GENETIC POLYMORPHISMS IN IL-7 AND IL-7R ARE CORRELATED WITH LUNG CANCER RISK IN THE CHINESE HAN POPULATION

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PURPOSE: IL-7/IL-7R axis participates in the initiation and progression of lung cancer (LC). This study aimed to explore the potential influence of IL-7/IL-7R polymorphisms on LC risk.

PATIENTS AND METHODS: In total, 1,010 participants (507 LC patients and 503 healthy controls) were enrolled. Five single-nucleotide polymorphisms (SNPs) in IL-7R and one SNP in IL-7 were genotyped in included samples with Agena MassARRAY system. OR and 95% CIs were computed by logistic regression analysis after adjusting for age and gender. Stratified analyses with demographic and clinical characteristics were also performed. Finally, linkage disequilibrium (LD) analysis was conducted with the PLINK version 1.07 software.

RESULTS: IL-7R rs10053847 variant was related to a decreased LC risk under the allele gene (OR = 0.78, P = 0.043) and additive model (OR = 0.77, P = 0.042). The results of stratified analysis indicated that this SNP was associated with a lower LC risk among nonsmokers (AA/GG: OR = 0.09, P = 0.033; AA/AG+GG: OR = 0.10, P = 0.037) or nondrinkers (AA/GG: OR = 0.07, P = 0.047; AA/AG+GG: OR = 0.18, P = 0.049). Moreover, carriers of IL-7R rs10213865-C allele had an increased lung adenocarcinoma risk (CA/AA: OR = 1.60, P = 0.011; CC+CA/AA: OR = 1.62, P = 0.007; CA/CA/AA: OR = 1.50, P = 0.007). Additionally, AGAA haplotype (rs10213865, rs969129, rs118137916 and rs10053847) increased LC risk (OR = 1.30, P = 0.041).

CONCLUSION: IL-7R rs10053847 was correlated with a decreased LC risk, while IL-7R rs10213865 was correlated with an elevated lung adenocarcinoma risk, implying these two SNPs might play essential roles in LC risk evaluation.

KEYWORDS: lung cancer, IL-7R, IL-7, polymorphisms, cancer susceptibility, case-control study

INTRODUCTION

Lung cancer (LC) has been regarded as one of the multifactorial disorders and remained a considerable public health challenge around the world. It is estimated that approximately 2.09 million cases were diagnosed worldwide in 2018. Moreover, the mortality rate is relatively higher in China than most other countries and predicted to continuously increase before 2030. Currently, although numerous investigators have emphasized that genetic and environmental factors participate in the progression of LC, the detailed pathogenesis of LC has not been fully elaborated. Several research groups claimed that there were strong associations between genetic variations and the occurrence and development of LC in the past few years.
IL-7, a pleiotropic cytokine primarily secreted by stromal cells, is involved in several cell biological processes such as lymphangiogenesis, cell proliferation and apoptosis through binding to its receptor (IL-7R).\(^8\),\(^9\) Increasing studies have found that IL-7 and IL-7R participate in the development of various cancers including LC by mediating multiple cell signaling pathways.\(^10\),\(^11\) Andersson et al previously found that IL-7 could significantly diminish tumor burdens via enhancing the specific chemokine receptor-dependent T-cell antitumor activity in LC progression.\(^12\) Jian et al pointed out that IL-7R interacted with some autophagy-associated molecules to activate the signaling pathways in cell apoptotic process of LC.\(^13\) Liu et al also argued that IL-7/IL-7R axis might be responsible for LC cell apoptosis regulation and survival outcomes.\(^14\) Recently, overwhelming evidence has explored the relationships between SNPs (single-nucleotide polymorphisms) in many tumor-related genes and LC risk.\(^15\),\(^16\) Van Dyke et al suggested that IL7R rs1494555 and rs7737000 variants were significantly linked to a higher risk of non-small LC among Caucasians.\(^17\) However, the underlying impact of IL-7/IL-7R polymorphisms (rs10213865, rs969129, rs118137916, rs10053847 and rs6451231 in IL-7R and rs117173992 in IL-7) on the prevalence of LC has not been clarified.

Therefore, we carried out an association analysis based on a Chinese Han population to evaluate the potential correlations between IL-7/IL-7R SNPs and the risk of LC.

Materials and methods

Study subjects
A total of 1,010 participants (507 patients suffering from LC and 503 cancer-free controls) were consecutively enrolled from Shaanxi Provincial Cancer Hospital. All cases were newly diagnosed and histologically confirmed lung carcinoma. Patients did not receive chemotherapy or radiotherapy before collecting samples. Patients with prior cancer history were excluded from this study. Meanwhile, all control subjects underwent medical examinations in the same hospital and did not have any family history of LC or other diseases. All eligible participants were all genetically unrelated to each other. The detailed demographic and the clinical data were subsequently obtained according to the pre-established standardized questionnaire, medical record and/or the face-to-face interviews, primarily including age, gender, body mass index (BMI), smoking and drinking status, pathological type, lymph nodes metastasis and TNM staging. This work was supported by Ethics Committee of Shaanxi Provincial Cancer Hospital and the written informed consent was acquired from each participant. All experiments were conducted in accordance with the World Medical Association Declaration of Helsinki.

SNP selection and genotyping
Two cancer-associated genes (IL-7R and IL-7) were selected to evaluate the correlation between their polymorphisms and the susceptibility to LC. Peripheral blood samples (5 mL) were collected from each subject, and genomic DNA was extracted using GoldMag whole-blood genomic DNA purification kit (GoldMag Co. Ltd., Xi’an, China) according to the manufacturer’s recommendations. The candidate SNPs of IL-7R and IL-7 were selected based on the 1,000 Genomes Project database (https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/) and dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/) according to thresholds of minor allele frequency (MAF) > 0.05 in Chinese Han population. Ultimately, six SNPs (rs10213865, rs969129, rs118137916, rs10053847 and rs6451231 in IL-7R and rs117173992 in IL-7) were identified and genotyped using MassARRAY system (Agena, San Diego, CA, USA) as reported in previous publications by two independent researchers.\(^18\),\(^19\) The specific primers for each polymorphism are displayed in Table S1. Meanwhile, nearly 10% of samples were randomly selected to repeat genotyping, and the reproducibility was 100%. Additionally, the functional prediction analyses of these SNPs were carried out using the web-based HaploReg v4.1 software (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) and SNPinfo Web Server (https://snpinfo.niehs.nih.gov/).

Statistical analyses
We utilized the Pearson’s \(\chi^2\) test and Student’s \(t\) test to assess differences in demographic data (age, gender, BMI, smoking and drinking status) between cases and controls. Hardy–Weinberg equilibrium (HWE) analyses of each SNP were performed by comparing the observed and expected genotype frequencies among controls using the Fisher’s exact test. ORs and their 95% CIs were estimated by the logistic regression analysis with adjustment for age and gender. Multiple genetic models (dominant, recessive and additive model) were adopted to explore the relationships of IL-7R and IL-7 polymorphisms and LC risk using PLINK v1.07 software. Additionally, the stratified analyses in terms of several confounding factors such as age, gender, body mass index (BMI), smoking and drinking status, pathological type, lymph nodes metastasis and TNM stage were also
conducted. Finally, the pairwise LD and haplotype analysis were carried out using PLINK v1.07 software and Haploview v4.2 software. All statistical analyses were performed by SPSS v 18.0 software (Armonk, New York City, NY, USA), and two-sided $P<0.05$ indicated statistical significance. We used power and sample size (PS) calculation software (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize) to calculate the expected sample size and the power values.20

Results

Participant characteristics and SNP identification

As exhibited in Table 1, there were 507 LC patients (352 males and 155 females; median age: 60.79±9.96 years) and 503 healthy controls (354 males and 149 females; median age: 59.94±9.58 years) in the present work. No significantly statistical differences on age, gender and smoking status were observed between cases and control groups (age: $P=0.164$; gender: $P=0.742$; smoking status: $P=0.164$; Table 1). However, BMI and drinking status were dramatically different between the two groups ($P<0.001$). Five candidate SNPs in $IL-7R$ (rs10213865, rs969129, rs118137916, rs10053847 and rs6451231) and one SNP in $IL-7$ (rs117173992) were successfully genotyped as displayed in Table 2. The observed genotype frequency of all tested SNPs in control groups was strongly accorded with HWE ($P>0.05$). Notably, the frequency distribution of $IL-7R$ rs10053847-A allele was remarkably lower in LC patients than health controls ($OR =0.78, 95\% CI: 0.62–0.99, P=0.043, power =52.50\%$), suggesting that this SNP served as a protective factor for the susceptibility to LC.

LC risk evaluation

To further evaluate the correlations of SNPs in $IL-7R$ and $IL-7$ with LC risk, multiple inheritance models (genotype, dominant, recessive and additive models) were performed using logistic regression analyses with adjustment for age and gender (Table 3). The results also showed that carriers of $IL-7R$ rs10053847 mutant allele had a decreased LC risk under additive model ($OR =0.77, 95\% CI: 0.60–0.99, P=0.042$). No significant associations were detected between other SNPs and the susceptibility to LC ($P>0.05$).

Stratified analyses were carried out to estimate relationships between these polymorphisms and several demographic characteristics (Tables 4 and S2–S6). There were no significant associations between SNPs in $IL-7R$ and $IL-7$ and three demographic variables (age, gender and BMI; $P>0.05$; Tables S2–S4). Interestingly, for $IL-7R$ rs10053847 A → G, AA genotype was predominantly related to a reduced risk of LC among non-smokers (AA/AG: OR =0.09, 95% CI: 0.01–0.83, $P=0.033$, power =97.13%; AA/AG+GG: OR =0.10, 95% CI: 0.01–0.87, $P=0.037$, power =96.70%; Table 4). Similarly, we also found that $IL-7R$ rs10053847-A allele decreased the incidence of LC in nondrinkers under homozygote and recessive models (AA/AG: OR =0.17, 95% CI: 0.03–0.98, $P=0.047$, power =88.31%; AA/AG+GG: OR =0.18, 95% CI: 0.03–0.99, $P=0.049$, power =87.25%;

### Table 1 Characteristics of cases and cancer-free controls

| Variables                  | Cases (n=507) | Control (n=503) | $P$-value |
|----------------------------|---------------|-----------------|-----------|
| Age, years (mean ± SD)     |               |                 |           |
| >60 years                  | 60.79±9.96    | 59.94±9.58      | 0.164     |
| ≤60 years                  | 272 (53.6%)   | 274 (54.5%)     |           |
|                            | 235 (46.4%)   | 229 (45.5%)     |           |
| Gender                     |               |                 | 0.742     |
| Male                       | 352 (69.4%)   | 354 (70.4%)     |           |
| Female                     | 155 (30.6%)   | 149 (29.6%)     |           |
| BMI (kg/m$^2$)             |               |                 | <0.001*   |
| <24                        | 316 (62.3%)   | 138 (27.4%)     |           |
| ≥24                        | 177 (34.9%)   | 151 (30.0%)     |           |
| Unavailable                | 14 (2.8%)     | 214 (42.5%)     |           |
| Smoking                    |               |                 | 0.164     |
| Yes                        | 250 (49.3%)   | 158 (31.4%)     |           |
| No                         | 251 (49.5%)   | 129 (25.6%)     |           |
| Unavailable                | 6 (1.2%)      | 216 (42.9%)     |           |
| Drinking                   |               |                 | <0.001*   |
| Yes                        | 114 (22.5%)   | 110 (21.9%)     |           |
| No                         | 356 (70.2%)   | 120 (23.9%)     |           |
| Unavailable                | 37 (7.3%)     | 273 (54.3%)     |           |
| Pathological type          |               |                 |           |
| Squamous carcinoma         | 119 (23.5%)   |                 |           |
| Adenocarcinoma             | 188 (37.1%)   |                 |           |
| Unavailable                | 200 (39.4%)   |                 |           |
| Lymph node metastasis      |               |                 |           |
| Positive                   | 213 (42.0%)   |                 |           |
| Negative                   | 83 (16.4%)    |                 |           |
| Unavailable                | 211 (41.6%)   |                 |           |
| TNM stage                  |               |                 |           |
| III–IV                     | 260 (51.3%)   |                 |           |
| I–II                       | 84 (16.6%)    |                 |           |
| Unavailable                | 163 (32.1%)   |                 |           |

Notes: *$P<0.05$ was considered statistically significant.
Abbreviation: BMI, body mass index.
However, there was no statistical difference between other SNPs and smoking and drinking status ($P>0.05$, Tables S5 and S6).

Additionally, carriers of IL-7R rs10053847 mutant allele had a lower risk of lung adenocarcinoma in additive model (OR =0.67, 95% CI: 0.47–0.95, $P=0.025$; Table 5). Conversely, IL-7R rs10213865 polymorphism was observed with a dramatically elevated the incidence of lung adenocarcinoma (CA/AA: OR =1.60, 95% CI: 1.11–2.29, $P=0.011$, power =93.15%; CC+CA/AA: OR =1.62, 95% CI: 1.14–2.29, $P=0.007$, power =95.33%; CC/CA/AA: OR =1.50, 95% CI: 1.11–2.01, $P=0.007$; Table 5) according to the stratification analysis with pathology type (Table 5 and Table S7). However, no significant relationships between these two SNPs and other clinic-pathological features (lymph nodes metastasis and TNM stage) were found ($P>0.05$; Table S8). In addition, there was also no statistical difference between remaining SNPs (rs969129, rs118137916 and rs6451231 in IL-7R; rs117173992 in IL-7) and these clinical characteristics (pathology type, lymph node metastasis and TNM stage; $P>0.05$; Tables S7 and S8).

### Haplotype analysis of IL-7R polymorphisms

Linkage disequilibrium (LD) and corresponding haplotypes of IL-7R SNPs were further analyzed to estimate the association between this gene and the prevalence of LC. The results suggested that the high LD block was composed of four IL-7R polymorphisms (rs10213865, rs969129, rs118137916 and rs10053847) which formed five haplotypes (AGAA, ATGG, CGAG, AGAG and ATAG; Figure 1). Furthermore, logistic regression analysis based on haplotype was performed to investigate the impact of these haplotypes on the incidence of LC. We noted that there was a significant correlation between AGAA haplotype and an increased LC risk (OR =1.30, 95% CI: 1.01–1.66, $P=0.041$; Table 6).

### Discussion

In this present work, we first examined the relationships between IL-7/IL-7R polymorphisms and the risk of LC in a Chinese Han population. Our findings revealed that IL-7R rs10053847 and rs10213865 variants were predominately correlated with LC susceptibility, while no significant association of IL-7 polymorphism and LC risk was observed. To our best knowledge, this is the first study to provide evidence of the potential role of the IL-7R variants in LC risk. Combined with the previous
Table 3: Relationships of polymorphisms in IL-7R and IL-7 genes and lung cancer susceptibility

| Gene symbol | SNPs     | Model   | Genotype | Cases (%) | Controls (%) | OR (95% CI)* | P-value* |
|-------------|----------|---------|----------|-----------|--------------|--------------|----------|
| IL-7R       | rs10213865 | Genotypes | CC       | 19 (3.7%) | 16 (3.2%)    | 1.28 (0.65–2.54) | 0.479    |
|             |          |         | CA       | 164 (32.3%) | 147 (29.2%)  | 1.16 (0.89–1.52) | 0.280    |
|             |          |         | AA       | 324 (63.9%) | 340 (67.6%)  | 1.00          |          |
|             |          | Dominant | CC+CA    | 183 (36.1%) | 163 (32.1%)  | 1.17 (0.90–1.52) | 0.232    |
|             |          |         | AA       | 324 (63.9%) | 340 (67.6%)  | 1.00          |          |
|             |          | Recessive| CC       | 19 (3.7%) | 16 (3.2%)    | 1.22 (0.62–2.41) | 0.562    |
|             |          |         | CA+AA    | 488 (96.3%) | 487 (96.8%)  | 1.00          |          |
|             |          | Additive | CC+CA+AA | -         | -            | 0.15 (0.92–1.44) | 0.223    |
| IL-7R       | rs969129  | Genotypes | GG       | 101 (19.9%) | 102 (20.3%)  | 1.07 (0.74–1.53) | 0.730    |
|             |          |         | GT       | 271 (53.5%) | 257 (51.1%)  | 1.12 (0.83–1.49) | 0.458    |
|             |          |         | TT       | 135 (26.6%) | 144 (28.6%)  | 1.00          |          |
|             |          | Dominant | GG+GT    | 372 (73.4%) | 359 (71.4%)  | 1.10 (0.84–1.45) | 0.490    |
|             |          |         | TT       | 135 (26.6%) | 144 (28.6%)  | 1.00          |          |
|             |          | Recessive| GG       | 101 (19.9%) | 102 (20.3%)  | 0.99 (0.73–1.35) | 0.959    |
|             |          |         | GT+TT    | 406 (80.1%) | 404 (79.7%)  | 1.00          |          |
|             |          | Additive | GG+GT+TT | -         | -            | 1.04 (0.87–1.24) | 0.675    |
| IL-7R       | rs118137916 | Genotypes | GG       | 0         | 3 (0.6%)     | /            | /        |
|             |          |         | GA       | 86 (17.0%) | 80 (15.9%)   | 1.08 (0.77–1.50) | 0.662    |
|             |          |         | AA       | 421 (83.0%) | 420 (84.1%)  | 1.00          |          |
|             |          | Dominant | GG+GA    | 86 (17.0%) | 83 (16.5%)   | 1.04 (0.75–1.45) | 0.821    |
|             |          |         | AA       | 421 (83.0%) | 420 (84.1%)  | 1.00          |          |
|             |          | Recessive| GG       | 0         | 3 (0.6%)     | /            | /        |
|             |          |         | GA+AA    | 507 (100%) | 500 (99.4%)  | 1.00          |          |
|             |          | Additive | GG+GA+AA | -         | -            | 1.00 (0.72–1.38) | 0.979    |
| IL-7R       | rs10053847 | Genotypes | AA       | 6 (0.08%) | 12 (2.4%)    | 0.47 (0.17–1.26) | 0.131    |
|             |          |         | AG       | 133 (26.2%) | 153 (30.1%)  | 0.80 (0.61–1.06) | 0.116    |
|             |          |         | GG       | 368 (72.6%) | 338 (67.5%)  | 1.00          |          |
|             |          | Dominant | AA+AG    | 139 (27.4%) | 165 (32.8%)  | 0.78 (0.59–1.02) | 0.068    |
|             |          |         | GG       | 368 (72.6%) | 338 (67.5%)  | 1.00          |          |
|             |          | Recessive| AA       | 6 (0.08%) | 12 (2.4%)    | 0.50 (0.18–1.34) | 0.166    |
|             |          |         | AG+GG    | 501 (98.8%) | 491 (97.6%)  | 1.00          |          |
|             |          | Additive | AA+AG+GG | -         | -            | 0.77 (0.60–0.99) | 0.042*   |
| IL-7R       | rs6451231  | Genotypes | CC       | 71 (14.0%) | 71 (14.1%)   | 1.01 (0.73–1.59) | 0.721    |
|             |          |         | CT       | 258 (50.9%) | 250 (49.2%)  | 1.10 (0.83–1.44) | 0.508    |
|             |          |         | TT       | 168 (33.1%) | 178 (35.1%)  | 1.00          |          |
|             |          | Dominant | CC+CT    | 329 (64.9%) | 321 (63.8%)  | 1.09 (0.84–1.42) | 0.510    |
|             |          |         | TT       | 168 (33.1%) | 178 (35.1%)  | 1.00          |          |
|             |          | Recessive| CC       | 71 (14.0%) | 71 (14.1%)   | 1.02 (0.71–1.45) | 0.929    |
|             |          |         | CT+TT    | 426 (84.0%) | 428 (85.1%)  | 1.00          |          |
|             |          | Additive | CC+CT+TT | -         | -            | 1.05 (0.87–1.27) | 0.606    |
| IL-7        | rs117173992 | Genotypes | GG       | 2 (0.04%) | 4 (0.08%)    | 0.53 (0.10–2.90) | 0.462    |
|             |          |         | GA       | 82 (16.2%) | 71 (35.1%)   | 1.16 (0.82–1.65) | 0.389    |
|             |          |         | AA       | 422 (83.2%) | 428 (84.0%)  | 1.00          |          |
|             |          | Dominant | GG+GA    | 84 (16.6%) | 75 (14.9%)   | 0.13 (0.80–1.59) | 0.479    |
|             |          |         | AA       | 422 (83.2%) | 428 (84.0%)  | 1.00          |          |
|             |          | Recessive| GG       | 2 (0.04%) | 4 (0.08%)    | 0.52 (0.09–2.84) | 0.446    |
|             |          |         | GA+AA    | 504 (99.4%) | 499 (99.2%)  | 1.00          |          |

Notes: Bold values are statistically significant. *P-values, OR and 95% CI were computed by logistic regression analysis with adjustments for age and gender. aIndicates statistical significance (P<0.05). bIndicates the P-values were unavailable due to the absence of frequency of allele or genotype.

Abbreviation: SNPs, single-nucleotide polymorphisms.
studies, this association may be a promising starting point on the association of IL-7R polymorphism with LC formation and progression and provide data for the construction of a genetic panel for the prediction of LC risk in China.

IL-7R, located on chromosome 5p13, plays crucial roles in human diseases including malignancies. IL-7R has been demonstrated to be implicated with the molecular mechanisms of LC. Ming et al found that IL-7/IL-7R might promote lymphangiogenesis in LC by increasing the expression levels of specific vascular endothelial growth factor and stimulating the c-Fos/c-Jun pathway. Another research suggested that IL-7/IL-7R could elevate cyclin D1 expression through activating the AP1 signaling pathway to accelerate LC cell proliferation. More interestingly, numerous studies highlighted that IL-7R polymorphisms were involved in the initiation and development of several diseases in the recent years. However, the potential influence of IL-7R variants on the prevalence of LC has not been uncovered.

Herein, we conducted an association analysis between IL-7/IL-7R polymorphisms and LC risk in a Chinese Han population and found that IL-7R rs10053847 dramatically decreased the risk of LC under the additive model. rs10053847-A allele was predominately correlated with a lower incidence of LC among nonsmokers or nondrinkers, which further provided evidence that there was correlative effect between IL-7R polymorphisms and tobacco smoke exposure on the risk of LC.

In addition, this SNP also significantly reduced the risk of lung adenocarcinoma in additive model. Therefore, we speculated that an allele of IL-7R rs10053847 acted as protective factors against LC occurrence. However, our stratified analysis revealed that another SNP in IL-7R (rs10213865) increased the susceptibility to lung adenocarcinoma under the heterozygous mutation, dominant and additive models. Moreover, there no significant difference was observed in other clinical features. Thus, it was inferred that IL-7R rs10213865 variant might only confer the risk

Table 4 The associations between IL-7R rs10053847 and the risk of lung cancer stratified by smoking and drinking status

| Model          | Smoking                  | No smoking               | Smoking                  | No smoking               |
|----------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                | Cases | Controls | OR (95% CI)\(^a\) | P-value\(^a\) | Cases | Controls | OR (95% CI)\(^a\) | P-value\(^a\) | Cases | Controls | OR (95% CI)\(^a\) | P-value\(^a\) |
| Genotypes      |       |          |                    |                       |       |          |                    |                       |       |          |                    |                       |
|                | 5     | 2        | 1.46 (0.27–7.69)    | 0.656                  | 1     | 5        | 0.09 (0.01–0.83)   | 0.033\(*\)          | 1     | 5        | 0.09 (0.01–0.83)   | 0.033\(*\)          |
|                | 65    | 42       | 0.95 (0.60–1.50)    | 0.811                  | 66    | 36       | 0.85 (0.52–1.38)   | 0.507                  |
|                | 180   | 114      | 1.00               |                        | 184   | 88       | 1.00               |                        |
| Dominant       | 70    | 44       | 0.97 (0.62–1.52)    | 0.892                  | 67    | 41       | 0.76 (0.47–1.22)   | 0.251                  |
|                | 180   | 114      | 1.00               |                        | 184   | 88       | 1.00               |                        |
| Recessive      | 5     | 2        | 1.73 (0.95–3.17)    | 0.075                  | 1     | 5        | 0.10 (0.01–0.87)   | 0.037\(*\)          | 1     | 5        | 0.10 (0.01–0.87)   | 0.037\(*\)          |
|                | 245   | 156      | 1.00               |                        | 250   | 124      | 1.00               |                        |
| Additive       | -     | -        | 1.00 (0.66–1.51)    | 1.000                  | -     | -        | 1.01 (0.73–1.41)   | 0.950                  |

Notes: Bold values are statistically significant. \(^a\)P-values, OR and 95% CI were computed by logistic regression analysis with adjustments for age and gender. \(^*\)Indicates statistical significance (\(P<0.05\)).

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Table 4 The associations between IL-7R rs10053847 and the risk of lung cancer stratified by smoking and drinking status

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| Model          | Smoking                  | No smoking               | Smoking                  | No smoking               |
|----------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                | Cases | Controls | OR (95% CI)\(^a\) | P-value\(^a\) | Cases | Controls | OR (95% CI)\(^a\) | P-value\(^a\) | Cases | Controls | OR (95% CI)\(^a\) | P-value\(^a\) |
| Genotypes      |       |          |                    |                       |       |          |                    |                       |       |          |                    |                       |
|                | 4     | 1        | 2.88 (0.29–28.67)   | 0.366                  | 2     | 4        | 0.17 (0.03–0.98)   | 0.047\(*\)          | 2     | 4        | 0.17 (0.03–0.98)   | 0.047\(*\)          |
|                | 28    | 34       | 0.65 (0.35–1.21)    | 1.000                  | 94    | 33       | 0.93 (0.58–1.48)   | 0.745                  |
|                | 82    | 75       | 1.00               |                        | 260   | 83       | 1.00               |                        |
| Dominant       | 32    | 35       | 0.71 (0.39–1.31)    | 0.278                  | 96    | 37       | 0.85 (0.54–1.34)   | 0.477                  |
|                | 82    | 75       | 1.00               |                        | 260   | 83       | 1.00               |                        |
| Recessive      | 4     | 1        | 3.27 (0.33–32.09)   | 0.310                  | 2     | 4        | 0.18 (0.03–0.99)   | 0.049\(*\)          | 2     | 4        | 0.18 (0.03–0.99)   | 0.049\(*\)          |
|                | 110   | 109      | 1.00               |                        | 354   | 116      | 1.00               |                        |
| Additive       | -     | -        | 0.83 (0.49–1.43)    | 0.510                  | -     | -        | 0.78 (0.51–1.18)   | 0.238                  |

Notes: Bold values are statistically significant. \(^a\)P-values, OR and 95% CI were computed by logistic regression analysis with adjustments for age and gender. \(^*\)Indicates statistical significance (\(P<0.05\)).
for developing lung adenocarcinoma. More notably, the haplotype analysis implied that AGAA haplotype (rs10213865, rs969129, rs118137916 and rs10053847) was associated with a decreased LC risk, which further supported the conclusion that these two polymorphisms (rs10213865 and rs10053847) in IL-7R played vital roles in LC risk assessment. Although IL-7 was also found to participate in the pathogenesis of LC,30–32 there was no correlation between IL-7 rs117173992 and the risk of LC. Additional analyses of the relationship between this SNP and the incidence of LC are still required to verify in the future.

Certainly, there are still limitations in the current study. First, the study was performed using the hospital-based samples; therefore, the sample bias might be confounding factors for our findings. Second, the exhaustive functional analysis of these SNPs should be investigated to explain our results. Finally, the prognostic analysis of selected IL-7/IL-7R polymorphisms is needed to carry out in order to evaluate the survival outcomes of LC patients with these SNPs.

Conclusion
In conclusion, our results implied that IL-7R rs10053847 polymorphism was closely related to a decreased risk of LC, whereas carriers of IL-7R rs10213865-C allele showed an elevated adenocarcinoma risk, which would provide new evidence for prevention and diagnosis of LC. However, relevant functional study still needs to be undertaken in future.

Table 5 Relationships of IL-7R rs10053847 and rs10213865 and pathology type risk of lung cancer

| SNP       | Squamous carcinoma | Adenocarcinoma |
|-----------|--------------------|----------------|
|           | Cases (n=119)      | Controls (n=503) | OR (95% CI) | P-value | Cases (n=188) | Controls (n=503) | OR (95% CI) | P-value |
|           | Homozygote         |               | 2 (2%) | 12 (2%) | 0.75 (0.16–3.56) | 0.722 | 1 (0.5%) | 12 (2%) | 0.19 (0.02–1.48) | 0.113 |
|           | Heterozygote       |               | 35 (29%) | 153 (30%) | 0.95 (0.61–1.50) | 0.722 | 46 (24%) | 153 (30%) | 0.72 (0.49–1.06) | 0.096 |
|           | Dominant           |               | 37 (31%) | 165 (33%) | 0.94 (0.60–1.46) | 0.784 | 47 (25%) | 165 (33%) | 0.68 (0.46–1.00) | 0.048* |
|           | Recessive          |               | 2 (2%) | 12 (2%) | 0.77 (0.16–3.60) | 0.735 | 1 (2%) | 12 (2%) | 0.21 (0.03–1.62) | 0.134 |
|           | Additive           |               | - | - | 0.93 (0.62–1.39) | 0.732 | - | - | 0.67 (0.47–0.95) | 0.025* |

Note: Bold values are statistically significant. *P-values, odd ratios and their 95% CI were estimated by unconditional logistic regression models with the adjustment for age and gender. *Indicates statistical significance (P<0.05).
Table 6 Associations of haplotype of IL-7R and the risk of lung cancer

| Haplotype | Frequency | $\chi^2$ | P-value | Adjusted by age OR (95% CI) | P-value |
|-----------|-----------|---------|---------|----------------------------|---------|
| AGAA      | 0.86/0.83 | 4.11    | 0.043*  | 1.30 (1.01–1.66)            | 0.041*  |
| ATGG      | 0.08/0.09 | 0.00    | 0.957   | 1.00 (0.72–1.38)            | 0.979   |
| CGAG      | 0.80/0.82 | 1.50    | 0.221   | 0.87 (0.69–1.09)            | 0.223   |
| AGAG      | 0.87/0.89 | 0.96    | 0.162   | 0.82 (0.62–1.08)            | 0.152   |
| ATAG      | 0.45/0.46 | 0.12    | 0.733   | 0.96 (0.81–1.15)            | 0.687   |

Notes: Haplotypes were identified with the order of rs10213865, rs969129, rs118137916 and rs10053847. Bold values are statistically significant. *P-values, OR and 95% CI were computed by logistic regression analysis with adjustments for age and gender. *Indicates statistical significance (P<0.05).

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Disclosure
The authors report that they have no conflicts of interest in regard to this work.

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