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Original Article

Variants in multi-gene polymorphism association analysis of lung cancer in the Chinese Han population

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Abstract: Lung cancer (LC) is a common malignant tumor that is influenced by an interaction between genetic and environmental factors. Until now, the inherited factors of lung cancer have not been clear. Our study selected 16 tag single nucleotide polymorphisms (tSNPs) to investigate whether they were associated with lung cancer in the Han population. In this Han Chinese case-control study, we genotyped 554 cases and 696 controls using Sequenom MassARRAY technology and analyzed their associations with the cancer using χ^2 test, SNPStats software, and Microsoft Excel. Based on χ^2 tests, RBMS3-rs1530057 (P=0.05), TP63-rs4488809, rs10937405 (P=0.013, P=0.014), VTI1A-rs7086803 (P=0.03) and RAD52-rs10849605 (P=0.008) correlate with lung cancer risk. In the genetic model analyses, increased risk for lung cancer was associated with the genotypes "TT" in rs4488809 (OR=1.38, 95% CI, 1.03-1.86; P=0.033) in the recessive model and under the log-additive model (OR=1.2, 95% CI=1.00-1.43, P=0.046). Also, our analysis revealed the genotype "C/C" in rs10849605 was associated with increased risk of lung cancer under the codominant model (OR=1.71, 95% CI=1.13-2.58, P=0.039), the recessive model (OR=1.62, 95% CI=1.10-2.39, P=0.015), and under the log-additive model (P=0.021, OR=1.25, 95% CI=1.03-1.50). We found four genes (RBMS3, TP63, VTI1A and RAD52) are associated with lung cancer susceptibility. In combination with previous reports, our results suggest that these genes may be associated with lung cancer in the Han population.

Keywords: Lung cancer, tag single nucleotide polymorphism (tSNP), case-control study

Introduction

Lung cancer, a leading cause of cancer-related mortality, is one of the most common tumors throughout the world. It is a major cause of cancer death worldwide with >1 million deaths each year. In china, the incidence and mortality rates of lung cancer increased rapidly in the last three decades, which imposes an enormous burden on patients, health-care professionals, and society [1]. Tobacco smoke, environmental pollution, occupational exposures, and preexisting lung disease increase the risk of lung cancer. However, patients have been diagnosed with lung cancer in the absence of these risk factors [2]. Studies have emphasized identification of the relationship between germline polymorphisms and susceptibility to lung cancer, so that we can use molecular markers to classify carcinoma of the lungs in more homogenous groups.

In the present study, we selected 16 SNPs which have previously been reported to be associated with the lung cancer susceptibility to investigate and validate their potential association with lung cancer risk. An extensive association analysis was conducted in a case-control study in a Han Chinese population. Our data provided considerable evidence for the association between common SNPs and lung cancer susceptibility.

Materials and methods

Study population

We recruited 554 lung cancer patients and 696 controls for the case-control study from Xi'an

Table 1. Basic characteristics of case and control patients

Characteristics	Cases (n=554)		Control (n=696)	
Age (means ± SD, year)	58.17±10.53		48.57±9.47	
Sex				
Male	416	75.1	392	56.3
Female	138	24.9	304	43.7

city, the capital of Shanxi province. Cases were recruited from the First Affiliated Hospital of Xi'an Jiao Tong University. Eligible cases were newly diagnosed with lung cancer, lived in Xi'an city for 10 years or more, medically in stable condition and willing to participate in the study. All included patients had histopathologically confirmed primary lung cancer. Control subjects were randomly recruited from the health centers of the hospitals during the same period. We excluded cases that underwent radiotherapy or chemotherapy as well as controls with chronic disease. All of the participants were genetically unrelated ethnic Han Chinese from Shanxi Province and provided written informed consent for their participation in the present study. The protocols for this study were conducted according to the Declaration of Helsinki and were approved by the Ethical Committee of the Medical College, Xi'an Jiaotong University. All subjects signed informed consent forms.

Demographic and related clinical data of the study population was collected by a face-to-face questionnaire and medical case record. Five milliliters of whole blood were collected from each subject into tubes containing ethylenediaminetetraacetic acid (EDTA) at the time of initial diagnosis. After centrifugation, the samples were stored at -80°C until further use.

tSNP selection and genotyping

A total of 16 candidate tSNPs from nine genes were selected for our study, each with a MAF greater than 5% in the HapMap Chinese Han Beijing population. DNA was extracted from the peripheral blood using the GoldMag® Whole Blood Genomic DNA Extraction kit (GoldMag Ltd. Xi'an, China) according to the manufacturer's instructions. The concentrations were measured using the NanoDrop™ 2000 (Thermo Scientific. Waltham, Massachusetts, USA). A Sequenom MassARRAY® mass spectrometry analyzer (Sequenom, San Diego, CA, USA) was used to genotyping and data were managed using Sequenom Typer 4.0 Software (Sequenom, San Diego, CA, USA) [3, 4].

Statistical analysis

Statistical analyses were performed using Microsoft Excel and statistical software (SPSS 18.0, Chicago, IL). All *p* values in this study were two-sided. A *p*-value of less than 0.05 was considered the threshold for statistical significance. Hardy-Weinberg equilibrium (HWE) of each tSNP in control group was tested by Fisher's exact test [5]. Allele frequencies and genotype frequencies for each SNP of patients and control subjects were compared using the Chi squared test. Unconditional logistic regression analysis were performed to obtain the odds ratios (ORs) for risk of lung cancer and their 95% confidence intervals (CI), adjusted for age and sex [6]. Associations between genotypes and lung cancer risk were tested in different genetic models (codominant, dominant, recessive, and log-additive) by SNPStats website software http://bioinfo.iconcologia.net/snpstats/start.htm [7].

Results

The present study comprised 554 lung cancer (138 females, 416 males; median age 58.17 years) cases and 696 controls (304 females, 392 males; median age 48.57 years). There was a significant difference between the cases and controls in terms of gender and mean age distribution (**Table 1**). As listed in the **Table 2**, the basic characteristics of the SNPs in the study population are clearly shown. One locus (rs6089953) was removed because it did not fit HWE in the control subjects. The association between SNP genotypes and the susceptibility of alleles to lung cancer was all performed by Pearson χ^2 test.

We hypothesized that the minor allele of each SNP was a risk factor compared with the wild-type allele. Four genetic analysis models (codominant, dominant, recessive and log-additive) were applied to assess the association between SNPs and lung cancer risks using the unconditional logistic-regression analysis. Based on χ^2 tests, RBMS3-rs1530057 (P=0.05), TP63-rs4488809, rs10937405 (P=0.013, P=0.014), VTI1A-rs7086803 (P=0.03) and RAD52-rs10849605 (P=0.008) correlate with lung cancer risk. In the genetic model analyses, in **Table 3** increased risk for lung cancer was

Table 2. Basic information of candidate tSNPs in this study

SNP	Gene name	Position	Base change	MAF Case	MAF control	p HWE	ORs	95% CI	*p*-value
rs2808630	CRP	159680868	C/T	0.159	0.171	0.279	0.91	0.74-1.13	0.404
rs10197940		152253918	C/T	0.467	0.490	0.94	0.91	0.78-1.07	0.246
rs1530057	RBMS3	29575463	A/C	0.060	0.080	0.114	0.73	0.53-1	0.05
rs4488809	TP63	189356261	T/C	0.510	0.460	0.819	1.22	1.04-1.43	0.013
rs10937405	TP63	189383183	T/C	0.266	0.311	0.111	0.8	0.67-0.96	0.014
rs7626795	IL1RAP	190350461	G/A	0.204	0.196	0.81	1.05	0.86-1.28	0.638
rs3817963	BTNL2	32400310	G/A	0.252	0.246	0.919	1.03	0.86-1.24	0.74
rs9387478		117786180	A/C	0.475	0.466	0.171	1.03	0.88-1.21	0.674
rs9390123	PHACTR2	143943314	C/T	0.366	0.398	0.179	0.87	0.74-1.03	0.107
rs1926203	ACTA2	90727334	T/G	0.156	0.157	0.774	0.99	0.8-1.24	0.956
rs7086803	VTI1A	114498476	A/G	0.291	0.252	0.763	1.22	1.02-1.45	0.03
rs10849605	RAD52	1064438	C/T	0.371	0.320	0.542	1.25	1.06-1.48	0.008
rs753955		24293859	C/T	0.338	0.355	0.508	0.93	0.79-1.1	0.397
rs748404	TGM5	43559231	C/T	0.073	0.067	0.539	1.1	0.81-1.5	0.539
rs8034191	AGPHD1	78806023	C/T	0.032	0.032	1	1	0.64-1.57	0.995
rs9635542	SEC14L5	5001380	G/A	0.446	0.435	0.643	1.04	0.89-1.22	0.596
rs7216064	BPTF	65898809	G/A	0.432	0.428	1	1.02	0.87-1.19	0.823
rs13181	KLC3	45854919	G/T	0.087	0.091	0.643	0.95	0.72-1.26	0.735
rs6089953	STMN3	62291008	G/A	0.261	0.240	0.007	1.12	0.93-1.34	0.23
rs6062302	TNFRSF6B	62320968	C/T	0.274	0.245	0.125	1.16	0.97-1.39	0.099
rs2236507	TNFRSF6B	62323006	C/G	0.264	0.240	0.021	1.13	0.94-1.36	0.18
rs2297441	TNFRSF6B	62327582	A/G	0.335	0.310	0.25	1.13	0.95-1.33	0.17
rs36600	MTMR3	30337586	T/C	0.147	0.140	0.433	1.06	0.85-1.33	0.618

MAF minor allele frequency, OR odds ratio, CI confidence interval. *P<0.05 indicates statistical significance.

associated with the genotypes "TT" in rs4488809 (OR=1.38, 95% CI, 1.03-1.86; P=0.033) in the recessive model and under the log-additive model (OR=1.2, 95% CI=1.00-1.43, P=0.046). In **Table 4**, our analysis revealed the genotype "C/C" in rs10849605 was associated with increased risk of lung cancer under the codominant model (OR=1.71, 95% CI=1.13-2.58, P=0.039), the recessive model (OR=1.62, 95% CI=1.10-2.39, P=0.015), and under the log-additive model (P=0.021, OR=1.25, 95% CI=1.03-1.50). We found four genes (RBMS3, TP63, VTI1A and RAD52) are associated with lung cancer susceptibility.

Discussion

We genotyped 16 tSNPs and found four tSNPs that were associated with LC, which suggested that three genes may contribute to LC in the Han population.

RNA-binding motif, single-stranded interacting protein 3 (RBMS3) is identified as a candidate tumor suppressor gene. On the one side, deletion of the short arm of chromosome 3 is one of the most frequent genetic alterations in lung cancers [8-12]. Furthermore, RBMS3 which is located on human short arm of chromosome 3 [13, 14], is a gene that encodes an RNA-binding protein that belongs to the c-Myc family of single-stranded RNA-binding proteins [15]. Moreover, the recent studies reported that RBMS3 was downregulated at both the mRNA and protein levels in lung cancer, suggesting that RBMS3 might play a pivotal role in the lung cancer development and progression. C-Myc is a common proto-oncogene that promotes proliferation, malignant transformation and progression of tumors through transcriptional regulation of its target genes [16, 17]. RBMS3 may act independently of the canonical Wnt1/b-catenin signaling pathway possibly by directly binding to the promoter region of c-Myc and regulating its expression.

rs4488809 and rs10937405 are located at the first intron of Tumor protein p63 (TP63) at chromosome 3q28. We found that rs4488809

Table 3. Relationship between rs4488809 and the risk of LC (adjusted by sex + age)

Model	Genotype	Control	Case	OR (95% CI)	*p* value	AIC	BIC
Co-dominant	C/C	201 (28.9%)	138 (24.9%)	1	0.092	1427.4	1453
	C/T	349 (50.2%)	267 (48.2%)	1.07 (0.79-1.46)			
	T/T	145 (20.9%)	149 (26.9%)	1.45 (1.01-2.07)			
Dominant	C/C	201 (28.9%)	138 (24.9%)	1	0.25	1428.9	1449.4
	C/T-T/T	494 (71.1%)	416 (75.1%)	1.18 (0.89-1.58)			
Recessive	C/C-C/T	550 (79.1%)	405 (73.1%)	1	0.033	1425.6	1446.1
	T/T	145 (20.9%)	149 (26.9%)	1.38 (1.03-1.86)			
Log-additive	---	---	---	1.20 (1.00-1.43)	0.046	1426.2	1446.7

Table 4. Relationship between rs10849605and the risk of LC (adjusted by sex + age)

Model	Genotype	Control	Case	OR (95% CI)	*p* value	AIC	BIC
Codominant	T/T	318 (45.7%)	224 (40.5%)	1	0.039	1424.6	1450.2
	T/C	311 (44.7%)	248 (44.9%)	1.12 (0.85-1.46)			
	C/C	67 (9.6%)	81 (14.7%)	1.71 (1.13-2.58)			
Dominant	T/T	318 (45.7%)	224 (40.5%)	1	0.12	1426.7	1447.2
	T/C-C/C	378 (54.3%)	329 (59.5%)	1.22 (0.95-1.58)			
Recessive	T/T-T/C	629 (90.4%)	472 (85.3%)	1	0.015	1423.2	1443.7
	C/C	67 (9.6%)	81 (14.7%)	1.62 (1.10-2.39)			
Log-additive	---	---	---	1.25 (1.03-1.50)	0.021	1423.8	1444.3

was associated with increased lung cancer risk, which was same with the previous studies. Whereas, we confirmed that rs10937405 was associated with decreased risk. Rs10937405 variant which confered a harmful effect on LC was previously reported in a GWAS conducted in Japan and South Korea [18], but because we studied a different ethnic group, our results is different. TP63 is a member of the tumor suppressor P53 gene family, which is pivotal to cellular differentiation and responsiveness to cellular stress. TP63 is expressed mainly in two isoforms, the TA and N-terminal-truncated (ΔN) forms. The TAp63 isoforms are transcribed using a promoter-located upstream of exon 1 of the gene, whereas expression of the ΔNp63 isoforms are regulated by a promoter within intron 3 of TP63 [19]. Exposure of cells to DNA damage leads to induction of TP63 and both isoforms have the ability to transactivate TP53 target genes, hence impacting on cellular responsiveness to DNA damage [20, 21]. The rs10937405 and rs4488809 may impact TP63 expression directly or indirectly through different way.

The association signal rs7086803 maps to intron 7 of the Vps10p tail interacting 1A (VTI1A) gene at chromosome 10q25.2, which has been involve in lung carcinogenesis. Loss of VTI1A activity has been reported to reduce high-frequency spontaneous neurotransmitter release and rapid progressive neuro-degeneration in the peripheral ganglia [22, 23]. VTI1A is also involved in Acrp30-containing vesicles in adipocytes, and lower amounts of VTI1A in cultured adipocytes can inhibit adiponectin secretion [24]. Lower amounts of adiponectin have previously been associated with advanced lung cancer [24, 25].

rs10849605 is located at chromosome 12p 13.33, a locus that contains the RAD52 gene. A key role of RAD52 is to provide cells with a level of redundancy in DNA repair [26]. RAD52 is therefore particularly important in cells deficient in the BRCA1-PALB2-BRCA2 pathway, providing an alternate mechanism for DNA repair [27, 28]. Targeted inhibition of RAD52 in BRCA2 deficient cells results in genomic instability and cell growth inhibition, leading to the suggestion of RAD52 as a potential therapeutic target using synthetic lethality approaches [29].

Several limitations in our study should be acknowledged. On the one hand, despite our ability to identify genetic associations with LC, we were not able to elucidate causal mechanisms. And on the other side, the most important limitation of study was the sample size and

patients were not subgrouped by age or gender. Furthermore, we may have needed more participants to detect interactions between the risk factors and genetic polymorphisms in association with lung cancer.

Conclusion

In conclusion, our study described the association between RBMS3-rs1530057, TP63-rs4488809, rs10937405, VTI1A-rs7086803, RAD52-rs10849605 and lung cancer risk in the Han population. Further studies on the association of these genes with lung cancer in affiliation with risk factors are warranted in larger studies and in different populations. Additionally, the functional mechanisms of the four genes need to be studied further to better understand their role in risk of lung cancer.

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Disclosure of conflict of interest

None.

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