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A Study on the Association Between *Siglec-1* Gene Polymorphism and Susceptibility in Patients with Chronic Obstructive Pulmonary Disease in Luohe Area

Juan Cao[1,2], Chun'e Wang[3], Bing Zhao[2], Yi Zheng[1,2], Sensen Li[1,2]*

[1]School of Medicine of Huanghuai University, Zhumadian 463000, Henan Province, China
[2]Affiliated Zhumadian Central Hospital of Huanghuai University, Zhumadian 463000, Henan Province, China
[3]Jiyang District People's Hospital, Jinan 251400, Shandong Province, China

***Corresponding author:** Sensen Li, lsswcy@163.com

Abstract: *Objective:* To analyze the association between *Siglec-1* gene polymorphism and susceptibility to chronic obstructive pulmonary disease (COPD) in the population of the Luohe area. *Methods:* A case-control study (150 COPD patients and 150 healthy controls) was conducted to analyze the *Siglec-1* allele in two groups of individuals using single nucleotide polymorphism (SNP) high-throughput detection technology, and the frequencies of each allele were compared. *Results:* The frequency of rs611847 heterozygous A/G genotype in COPD patients was significantly lower in females than in healthy controls (OR = 0.282, 95% CI = 0.085–0.938, P = 0.039); among smokers, the frequency of rs3859664 and rs6084444 genotypes in COPD patients was significantly higher than that in the healthy control group (OR = 2.028, 95% CI = 1.111–3.704, P = 0.021; OR = 1.836, 95% CI = 1.033–3.262, P = 0.038). *Conclusion:* Among the COPD population in the Luohe area, there is a significant correlation between the genotypes of three SNPs loci, rs3859664, rs6084444, and rs611847 and susceptibility to COPD in different subgroups of the population. The rs3859664 A/G-A/A and rs6084444 A/G-G/G genotypes can increase the risk of COPD in smokers; the rs611847 heterozygous A/G genotype can reduce the risk of COPD in both female and smoking populations.

Keywords: Chronic obstructive pulmonary disease; *Siglec-1*; Gene frequency

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by persistent airflow restriction, and is associated with chronic inflammatory reactions caused by harmful particles or gases. As a multifactorial constitutive disease with inflammation at its core, various stimuli that induce inflammatory reactions in the airways and lung parenchyma can affect the overall development process of the disease [1-3]. Therefore, it is particularly important to analyze the factors related to the inflammatory response of COPD patients from

multiple perspectives in order to discover potential therapeutic targets.

Siglec-1, also known as CD169, is a type I transmembrane protein of the sialic immunoglobulin lectin family, mainly expressed on macrophages and dendritic cells in specific tissues. It not only mediates cell adsorption but also promotes the occurrence of inflammatory reactions [4,5]. The rs3859664 locus is the intron of the *Siglec-1* gene. Researchers found that individuals carrying the rs3859664/A allele produced lower IL-1β when stimulated with BCG in a tuberculosis case/control cohort in the Brazilian Amazon region, suggesting that *Siglec-1* gene polymorphism may be associated with complex inflammatory signaling pathways [6]. However, currently, the correlation between *Siglec-1* gene polymorphism and COPD inflammatory response has not yet been reported. This study aims to investigate the genetic polymorphism of COPD patients in the Luohe area and explore the relationship between *Siglec-1* gene polymorphism and COPD inflammatory response.

2. Materials and methods

2.1. General information

A total of 300 individuals with COPD and health controls in the Luohe area were selected as the research subjects from March 2021 to March 2022. Through the hospital information management system, electronic medical records were accessed to collect clinical data, including age, gender, smoking history, lymphocyte count, neutrophil count, and eosinophil count. Inclusion criteria: the diagnosis of COPD complies with the 2020 Global Strategy for the Diagnosis, Treatment, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD2020) [7]. Exclusion criteria: cases of combined infections, immune diseases, and other factors that affect the progression of COPD-related diseases. The project application has been approved by the Ethics Committee of the First People's Hospital of Luohe City, and all research subjects have filled out informed consent forms.

2.2. Candidate single nucleotide polymorphism (SNP) strategies

This study obtained relevant candidate loci through NCBI dbSNP database and HapMap SNP database. The screening criteria are as follows: (1) In the Han Chinese population, the minor allele frequency (MAF) is greater than 5%, and the heterozygosity is greater than 0.10; (2) Those related to lung infectious diseases or immune diseases reported in relevant literature are preferred to be included. On this basis, SNPinfo and FASTSNP bioinformatics websites were used for functional prediction, and ultimately seven SNP loci were selected for the study: rs611847, rs656635, rs735294, rs1046919, rs3859664, rs6084444, and rs73608192.

2.3. Methods

The *Siglec-1* gene locus polymorphism was detected using target region resequencing combined with multiplex polymerase chain reaction (PCR) and high-throughput sequencing techniques. The specific method was to extract genomic DNA using the traditional phenol-chloroform extraction method and use it as a template. Subsequently, specific primers were designed for the *Siglec-1* allele loci to be detected, and multiplex PCR amplification was performed in a single tube. The PCR primers, PCR reaction conditions, and sequencing methods are shown in **Table 1**.

Table 1. Multiple PCR primers for the *Siglec-1* gene locus

Gene loci	Position	Multiple PCR primers
rs611847	3,703,375	Forward primer: CTCACAGAAGTAGAAGCCAGTATC Reverse primer: CTCCCTATGCTGCCCTTG
rs656635	3,687,435	Forward primer: GGAATAAGGATGCTGACAACATC Reverse primer: AAAAAGGTTTGGTGTTTTCCTAGG
rs735294	3,704,313	Forward primer: AAAGCTCAGTCCTAAGGAAGTATG Reverse primer: CATTGGGAAGCAGAAAACTACAG
rs1046919	3,687,178	Forward primer: CAATGGAGCATGAAAATGAATGAG Reverse primer: CTTGAGTGGGCTAGTGACTC
rs3859664	3,691,244	Forward primer: TTCTTATACAACTTGCAGGATGAG Reverse primer: TGTGCTCTGTGAGTGTGAAC
rs6084444	3,710,937	Forward primer: CACTCCCATCACATAATGTAGAGG Reverse primer: CTCAACTCCAGGCTTTCAAAC
rs73608192	3,712,917	Forward primer: GCAAAGTGAGAAATGGAGTGG Reverse primer: CTGAATGGCTTGGAGAATAACTG

Subsequently, different samples were distinguished using different Barcode primers and high-throughput sequencing was performed on the amplicons. The sequencing results used bioinformatics methods to distinguish different samples and ultimately obtain mutation information for each locus. The workflow of sequencing data quality control included steps such as nucleic acid extraction and detection, library construction and testing, and machine sequencing. These steps were strictly controlled to ensure the accuracy of sequencing data.

2.4. Statistical processing

All data were managed and analyzed using SPSS19.0 software. The analysis methods included independent sample *t*-test or chi-square test for general demographic characteristics; using direct counting method to calculate allele and genotype frequencies, and comparing allele frequencies between groups using chi-square test; multivariate analysis using logistic regression, i.e. odds ratio, OR and 95% confidence interval, CI. All statistical tests were bilateral probability tests, and $P < 0.05$ indicates statistical significance; introducing Bonferroni correction in multi-group and multi-genotype analysis, adjusted $P > 0.0125$.

3. Results

3.1. Basic characteristics of the research subjects

The comparison of general information between two groups including age, gender, and smoking history, showed no statistically significant difference ($P > 0.05$), indicating comparability (**Table 2**).

Table 2. Demographic characteristics of COPD group and healthy control group in Luohe district

Variable	Control group	Case group	t/c^2 value	*P* value
	Healthy control group (*n* = 150)	COPD group (*n* = 150)		
Age (years)	72.31 ± 8.142	72.26 ± 7.165	1.336	0.183
Gender			0.384	0.536
Female	27 (15.3%)	23 (18%)		
Male	123 (84.7%)	127 (82%)		
Smoking history			0.4376	0.539
Yes	103 (65.4%)	98 (65.3%)		
No	47 (34.6%)	52 (31.3%)		

3.2. Hardy-Weinberg equilibrium (HWE) inspection

In this study, the MAF values of seven SNP loci (rs611847, rs656635, rs735294, rs1046919, rs3859664, rs6084444, and rs73608192) in the healthy control group were all greater than 5%, and the HWE test in the healthy control group met the requirements; the *P* values were 0.87, 0.06, 0.36, 0.37, 0.10, 0.51, and 0.97, respectively, indicating that the healthy control population included in this study is representative.

3.3. Association analysis between *Siglec-1* gene polymorphism and susceptibility to COPD

In this study, the distribution of genotypes and alleles of seven SNP loci (rs611847, rs656635, rs735294, rs1046919, rs3859664, rs6084444, and rs73608192) in the two populations is shown in **Table 3**. In the codominant model, explicit model, implicit model, and superdominant model analysis, after adjusting for age, gender, and smoking history, logistic regression analysis did not find a significant correlation between the distribution of seven SNP loci genotypes and susceptibility to COPD (Bonferroni correction was introduced in multi-group and multi-genotype analysis), adjusted $P > 0.0125$).

3.4. Layered analysis

This study investigated the effects of age, gender, and smoking history on the association between seven SNP locus genotypes and susceptibility to COPD, as shown in **Table 4**.

Table 3. Association analysis between *Siglec-1* gene polymorphism and susceptibility to COPD

SNP site	Mode	Genotype	COPD group [cases (%)]	Healthy control group [cases (%)]	OR (95% CI)	*P* value
rs611847	Codominance	G/G	68 (45.3)	61 (40.7)	1.00	0.333
		A/G	58 (39.2)	70 (46.7)	1.42 (0.86–2.35)	0.170
		A/A	23 (15.5)	19 (12.7)	0.99 (0.49–2.02)	0.977
	Dominance	G/G	67 (45.3)	61 (40.7)	1.00	0.274
		A/G-A/A	81 (54.7)	89 (59.3)	1.30 (0.81–2.08)	
	Implicit	G/G-A/G	125 (84.5)	131 (87.3)	1.00	0.571
		A/A	23 (15.5)	19 (12.7)	0.83 (0.43–1.60)	
	Superdominant	G/G-A/A	90 (60.8)	80 (53.3)	1.00	0.138
		A/G	58 (39.2)	70 (46.7)	1.42 (0.89–2.27)	

Table 4 (Continued)

SNP site	Mode	Genotype	COPD group [cases (%)]	Healthy control group [cases (%)]	OR (95% CI)	*P* value
rs656635	Codominance	G/G	49 (32.9)	54 (36.2)	1.00	0.602
		T/G	80 (53.7)	80 (53.7)	0.91 (0.55–1.51)	0.722
		T/T	20 (13.4)	15 (10.1)	0.67 (0.31–1.46)	0.314
	Dominance	G/G	49 (32.9)	54 (36.2)	1.00	0.549
		T/G-T/T	100 (67.1)	95 (63.8)	0.86 (0.53–1.40)	
	Implicit	G/G-T/G	129 (86.6)	134 (89.9)	1.00	0.346
		T/T	20 (13.4)	15 (10.1)	0.71 (0.35–1.45)	
	Superdominant	G/G-T/T	69 (46.3)	69 (46.3)	1.00	0.971
		T/G	80 (53.7)	80 (53.7)	0.99 (0.63–1.57)	
rs735294	Codominance	T/T	77 (51.3)	77 (51.3)	1.00	0.950
		T/C	65 (43.3)	64 (42.7)	0.94 (0.58–1.51)	0.792
		C/C	8 (5.3)	9 (6.0)	1.06 (0.39–2.92)	0.906
	Dominance	T/T	77 (51.3)	77 (51.3)	1.00	0.833
		T/C-C/C	73 (48.7)	73 (48.7)	0.95 (0.60–1.51)	
	Implicit	T/T-T/C	142 (94.7)	141 (94.0)	1.00	0.857
		C/C	8 (5.3)	9 (6.0)	1.10 (0.40–2.93)	
	Superdominant	T/T-C/C	85 (56.7)	86 (57.3)	1.00	0.767
		T/C	65 (43.3)	64 (42.7)	0.93 (0.59–1.48)	
rs1046919	Codominance	A/A	72 (48.3)	65 (43.6)	1.00	0.751
		A/G	59 (39.6)	63 (42.3)	1.15 (0.70–1.88)	0.576
		G/G	18 (12.1)	21 (14.1)	1.28 (0.62–2.62)	0.507
	Dominance	A/A	72 (48.3)	65 (43.6)	1.00	0.481
		A/G-G/G	77 (51.7)	84 (56.4)	1.18 (0.75–1.87)	
	Implicit	A/A-A/G	131 (87.9)	128 (85.9)	1.00	0.610
		G/G	18 (12.1)	21 (14.1)	1.19 (0.61–2.36)	
	Superdominant	A/A-G/G	90 (60.4)	86 (57.7)	1.00	0.716
		A/G	59 (39.6)	63 (42.3)	1.09 (0.68–1.74)	
rs3859664	Codominance	G/G	43 (30.3)	60 (40.0)	1.00	0.131
		A/G	61 (43.0)	48 (32.0)	0.57 (0.33–0.99)	0.046
		A/A	38 (26.8)	42 (28.0)	0.81 (0.45–1.46)	0.482
	Dominance	G/G	43 (30.3)	60 (40.0)	1.00	0.099
		A/G-A/A	99 (69.7)	90 (60.0)	0.66 (0.41–1.08)	
	Implicit	G/G-A/G	104 (73.2)	108 (72.0)	1.00	0.782
		A/A	38 (26.8)	42 (28.0)	0.93 (0.55–1.56)	
	Superdominant	G/G-A/A	81 (57.0)	102 (68.0)	1.00	0.058
		A/G	61 (43.0)	48 (32.0)	1.60 (0.98–2.59)	

Table 4 (Continued)

SNP site	Mode	Genotype	COPD group [cases (%)]	Healthy control group [cases (%)]	OR (95% CI)	*P* value
rs6084444	Codominance	AA	86 (57.7)	98 (65.3)	1.00	0.362
		AG	59 (39.6)	48 (32.0)	0.71 (0.44–1.14)	0.154
		GG	4 (2.7)	4 (2.7)	0.91 (0.22–3.76)	0.891
	Dominance	A/A	86 (57.7)	98 (65.3)	1.00	0.166
		A/G-G/G	63 (42.3)	52 (34.7)	0.72 (0.45–1.15)	
	Implicit	A/A-A/G	145 (97.3)	146 (97.3)	1.00	0.971
		G/G	4 (2.7)	4 (2.7)	1.03 (0.25–4.22)	
	Superdominant	A/A-G/G	90 (60.4)	102 (68.0)	1.00	0.156
		A/G	59 (39.6)	48 (32.0)	0.71 (0.44–1.14)	
rs73608192	Codominance	GG	97 (65.5)	111 (74.0)	1.00	0.288
		CG	48 (32.4)	36 (24.0)	0.66 (0.40–1.11)	0.115
		CC	3 (2.0)	3 (2.0)	0.92 (0.18–4.73)	0.924
	Dominance	G/G	97 (65.5)	111 (74.0)	1.00	0.126
		C/G-C/C	51 (34.5)	39 (26.0)	0.68 (0.41–1.12)	
	Implicit	G/G-C/G	145 (98.0)	147 (98.0)	1.00	0.961
		C/C	3 (2.0)	3 (2.0)	1.04 (0.21–5.30)	
	Superdominant	G/G-C/C	100 (67.6)	114 (76.0)	1.00	0.115
		C/G	48 (32.4)	36 (24.0)	0.66 (0.40–1.11)	

Table 4. Stratified analysis of the correlation between *Siglec-1* gene polymorphism and susceptibility to COPD

SNP site	Subgroup	Genotype	COPD group [cases (%)]	Healthy control group [cases (%)]	OR (95% CI)	*P* value
rs611847	Female	G/G-A/A	17 (73.9)	12 (44.4)	1.00	0.039
		A/G	6 (26.1)	15 (55.6)	0.282 (0.085–0.938)	
	Male	G/G-A/A	73 (58.4)	68 (55.3)	1.00	0.620
		A/G	52 (41.6)	55 (44.7)	0.881 (0.533–1.456)	
	Smoking	G/G-A/A	67 (69.8)	54 (52.4)	1.00	0.013
		A/G	29 (30.2)	49 (47.6)	0.477 (0.266–0.854)	
	Non-smoking	G/G-A/A	23 (44.2)	26 (55.3)	1.00	0.271
		A/G	29 (55.8)	21 (44.7)	1.561 (0.706–3.453)	
rs3859664	Smoking	G/G	25 (26.9)	44 (42.7)	1.00	0.021
		A/G-A/A	68 (73.1)	59 (57.3)	2.028 (1.111–3.704)	
	Non-smoking	G/G	18 (36.7)	16 (34.0)	1.00	0.783
		A/G-A/A	31 (63.3)	31 (66.0)	0.889 (0.385–2.054)	
rs6084444	Smoking	A/A	52 (53.6)	70 (68.0)	1.00	0.038
		A/G-G/G	45 (46.4)	33 (32.0)	1.836 (1.033–3.262)	
	Non-smoking	A/A	34 (65.4)	28 (59.6)	1.00	0.551
		A/G-G/G	18 (34.6)	19 (40.4)	0.780 (0.345–1.764)	

The study did not find any effect of age on the association between the genotype of seven SNP loci and susceptibility to COPD.

However, when examining gender factors, it was found that the frequency of rs611847 heterozygous A/G genotype in COPD patients was significantly lower in females than in healthy controls (OR = 0.282, 95% CI = 0.085–0.938, $P = 0.039$). This indicates that the rs611847 heterozygous A/G genotype has a protective effect in female COPD patients.

Examining smoking history factors, explicit model analysis showed that in the smoking population, the frequency of rs3859664 and rs6084444 genotypes in COPD patients was significantly higher than that in the healthy control group (OR = 2.028, 95% CI = 1.111–3.704, $P = 0.021$; OR = 1.836, 95% CI = 1.033–3.262, $P = 0.038$), indicating that among smokers, there is a significant correlation between the rs3859664 and rs6084444 genotypes and increased risk of COPD. Superdominant model analysis found that among smokers, the frequency of rs611847 heterozygous A/G genotype in COPD patients was significantly lower than that in the healthy control group (OR = 0.477, 95% CI = 0.266–0.854, $P = 0.013$). This indicates that the rs611847 heterozygous A/G genotype has a protective effect on COPD patients in the smoking population.

4. Discussion

COPD is a reactive disease characterized by abnormal airway inflammation. COPD patients exhibit differences in the clinical course after exposure to smoke, dust, and viral or bacterial infections. In addition to being related to external stimuli themselves, what is more important is that different individuals have varying immune responses to external stimuli. This susceptibility difference is mainly related to immune status and positive and negative immune responses [8,9].

The Siglecs family is a transmembrane molecular protein expressed on the surface of immune cells, which regulates immune responses such as cell adhesion and signal transduction by binding to polysaccharides containing sialic acid residues [10]. Its allele polymorphism is the most important genetic factor determining the host's immune response and the ability of different individuals to respond to antigens. Siglec-1 is an important transmembrane receptor molecule expressed on immune cells, playing a regulatory role in multiple stages and steps of macrophage immune response. Previous studies have shown that Sigelc-1 expression increases in COPD patients, which in turn promotes COPD inflammatory response by regulating downstream NF-κB signaling pathways [11,12]. In addition, there have been no research reports on the association between *Siglec-1* gene polymorphism and pulmonary inflammatory diseases. Therefore, as an important regulatory site for immune responses such as cell adhesion and signal transduction, the relevance of the *Sigelc-1* gene in the inflammatory response of COPD needs to be further studied and explored [13,14].

This study explored seven SNPs loci (rs611847) on the *Sigelc-1* gene in the Han population of Luohe region, China, using four models: codominant, dominant, recessive, and superdominant. The association between rs611847, rs656635, rs735294, rs1046919, rs3859664, rs6084444, and rs73608192 and the occurrence of COPD shows that there is a significant correlation between the genotypes of three SNPs loci, rs3859664, rs6084444, and rs611847 and susceptibility to COPD in different subgroups of the population.

In this study, through the analysis of the superdominant model, it was found that the rs611847 heterozygous A/G genotype showed a superdominant effect in both female and smoking populations, suggesting that the G → A mutation of the rs611847 base can reduce the risk of COPD in female and smoking populations. This study is still the first to discover this. In addition, studies have reported that *in vivo* cytokines such as interferon-beta (IFN-β), interferon-gamma (IFN-γ), and interleukin-4 (IL-4) can mediate the expression of the *Siglec-1*

gene through glucocorticoid receptors [15]. It is speculated that the protective effect of the rs611847 base G → A mutation on the female population may be related to differences in glucocorticoid expression levels between male and female populations, and future correlation studies can be conducted.

In this study, through explicit model analysis, it was found that the rs3859664 A/G-A/A and rs6084444 A/G-G/G genotypes can increase the risk of COPD in smokers. There have been few research reports on the rs3859664 locus in recent years. For example, a researcher analyzed the relationship between *Siglec-1* gene single nucleotide polymorphisms and tuberculosis susceptibility and transition in a tuberculosis case/control cohort in the Amazon region of Brazil. The results showed that rs3859664 small allele A significantly increased the incidence rate of active pulmonary tuberculosis patients. Further exploration found that carriers of *Siglec-1* rs3859664 single nucleotide polymorphism G → A mutation group produced less IL-1 β than non-carriers, suggesting that it may be related to the complex signal pathway of Siglec-1 inflammation [6]. Based on previous research and literature research, it is speculated that the intron rs3859664 of the *Siglec-1* gene can reduce gene mRNA expression by affecting splicing site activity through G → A mutation, thereby affecting the NF-κB signaling pathway and correspondingly reducing the expression of pro-inflammatory cytokine IL-1β, ultimately achieving the goal of affecting the progression of COPD inflammation. However, research on the single nucleotide polymorphism of intron rs6084444 has not been reported yet. Therefore, it is necessary to conduct future research on the impact of the A → G mutation at the rs6084444 site on the complex signaling pathway of Siglec-1 inflammation.

5. Conclusion

In summary, this study screened rs611847 from the *Siglec-1* gene in the COPD population in Luohe area. There is a significant correlation between the genotypes of three SNPs loci, rs3859664, rs6084444, and rs611847 and susceptibility to COPD in different subgroups. Among them, the rs3859664 A/G-A/A and rs6084444 A/G-G/G genotypes can increase the risk of COPD in smokers; the rs611847 heterozygous A/G genotype can reduce the risk of COPD in both female and smoking populations.

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Disclosure statement

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