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Association between *ADRB2*, *IL33*, and *IL2RB* gene polymorphisms and lung cancer risk in a Chinese Han population

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ABSTRACT

Purpose: This study aimed to explore the associations between polymorphisms of a very important pharmacogene, *ADRB2*, two inflammation-related genes, *IL33* and *IL2RB*, and the risk of lung cancer.

Methods: Six polymorphisms of *ADRB2*, *IL33*, and *IL2RB* were genotyped in 300 lung cancer patients and 300 healthy controls using MassARRAY. The relationship between genotypes and lung cancer risk was evaluated using chi-square tests.

Results: The minor allele of rs1042711 was a risk allele for lung cancer, whereas the minor alleles of rs7025417 and rs5756523 had protective effects against lung cancer ($p < 0.05$). The CT genotype of rs1042711 and the GT genotype of rs1560642 were associated with increased risk of lung cancer, whereas the CC and AA genotypes of rs7025417 and the CT and CC genotypes of rs5756523 were associated with decreased disease risk ($p < 0.05$). Genetic model analysis shows that rs1042711 and rs1560642 were associated with increased risk of lung cancer; whereas rs7025417, rs5756523, and rs2284033 were associated with decreased disease risk ($p < 0.05$). Stratification analysis showed that rs1042711 and rs1560642 were associated with increased risk of lung cancer in nonsmokers and smokers, respectively, whereas rs7025417 and rs5756523 were associated with decreased disease risk in both subgroups ($p < 0.05$).

Conclusion: Our results shed new light on the association between polymorphisms of *ADRB2*, *IL33*, and *IL2RB* and the risk of lung cancer.

1. Introduction

According to the 2018 Global Cancer Statistics, lung cancer is one of the most malignant cancers, with considerably high morbidity and mortality and accounting for 11.6% of total cancer patients and 18.4% of cancer-related deaths [1]. In China, lung cancer accounted for 18.1% of total diagnosed cancer cases, and 24.1% of total cancer deaths [2]. Even though cigarette smoking contributed to more than 85% of lung cancer, a recent study demonstrated that genetic susceptibility also plays an important role in the pathogenesis of lung cancer [3]. Genome-wide association studies (GWAS) have identified several regions associated with lung cancer risk in various populations; examples of such regions include *TERT* and *CLPTM1L* at 5p15, *CHRNA3* and *CHRNA5* at 15q25, and *MIPEP-TNFRSF19* at 13q12.12 [4–6]. However, it is necessary to search for additional single nucleotide polymorphisms (SNPs) that can better aid in the early screening of lung cancer.

Inflammation, airflow obstruction, and their interaction may be involved in the pathogenesis of lung cancer [7]. Deregulated inflammation can give rise to the epithelial-to-mesenchymal transition of bronchial epithelial cells and to lung carcinogenesis [8]. In addition, chronic inflammation in airways can activate tumor alveolar macrophages, promoting pulmonary carcinogenesis [9]. Chronic obstructive pulmonary disease (COPD) is characterized by excessive inflammation and airflow obstruction, and is an independent risk factor for lung cancer [10].

ADRB2, a very important pharmacogene (VIP gene), encodes the β2-adrenergic receptor [11]. *ADRB2* is highly expressed in bronchial smooth muscle cells, and activation of the beta2-adrenergic receptor may give rise to bronchodilation [12]. *ADRB2* polymorphisms have been associated with risk of COPD [13,14]. However, to date, there is little evidence showing associations between *ADRB2* polymorphisms and risk of lung cancer. Considering its pharmacogene function and

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Table 1
Baseline information of the participants.

Variables	Case (N = 300)	Control (N = 300)	χ^2/t	*p*
Gender (%)			0.167	0.683[a]
Male	155 (51.7)	150 (50.0)		
Female	145 (48.3)	150 (50.0)		
Age (mean ± SD), years	57.86 ± 10.24	58.38 ± 10.65	0.946	0.157[b]
BMI (mean ± SD), kg/m^2	24.32 ± 3.64	24.15 ± 3.79	0.784	0.188[b]
Smoking (%)			0.167	0.683 [a]
Yes	148 (49.3)	143 (47.7)		
No	152 (50.7)	157 (52.3)		

[a] *p* value was calculated using Pearson's chi-square tests.
[b] *p* value was calculated using student *t* tests.

close association with COPD, we speculated that *ADRB2* polymorphisms might be associated with lung cancer risk.

Interleukin (IL), produced by leukocytes, participate in inflammatory responses by mediating the activation, proliferation, and differentiation of T and B cells [15]. Previous studies have shown that abnormal expression and genetic variants of *IL33* are involved in the pathogenesis of asthma and COPD [16,17]. However, association between *IL33* polymorphisms and risk of lung cancer remains to be verified. In addition, *IL2RB* encodes IL-2Rβ, a subunit of IL-2R, which has an important role in signal transduction in the immune response process [18]. Polymorphisms of *IL2RB* have been associated with asthma risk [19]. To better reveal the important role of IL-33 and IL2R in lung cancer, we selected *IL33* and *IL2RB* as candidate genes to conduct this association study.

In this study, we selected six tag SNPs in *ADRB2* (rs1042711 and rs1560642), *IL33* (rs7025417 and rs1317230), and *IL2RB* (rs5756523 and rs2284033) to investigate their association with lung cancer risk. The results have the potential to be useful in the early screening of lung cancer.

2. Materials and methods

2.1. Subjects

In this study, 300 lung cancer patients and 300 healthy controls were recruited at Xi'an Hospital of Traditional Chinese Medicine. The diagnosis of lung cancer was established by histopathological examination of biopsy or resected tissue specimens. The patients who had received chemo or radiotherapy were excluded. The healthy controls were enrolled from cancer-free individuals at the same hospital, and were gender and age matched with the cancer cases. We obtained written informed consent from all subjects. The study design was approved by the Ethics Committee of Xi'an Hospital of Traditional Chinese Medicine.

2.2. Genotyping

Six tag SNPs in *ADRB2, IL33*, and *IL2RB* were selected. These SNPs had minor allele frequencies (MAFs) > 5% in the East Asian populations of 1000 Genomes. DNA was extracted from blood samples using the QIAamp DNA Blood Midi Kit (QIAGEN, Germany). Primers were designed using the Sequenom MassARRAY Assay Design 3.0 software [20–22]. SNP genotyping was performed using Sequenom MassARRAY RS1000 (Sequenom, San Diego, CA).

2.3. Statistical analyses

Statistical analyses were performed using SPSS 21.0 statistical package (SPSS, Chicago, IL, USA). Allele frequencies in the controls were tested for departure from Hardy-Weinberg Equilibrium (HWE). Differences in the demographic variables and allele frequencies between cases and controls were evaluated using chi-square tests and Welch's t tests. Associations between the genotypes and lung cancer risk were evaluated using unconditional logistic regression analysis and are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was established when $p < 0.05$.

3. Results

Baseline information of the participants is described in Table 1. The mean age of the patients was 57.86 ± 10.24 years and that of the controls was 58.38 ± 10.65 years. There was no significant difference in the distribution of gender, age, or BMI between the cases and controls ($p > 0.05$), indicating that the two groups were comparable.

The allele frequencies of candidate SNPs in cases and controls and the associations with lung cancer risk are listed in Table 2. All SNPs were at HWE ($p > 0.05$). The MAF of rs1042711 was higher in lung cancer cases than in healthy controls (0.17 versus 0.12), which indicates that the rs104271-C allele was a risk allele for lung cancer (OR = 1.45, 95%CI = 1.05–2.02, $p = 0.025$). In contrast, the MAFs of rs7025417 and rs5756523 were lower in cases than in controls, which indicates that the minor alleles of rs7025417 and rs5756523 had protective effects against the risk of lung cancer ($OR_{rs7025417} = 0.71$, 95%CI = 0.56–0.91, $p = 0.005$; $OR_{rs5756523} = 0.64$, 95%CI = 0.51–0.81, $p = 0.001$).

The genotype frequencies of candidate SNPs are shown in Table 3. The CT genotype frequency of rs1042711 was higher in cases than in controls and associated with 1.67-fold increased risk of lung cancer (95%CI = 1.13–2.45, $p = 0.032$). The GT genotype of rs1560642 was associated with 1.81-fold increased risk of lung cancer (95%CI = 1.19–2.74, $p = 0.006$). In contrast, the CC and AA genotypes of rs7025417, and the CT and CC genotypes of rs5756523, were all associated with decreased risk of lung cancer ($p < 0.05$).

Associations between candidate SNPs and lung cancer risk were also evaluated in three genetic models (Table 4). A total of five SNPs were identified as having association with lung cancer risk under different

Table 2
Allele frequencies in cases and controls and association with risk of lung cancer.

SNP ID	Gene	Chromosome	Position	Minor/major Alleles	MAF		*p*-HWE	OR (95% CI)	p^a
					Case	Control			
rs1042711	ADRB2	5	148,826,785	C/T	0.17	0.12	0.59	1.45 (1.05–2.02)	0.025*
rs1560642	ADRB2	5	148,888,172	T/G	0.50	0.48	0.36	1.08 (0.84–1.36)	0.489
rs7025417	IL33	9	6,240,084	C/T	0.32	0.40	0.90	0.71 (0.56–0.91)	0.005*
rs1317230	IL33	9	6,251,012	C/A	0.45	0.44	0.64	1.03 (0.82–1.30)	0.896
rs5756523	IL2RB	22	37,117,508	C/T	0.34	0.44	0.48	0.64 (0.51–0.81)	0.001*
rs2284033	IL2RB	22	37,137,994	G/A	0.33	0.37	0.90	0.87 (0.68–1.10)	0.235

SNP: single nucleotide polymorphism, MAF, minor allele frequency; OR: odds ratio, CI: confidence interval, HWE: Hardy–Weinberg equilibrium.
p values were calculated using two-sided Chi-squared tests and adjusted by gender and age.
* $p < 0.05$ indicates statistical significance.

Table 3
Genotype frequencies of the SNPs and association with risk of lung cancer.

SNP ID	Genotype	Genotype frequencies		Without adjustment		With adjustment	
		Control (%)	Case (%)	OR (95%CI)	*p*	OR (95%CI)	*p*
	T/T	233 (77.7%)	204 (68.9%)	1		1	
rs1042711	C/T	62 (20.7%)	86 (29.1%)	1.58 (1.09–2.31)	0.052	1.67 (1.13–2.45)	0.032*
	C/C	5 (1.7%)	6 (2%)	1.37 (0.41–4.56)		1.19 (0.35–4.09)	
	G/G	78 (26%)	52 (17.4%)	1		1	
rs1560642	G/T	158 (52.7%)	196 (65.8%)	1.86 (1.24–2.80)	0.004	1.81 (1.19–2.74)	0.006*
	T/T	64 (21.3%)	50 (16.8%)	1.17 (0.70–1.95)		1.12 (0.66–1.88)	
	T/T	107 (35.7%)	144 (48.6%)	1		1	
rs7025417	T/C	146 (48.7%)	113 (38.2%)	0.58 (0.41–0.82)	0.006	0.56 (0.39–0.80)	0.005*
	C/C	47 (15.7%)	39 (13.2%)	0.62 (0.38–1.01)		0.66 (0.40–1.09)	
	A/A	91 (30.3%)	95 (32%)	1		1	
rs1317230	C/A	153 (51%)	137 (46.1%)	0.86 (0.59–1.24)	0.440	0.87 (0.60–1.27)	0.370
	C/C	56 (18.7%)	65 (21.9%)	1.11 (0.70–1.76)		1.19 (0.75–1.90)	
	T/T	89 (29.7%)	136 (45.3%)	1		1	
rs5756523	C/T	155 (51.7%)	125 (41.7%)	0.53 (0.37–0.75)	< 0.001	0.52 (0.36–0.75)	< 0.001*
	C/C	56 (18.7%)	39 (13%)	0.46 (0.28–0.74)		0.46 (0.28–0.75)	
	A/A	121 (40.3%)	123 (41.3%)	1		1	
rs2284033	A/G	138 (46%)	151 (50.7%)	1.08 (0.77–1.51)	0.078	1.06 (0.75–1.50)	0.093
	G/G	41 (13.7%)	24 (8.1%)	0.58 (0.33–1.01)		0.57 (0.32–1.02)	

SNP: Single nucleotide polymorphism; OR: odds ratio; 95%CI: 95% confidence interval.
p values were calculated using unconditional logistic regression analysis with adjustments for age and gender.
* $p < 0.05$ indicates statistical significance.

Table 4
Association between SNPs and risk of lung cancer in three genetic models (adjusted by gender and age).

SNP	Model	Genotype	Genotype frequencies		Without adjustment		With adjustment	
			Control	Case	OR (95% CI)	*p*	OR (95% CI)	*p*
rs1042711	Dominant	T/T	233 (77.7%)	204 (68.9%)	1	0.016	1	0.010*
		C/T-C/C	67 (22.3%)	92 (31.1%)	1.57 (1.09–2.26)		1.63 (1.12–2.37)	
	Recessive	T/T-C/T	295 (98.3%)	290 (98%)	1	0.740	1	0.930
		C/C	5 (1.7%)	6 (2%)	1.22 (0.37–4.04)		1.05 (0.31–3.59)	
	Log-additive	—	—	—	1.47 (1.05–2.04)	0.023	1.50 (1.06–2.11)	0.019*
rs1560642	Dominant	G/G	78 (26%)	52 (17.4%)	1	0.011	1	0.020*
		G/T-T/T	222 (74%)	246 (82.5%)	1.66 (1.12–2.47)		1.61 (1.08–2.40)	
	Recessive	G/G-G/T	236 (78.7%)	248 (83.2%)	1	0.160	1	0.130
		T/T	64 (21.3%)	50 (16.8%)	0.74 (0.49–1.12)		0.72 (0.48–1.10)	
	Log-additive	—	—	—	1.10 (0.86–1.42)	0.440	1.08 (0.83–1.39)	0.560
rs7025417	Dominant	T/T	107 (35.7%)	144 (48.6%)	1	0.001	1	0.002*
		T/C-C/C	193 (64.3%)	152 (51.4%)	0.59 (0.42–0.81)		0.58 (0.42–0.81)	
	Recessive	T/T-T/C	253 (84.3%)	257 (86.8%)	1	0.390	1	0.610
		C/C	47 (15.7%)	39 (13.2%)	0.82 (0.52–1.29)		0.88 (0.55–1.41)	
	Log-additive	—	—	—	0.73 (0.58–0.92)	0.007	0.74 (0.58–0.94)	0.012*
rs1317230	Dominant	A/A	91 (30.3%)	95 (32%)	1	0.660	1	0.810
		C/A-C/C	209 (69.7%)	202 (68%)	0.93 (0.65–1.31)		0.96 (0.67–1.36)	
	Recessive	A/A-C/A	244 (81.3%)	232 (78.1%)	1	0.330	1	0.220
		C/C	56 (18.7%)	65 (21.9%)	1.22 (0.82–1.82)		1.29 (0.86–1.95)	
	Log-additive	—	—	—	1.03 (0.82–1.29)	0.790	1.07 (0.85–1.34)	0.590
rs5756523	Dominant	T/T	89 (29.7%)	136 (45.3%)	1	< 0.001	1	< 0.001*
		C/T-C/C	211 (70.3%)	164 (54.7%)	0.51 (0.36–0.71)		0.50 (0.36–0.71)	
	Recessive	T/T-C/T	244 (81.3%)	261 (87%)	1	0.057	1	0.067
		C/C	56 (18.7%)	39 (13%)	0.65 (0.42–1.02)		0.66 (0.42–1.03)	
	Log-additive	—	—	—	0.64 (0.51–0.81)	< 0.001*	0.64 (0.50–0.81)	< 0.001*
rs2284033	Dominant	A/A	121 (40.3%)	123 (41.3%)	1	0.810	1	0.750
		A/G-G/G	179 (59.7%)	175 (58.7%)	0.96 (0.69–1.33)		0.95 (0.68–1.32)	
	Recessive	A/A-A/G	259 (86.3%)	274 (92%)	1	0.027	1	0.031*
		G/G	41 (13.7%)	24 (8.1%)	0.55 (0.33–0.94)		0.56 (0.32–0.96)	
	Log-additive	—	—	—	0.86 (0.67–1.10)	0.220	0.85 (0.66–1.09)	0.210

SNP: Single nucleotide polymorphism; ORs, odds ratios; CI: confidence interval.
p values were calculated using unconditional logistic regression analysis with adjustments for age and gender.
* $p < 0.05$ indicates statistical significance.

models: the minor allele C of rs1042711 was associated with increased risk of lung cancer under dominant and log-additive models ($p < 0.05$); the minor allele T of rs1560642 was also associated with increased risk of lung cancer under the dominant model ($p < 0.05$); the minor allele C of rs7025417 and rs5756523 had a protective role against lung cancer under dominant and log-additive models ($p < 0.05$); and the minor allele G of rs2284033 was associated with decreased risk of lung cancer under the recessive model ($p < 0.05$).

We also conducted a stratification analysis by smoking status (Table 5). In nonsmokers, the C allele of rs1042711 was associated with increased risk of lung cancer, whereas the C alleles of rs7025417 and rs5756523 were associated with decreased risk of lung cancer

Table 5
Association of candidate SNPs with susceptibility to lung cancer stratified by smoking status.

SNP	Model	Genotype	Nonsmokers		Smokers	
			OR (95% CI)	*p*	OR (95% CI)	*p*
rs1042711	Dominant	T/T	1	0.052	1	0.091
		C/T-C/C	1.64 (0.99–2.70)		1.63 (0.92–2.88)	
	Recessive	T/T-C/T	1	0.300	1	0.340
		C/C	2.43 (0.43–13.60)		0.41 (0.07–2.57)	
	Log-additive	—	1.60 (1.01–2.51)	0.042	1.39 (0.83–2.32)	0.0210
rs1560642	Dominant	G/G	1	0.520	1	0.003
		G/T-T/T	1.19 (0.70–2.01)		2.57 (1.37–4.84)	
	Recessive	G/G-G/T	1	0.310	1	0.180
		T/T	0.38 (0.20–1.10)		1.55 (0.81–2.96)	
	Log-additive	—	0.77 (0.55–1.09)	0.140	1.78 (1.18–2.70)	0.005
rs7025417	Dominant	T/T	1	0.028	1	0.023
		T/C-C/C	0.60 (0.38–0.95)		0.57 (0.34–0.93)	
	Recessive	T/T-T/C	1	0.820	1	0.300
		C/C	1.07 (0.59–1.95)		0.67 (0.32–1.43)	
	Log-additive	—	0.80 (0.59–1.10)	0.170	0.67 (0.46–0.96)	0.029
rs1317230	Dominant	A/A	1	0.430	1	0.590
		C/A-C/C	0.82 (0.51–1.33)		1.15 (0.69–1.94)	
	Recessive	A/A-C/A	1	0.520	1	0.240
		C/C	1.19 (0.70–2.04)		1.46 (0.77–2.77)	
	Log-additive	—	0.98 (0.72–1.33)	0.890	1.20 (0.84–1.71)	0.310
rs5756523	Dominant	T/T	1	0.001	1	0.019
		C/T-C/C	0.46 (0.29–0.74)		0.55 (0.33–0.91)	
	Recessive	T/T-C/T	1	0.630	1	0.028
		C/C	0.86 (0.46–1.59)		0.48 (0.25–0.93)	
	Log-additive	—	0.66 (0.47–0.91)	0.005	0.61 (0.43–0.87)	0.005
rs2284033	Dominant	A/A	1	0.420	1	0.170
		A/G-G/G	1.21 (0.77–1.90)		0.71 (0.43–1.16)	
	Recessive	A/A-A/G	1	0.0110	1	0.130
		G/G	0.56 (0.27–1.16)		0.53 (0.23–1.21)	
	Log-additive	—	0.97 (0.70–1.36)	0.860	0.71 (0.48–1.04)	0.078

SNP: Single nucleotide polymorphism; ORs, odds ratios; CI: confidence interval.
p values were calculated using unconditional logistic regression analysis with adjustments for age and gender.
$^{*}p < 0.05$ indicates statistical significance.

($p < 0.05$). In smokers, the T allele of rs1560642 was associated with increased risk of lung cancer, and the C alleles of rs7025417 and rs5756523 were associated with decreased risk of lung cancer ($p < 0.05$).

4. Discussion

Identification of susceptible SNPs is a helpful approach to early screening of lung cancer because of its convenience and low-cost process in identifying the high-risk population [23]. At present, an increasing number of biomedical companies provide the service of early screening for lung cancer. However, the SNPs currently associated with lung cancer are not sufficient to fully explain the genetic predisposition to the disease. In this study, we explored the association between a VIP gene, *ADRB2*, and two inflammation-related genes, *IL33* and *IL2RB*, and lung cancer risk, and identified two SNPs associated with increased risk of lung cancer and three SNPs associated with decreased risk of lung cancer.

ADRB2 encodes the β2-adrenergic receptor, which plays a biological function in muscle relaxation in the lungs [24]. Previous studies have reported that *ADRB2* gene variants may influence the severity of cystic fibrosis (CF) and lead to different responses to bronchodilators in CF patients and budesonide/formoterol in COPD patients [25,26]. Rs1042711 is located in the 5′ upstream region of *ADRB2*, and is a non-synonymous mutation (Arg19Cys) [27]. Zhao et al. [14] reported that the TT genotype of rs1042711 may be a risk factor for COPD, whereas Guo et al. [28] identified no association between rs1042711 and risk of asthma in children in a meta-analysis study. We identified the minor allele C of rs1042711 to be associated with increased risk of lung cancer, suggesting that *ADRB2*-rs1042711 may be involved in the development of lung cancer by altering the biological function of *ADRB2* in the lung. In addition, we showed that the minor allele T of rs1560642 in *ADRB2* was also associated with increased risk of lung cancer. However, there is no previous study on this SNP, and therefore the association between rs1560642 and lung cancer risk needs to be replicated in a larger population.

IL-33 belongs to the IL-1 family, and plays various and important roles in the immune response. Genetic polymorphisms of *IL33* and the abnormal levels of IL-33 may be involved in several types of diseases, including cancer [17,29,30]. Rs7025417 is located in the promoter of *IL33*, which can influence the expression of IL-33 [31]. Wang et al. reported that rs7025417 may have a protective effect against the development of osteosarcoma by down-regulating the expression of IL-33 [32]. We also demonstrated the protective role of the rs7025417-C allele against lung cancer, suggesting that rs7025417 may also affect the development of the disease by influencing the levels of IL-33.

IL-2R contains three subunits: α, β, and γ_c. IL2Rβ is encoded by *IL2RB*, which influences the affinity of IL-2R [33]. A GWAS study identified rs2284033 as being associated with 1.12-fold increased risk of asthma [34]. Jia et al. reported that rs2281089 in *IL2RB* is related to decreased risk of lung cancer [15]. In this study, we confirmed that the GG phenotype of rs2284033 may protect individuals against lung cancer, suggesting the protective role of *IL2RB* in the development of the disease. The different roles of *IL2RB* in asthma and lung cancer may result from different pathogenesis. We also showed that the minor allele of rs5756523 in *IL2RB* was associated with decreased risk of lung cancer, which needs to be further confirmed in a larger population.

Smoking is an independent risk factor for lung cancer, and thus we further analyzed the association between candidate SNPs and lung cancer risk in nonsmokers and smokers. Notably, rs1042711 was associated with increased risk of lung cancer in all participants of the nonsmoker subgroup, but showed no association in the smoker

subgroup. Similarly, rs1560642 was associated with increased risk of lung cancer in all participants of the smoker subgroup, but not in the nonsmoker subgroup. A previous study reported that the effects of genetic factors and their interaction with environmental factors on lung cancer in nonsmokers is different from those in smokers to a large extent [35], which may explain the different results between nonsmokers and smokers in our study. In addition, rs2284033 showed no association with lung cancer risk in either subgroup, which could be a result of the limited sample size in our study.

This study has some limitations. Firstly, the sample size was modest; genetic association studies for lung cancer usually recruit much larger samples because of the high incidence of the disease. Secondly, although we identified several susceptibility SNPs, the underlying mechanism needs to be confirmed by functional studies. Finally, the reasonable application of such susceptibility SNPs in the clinic is still a challenge, which may be resolved by obtaining a comprehensive genetic background of lung cancer and a permissive policy in the future.

In conclusion, we identified *ADRB2* polymorphisms (rs1042711 and rs1560642) that were associated with increased risk of lung cancer, and polymorphisms in *IL33* (rs7025417) and *IL2RB* (rs5756523 and rs2284033) that were associated with decreased disease risk. Further studies should focus on the functional role of these genes in lung cancer cell lines and animal models; uncovering the underlying mechanism may shed new light on the pathogenesis of this disease.

Declaration of Competing Interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105930.

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