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ORIGINAL RESEARCH

Immune Response-Related Genes – *STAT4, IL8RA* and *CCR7* Polymorphisms in Lung Cancer: A Case–Control Study in China

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Purpose: This study aimed to evaluate the associations between immune response-related genes – *STAT4, IL8RA* and *CCR7* polymorphisms and risk of lung cancer.

Methods: Seven polymorphisms of *STAT4, IL8RA* and *CCR7* were genotyped in 350 cases and 350 controls using a MassARRAY platform.

Results: The *STAT4* rs1400656-G and rs7574865-T alleles may decrease the susceptibility to lung cancer ($p_{rs1400656}$= 0.020; $p_{rs7574865}$= 0.014); while *IL8RA* rs1008562-C and *CCR7* rs3136685-T alleles may increase the risk of disease ($p_{rs1008562}$< 0.001; $p_{rs3136685}$= 0.018). The *STAT4* rs1400656-GA and rs7574865-GT genotypes were determined as protective genotypes against lung cancer risk ($p_{rs1400656}$= 0.048; $p_{rs7574865}$= 0.042). However, *IL8RA* rs1008562-CG/GG and *CCR7* rs3136685-TT genotypes were significantly associated with an elevated risk of disease ($p_{rs1008562}$< 0.0001; $p_{rs3136685}$= 0.020). Genetic model analysis revealed that *STAT4* rs1400656 and rs7574865 were relate to a declining risk of disease under dominant and log-additive models (rs1400656: p_{dominant} = 0.014, $p_{\text{log-additive}}$= 0.016; rs7574865: p_{dominant} = 0.013, $p_{\text{log-additive}}$= 0.013). In contrast, *IL8RA* rs1008562 exhibited a strong correlation with an elevated risk of lung cancer under all three models (p_{dominant} < 0.0001, $p_{\text{recessive}}$ = 0.011, $p_{\text{log-additive}}$< 0.0001). Moreover, *CCR7* rs3136685 was correlated with an increased risk of disease under recessive and log-additive models ($p_{\text{recessive}}$ = 0.007, $p_{\text{log-additive}}$= 0.019); and *CCR7* rs17708087 was also identified as a risk factor in the dominant model (p = 0.038).

Conclusion: These results widen the scope of knowledge about the association between *STAT4, IL8RA* and *CCR7* polymorphisms and risk of lung cancer.

Keywords: lung cancer, signal transducers and activators of transcription 4, *STAT4*, interleukin 8-receptor alpha, *IL8RA*, Chemokine (C-C motif) receptor 7, *CCR7*, single nucleotide polymorphisms, SNPs

Introduction

Lung cancer is the most common diagnosed malignant tumor, with the fastest growing morbidity and mortality rates compared with other types of tumors.[1] The 5-year survival rate for lung cancer patients depends on the stage when they were diagnosed: early detection and treatment can significantly improve the prognosis of patients.[2] Lung cancer has obvious familial aggregation and genetic predisposition.[3] Thus, identification of individuals with a high risk of lung cancer will help people focus on their body health; and a personalized and comprehensive response plan, including tobacco prevention, healthy diet, proper exercise, periodic physical

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examination and so on, will finally decrease the incidence of disease. With the awareness of genetic counseling, single nucleotide polymorphisms (SNPs) are extensively used to evaluate the susceptibility to cancer.[4–6] However, it still needs a great effort to find more SNPs to draw the genetic map of lung cancer.

The Nobel Prize on tumor immunotherapy provided us clues that SNPs on immune response related genes may influence the genetic predisposition to lung cancer to a large extent.[7] In this study, we focused on three immune response related genes: signal transducers and activators of transcription 4 (*STAT4*), interleukin 8-receptor alpha (*IL8RA*) and Chemokine (C-C motif) receptor 7 (*CCR7*). *STAT4* can change the tumor microenvironment by influencing the level of growth factors and cytokines, which may have indirect effects on tumor cell growth and apoptosis.[8] *IL8RA* may have associations with serum IgE levels, and *IL8RA* polymorphisms were associated with risk of bronchial asthma.[9] *CCR7* can induce cells to lymphoid organs, and its expression is associated with lymph node metastasis of cancer.[10] However, to date, few studies focus on the *STAT4, IL8RA* and *CCR7* polymorphisms in lung cancer.

Seven SNPs were chosen as candidate SNPs in this study: rs1400656, rs7574865, rs11685878 on *STAT4*; rs1008562 and rs3138060 on *IL8RA*; and rs3136685 and rs17708087 on *CCR7*. A case-control study in an Indian population reported that rs1400656 might affect genetic susceptibility to asthma.[11] rs7574865 and rs11685878 have been investigated in the virus infection and clearance in a Chinese population.[12] rs1008562 was correlated with an increased risk of colorectal cancer,[13] and rs3138060 was related to bacterial infection in the urinary tract.[14] The rs3136685 was selected because of its correlation with prostate cancer risk,[15] and rs17708087 may exert an influence on myocardial infarction.[16] In this study, we genotyped these genetic polymorphisms in lung cancer patients and healthy controls, and aimed at improving our understanding of genetic predisposition to lung cancer.

Subjects and Methods

Subjects

A total of 350 lung cancer cases and 350 healthy controls were collected at the General Hospital of Ningxia Medical University. The diagnosis of lung cancer was established by histopathological examination of biopsy or resected tissue specimens. All the cases were more than 18 years old and had no history of any malignancy. The patients who had received chemo or radiotherapy were excluded. The controls were recruited at the physical examination center of our hospital, with no history of any malignant disorder or serious disease. Controls who were under 18 years old were excluded.

The sample size was calculated using Sampsize online tool (http://sampsize.sourceforge.net/iface/s3.html), and followed by the conditions: α=0.05, power=0.90, and expected OR=1.8. The calculated sample size was 318 in both the case and control groups. The sample size was therefore sufficient.

The basic characteristics of the participants are described in Table 1. The cases include 180 males and 170 females, 187 smokers and 163 nonsmokers, with a mean age of 56.9 years; and the control group contains 175 males and 175 females, 180 smokers and 170 nonsmokers, with a mean age of 58.1 years. No significant difference was observed in the distribution of sex, age, or smoking status between the two groups ($p > 0.05$).

Two milliliters of whole blood was collected from each subject into tubes containing ethylenediaminetetraacetic acid. After centrifugation, the samples were stored at −80 °C until further use.

Table 1 The Basic Characteristics of the Participants

Variables	Case (%) (n = 350)	Control (%) (n = 350)	$\chi 2/t$	*p*
Sex (%)			0.143	0.705
Male	180 (51.4)	175 (50.0)		
Female	170 (48.6)	175 (50.0)		
Age (mean ±SD), years	56.9±10.9	58.1±9.8	−1.513	0.131
Smoking (%)			0.281	0.596
Yes	187 (53.4)	180 (51.4)		
No	163 (46.6)	170 (48.6)		

We obtained written informed consent from each subject, and the study was approved by the Ethics Department of General Hospital of Ningxia Medical University and carried out in accordance with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

SNP Selection and Genotyping

Seven tag SNPs in immune response genes *STAT4, IL8RA* and *CCR7* were selected based on previous association studies on cancers and pulmonary disease. All of the SNPs are with minor allele frequency (MAF) > 5% in Asian populations of the NCBI database. Tag SNPs were selected with linkage disequilibrium (LD) greater than 0.8 using HaploView.

DNA was extracted using a PureLink™ Pro 96 Genomic DNA Purification Kit (Invitrogen, Carlsbad, CA). Primers were designed using Sequenom MassARRAY Assay Design 3.0 software and listed in Table 2. Genotyping was performed on Mass ARRAY iPLEX (Sequenom, San Diego, CA, USA) platform using a matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometer. The results were output by Sequenom TYPER 4.0 software.[17]

Statistical Analysis

Statistical analysis was performed with SPSS package version 20.0 (SPSS, Chicago, IL, USA). Minor allele frequencies (MAFs) of each SNP were checked for divergence from Hardy–Weinberg equilibrium (HWE). HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) was used to predict the potential functions of the SNPs. Allele and genotype frequencies in the cases and controls were evaluated using Chi-square tests. The association between SNPs and lung cancer risk were evaluated using SNPstats (https://www.snpstats.net/start.htm) and expressed by odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was established when $p < 0.05$.

Results

The position of candidate SNPs and predicted function are listed in Table 3. The predicted function according to the HaploReg database showed that the seven SNPs were involved in the changes of reference epigenomes (regulation of the promoter and/or enhancer histone), regulatory motifs, and expression quantitative trait loci (eQTL).

The MAFs of SNPs in cases and controls are listed in Table 4. All SNPs were consistent with HWE ($p > 0.05$). Comparing the MAF of each SNP between cases and controls, we found that four SNPs had potential influence on lung cancer risk: rs1400656, rs7574865, rs1008562 and rs3136685. The minor alleles of rs1400656 and rs7574865 may decrease the susceptibility to lung cancer (rs1400656: OR = 0.694, 95% CI: 0.510–0.945, $p = 0.020$; rs7574865: OR = 0.735, 95% CI: 0.574–0.941, $p = 0.014$). However, the minor alleles of rs1008562 and rs3136685 may increase the risk of lung cancer (rs1008562: OR = 1.655, 95% CI: 1.332–2.057, $p < 0.001$; rs3136685: OR = 1.309, 95% CI: 1.048–1.634, $p = 0.018$).

The genotype frequencies of SNPs among cases and controls are presented in Table 5. Compared with the AA genotype, the GA genotype frequency of rs1400656 was lower in cases than in controls, thus the GA of rs1400656 was considered as a protective genotype against lung cancer risk (OR = 0.66, 95% CI: 0.46–0.94, $p = 0.048$). Moreover, the GT genotype of rs7574865 was also correlated with a reduced risk of lung cancer (OR = 0.70, 95% CI: 0.51–0.96, $p = 0.042$). However, the CG and GG genotypes of rs1008562 were significantly associated with a 1.92-fold and 2.50-fold increased risk of disease, respectively ($p < 0.0001$). The TT genotype of rs3136685 was also correlated with a 2.09-fold elevated risk of disease (95% CI: 1.23–3.54, $p = 0.020$).

The effects of candidate SNPs on the risk of lung cancer were further evaluated under genetic models (Table 6). The minor alleles of rs1400656 and rs7574865 were related to a declining risk of disease under dominant and log-additive models (rs1400656: $p_{\text{dominant}} = 0.014$, $p_{\text{log-additive}} = 0.016$; rs7574865: $p_{\text{dominant}} = 0.013$, $p_{\text{log-additive}} = 0.013$). In contrast, the allele C of rs1008562 exhibited a strong correlation with an elevated risk of lung cancer under all three models ($p_{\text{dominant}} < 0.0001$, $p_{\text{recessive}} = 0.011$, $p_{\text{log-additive}} < 0.0001$). The allele T of rs3136685 was correlated with an elevated risk of disease under recessive and log-additive models ($p_{\text{recessive}} = 0.007$, $p_{\text{log-additive}} = 0.019$). In addition, the allele G of rs17708087 was also identified as a risk allele in the dominant model ($p = 0.038$).

Smoking is an important risk factor for lung cancer. So a stratification analysis was conducted (Table 7). The rs1400656 polymorphism was correlated to a reduced risk of disease in smokers ($p_{\text{dominant}} = 0.019$, $p_{\text{log-additive}} = 0.015$), while rs7574865 exhibited a declining risk of disease in nonsmokers ($p_{\text{dominant}} = 0.046$, $p_{\text{log-additive}} = 0.031$). In contrast, rs1008562 polymorphism was associated with an elevated risk of disease in both subgroups

Table 2 The Primers Used in This Study

SNP_ID	1st-PCRP	2nd-PCRP	UEP_SEQ
rs1400656	ACGTTGGATGATAATATAAAAAAGCCTTTA	ACGTTGGATGACTTTACTTTTCCCCAAAC	TTCCCCAAACCTGGTG
rs7574865	ACGTTGGATGAAAAATCCCCCTGAAATTCC	ACGTTGGATGGCAGTAAAAGTATGAAAAG	GGTGACCAAAATGT
rs11685878	ACGTTGGATGGCAGGATTTTCTCAGTGTAA	ACGTTGGATGCCCTCACAATCTTATCCTCC	CAAAAGATGGGTTGTTTTC
rs1008562	ACGTTGGATGAGCCTTATAGCTACTAAGCC	ACGTTGGATGGAGACTTTGGAATGGGATAAG	AGGCCTGGAATGAATAT
rs3138060	ACGTTGGATGCTTCACCTGCTAACTCCATG	ACGTTGGATGTCATTTCTGTGGGAGCTGAG	CCTCTCTTGTGACCA
rs3136685	ACGTTGGATGTCCTCTTCACCTGCTAACTC	ACGTTGGATGTGTGGGAGCTGAGGATTTCT	TCCTCTCTTGTGACCA
rs17708087	ACGTTGGATGCGTGCTCCCACTTGCTAGA	ACGTTGGATGCCTGAACCCACTTTCTAAACTCA	GTTAAGCAACATTCCAG

(smokers: $p_{\text{dominant}} = 0.001$, $p_{\text{log-additive}} = 0.003$; nonsmokers: $p_{\text{dominant}} = 0.003$, $p_{\text{log-additive}} = 0.001$). In addition, rs3136685 has influence on lung cancer risk only in nonsmokers ($p_{\text{dominant}} = 0.033$, $p_{\text{recessive}} = 0.027$, $p_{\text{log-additive}} = 0.008$).

Discussion

Immune response has always been the research hotspot in the study of cancer prevention and treatment in the last few years.[18] In this study, we took immune response genes *STAT4, IL8RA* and *CCR7* as the starting point, and explored the association between seven SNPs on these genes and lung cancer risk. We identified that two SNPs (*STAT4* rs1400656 and rs7574865) had a protective role against the risk of disease, and three SNPs (*IL8RA* rs1008562, *CCR7* rs3136685 and rs17708087) may increase the risk of disease.

STAT4 is involved in a variety of immune response processes, including production of interferon-γ (IFN-γ), signal transduction of IL-12, -23, IFN and other cytokines in immune cells, differentiation and activation of immune cells, and so on.[19] *STAT4* polymorphisms have been extensively investigated in several kinds of immune regulation disorders, such as rheumatoid arthritis, polymyositis/dermatomyositis, intestinal Behcet's disease, and systemic lupus erythematous.[20–22] In recent years, the important role of *STAT4* polymorphisms has been gradually found in the genesis and progression of liver cancer. A meta-analysis reported that rs7574865 G allele was correlated with an increased risk of HBV-induced liver cancer.[23] We identified that minor allele T of rs7574865 might be a protective allele for the risk of lung cancer, suggesting that rs7574865 polymorphism may have a similar influence on the occurrence of cancer. In addition, we also determined rs1400656 G allele as a protective allele against the risk of disease. However, due to the limited literature, the protective effects of rs1400656 and rs7574865 on lung cancer need to be further verified.

IL8RA (also known as CXCR1) is one of the receptors of IL8 (also known as CXCL8). Their binding proteins take part in the initiation and progression of several kinds of cancers via PI3K and MAPK pathway.[24] Stimulation of IL8 in lung cancer cells was mediated by *IL8RA* and EGFR to a large extent.[25] Lee et al have reported that the interaction of *IL8RA* rs2234671 (C/G) and smoke exposure was substantially correlated with the lung cancer risk.[26] Slattery et al demonstrated that *IL8RA* rs1008562 in the CHIEF pathway had significant associations with

Table 3 Basic Information and Predicted Functions of Candidate SNPs

SNP	Gene	Chromosome	Position	Alleles	HaploReg Annotations
rs1400656	*STAT4*	2	191,070,307	A>G	Enhancer histone mark, motifs changed
rs7574865	*STAT4*	2	191,099,907	G>T	Enhancer histone mark, motifs changed, eQTL hits
rs11685878	*STAT4*	2	191,144,729	C>T	Enhancer histone mark, motifs changed, eQTL hits
rs1008562	*IL8RA*	2	218,162,249	G>C	motifs changed, eQTL hits
rs3138060	*IL8RA*	2	218,166,777	G>C	Promoter and enhancer histone marks, motifs changed, eQTL hits
rs3136685	*CCR7*	17	40,563,547	C>T	Promoter and enhancer histone marks, motifs changed, eQTL hits
rs17708087	*CCR7*	17	40,514,261	A>G	Enhancer histone mark, motifs changed, eQTL hits

Abbreviations: SNP, single nucleotide polymorphism; eQTL, expression quantitative trait locus.

Table 4 Allele Frequency Distributions Among Lung Cancer Cases and Healthy Controls

SNP	Gene	MAF-Case	MAF-Control	HWE *p*	OR (95% CI)	*p*
rs1400656	*STAT4*	0.12	0.16	0.99	0.694(0.510–0.945)	0.020*
rs7574865	*STAT4*	0.21	0.27	0.50	0.735(0.574–0.941)	0.014*
rs11685878	*STAT4*	0.45	0.49	0.99	0.857(0.694–1.057)	0.148
rs1008562	*IL8RA*	0.44	0.33	0.47	1.655(1.332–2.057)	<0.001*
rs3138060	*IL8RA*	0.18	0.17	0.71	1.030(0.782–1.356)	0.833
rs3136685	*CCR7*	0.37	0.31	0.10	1.309(1.048–1.634)	0.018*
rs17708087	*CCR7*	0.40	0.36	0.16	1.186(0.955–1.472)	0.123

Note: *$p < 0.05$ indicates statistical significance.
Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium.

Table 5 Genotype Frequency Distributions Among Lung Cancer Cases and Healthy Controls

SNP	Genotype	Control (%)	Case (%)	OR (95% CI)	*p*
rs1400656	A/A G/A G/G	248 (70.9%) 93 (26.6%) 9 (2.6%)	275 (78.6%) 69 (19.7%) 6 (1.7%)	1.00 0.66 (0.46–0.94) 0.59 (0.20–1.68)	0.048*
rs7574865	G/G G/T T/T	186 (53.1%) 142 (40.6%) 22 (6.3%)	219 (62.6%) 115 (32.9%) 16 (4.6%)	1.00 0.70 (0.51–0.96) 0.59 (0.30–1.16)	0.042*
rs11685878	C/C C/T T/T	91 (26%) 175 (50%) 84 (24%)	98 (28%) 188 (53.7%) 64 (18.3%)	1.00 1.02 (0.72–1.46) 0.71 (0.46–1.10)	0.170
rs1008562	G/G C/G C/C	162 (46.3%) 148 (42.3%) 40 (11.4%)	103 (29.4%) 183 (52.3%) 64 (18.3%)	1.00 1.92 (1.38–2.67) 2.50 (1.57–3.98)	<0.0001*
rs3138060	G/G C/G C/C	237 (67.7%) 104 (29.7%) 9 (2.6%)	235 (67.1%) 105 (30%) 10 (2.9%)	1.00 1.03 (0.74–1.42) 1.09 (0.44–2.74)	0.970
rs3136685	C/C C/T T/T	161 (46%) 163 (46.6%) 26 (7.4%)	142 (40.6%) 159 (45.4%) 49 (14%)	1.00 1.11 (0.81–1.52) 2.09 (1.23–3.54)	0.020*
rs17708087	A/A A/G G/G	151 (43.1%) 148 (42.3%) 51 (14.6%)	125 (35.7%) 172 (49.1%) 53 (15.1%)	1.00 1.42 (1.03–1.97) 1.26 (0.80–1.99)	0.100

Note: *$p < 0.05$ indicates statistical significance.
Abbreviations: OR, odds ratio; CI, confidence interval.

Table 6 Association Between Candidate SNPs and Risk of Lung Cancer in Three Genetic Models

SNP	Model	Genotype	Control	Case	OR (95% CI)	*p*
rs1400656	Dominant	A/A	248 (70.9%)	275 (78.6%)	1	0.014*
		G/A-G/G	102 (29.1%)	75 (21.4%)	0.65 (0.46–0.92)	
	Recessive	A/A-G/A	341 (97.4%)	344 (98.3%)	1	0.410
		G/G	9 (2.6%)	6 (1.7%)	0.65 (0.23–1.85)	
	Log-additive	—	—	—	0.69 (0.50–0.93)	0.016*
rs7574865	Dominant	G/G	186 (53.1%)	219 (62.6%)	1	0.013*
		G/T-T/T	164 (46.9%)	131 (37.4%)	0.68 (0.51–0.92)	
	Recessive	G/G-G/T	328 (93.7%)	334 (95.4%)	1	0.250
		T/T	22 (6.3%)	16 (4.6%)	0.68 (0.35–1.32)	
	Log-additive	—	—	—	0.73 (0.57–0.94)	0.013*
rs11685878	Dominant	C/C	91 (26%)	98 (28%)	1	0.630
		C/T-T/T	259 (74%)	252 (72%)	0.92 (0.66–1.29)	
	Recessive	C/C-C/T	266 (76%)	286 (81.7%)	1	0.059
		T/T	84 (24%)	64 (18.3%)	0.70 (0.49–1.01)	
	Log-additive	—	—	—	0.86 (0.69–1.06)	0.160
rs1008562	Dominant	G/G	162 (46.3%)	103 (29.4%)	1	<0.0001*
		C/G-C/C	188 (53.7%)	247 (70.6%)	2.05 (1.50–2.79)	
	Recessive	G/G-C/G	310 (88.6%)	286 (81.7%)	1	0.011*
		C/C	40 (11.4%)	64 (18.3%)	1.73 (1.13–2.66)	
	Log-additive	—	—	—	1.66 (1.33–2.07)	<0.0001*
rs3138060	Dominant	G/G	237 (67.7%)	235 (67.1%)	1	0.840
		C/G-C/C	113 (32.3%)	115 (32.9%)	1.03 (0.75–1.42)	
	Recessive	G/G-C/G	341 (97.4%)	340 (97.1%)	1	0.860
		C/C	9 (2.6%)	10 (2.9%)	1.08 (0.43–2.71)	
	Log-additive	—	—	—	1.03 (0.78–1.37)	0.820
rs3136685	Dominant	C/C	161 (46%)	142 (40.6%)	1	0.150
		C/T-T/T	189 (54%)	208 (59.4%)	1.25 (0.92–1.68)	
	Recessive	C/C-C/T	324 (92.6%)	301 (86%)	1	0.007*
		T/T	26 (7.4%)	49 (14%)	1.98 (1.20–3.27)	
	Log-additive	—	—	—	1.31 (1.04–1.65)	0.019*
rs17708087	Dominant	A/A	151 (43.1%)	125 (35.7%)	1	0.038*
		A/G-G/G	199 (56.9%)	225 (64.3%)	1.38 (1.02–1.87)	
	Recessive	A/A-A/G	299 (85.4%)	297 (84.9%)	1	0.820
		G/G	51 (14.6%)	53 (15.1%)	1.05 (0.69–1.60)	
	Log-additive	—	—	—	1.19 (0.96–1.47)	0.120

Note: *$p < 0.05$ indicates statistical significance.
Abbreviations: OR, odds ratio; CI, confidence interval.

rectal cancer.[27] In this study, we found that rs1008562 exhibited a strong relationship with the risk of lung cancer, suggesting that rs1008562 polymorphism may also exert an influence on the development of lung cancer via the network of the CHIEF pathway.

CCR7 has two ligands CCL19 and CCL21, which are mainly expressed in lymphatic organs. *CCR7* can induce immune cells towards the lymphatic organs, which means it plays a crucial role in the migration of tumor cells.[28] Wang et al has found that the up-regulation of HIF-1α and HIF-2α could improve the expression of *CCR7* under hypoxia conditions, and led to the metastasis of lung cancer.[29] In this study, we compared the *CCR7* rs3136685 and rs17708087 polymorphisms between lung cancer patients and a heathy control, and found that both polymorphisms had a strong correlation with lung cancer risk, suggesting they might be used as biomarkers to identify the high-risk groups. Moreover, considering the

Table 7 Association of Candidate SNPs with the Risk of Lung Cancer in Smokers and Nonsmokers

SNP	Model	Smokers		Nonsmokers	
		OR (95% CI)	*p*	OR (95% CI)	*p*
rs1400656	Dominant	0.57 (0.36–0.91)	0.019*	0.75 (0.45–1.26)	0.280
	Recessive	0.41 (0.08–2.14)	0.270	1.04 (0.25–4.24)	0.960
	Log-additive	0.59 (0.38–0.91)	0.015*	0.81 (0.52–1.26)	0.350
rs7574865	Dominant	0.75 (0.49–1.14)	0.180	0.64 (0.41–0.99)	0.046*
	Recessive	0.86 (0.37–2.01)	0.720	0.49 (0.16–1.49)	0.200
	Log-additive	0.81 (0.58–1.14)	0.230	0.66 (0.45–0.97)	0.031*
rs11685878	Dominant	0.96 (0.60–1.53)	0.870	0.89 (0.55–1.44)	0.630
	Recessive	0.77 (0.46–1.31)	0.340	0.63 (0.38–1.06)	0.081
	Log-additive	0.90 (0.66–1.22)	0.500	0.81 (0.60–1.10)	0.180
rs1008562	Dominant	2.06 (1.33–3.19)	0.001*	1.97 (1.25–3.08)	0.003*
	Recessive	1.50 (0.83–2.71)	0.180	1.98 (1.06–3.71)	0.029*
	Log-additive	1.60 (1.17–2.19)	0.003*	1.68 (1.22–2.32)	0.001*
rs3138060	Dominant	0.66 (0.42–1.02)	0.058	1.77 (0.91–2.85)	0.056
	Recessive	0.57 (0.18–1.79)	0.330	5.34 (0.62–46.24)	0.077
	Log-additive	0.69 (0.47–1.00)	0.051	1.79 (0.955–2.77)	0.058
rs3136685	Dominant	1.00 (0.66–1.51)	0.990	1.61 (1.04–2.50)	0.033*
	Recessive	1.78 (0.93–3.44)	0.079	2.38 (1.08–5.23)	0.027*
	Log-additive	1.14 (0.84–1.54)	0.410	1.59 (1.13–2.25)	0.008*
rs17708087	Dominant	1.39 (0.91–2.12)	0.120	1.35 (0.86–2.10)	0.190
	Recessive	1.05 (0.62–1.80)	0.850	1.05 (0.53–2.06)	0.890
	Log-additive	1.18 (0.89–1.56)	0.250	1.19 (0.85–1.67)	0.300

Note: *$p < 0.05$ indicates statistical significance.
Abbreviations: OR, odds ratio; CI, confidence interval.

specific role of *CCR7* on metastasis, we will further investigate the association between its polymorphisms and prognosis of lung cancer patients in a future study.

The effects of genetic polymorphisms on lung cancer risk can be significantly different in smokers and nonsmokers,[30] so we conduct a stratification analysis. The rs1008562 polymorphism was associated with risk of disease in both of subgroups, suggesting that rs1008562 polymorphism was a significant risk factor. While rs1400656, rs7574865 and rs3136685 were significant only in one subgroup, we speculated it may be due to the limited sample size.

Although the present study provided novel susceptible SNPs for lung cancer, it has some inevitable disadvantages. Firstly, we were unable to collect information about the pathological types and treatment regimens, and therefore, we cannot conduct the stratification analysis according to pathological type, and evaluate the effect of these polymorphisms on the response to treatment. Secondly, the current results are insufficient to explain the molecular pathogenesis of the disease. Thirdly, the sample size was modest, and the allele and genotype frequency of SNPs could be variable among different populations, thus the results identified here should be verified in a larger sample size and different populations.

In conclusion, we found that two SNPs (*STAT4* rs1400656 and rs7574865) had a protective role against the risk of lung cancer, and three SNPs (*IL8RA* rs1008562, *CCR7* rs3136685 and rs17708087) may increase the risk of disease. These results widen the scope of knowledge about the association between immune response genes, *STAT4, IL8RA* and *CCR7* polymorphisms, and risk of the disease.

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Disclosure

The authors declare that they have no competing interests.

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