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Genetic polymorphisms of *IL-10*, *IL-18* and *IL12B* are associated with risk of non-small cell lung cancer in a Chinese Han population

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ABSTRACT

Purpose: IL-10, IL-18 and IL-12 are reported to participate in the inflammation process. The potential influences of *IL-10*, *IL-18* and *IL-12* polymorphisms on non-small cell lung cancer (NSCLC) risk were explored in this study.
Methods: Six candidate SNPs from 500 NSCLC patients and 500 controls were genotyped. The correlation between the SNPs and NSCLC risk was evaluated by logistic regression analysis.
Results: Comparisons of the allele and genotype frequencies showed that five SNPs were correlated with NSCLC risk. The minor allele 'G' of *IL-18* rs5744256 and rs1834481 and *IL-10* rs3021094 was correlated with a decreased risk of NSCLC ($p < 0.05$). In contrast, the minor allele 'T' of *IL-18* rs5744224 and the minor allele 'G' of *IL-12B* rs3212227 were correlated with an increased risk of NSCLC ($p < 0.05$). By genetic model analysis, we found that rs5744256 and rs1834481 were associated with a decreased risk of NSCLC under dominant and log-additive models ($p < 0.05$). Rs3021094 was correlated with a decreased risk of NSCLC under all three models ($p < 0.05$). In contrast, rs5744224 was associated with an increased risk of NSCLC under the recessive model ($p = 0.005$), and rs3212227 was associated with an increased risk of NSCLC under all three models ($p < 0.05$). Finally, the GGA haplotype of rs5744256, rs1834481 and rs5744224 and the GT haplotype of rs3021094 and rs3790622 were associated with a decreased risk of NSCLC ($p < 0.05$).
Conclusion: Our results provided new candidate SNPs for the prediction and prevention of NSCLC.

1. Introduction

Lung cancer (LC) is the most common type of cancer worldwide and exhibits the highest morbidity and mortality. According to global cancer statistics, in 2018, there were more than two million new cases and almost two million deaths from LC [1]. In China, LC is also ranked highest for cancer death, resulting in a heavy economic and mental burden for patients and their families [2]. Early diagnosis and prevention of LC are important to improve the prognosis of patients [3]. In recent years, researchers have identified many single nucleotide polymorphisms (SNPs) associated with risk of LC, and some organizations currently provide genetic counseling regarding LC risk based on these SNPs [4–6]. However, the existing SNPs are still not sufficient to explain the genetic factors of LC, and it is important to identify additional SNPs to better understand the molecular mechanism and for prediction and early prevention of LC.

It is widely accepted that the occurrence and development of cancers are closely associated with chronic inflammation in the human body [7]. Interleukin (IL) is a type of lymphokine that is produced by the interaction between leukocytes and immune cells and plays important roles in the inflammation process. IL-10, IL-18 and IL-12 have been intensively reported to participate in stimulating T cell proliferation, enhancing natural killer cell activity, and promoting cytokine production. Wang et al. found that the IL-10 level in exosomes of LC cells was increased, and IL-10 was involved in the migration of tumor cells [8]. Timperi et al. reported that IL-18 can produce a pro-inflammatory condition in the tumor microenvironment of non-small cell lung cancer (NSCLC) and that the IL-18 receptor may represent the functional tumor-infiltrating $CD8^+$ T cell level in NSCLC patients [9]. In addition, Yue et al. found that the curative effect of IL-12 on LC was even better than that of paclitaxel and cisplatin doublet chemotherapy [10]. These previous studies showed that IL-10, IL-18 and IL-12 may play a substantial role in the development and progression of LC. At the gene, several SNPs in the *IL-10*, *IL-18* and *IL12* genes have been

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reported to be associated with the risk of LC, including rs1800871 in *IL-10*, rs187238 and rs1946518 in *IL-18*, and rs2243115 in *IL-12A* [11–13]. We examined several candidate SNPs to identify novel SNPs on these three genes that indicate susceptibility to LC.

The SNPs rs3021094 and rs3790622 in *IL-10* were found to be correlated with a decreased risk of tuberculosis in the Chinese Han population, while there is little information on their association with LC risk [14]. Rs3212227 in the 3′ UTR region of *IL-12B* was reported to be associated with the risk of gastric and cervical cancer [15,16] and was also examined in our study. Rs5744256 and rs1834481, two intronic SNPs in *IL-18*, were selected based on their functional effects, and both are significantly associated with plasma IL-18 levels [17]. Rs5744224 in the promoter region of *IL-18* was also selected as a candidate SNP. NSCLC is the most common type of LC and accounts for approximately 85% of all LC cases. In the present study, we detected rs3021094, rs3790622, rs3212227, rs5744256, rs1834481 and rs5744224 polymorphisms in 500 NSCLC patients and 500 healthy controls and investigated the association between the above SNPs and risk of NSCLC.

2. Materials and methods

2.1. Subjects

The subjects of this study included 500 NSCLC patients and 500 controls. All participants were of Chinese Han ethnicity and were recruited at our hospital. The patients were diagnosed with NSCLC by histopathological examination of biopsy specimens. The control group included randomly selected healthy individuals with no history of cancer. This study was approved by the ethics committee of the hospital. All participants provided written informed consent.

2.2. Genotyping

Six SNPs in *IL-18*, *IL-10* and *IL-12B* were selected based on previous association studies. The minor allele frequencies (MAFs) of these SNPs are greater than 5% in East Asian populations according to the 1000 Genomes database. Genomic DNA was extracted using a QIAamp DNA Blood Midi Kit (QIAGEN, Germany). Primers were designed using Sequenom MassARRAY Assay Design 3.0 software [18–20]. SNP genotyping was performed by a Sequenom MassARRAY RS1000 (Sequenom, SanDiego, CA).

2.3. Statistical analyses

Statistical analyses were performed with the SPSS 21.0 statistical package (SPSS, Chicago, IL, USA). Allele frequencies in the control group were checked for divergence from Hardy–Weinberg Equilibrium (HWE). The differences in allele and genotype frequencies between the case and control groups were evaluated by chi-square tests. Associations between the genotypes and NSCLC risk were estimated by calculating the odds ratios (ORs) and 95% confidence intervals (CIs) from an unconditional logistic regression analysis. Additionally, the linkage disequilibrium (LD) and haplotypes were evaluated using Haploview v4.2 software. Statistical significance was established when $p < 0.05$.

3. Results

The present study includes 500 NSCLC cases and 500 healthy controls. The demographics of the participants are described in Table 1. The mean age of the participants was 57.74 ± 10.35 years in the case group and 57.12 ± 10.76 years in the control group. No significant difference was observed in the distribution of gender or age between the case and control groups ($p > 0.05$).

The basic information of the candidate SNPs is shown in Table 2. All SNPs were consistent with HWE ($p > 0.05$). The frequency of the 'G' allele of rs5744256 was significantly lower in the NSCLC case group than in the control group (0.26 versus 0.31), which suggested that the 'G' allele of rs5744256 may be a protective allele against NSCLC risk (OR = 0.76, 95% CI = 0.62–0.93, $p = 0.011$). Similarly, the 'G' alleles of rs1834481 and rs3021094 were both protective against NSCLC risk ($OR_{rs1834481} = 0.75$, 95% CI = 0.59–0.92, $p = 0.007$; $OR_{rs3021094} = 0.65$, 95% CI = 0.56–0.88, $p = 0.001$). However, the frequency of the 'G' allele of rs3212227 was significantly higher in the NSCLC case group than in the control group (0.52 versus 0.44), which suggested that the 'G' allele of rs3212227 may be a risk allele for NSCLC (OR = 1.35, 95% CI = 1.11–1.63, $p = 0.001$).

Table 1
Basic characteristics of the case and control groups.

Variables	Case (N = 500)	Control (N = 500)	X^2/t	p
Gender (%)			0.048	0.826[a]
Male	374 (74.8)	377 (75.4)		
Female	126 (25.2)	123 (24.6)		
Age (mean ± SD)	57.74 ± 10.35	57.12 ± 10.76	0.931	0.352[b]

[a] p value was calculated from Pearson's chi-square tests.
[b] p value was calculated by Student's t tests.

The genotype frequencies of candidate SNPs are provided in Table 3. Compared to the AA genotype, the GG genotype frequency of rs5744256 in the case group was different from that of the control group (GG vs. AA: OR = 0.59, 95% CI = 0.37–0.95, $p = 0.039$), which suggested that the GG genotype of rs5744256 decreases NSCLC risk. Similarly, the CG and GG genotypes of rs1834481 and the GT and GG genotypes of rs3021094 were associated with a decreased risk of NSCLC ($p < 0.05$). However, the TT genotype of rs5744224 and the GG genotype of rs3212227 were both associated with increased risk of NSCLC ($p < 0.05$).

A total of five SNPs were correlated with NSCLC risk under three genetic models (Table 4). The minor 'G' alleles of rs5744256 and rs1834481 were associated with decreased risk of NSCLC under the dominant and log-additive models ($p < 0.05$). The minor allele 'G' of rs3021094 was also correlated with a decreased risk of NSCLC under all three models ($p < 0.05$). In contrast, the minor allele 'T' of rs5744224 was associated with a 1.56-fold increased risk of NSCLC under a recessive model ($p = 0.005$), and the minor allele 'G' of rs3212227 was associated with an increased risk of NSCLC under all three models ($p < 0.05$).

LD and haplotypes of *IL-18* and *IL-10* SNPs were further analyzed to evaluate the association with NSCLC risk (Figs. 1 and 2). We found two LD blocks that consisted of three SNPs on *IL-18* (rs5744256, rs1834481 and rs5744224) and two SNPs on *IL-10* (rs3021094 and rs3790622). Furthermore, the impact of haplotypes on the risk of NSCLC was evaluated (Table 5). We found that the GGA haplotype consisting of rs5744256, rs1834481 and rs5744224 was associated with 0.76-fold decreased risk of NSCLC (95% CI: 0.61–0.95, $p = 0.014$), and the GT haplotype consisting of rs3021094 and rs3790622 was associated with 0.67-fold decreased risk of NSCLC (95% CI: 0.55–0.82, $p = 0.001$).

4. Discussion

In the past ten years, great interest has been expressed in the development of biomarkers for prediction and early diagnosis of LC [21]. Many studies are still underway to identify genes and SNPs that are susceptible to LC. In the present study, we focused on the IL-related genes *IL-10*, *IL-18* and *IL-12B* and investigated their association with the risk of LC. Five SNPs were identified. The G alleles of rs5744256, rs1834481 and rs3021094 were found to have protective effects against the risk of LC, while the T allele of rs5744224 and the G allele of rs3212227 were correlated with elevated LC risk.

IL-10 is a cytokine secreted by monocytes and lymphocytes that can down-regulate Th1 cytokine and MHC class II Ag levels. Genetic

Table 2
Allele frequencies in the case and control groups and odds ratio estimates for NSCLC.

SNP ID	Gene	Chromosome	Position	Minor/Major Alleles	MAF		*p*-HWE	OR (95% CI)	p^a
					Case	Control			
rs5744256	*IL-18*	chr11	112152125	G/A	0.26	0.31	0.98	0.76 (0.62–0.93)	0.011*
rs1834481	*IL-18*	chr11	112153104	G/C	0.24	0.29	0.75	0.75 (0.59–0.92)	0.007*
rs5744224	*IL-18*	chr11	112164936	T/A	0.47	0.43	0.08	1.21 (0.99–1.43)	0.078
rs3021094	*IL-10*	chr1	206771607	G/T	0.27	0.35	0.92	0.65 (0.56–0.88)	0.001*
rs3790622	*IL-10*	chr1	206771818	A/G	0.07	0.07	0.99	1.02 (0.66–1.53)	0.722
rs3212227	*IL-12B*	chr5	159315942	G/T	0.52	0.44	0.97	1.35 (1.11–1.63)	0.001*

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

polymorphisms of *IL-10* have been associated with several types of cancers, including gastric, colorectal, lung, prostate, and cervical cancers [22–25]. For regarding LC risk, rs1800896 (−1082G/A), rs1800871 (−819C/T), and rs1800872 (−592C/A) in the *IL-10* promoter are the most widely studied SNPs [26]. Two intronic SNPs, rs3021094 and rs3790622, in *IL-10* were examined in this study. Ting et al. found that the GG genotype of rs3021094 was correlated with an elevated risk of death in colorectal cancer patients [27]. He et al. reported that both minor alleles of rs3021094 and rs3790622 were correlated with a declining risk of tuberculosis [14]. We found that the GG genotype of rs3021094 was correlated with a 0.46-fold decreased risk of NSCLC, while no significant result was found for rs3790622. However, the results identified here were preliminary and still need to be replicated in future studies.

IL-18 is a pro-inflammatory cytokine that enhances NK cell activity and induces interferon-γ production. A previous study showed that rs187238 and rs1946518 in *IL-18* were correlated with cancer risk in different populations [12]. In our study, rs5744256, rs1834481 and rs5744224 were selected for analysis. Both of rs5744256 and rs1834481 were associated with the IL-18 level [17]. Santos et al. reported that rs5744256 can slow the development of anemia [28], and Palmieri et al. reported that the C allele of rs1834481 was associated with increased risk of ovarian cancer in non-Hispanic white women [29]. We found that the G alleles of rs5744256 and rs1834481 were correlated with a decreased risk of NSCLC, suggesting the minor G alleles of rs5744256 and rs1834481 may play a protective role against the development of NSCLC by influencing the plasma IL-18 level in patients. In addition, we found that the TT genotype of rs5744224 may increase the risk of NSCLC under the recessive model. However, to date, there is little information on rs5744224, and further studies are needed to confirm the results.

IL-12, encoded by *IL12A* and *IL-12B*, is a cytokine that acts on T and NK cells. Previous studies have reported several SNPs in *IL12A* and *IL-12B* that are correlated with brain, liver, colorectal, breast, cervical and bladder cancers [30–34]. Among those SNPs, rs3212227 (+1188A/C) has been associated with various cancers and diseases [35,36]. We sought to illustrate the association between rs3212227 and the risk of LC, and as a result, we found that the minor allele G was associated with the risk of NSCLC under all three genetic models, suggesting that rs3212227 may be a good candidate SNP for prediction of NSCLC.

Although the present study identified five SNPs on IL-related genes associated with NSCLC risk in a relatively large sample, there are still some limitations of the study. Our study did not include environmental factors such as smoking and dust exposure; therefore, we cannot perform an interaction analysis between genetic and environmental factors. Furthermore, we failed to collect the clinical information of NSCLC

Table 3
Genotype frequencies of SNPs and their associations with NSCLC risk.

SNP ID	Genotype	Genotype frequencies		Without adjustment		With adjustment	
		Case (%)	Control (%)	OR (95%CI)	*p*	OR (95%CI)	*p*
rs5744256	AA	273 (54.6)	235 (47.5)	1.00		1.00	
	AG	194 (38.8)	212 (42.8)	0.79 (0.61–1.02)	0.040*	0.79 (0.61–1.02)	0.039*
	GG	33 (6.6)	48 (9.7)	0.59 (0.37–0.95)		0.59 (0.37–0.95)	
rs1834481	CC	291 (58.2)	249 (50.3)	1.00		1.00	
	CG	180 (36)	202 (40.8)	0.76 (0.59–0.99)	0.022*	0.76 (0.59–0.99)	0.022*
	GG	29 (5.8)	44 (8.9)	0.56 (0.34–0.93)		0.56 (0.34–0.93)	
rs5744224	AA	148 (29.7)	150 (30.2)	1.00		1.00	
	AT	232 (46.5)	264 (53.1)	0.89 (0.67–1.19)	0.014*	0.89 (0.67–1.19)	0.015*
	TT	119 (23.8)	83 (16.7)	1.45 (1.01–2.08)		1.45 (1.01–2.08)	
rs3021094	TT	262 (52.6)	211 (42.3)	1.00		1.00	
	GT	202 (40.6)	228 (45.7)	0.71 (0.55–0.93)	< 0.001*	0.71 (0.55–0.93)	< 0.001*
	GG	34 (6.8)	60 (12.0)	0.46 (0.29–0.72)		0.45 (0.28–0.71)	
rs3790622	GG	428 (85.6)	433 (86.6)	1.00		1.00	
	AG	70 (14.0)	65 (13)	1.09 (0.76–1.57)	0.900	1.09 (0.76–1.57)	0.890
	AA	2 (0.4)	2 (0.4)	1.01 (0.14–7.22)		0.98 (0.14–7.00)	
rs3212227	TT	125 (25.0)	152 (30.8)	1.00		1.00	
	GT	233 (46.6)	245 (49.6)	1.16 (0.86–1.56)	0.003*	1.16 (0.86–1.57)	0.003*
	GG	142 (28.4)	97 (19.6)	1.78 (1.25–2.53)		1.80 (1.26–2.55)	

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

Table 4
Association between SNPs and risk of NSCLC in multiple inheritance models (adjusted by gender and age).

SNP	Model	Genotype	Genotype frequencies		Without adjustment		With adjustment	
			Case (%)	Control (%)	OR (95% CI)	*p*	OR (95% CI)	*p*
rs5744256	Dominant	AA	273 (54.6)	235 (47.5)	1	0.024*	1	0.024*
		AG/GG	227 (45.4)	260 (52.5)	0.75 (0.59–0.96)		0.75 (0.59–0.96)	
	Recessive	AA/AG	467 (93.4)	447 (90.3)	1	0.073	1	0.070
		GG	33 (6.6)	48 (9.7)	0.66 (0.41–1.04)		0.65 (0.41–1.04)	
	Log-additive	—	—	—	0.78 (0.64–0.95)	0.012*	0.78 (0.64–0.94)	0.011*
rs1834481	Dominant	CC	291 (58.2)	249 (50.3)	1	0.012*	1	0.012*
		CG/GG	209 (41.8)	246 (49.7)	0.73 (0.57–0.93)		0.73 (0.56–0.93)	
	Recessive	CC/CG	471 (94.2)	451 (91.1)	1	0.061	1	0.061
		GG	29 (5.8)	44 (8.9)	0.63 (0.39–1.03)		0.63 (0.39–1.03)	
	Log-additive	—	—	—	0.76 (0.62–0.92)	0.006*	0.76 (0.62–0.92)	0.006*
rs5744224	Dominant	AA	148 (29.7)	150 (30.2)	1	0.860	1	0.850
		AT/TT	351 (70.3)	347 (69.8)	1.03 (0.78–1.34)		1.03 (0.78–1.35)	
	Recessive	AA/AT	380 (76.2)	414 (83.3)	1	0.005*	1	0.005*
		TT	119 (23.9)	83 (16.7)	1.56 (1.14–2.14)		1.56 (1.14–2.13)	
	Log-additive	—	—	—	1.17 (0.98–1.40)	0.084	1.17 (0.98–1.40)	0.086
rs3021094	Dominant	TT	262 (52.6)	211 (42.3)	1	0.001*	1	0.001*
		GT/GG	236 (47.4)	288 (57.7)	0.66 (0.51–0.85)		0.66 (0.51–0.85)	
	Recessive	TT/GT	464 (93.2)	439 (88)	1	0.005*	1	0.004*
		GG	34 (6.8)	60 (12)	0.54 (0.35–0.83)		0.53 (0.34–0.82)	
	Log-additive	—	—	—	0.69 (0.57–0.84)	< 0.001*	0.69 (0.57–0.83)	< 0.001*
rs3790622	Dominant	GG	428 (85.6)	433 (86.6)	1	0.650	1	0.650
		AG/AA	72 (14.4)	67 (13.4)	1.09 (0.76–1.56)		1.09 (0.76–1.56)	
	Recessive	GG/AG	498 (99.6)	498 (99.6)	1	0.988	1	0.970
		AA	2 (0.4)	2 (0.4)	1.00 (0.14–7.13)		0.97 (0.14–6.91)	
	Log-additive	—	—	—	1.08 (0.77–1.52)	0.660	1.08 (0.77–1.52)	0.66
rs3212227	Dominant	TT	125 (25)	152 (30.8)	1	0.042*	1	0.039*
		GT/GG	375 (75)	342 (69.2)	1.33 (1.01–1.76)		1.34 (1.01–1.77)	
	Recessive	TT/GT	358 (71.6)	397 (80.4)	1	0.001*	1	0.001*
		GG	142 (28.4)	97 (19.6)	1.62 (1.21–2.18)		1.63 (1.21–2.19)	
	Log-additive	—	—	—	1.33 (1.11–1.58)	0.001*	1.33 (1.12–1.59)	0.001*

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

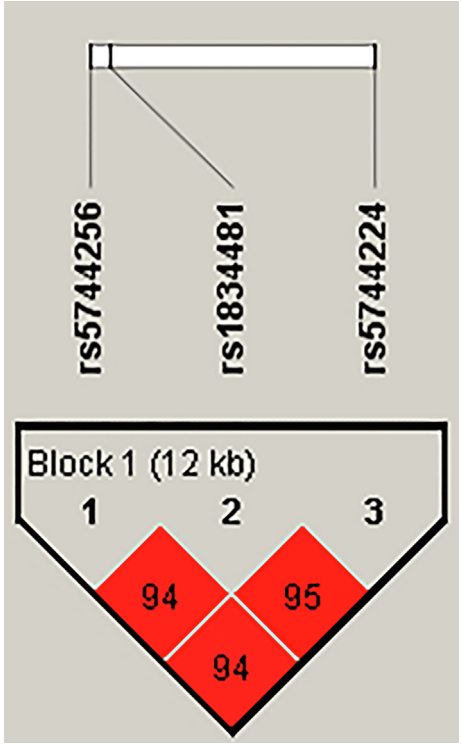

Fig. 1. Haplotype block map for SNPs in *IL-18*.

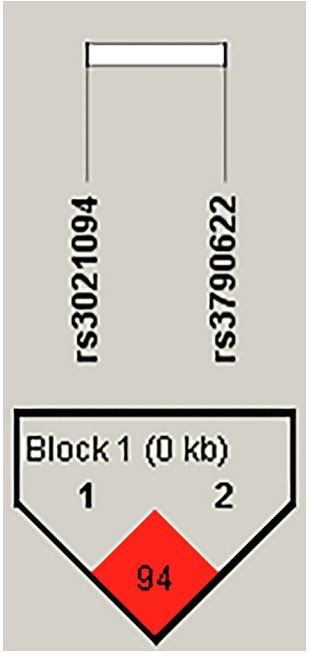

Fig. 2. Haplotype block map for SNPs in *IL-10*.

Table 5
Haplotype frequencies of the SNPs and associations with NSCLC risk.

Gene	SNP	Haplotypes	Frequencies		Without adjustment		With adjustment	
			Case	Control	OR (95% CI)	*p*	OR (95% CI)	*p*
IL-18	rs5744256/rs1834481/rs5744224	ACT	0.464	0.425	1	—	1	—
		ACA	0.269	0.250	0.98 (0.78–1.22)	0.820	0.98 (0.78–1.22)	0.840
		GGA	0.227	0.273	0.76 (0.61–0.94)	0.014*	0.76 (0.61–0.95)	0.014*
		GCA	0.026	0.030	0.76 (0.43–1.34)	0.340	0.76 (0.43–1.33)	0.330
IL-10	rs3021094/rs3790622	TT	0.656	0.583	1	—	1	—
		GT	0.270	0.348	0.68 (0.55–0.82)	0.001*	0.67 (0.55–0.82)	0.001*
		TG	0.072	0.068	0.91 (0.63–1.30)	0.600	0.91 (0.63–1.30)	0.600

P values, ORs and 95% CIs were computed by logistic regression analysis with adjustments for age and gender.
* Indicates statistical significance ($P < 0.05$).

patients, which led to a lack of stratification analysis.

In summary, the present study found that the minor G alleles of rs5744256, rs1834481 and rs3021094 may have a protective effect against the risk of NSCLC, while the minor alleles of rs5744224 and rs3212227 may increase the risk of NSCLC. Our results shed new light on the genetic predisposition of NSCLC and provide new candidate SNPs for the prediction and prevention of NSCLC.

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Declaration of Competing Interest

None.

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