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} < 0.001; 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_{log-additive} = 0.016; rs7574865: p_{dominant} = 0.013, p_{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_{recessive} = 0.011, p_{log-additive} < 0.0001). Moreover, CCR7 rs3136685 was correlated with an increased risk of disease under recessive and log-additive models (p_{recessive} = 0.007, p_{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 moti) 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...
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. 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. 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. IL8RA may have associations with serum IgE levels, and IL8RA polymorphisms were associated with risk of bronchial asthma. CCR7 can induce cells to lymphoid organs, and its expression is associated with lymph node metastasis of cancer. 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. rs7574865 and rs11685878 have been investigated in the virus infection and clearance in a Chinese population. rs1008562 was correlated with an increased risk of colorectal cancer, and rs3138060 was related to bacterial infection in the urinary tract. The rs3136685 was selected because of its correlation with prostate cancer risk, and rs17708087 may exert an influence on myocardial infarction. 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 Sampsie online tool (http://sampsie.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 non-smokers, with a mean age of 56.9 years; and the control group contains 175 males and 175 females, 180 smokers and 170 non-smokers, 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) | χ2/φ | p |
|-----------|--------------------|-----------------------|------|---|
| Sex (%)   |                    |                       |      |   |
| Male      | 180 (51.4)         | 175 (50.0)            | 0.143| 0.705|
| Female    | 170 (48.6)         | 175 (50.0)            |      |   |
| Age (mean ±SD), years | 56.9±10.9 | 58.1±9.8 | −1.513 | 0.131 |
| Smoking (%) |                    |                       |      |   |
| Yes       | 187 (53.4)         | 180 (51.4)            | 0.281| 0.596|
| 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.\(^1\)

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

**Discussion**

Immune response has always been the research hotspot in the study of cancer prevention and treatment in the last few years. 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. **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 erythematosus. 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. 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. Stimulation of IL8 in lung cancer cells was mediated by *IL8RA* and EGFR to a large extent. Lee et al have reported that the interaction of *IL8RA* rs2234671 (C/G) and smoke exposure was substantially correlated with the lung cancer risk. 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 | 248 (70.9%) | 275 (78.6%) | 1.00 | 0.048* |
|          | G/A | 93 (26.6%) | 69 (19.7%) | 0.66 (0.46–0.94) | 0.59 (0.20–1.68) |
|          | G/G | 9 (2.6%) | 6 (1.7%) | 0.020* |
| rs7574865  | G/G | 186 (53.1%) | 219 (62.6%) | 1.00 | 0.042* |
|          | G/T | 142 (40.6%) | 115 (32.9%) | 0.067 (0.51–0.96) | 0.59 (0.30–1.16) |
|          | T/T | 22 (6.3%) | 16 (4.6%) | 0.170 |
| rs11685878 | C/C | 91 (26%) | 98 (28%) | 1.00 | 0.170 |
|          | C/T | 175 (50%) | 188 (53.7%) | 1.02 (0.72–1.46) | 0.71 (0.46–1.10) |
|          | T/T | 84 (24%) | 64 (18.3%) | 1.00 |
| rs1008562  | G/G | 162 (46.3%) | 103 (29.4%) | 1.00 | <0.0001* |
|          | C/G | 148 (42.3%) | 183 (52.3%) | 1.92 (1.38–2.67) | 2.50 (1.57–3.98) |
|          | C/C | 40 (11.4%) | 64 (18.3%) | 1.00 |
| rs3138060  | G/G | 237 (67.7%) | 235 (67.1%) | 1.00 | 0.970 |
|          | C/G | 104 (29.7%) | 105 (30%) | 1.03 (0.74–1.42) | 1.09 (0.44–2.74) |
|          | C/C | 9 (2.6%) | 10 (2.9%) | 0.970 |
| rs3136685  | C/C | 161 (46%) | 142 (40.6%) | 1.00 | 0.020* |
|          | C/T | 163 (46.6%) | 159 (45.4%) | 1.01 (0.81–1.52) | 2.09 (1.23–3.54) |
|          | T/T | 26 (7.4%) | 49 (14%) | 0.010 |
| rs17708087 | A/A | 151 (43.1%) | 125 (35.7%) | 1.00 | 0.100 |
|          | A/G | 148 (42.3%) | 172 (49.1%) | 1.42 (1.03–1.97) | 1.26 (0.80–1.99) |
|          | G/G | 51 (14.6%) | 53 (15.1%) | 1.00 |

**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 | 0.65 (0.46–0.92) | 0.014* |
|              |           | G/A-G/G  | 102 (29.1%) | 75 (21.4%)  |   |              |     |
|              |           | A/A-G/A  | 341 (97.4%) | 344 (98.3%) |   |              |     |
|              |           | G/G      | 9 (2.6%) | 6 (1.7%) |   |              |     |
|              | Recessive | —        | —       | —    | —           |     |
|              | Log-additive | —    | —       | —    | —           |     |
| rs7574865    | Dominant  | G/G      | 186 (53.1%) | 219 (62.6%) | 1 | 0.68 (0.51–0.92) | 0.013* |
|              |           | G/T-T/T  | 164 (46.9%) | 131 (37.4%) |   |              |     |
|              |           | G/G-G/T  | 328 (93.7%) | 334 (95.4%) |   |              |     |
|              |           | T/T      | 22 (6.3%) | 16 (4.6%) |   |              |     |
|              | Recessive | —        | —       | —    | —           |     |
|              | Log-additive | —    | —       | —    | —           |     |
| rs1168578    | Dominant  | C/C      | 91 (26%) | 98 (28%) | 1 | 0.92 (0.66–1.29) | 0.630 |
|              |           | C/T-T/T  | 259 (74%) | 252 (72%) |   |              |     |
|              |           | C/C-C/T  | 266 (76%) | 286 (81.7%) |   |              |     |
|              |           | T/T      | 84 (24%) | 64 (18.3%) |   |              |     |
|              | Recessive | —        | —       | —    | —           |     |
|              | Log-additive | —    | —       | —    | —           |     |
| rs1008562    | Dominant  | G/G      | 162 (46.3%) | 103 (29.4%) | 1 | 2.05 (1.50–2.79) | <0.0001* |
|              |           | G/C-G/C  | 188 (53.7%) | 247 (70.6%) |   |              |     |
|              |           | G/G-C/G  | 310 (88.6%) | 286 (81.7%) |   |              |     |
|              |           | C/C      | 40 (11.4%) | 64 (18.3%) |   |              |     |
|              | Recessive | —        | —       | —    | —           |     |
|              | Log-additive | —    | —       | —    | —           |     |
| rs3138060    | Dominant  | G/G      | 237 (67.7%) | 235 (67.1%) | 1 | 1.03 (0.75–1.42) | 0.840 |
|              |           | G/C-G/C  | 113 (32.3%) | 115 (32.9%) |   |              |     |
|              |           | G/G-C/G  | 341 (97.4%) | 340 (97.1%) |   |              |     |
|              |           | C/C      | 9 (2.6%) | 10 (2.9%) |   |              |     |
|              | Recessive | —        | —       | —    | —           |     |
|              | Log-additive | —    | —       | —    | —           |     |
| rs3136685    | Dominant  | C/C      | 161 (46%) | 142 (40.6%) | 1 | 1.25 (0.92–1.68) | 0.007* |
|              |           | C/T-T/T  | 189 (54%) | 208 (59.4%) |   |              |     |
|              |           | C/C-C/T  | 324 (92.6%) | 301 (86%)  |   |              |     |
|              |           | T/T      | 26 (7.4%) | 49 (14%) |   |              |     |
|              | Recessive | —        | —       | —    | —           |     |
|              | Log-additive | —    | —       | —    | —           |     |
| rs17708087   | Dominant  | A/A      | 151 (43.1%) | 125 (35.7%) | 1 | 1.38 (1.02–1.87) | 0.038* |
|              |           | A/G-G/G  | 199 (56.9%) | 225 (64.3%) |   |              |     |
|              |           | A/A-A/G  | 299 (85.4%) | 297 (84.9%) |   |              |     |
|              |           | G/G      | 51 (14.6%) | 53 (15.1%) |   |              |     |

Note: *p < 0.05 indicates statistical significance.

Abbreviations: OR, odds ratio; CI, confidence interval.

rectal cancer. 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. 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. In this study, we compared the *CCR7* rs3136685 and rs17708087 polymorphisms between lung cancer patients and a healthy 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
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, 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 speculate 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.

| SNP       | Model       | Smokers                                  | Non-smokers                             |
|-----------|-------------|------------------------------------------|-----------------------------------------|
|           | 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   | 0.40 (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   | 0.80 (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 (0.95–3.77) | 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.
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