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MALAT1 rs619586 A/G polymorphisms are associated with decreased risk of lung cancer

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Abstract

Lung cancer is the leading cause of cancer-associated mortality worldwide. Genetic factors are reported to play important roles in lung carcinogenesis. To evaluate genetic susceptibility, we conducted a hospital-based case-control study on the effects of functional single nucleotide polymorphisms (SNPs) in long non-coding RNAs (lncRNAs) and microRNAs on lung cancer development. A total of 917 lung cancer cases and 925 control subjects were recruited. The *MALAT1* rs619586 A/G genotype frequencies between patient and control groups were significantly different ($P<.001$), specifically, 83.85% vs 75.88% (AA), 15.60% vs 21.79% (AG), and 0.55% vs 2.32% (GG). When the homozygous genotype *MALAT1* rs619586 AA was used as the reference group, AG (AG vs AA: adjusted odds ratio [OR] 0.65, 95% confidential interval [CI] 0.51–0.83, $P=.001$) and GG genotypes were associated with significantly decreased risk of lung cancer (GG vs AA: adjusted OR 0.22, 95% CI 0.08–0.59, $P=.003$). In the dominant model, *MALAT1* rs619586 AG/GG variants were also associated with a significantly decreased risk of lung cancer (adjusted OR 0.61, 95% CI 0.48–0.78, $P<.001$). In the recessive model, when *MALAT1* rs619586 AA/AG genotypes were used as the reference group, the GG homozygous genotype was also associated with significantly decreased risk for lung cancer (adjusted OR 0.24, 95% CI 0.09–0.64, $P=.004$). *Hsa-miR-34b/c* rs4938723 T > C, *pri-miR-124-1* rs531564 C > G and *hsa-miR-423* rs6505162 C > A SNPs were not associated with lung cancer risk. Our collective data indicated that *MALAT1* rs619586 A/G SNPs significantly reduced the risk of lung cancer. Large-scale studies on different ethnic populations and tissue-specific biological characterization are required to validate the current findings.

Abbreviations: CI = confidential interval, lncRNAs = long non-coding RNAs, miRNA = microRNA, OR = odds ratio, SNPs = single nucleotide polymorphisms.

Keywords: long non-coding RNAs, lung cancer, microRNA, molecular epidemiology, polymorphisms

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We conducted a hospital based case–control study to evaluate the association between lncRNA variants MALAT1 rs619586 A/G and 3 microRNAs hsa-miR-34b/c rs4938723 T > C, pri-miR-124-1 rs531564 C > G and hsa-miR-423 rs6505162 C > A the susceptibility of lung cancer. Our results demonstrated that MALAT1 rs619586 A/G polymorphisms might be potential functional or causal SNPs for lung cancer.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Long non-coding RNAs (lncRNAs) are non-protein coding transcripts ranging from 200 bases to 100 kb involved in all aspects of gene regulation and biological processes. Under different physiological and pathological conditions, lncRNAs have diverse functions. lncRNAs regulate gene expression processes, including chromatin modification,[1] transcription and posttranscriptional processing[2] at various levels. Several lncRNAs have modulatory effects on cell homeostasis and proliferation while others function in apoptosis.[3] More recent studies have demonstrated critical roles of lncRNAs in carcinogenesis. In cancer cells, lncRNAs regulate transcriptional, posttranscriptional and epigenetic levels, the important cellular signaling pathways.[4] Most lncRNAs are RNA polymerase (Pol) II/Pol I-transcribing, while others transcribe RNA Pol III.[5] LncRNAs are involved in diverse cellular functions[6,7] as well as different mechanisms, with roles as decoys, guides and scaffolds.[8] Aberrant lncRNA expression contributes to progression of numerous tumors[9] and is considered an early event in some tumor types. A role of specific lncRNAs in glioma carcinogenesis has been reported based on data from microarray analysis.[10] LncRNAs additionally have important functions in lung, breast, and liver cancer development.[11] The well-characterized metastasis-associated lung adenocarcinoma transcript-1 (MALAT1) lncRNA is a nuclear-enriched abundant transcript expressed in the lungs, pancreas, nerve system and other healthy organs.[12] High expression of MALAT1 has also been detected in various cancer types, including lung cancer, endometrial stromal sarcoma, hepatocellular carcinoma, breast cancer and pancreatic cancer. Elevated expression of MALAT1 is associated with

hyperproliferation, metastasis, and poor prognosis. MALAT1 localizes to nuclear speckles, a subnuclear domain suggested to coordinate RNA polymerase II transcription, pre-mRNA splicing, and mRNA export.[13] Moreover, MALAT1 interacts with several pre-mRNA splicing factors including serine-arginine dipeptide-rich SR family splicing factors, such as SRSF1 (also known as ASF/SF2), SC35 (SRSF2), and SRSF3. The lncRNA further induces the expression of cell cycle genes and controls alternative splicing of pre-mRNAs by modulating the intranuclear distribution of SR splicing factors.[14] Interestingly, knockdown of MALAT1 has no impact on the formation, size, and number of nuclear speckles but results in decreased nuclear speckle association of several pre-mRNA splicing factors, including SRSF1.[10]

MicroRNAs (miRNAs) are tiny non-coding RNAs that act as posttranscriptional gene regulatory elements.[15] MiRNAs exert their effects by binding to the 3'-untranslated regions of target genes and downregulating their expression[16] and are reported to be important players in carcinogenesis.[17]

Genetic factors, such as single nucleotide polymorphisms (SNPs), may contribute to carcinogenesis.[18] SNPs in genomic miRNA sequences could influence miRNA-dependent regulation, affect the final levels and functions of miRNAs, and consequently alter tumor susceptibility.[19]

Members of the miR-34 family are direct p53 targets induced in response to DNA damage or oncogenic stress.[20] Down-regulation of mir-34b/c via methylation has been reported in colorectal cancer,[21] oral cancer,[22] and malignant melanoma.[23]*Hsa-miR-34b/c* rs4938723 SNP is located within the CpG island of pri-miR-34b/c and 423 bp upstream from the transcription start site is proposed to serve as the predicted binding site for GATA-X transcription factors.[24] The *Hsa-miR-34b/c* rs4938723 T>C polymorphism is associated with risk of nasopharyngeal carcinoma,[25] hepatocellular carcinoma,[26] colorectal cancer[27] and breast cancer survival.[28]

The rs531564 SNP in *pri-miR-124-1* is associated with increased risk of bladder cancer[29] and esophageal cancer in males.[30] Besides *hsa-miR-34b/c* rs4938723 T>C, *pri-miR-124-1* rs531564 C>G and *hsa-miR-423* rs6505162 C>A are associated with risk of different cancer types. For instance, the *hsa-miR-423* rs6505162 C>A polymorphism is reported to confer reduced breast cancer risk[31] and significantly associated with both overall and recurrence-free survival of colorectal cancer.[32]

To date, limited studies have focused on the influence of *MALAT1* rs619586 A/G, *hsa-miR-34b/c* rs4938723 T>C, *pri-miR-124-1* rs531564 C>G and *hsa-miR-423* rs6505162 C>A polymorphisms on susceptibility to lung cancer.[33] It is possible that functional genetic variations in lncRNAs contribute to lung cancer development. The main objective of this hospital-based case-control study was to evaluate the association between *MALAT1* rs619586 A/G, *hsa-miR-34b/c* rs4938723 T>C, *pri-miR-124-1* rs531564 C>G and *hsa-miR-423* rs6505162 C>A genotypes and lung cancer risk. We performed genotyping analyses for the 4 SNPs in 917 lung cancer and 925 cancer-free control subjects in a Chinese population.

2. Materials and methods

2.1. Isolation of DNA and genotyping

This case-control study was approved the Ethical Committee on Human Studies, Shanghai Chest Hospital (Shanghai, China). Written informed consent was provided by the participants. Subjects were selected from Shanghai Chest Hospital. Between April 2015 and October 2016, 917 non-small cell lung cancer patients were recruited consecutively, including 801 adenocarcinoma and 116 squamous cell carcinoma cases. All lung cancer cases were diagnosed using pathological methods. Exclusion criteria were as follows: patients previously diagnosed with cancer, small-cell lung cancer, any metastasized cancer and radiotherapy or chemotherapy. The study included 917 lung cancer cases and 925 cancer-free controls. Demographic data were collected from each subject using a pre-tested questionnaire, including sex, age at diagnosis, race, and related risk factors (including tobacco smoking and alcohol consumption).

2.2. Isolation of DNA and genotyping using ligation detection reaction

Blood sample collection, genomic DNA isolation and SNP genotyping were conducted using the ligation detection reaction (LDR) method with technical support from Shanghai Biowing Applied Biotechnology Company, as described previously.[34] The quality of genotyping for *MALAT1* rs619586 A/G, *miR-34b/c* rs4938723 T>C, *pri-miR-124-1* rs531564 C>G and *hsa-miR-423* rs6505162 C>A was high. For quality control, repeated analyses were conducted using 184 (10%) randomly selected samples with high DNA quality.

2.3. Statistical analyses

Student *t* test and χ^2 test were performed to assess the differences in distribution of selected variables, demographic characteristics, and genotypes for the 4 SNPs between lung cancer cases and controls. Using logistic regression analyses, the correlations between the 4 SNPs and risk of lung cancer were evaluated by calculating the crude odds ratio (ORs), adjusted ORs and corresponding 95% confidential intervals [CIs]. Hardy-Weinberg equilibrium (HWE) in controls was tested with an online calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Statistical analyses were performed with SAS (v 9.1.3) software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

The characteristics of cases and control subjects recruited for study are summarized in Table 1. In terms of age and sex, cases and controls appeared adequately matched ($P=.467$ and $P=.095$, respectively), as determined with the χ^2 test. No significant difference was detected in smoking rate ($P=.263$) and drinking status ($P=.284$) between the 2 groups, as shown in Table 1. Primary information on *MALAT1* rs619586 A/G SNPs is provided in Table 2. The genotyping success rate for *MALAT1* rs619586 A/G was 98.15% in all 1842 samples. The concordance rates of repeat analyses were 100% for both SNPs. Minor allele frequencies (MAFs) in our controls were similar to MAFs of these SNPs recorded in the Chinese database (Table 2). The observed genotype frequency for *MALAT1* rs619586 A/G polymorphisms was 0.132 in the controls in HWE ($P=.131$).

3.2. Associations between MALAT1 rs619586 A/G polymorphisms and the risk of lung cancer

The genotype frequencies of *MALAT1* rs619586 A/G were 83.85% (AA), 15.60% (AG), and 0.55% (GG) in the patient

Table 1

Distribution of selected demographic variables and risk factors in lung cancer cases and controls.

Variable	Cases (n = 917)		Controls (n = 925)		P^*
	n	%	n	%	
Age (yrs)					.467
<60	378	41.2	397	42.9	
≥60	539	58.8	528	57.1	
Age, yrs, mean ± SD	59.78 (±10.88)		60.06 (±7.58)		.521†
Sex					.095
Men	517	56.4	557	60.2	
Women	400	43.6	368	39.8	
Tobacco use					.263
Never	666	72.6	650	70.3	
Ever	251	27.4	275	29.7	
Alcohol use					.284
Never	674	73.5	700	75.7	
Ever	243	26.5	225	24.3	
Cancer pathology types					
Adenocarcinoma	801	87.4			
Squamous cell carcinoma	116	12.6			

* Two-sided χ^2 test.

† Student *t* test. The definition of "smokers": who smoked one cigarette per day for >1 year. The definition of "alcohol drinkers": who consumed alcohol more than 3 times a week for >6 months.

group and 75.88% (AA), 21.79% (AG), and 2.32% (GG) in the control group, which were significantly different ($P<.001$). When the *MALAT1* rs619586 AA homozygous genotype was used as the reference group, the AG genotype was associated with significantly decreased risk of lung cancer (AG vs AA: adjusted OR: 0.65, 95% CI: 0.51–0.83, $P=.001$) as well as the GG genotype (GG vs AA: adjusted OR: 0.22, 95% CI: 0.08–0.59, $P=.003$). In the dominant model, *MALAT1* rs619586 AG/GG variants were associated with significantly decreased risk of lung cancer, compared with the *MALAT1* rs619586 AA genotype (adjusted OR: 0.61, 95% CI: 0.48–0.78, $P<.001$). In the recessive model, when *MALAT1* rs619586 AA/AG genotypes were used as the reference group, the GG homozygous genotype was also associated with significantly decreased risk of lung cancer (adjusted OR: 0.24, 95% CI: 0.09–0.64, $P=.004$) (Table 3).

3.3. Associations between hsa-miR-34b/c rs4938723 T > C, pri-miR-124-1 rs531564 C > G and hsa-miR-423 rs6505162 C > A polymorphisms and the risk of lung cancer

The genotype distributions of *hsa-miR-34b/c* rs4938723 T > C, *pri-miR-124-1* rs531564 C > G and *hsa-miR-423* rs6505162 C > A in cases and control subjects are shown in Table 3. In single locus analyses, the genotype frequencies of *hsa-miR-34b/c* rs4938723 T > C were 44.4% (TT), 45.1% (TC), and 10.5% (CC) in patients and 42.2% (TT), 43.4% (TC), and 10.5% (CC) in control subjects. The difference between the 2 groups was not statistically significant ($P=.746$). In the recessive model, when *hsa-miR-34b/c* rs4938723 TT/TC genotypes were used as the reference group, the CC homozygous genotype was not associated with risk of lung cancer (CC vs TT/TC: adjusted

Table 2

Primary information for *MALAT1* rs619586 A/G, *pri-miR-124-1* rs531564 C > G, *hsa-miR-34b/c* rs4938723 T > C and *hsa-miR-423* rs6505162 C > A polymorphisms.

Genotyped SNPs	*MALAT1* rs619586 A/G	*pri-miR-124-1* rs531564 C > G	*hsa-miR-34b/c* rs4938723 T > C	*hsa-miR-423* rs6505162 C > A
Chromosome	11	8	11	17
Gene Official Symbol	ncRNA	MIR124-1	MIR34B/C	MIR423
Function	65498698	ncRNA	ncRNA	ncRNA
Chr Pos (Genome Build 36.3)	4	9798109	110887775	25468309
Regulome DB Score*	Y	5	5	1f
TFBS†	—	Y	Y	Y
Splicing (ESE or ESS)	—	—	—	Y
MAF‡ for Chinese in database	0.123	0.135	0.325	0.187
MAF in our controls (n = 925)	0.132	0.154	0.322	0.198
P value for HWE§ test in our controls	0.131	0.091	0.880	0.412
Genotyping method¶	LDR	LDR	LDR	LDR
% Genotyping value	98.15%	98.26%	99.40%	96.63%

* http://www.regulomedb.org/.

† TFBS = Transcription Factor Binding Site (http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm).

‡ MAF = minor allele frequency, from gnomAD-Exomes Asian.

§ HWE = Hardy–Weinberg equilibrium.

¶ LDR = Ligation Detection Reaction.

Table 3

Logistic regression analyses of associations between *MALAT1* rs619586 A/G, *pri-miR-124-1* rs531564 C > G, *hsa-miR-34b/c* rs4938723 T > C and *hsa-miR-423* rs6505162 C > A polymorphisms and risk of lung cancer.

	Cases (n=917)		Controls (n=925)					
Genotype	n	%	n	%	Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
MALAT1 rs619586 A/G								
AA	758	83.85	686	75.88	1.00 (reference value)		1.00 (reference value)	
AG	141	15.60	197	21.79	0.65 (0.51–0.82)	<.001	0.65 (0.51–0.83)	.001
GG	5	0.55	21	2.32	0.22 (0.08–0.58)	.002	0.22 (0.08–0.59)	.003
GG vs AG vs AA								<.001
AG/GG	146	16.15	218	24.12	0.61 (0.48–0.77)	<.001	0.61 (0.48–0.78)	<.001
AA/AG	899	99.45	883	97.68	1.00 (reference value)		1.00 (reference value)	
GG	5	0.55	21	2.32	0.23 (0.09–0.62)	.004	0.24 (0.09–0.64)	.004
G allele	151	8.35	239	13.22				
pri-miR-124-1 rs531564 C > G								
CC	672	73.6	648	72.2	1.00 (reference value)		1.00 (reference value)	
CG	214	23.4	221	24.6	0.93 (0.75–1.16)	.535	0.94 (0.76–1.17)	.569
GG	27	3.0	28	3.1	0.93 (0.54–1.60)	.792	0.94 (0.55–1.62)	.826
GG vs CG vs CC								.808
CG + GG	241	26.4	249	27.8	0.93 (0.76–1.15)	.514	0.94 (0.76–1.16)	.554
CC + CG	886	97.0	869	96.9	1.00		1.00	
GG	27	3.0	28	3.1	0.95 (0.55–1.62)	.839	0.96 (0.56–1.64)	.869
G allele	268	14.7	277	15.4				
hsa-miR-34b/c rs4938723 T > C								
TT	406	44.4	422	46.1	1.00 (reference value)		1.00 (reference value)	
TC	413	45.1	398	43.4	1.08 (0.89–1.31)	.444	1.08 (0.89–1.31)	.449
CC	96	10.5	96	10.5	1.04 (0.76–1.42)	.809	1.04 (0.76–1.42)	.817
CC vs TC vs TT								.746
TC + CC	509	55.6	494	53.9	1.07 (0.89–1.29)	.465	1.07 (0.89–1.29)	.472
TT + TC	819	89.5	820	89.5	1.00		1.00	
CC	96	10.5	96	10.5	1.00 (0.74–1.35)	.994	1.00 (0.74–1.35)	.999
C allele	605	33.1	590	32.2				
hsa-miR-423 rs6505162 C > A								
CC	573	64.6	571	63.9	1.00 (reference value)		1.00 (reference value)	
CA	277	31.2	291	32.6	0.95 (0.78–1.16)	.607	0.95 (0.77–1.16)	.591
AA	37	4.2	31	3.5	1.19 (0.73–1.94)	.490	1.21 (0.74–1.98)	.442
AA vs CA vs CC								.651
CA + AA	314	35.4	322	36.1	0.97 (0.80–1.18)	.772	0.97 (0.80–1.18)	.763
CC + CA	850	95.8	862	96.5	1.00		1.00	
AA	37	4.2	31	3.5	1.21 (0.74–1.97)	.443	1.24 (0.76–2.01)	.396
A allele	351	19.8	353	19.8				

* Adjusted for age, sex, smoking and drinking status.

OR: 1.00, 95% CI: 0.74–1.35, $P = .999$). Using the *hsa-miR-34b/c* rs4938723 TT homozygous genotype as the reference group, neither the TC genotype (TC vs TT: adjusted OR: 1.08, 95% CI: 0.89–1.31, $P = .449$) nor CC genotype (CC vs TT: adjusted OR: 1.04, 95% CI: 0.76–1.42, $P = .817$) were associated with risk of lung cancer. In the dominant model, *hsa-miR-34b/c* rs4938723 TC/CC variants were not associated with lung cancer risk, compared with the *hsa-miR-34b/c* rs4938723 TT genotype (adjusted OR: 1.07, 95% CI: 0.89–1.29, $P = .472$) (Table 3). Moreover, no association was observed between *pri-miR-124-1* rs531564 C > G and *hsa-miR-423* rs6505162 C > A polymorphisms and the risk of lung cancer (Table 3).

4. Discussion

In this hospital-based case-control study, we investigated the potential correlations of *MALAT1* rs619586 A/G, *hsa-miR-34b/c* rs4938723 T > C, *pri-miR-124-1* rs531564 C > G and *hsa-miR-423* rs6505162 C > A polymorphisms with susceptibility to lung cancer. Data from our multivariable logistic analyses supported the association of *MALAT1* rs619586 A/G polymorphisms with a decreased risk of lung cancer.

LncRNAs serve as precursors of small non-coding RNAs to produce microRNAs (miRNA) and endogenous small interfering RNAs or as a "miRNA sponge" to inhibit miRNA activity.[35,36] LncRNAs also act as scaffolds during the formation of cellular substructures or protein complexes.[37] Several lncRNAs have been shown to function as oncogenes or tumor suppressors. Previous research suggests that lncRNAs play integral roles in control of cellular growth, division and differentiation and use various mechanisms to control the cancer state. Perturbation of lncRNA expression can contribute to the development and progression of cancer. MALAT1 is a nuclear-enriched abundant transcript expressed in the lung, pancreas, nerve system and other healthy organs. Elevated expression of highly conserved MALAT1 has been detected in various cancer types, including lung cancer, endometrial stromal sarcoma, hepatocellular carcinoma, breast cancer and pancreatic cancer.[11]

The p53 gene regulates expression of miRNAs, in particular, miR-34 family members.[20] Members of the miR-34 family are

direct p53 targets induced in response to DNA damage or oncogenic stress.[20] MiR-34b (concomitantly with miR-34a and c) is silenced in numerous cancer types via DNA methylation of its promoter region.[38] Loss of miR-34 impairs TP53-mediated cell death via triggering Wnt signaling cascades while its overexpression induces apoptosis.[39–41] A tumor suppressor role of miR-34a has also been demonstrated in vivo.[42] Previous studies have reported down-regulation of mir-34b/c via methylation in colorectal cancer,[21] oral cancer,[22] and malignant melanoma.[23] An earlier rat model experiment additionally showed that inflammation modulates miRNA expression in vivo and alterations in miR-34b/c under an inflammatory microenvironment are influenced by p53.[43]

Hsa-miR-34b/c rs4938723 is located within the CpG island of pri-miR-34b/c and the position 423 bp upstream from the transcription start site is the predicted binding site for GATA-X transcription factors.[24] Polymorphisms of rs4938723C/T are located in the promoter region of pri-miR-34b/c in the CpG is land. Variations of rs4938723C to T may affect predicted GATA-X transcription factor binding and subsequent expression of target genes related to tumor differentiation and carcinogenesis. The *hsa-miR-34b/c* rs4938723 T > C polymorphism is associated with risk of nasopharyngeal carcinoma,[25] hepatocellular carcinoma,[26] colorectal cancer[27] and breast cancer survival.[28]

Several limitations of the present study need to be addressed when interpreting our findings. This was a hospital-based case-control study and selection bias may have inevitably occurred. Moreover, owing to the moderate sample sizes evaluated, our single case-control study had limited power to fully clarify the correlations of *MALAT1* and *hsa-miR-34b/c*, *pri-miR-124-1* and *hsa-miR-423* polymorphisms with susceptibility to lung cancer. To validate our findings, investigations with larger samples and detailed individual information should be undertaken. Finally, because lung cancer risk is affected by multiple environmental factors, gene-gene and gene-environment interactions, *MALAT1*, *hsa-miR-34b/c*, *pri-miR-124-1* and *hsa-miR-423* may be associated with differential degrees of genetic risk in different ethnicities and upon exposure to diverse environment-related risk factors.

In summary, our results provide evidence that *MALAT1* rs619586 A/G functional polymorphisms may serve as susceptibility loci for lung cancer. Further studies are required to validate or refute the results of this preliminary study.

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Author contributions

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