Cancer Management and Research

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ORIGINAL RESEARCH

Genetic polymorphisms in *IL-7* and *IL-7R* are correlated with lung cancer risk in the Chinese Han population

This article was published in the following Dove Press journal:
Cancer Management and Research

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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.[1] It is estimated that approximately 2.09 million cases were diagnosed worldwide in 2018.[2] Moreover, the mortality rate is relatively higher in China than most other countries and predicted to continuously increase before 2030.[3] Currently, although numerous investigators have emphasized that genetic and environmental factors participate in the progression of LC,[4,5] 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.[6,7]

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DovePress
http://doi.org/10.2147/CMAR.S202839

IL-7, a pleiotropic cytokine primarily secreted by stromal cells, is involved in the 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 purifcation 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 χ^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.

Table 1 Characteristics of cases and cancer-free controls

Variables	Cases (n=507)	Control (n=503)	*P*-value
Age, years (mean ± SD)	60.79±9.96	59.94±9.58	0.164
>60 years	272 (53.6%)	274 (54.5%)	
≤60 years	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.

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/GG: 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/GG: 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 2 Basic characteristics about candidate SNPs and associations with the risk of lung cancer in allele mode

Gene	SNPs	Chr: Position	Allele[a]	MAF		HWE[b]	OR (95% CI)	*P*-value[c]	Haploreg
				Case	Control				
IL-7R	rs10213865	5:35857748	C/A	0.199	0.178	1.000	1.15 (0.92–1.43)	0.222	DNAse, proteins bound, motifs changed, GRASP QTL hits, selected eQTL hits
IL-7R	rs969129	5: 35861166	G/T	0.466	0.458	0.590	1.03 (0.87–1.23)	0.711	Promoter histone marks, enhancer histone marks, DNAse, motifs changed, selected eQTL hits
IL-7R	rs118137916	5: 35863436	G/A	0.848	0.915	1.000	0.99 (0.73–1.36)	0.957	Promoter histone marks, enhancer histone marks, DNAse, proteins bound, motifs changed
IL-7R	rs10053847	5: 35878038	A/G	0.143	0.176	0.355	**0.78 (0.62–0.99)**	**0.043***	Motifs changed, GRASP QTL hits, selected eQTL hits
IL-7R	rs6451231	5:35878825	C/T	0.402	0.598	0.302	1.04 (0.87–1.25)	0.661	Enhancer histone marks, DNAse, motifs changed, selected eQTL hits
IL-7	rs117173992	8: 78779168	G/A	0.085	0.915	0.534	0.09 (0.79–1.50)	0.597	Motifs changed

Notes: Bold values are statistically significant. [a]Allele: The minor allele/the major allele. [b]*P*-values for the Hardy–Weinberger equilibrium (HWE) test. [c]*P*-values were calculated with Pearson's χ^2 tests. *P<0.05 and has statistical significance.
rs10213865: SNPinfo Web server; TFBS.
Abbreviations: SNP, single-nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium; eQTL, expression quantitative trait loci; GRASP, Genome-Wide Repository of Associations Between SNPs and Phenotypes; TFBS, transcription factor binding sites.

Table 4). 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 ofthe 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)[a]	*P*-value[a]
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%)	102 (20.3%)	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 (57.1%)	1.00	
		Dominant	GG+GA	86 (17.0%)	83 (16.5%)	1.04 (0.75–1.45)	0.821
			AA	421 (83.0%)	420 (57.1%)	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 (67.2%)	1.00	
		Dominant	AA+AG	139 (27.4%)	165 (32.8%)	0.78 (0.59–1.02)	0.068
			GG	368 (72.6%)	338 (67.2%)	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 (85.1%)	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%)		
		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	
		Additive	GG+GA+AA	-	-	1.09 (0.79–1.50)	0.607

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 ($P<0.05$). "/"represents the *P*-values were unavailable due to the absence of frequency of allele or genotype.
Abbreviation: SNPs, single-nucleotide polymorphisms.

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

Model	Smoking				No smoking			
	Cases	Controls	OR (95% CI)[a]	*P*-value[a]	Cases	Controls	OR (95% CI)[a]	*P*-value[a]
Genotypes	5 65 180	2 42 114	1.46 (0.27–7.69) 0.95 (0.60–1.50) 1.00	0.656 0.811	1 66 184	5 36 88	**0.09 (0.01–0.83)** 0.85 (0.52–1.38) 1.00	**0.033*** 0.507
Dominant	70 180	44 114	0.97 (0.62–1.52) 1.00	0.892	67 184	41 88	0.76 (0.47–1.22) 1.00	0.251
Recessive	5 245	2 156	1.73 (0.95–3.17) 1.00	0.075	1 250	5 124	**0.10 (0.01–0.87)** 1.00	**0.037***
Additive	-	-	1.00 (0.66–1.51)	1.000	-	-	1.01 (0.73–1.41)	0.950
Model	**Drinking**				**No drinking**			
	Cases	**Control**	**OR (95% CI)[a]**	***P*-value[a]**	**Cases**	**Controls**	**OR (95% CI)[a]**	***P*-value[a]**
Genotypes	4 28 82	1 34 75	2.88 (0.29–28.67) 0.65 (0.35–1.21) 1.00	0.366	2 94 260	4 33 83	**0.17 (0.03–0.98)** 0.93 (0.58–1.48) 1.00	**0.047*** 0.745
Dominant	32 82	35 75	0.71 (0.39–1.31) 1.00	0.278	96 260	37 83	0.85 (0.54 1.34) 1.00	0.477
Recessive	4 110	1 109	3.27 (0.33–32.09) 1.00	0.310	2 354	4 116	**0.18 (0.03–0.99)** 1.00	**0.049***
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 ($P<0.05$).

studies,[21] 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.[22,23] 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.[24] Another research suggested that *IL-7*/*IL-7R* could elevate cyclin D1 expression through activating the AP1 signaling pathway to accelerate LC cell proliferation.[25] More interestingly, numerous studies highlighted that *IL-7R* polymorphisms were involved in the initiation and development of several diseases in the recent years.[26–28] 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.[29] 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 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)[a]	*P*-value[a]	Cases (n=188)	Controls (n=503)	OR (95% CI)[a]	*P*-value[a]
***IL-7R* rs10053847**								
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***
***IL-7R* rs10213865**								
Homozygote	1 (0.8%)	16 (3%)	0.32 (0.04–2.54)	0.284	9 (5%)	16 (3%)	1.85 (0.79–4.36)	0.159
Heterozygote	40 (34%)	147 (29%)	1.16 (0.75–1.81)	0.500	73 (39%)	147 (26%)	**1.60 (1.11–2.29)**	**0.011***
Dominant	41 (34%)	163 (32%)	1.09 (0.71–1.68)	0.695	82 (44%)	163 (29%)	**1.62 (1.14–2.29)**	**0.007***
Recessive	1 (0.8%)	16 (3%)	0.31 (0.04–2.42)	0.263	9 (5%)	16 (3%)	1.58 (0.68–3.67)	0.293
Additive	-	-	1.00 (0.68–1.48)	0.991	-	-	**1.50 (1.11–2.01)**	**0.007***

Notes: Bold values are statistically significant. [a]*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 ($P<0.05$).

Figure 1 The haplotype block map for single-nucleotide polymorphisms in the *IL-7R*.

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 6 Associations of haplotype of *IL-7R* and the risk of lung cancer

Haplotype	Frequency	χ^2	*P*-value	Adjusted by age	
	case/control			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. [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).

Acknowledgments

We are grateful to the individuals who participated in this study. We also thank the clinicians and hospital staff who contributed to the sample and data collection for this study. We would also like to thank all those who contributed to this manuscript. This work was supported by the General Program of Applied Basic Research Projects-Joint Special Foundation from the Yunnan Provincial Science and Technology Department and the Kunming Medical University (2017FE468(−125)).

Disclosure

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

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