Mariani TJ, et al. FCER2: a pharmacogenetic basis for severe exacerbations in children with asthma. J Allergy Clin Immunol 2007;120:1285-91.
36. Park HW, Tantisira KG. Genetic Signatures of Asthma Exacerbation. Allergy Asthma Immunol Res 2017;9:191-9.
37. Karimi L, Vijverberg SJH, Farzan N, et al. FCER2 T2206C variant associated with FENO levels in asthmatic children using inhaled corticosteroids: The PACMAN study. Clin Exp Allergy 2019;49:1429-36.
38. Potaczek DP, Wang QH, Sanak M, et al. Interaction of functional FCER2 promoter polymorphism and phenotype-associated haplotypes. Tissue Antigens 2009;74:534-8.
39. Chan MA, Gigliotti NM, Aubin BG, et al. FCER2 (CD23) asthma-related single nucleotide polymorphisms yields increased IgE binding and Egr-1 expression in human B cells. Am J Respir Cell Mol Biol 2014;50:263-9.
40. Sharma V, Michel S, Gaertner V, et al. A role of FCER1A and FCER2 polymorphisms in IgE regulation. Allergy 2014;69:231-6.
41. Duong-Quy S, Le-Thi-Minh H, Nguyen-Thi-Bich H, et al. Correlations between exhaled nitric oxide, rs28364072 polymorphism of FCER2 gene, asthma control, and inhaled corticosteroid responsiveness in children with asthma. J Breath Res 2020;15:016012.

42. Keskin O, Farzan N, Birben E, et al. Genetic associations of the response to inhaled corticosteroids in asthma: a systematic review. Clin Transl Allergy 2019;9:2.
43. Koster ES, Maitland-van der Zee AH, Tavendale R, et al. FCER2 T2206C variant associated with chronic symptoms and exacerbations in steroid-treated asthmatic children. Allergy 2011;66:1546-52.
44. Veil-Picard M, Soumagne T, Vongthilath R, et al. Is atopy a risk indicator of chronic obstructive pulmonary disease in dairy farmers? Respir Res 2019;20:124.
45. Putcha N, Fawzy A, Matsui EC, et al. Clinical Phenotypes of Atopy and Asthma in COPD: A Meta-analysis of SPIROMICS and COPDGene. Chest 2020;158:2333-45.
46. Jin J, Liu X, Sun Y. The prevalence of increased serum IgE and Aspergillus sensitization in patients with COPD and their association with symptoms and lung function. Respir Res 2014;15:130.
47. Maspero J, Adir Y, Al-Ahmad M, et al. Type 2 inflammation in asthma and other airway diseases. ERJ Open Res 2022;8:00576-2021.
48. Çolak Y, Ingebrigtsen TS, Nordestgaard BG, et al. Plasma immunoglobulin E and risk of exacerbation and mortality in chronic obstructive pulmonary disease: A contemporary population-based cohort. Ann Allergy Asthma Immunol 2022;129:490-6.
49. Wu J, Lin R, Huang J, et al. Functional Fcgamma receptor polymorphisms are associated with human allergy. PLoS One 2014;9:e89196.
50. Gao PS, Heller NM, Walker W, et al. Variation in dinucleotide (GT) repeat sequence in the first exon of the STAT6 gene is associated with atopic asthma and differentially regulates the promoter activity in vitro. J Med Genet 2004;41:535-9.
51. Weidinger S, Gieger C, Rodriguez E, et al. Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus. PLoS Genet 2008;4:e1000166.
52. Potaczek DP, Michel S, Sharma V, et al. Different FCER1A polymorphisms influence IgE levels in asthmatics and non-asthmatics. Pediatr Allergy Immunol 2013;24:441-9.
53. Zhao S, Zhang W, Nie X. Association of β2-adrenergic receptor gene polymorphisms (rs1042713, rs1042714, rs1042711) with asthma risk: a systematic review and updated meta-analysis. BMC Pulm Med 2019;19:202.
54. Niu H, Niu W, Yu T, et al. Association of RAGE gene multiple variants with the risk for COPD and asthma in northern Han Chinese. Aging (Albany NY) 2019;11:3220-37.

Cite this article as: Zheng Z, Li J, Liu Y, Li L, Huang T, Huang Y, Song S, Gao J. Polymorphisms in the *FCER2* gene have associations with asthma and chronic obstructive pulmonary disease. J Thorac Dis 2023;15(2):589-599. doi: 10.21037/jtd-22-820

Supplementary

Table S1 Test of Hardy-Weinberg equilibrium of 10 SNPs

SNP name	Chromosome	Ref./Alt.*	HWpval[a]
rs2427837	1	G/A	1
rs1801274	1	T/C	0.7042
rs1050501	1	T/C	<0.0001
rs4950928	1	C/G	0.1422
rs1042713	5	A/G	0.1555
rs1042714	5	C/G	0.5271
rs12368672	12	C/G	0.09883
rs28364072	19	A/G	0.1768
rs2228137	19	C/T	0.3513
rs3760687	19	C/T	0.04289

* Ref./Alt.: Reference/Alternative. [a] HWpval: Hardy-Weinberg equilibrium P value.

https://dx.doi.org/10.21037/jtd-22-820