

# Association between *RTEL1* gene polymorphisms and COPD susceptibility in a Chinese Han population

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**Objective:** We investigated the association between single-nucleotide polymorphisms in regulation of telomere elongation helicase 1 (*RTEL1*), which has been associated with telomere length in several brain cancers and age-related diseases, and the risk of chronic obstructive pulmonary disease (COPD) in a Chinese Han population.

**Methods:** In a case-control study that included 279 COPD cases and 290 healthy controls, five single-nucleotide polymorphisms in *RTEL1* were selected and genotyped using the Sequenom MassARRAY platform. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression after adjusting for age and gender.

**Results:** In the genotype model analysis, we determined that rs4809324 polymorphism had a decreased effect on the risk of COPD (CC versus TT: OR =0.28; 95% CI =0.10–0.82;  $P=0.02$ ). In the genetic model analysis, we found that the “C/C” genotype of rs4809324 was associated with a decreased risk of COPD based on the codominant model (OR =0.33; 95% CI =0.13–0.86;  $P=0.022$ ) and recessive model (OR =0.32; 95% CI =0.12–0.80;  $P=0.009$ ).

**Conclusion:** Our data shed new light on the association between genetic polymorphisms of *RTEL1* and COPD susceptibility in the Chinese Han population.

**Keywords:** *RTEL1*, chronic obstructive pulmonary disease, COPD, gene polymorphisms, association study, case-control study

## Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation caused by chronic bronchitis, emphysema, and/or disease of small airways.<sup>1</sup> COPD is one of the leading causes of morbidity and mortality worldwide.<sup>2</sup> In The People's Republic of China, with the worsening of PM2.5, more and more people suffer from pulmonary disease and a large number died prematurely because of its complications. In the past few years, cigarette smoking is considered as the most significant risk factor of COPD; however, not all smokers will develop COPD.<sup>3</sup> The development of COPD is a result of the interaction between environment factors and a complex array of genetic traits.<sup>4</sup>

Regulator of telomere elongation helicase1 (*RTEL1*) is a DNA helicase crucial for regulation of telomere length that plays a role in a variety of fundamental cellular mechanisms such as DNA replication, genome stability, DNA repair, and telomere maintenance.<sup>5,6</sup> Several genome-wide association studies have revealed statistically significant associations between glioma susceptibility and single-nucleotide polymorphisms (SNPs) in *RTEL1*, such as rs4809324, rs6010620,<sup>7</sup> and rs2297440.<sup>8</sup> A recent study showed that mutations in *RTEL1* represent an important contributor to pulmonary

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fibrosis risk.<sup>9</sup> Moreover, *RTEL1* has been associated with airflow obstruction in a UK population.<sup>10</sup> However, little is known about the association between *RTEL1* polymorphisms and risk of COPD.

Hainan is located off the southern coast of the People's Republic of China and has little air pollution. People living in Hainan have longer average life expectancy than those living in heavily polluted areas. However, the incidence of COPD in the Hainan population is higher than that of other regions of the People's Republic of China. Therefore, to explore the contribution of genetic factors to the development of COPD in the Chinese population, we performed a case-control study to analyze the association between five SNPs in *RTEL1* and the risk of COPD in a Chinese Han population in Hainan.

## Materials and methods

### Study participants

All participants in our study were of Chinese Han population and living in Hainan. A total of 279 patients and 290 controls were consecutively recruited between June 2012 and July 2015 at the Hainan Province People's Hospital, People's Republic of China. There were no gender, age, or disease stage restrictions for case recruitment. All the cases were healthy before they were diagnosed with COPD. The diagnosis of COPD was confirmed according to the criteria established by the National Heart, Lung and Blood Institute/World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD).<sup>1</sup> The entry criteria for COPD cases were postbronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) <80% predicted and FEV<sub>1</sub>/forced vital capacity <70%. Patients were excluded from the study if they had other significant respiratory diseases such as lung cancer, pulmonary tuberculosis, cystic fibrosis, or bronchial asthma. The control group was randomly selected healthy individuals, which included current or ex-smokers with no known disease, no history of any disease, and no airflow limitation. All participants in the current study were not related by blood.

All of the participants provided written informed consent. The Human Research Committee for Approval of Research Involving Human Subjects, Hainan Province People's Hospital, approved the use of human blood samples in this study.

### SNP selection and genotyping

In this study, five SNPs in *RTEL1* were selected from previous studies for analysis.<sup>11,12</sup> The lower frequency alleles were coded as the minor allele. All of the SNPs had minor allele frequencies (MAFs) >5% in the HapMap Chinese Han Beijing population. Genomic DNA was isolated from whole-blood samples using the GoldMag-Mini Purification Kit (GoldMagCo. Ltd. Xi'an, People's Republic of China), and DNA concentrations were measured using the NanoDrop2000 (Thermo Scientific, Waltham, MA, USA). Sequenom MassARRAY Assay Design 3.0 software (San Diego, CA, USA) was used to design a multiplexed SNP Mass EXTENDED assay.<sup>13-15</sup> Genotyping was performed on a Sequenom MassARRAY RS1000 platform using the manufacturer's protocol. The PCR primers for each SNP are shown in Table 1. Data management and analysis was performed using the Sequenom Typer 4.0 Software.<sup>13,16</sup>

### Statistical analysis

We used Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and the SPSS 18.0 statistical package (SPSS, Chicago, IL, USA) to perform statistical analyses. All *P*-values presented in this study were two sided, and *P*=0.05 was considered the cutoff for statistical significance. Differences in the characteristics of the case and control study populations were analyzed using  $\chi^2$  tests for categorical variables and Welch's *t*-tests for continuous variables. In all analyses, the lower frequency allele was considered to be the "risk" allele. Control genotype frequencies for each SNP were tested for departure from Hardy-Weinberg Equilibrium using Fisher's exact tests. Allele and genotype frequencies in the cases and controls were compared using  $\chi^2$  tests.<sup>17</sup> Five models (log-additive, dominant, recessive, codominant, and

**Table 1** Primers used for this study

SNP ID	First PCR primer	Second PCR primer	UEP SEQ
rs6089953	ACGTTGGATGCCCTTCAAAGGACGATCGTT	ACGTTGGATGGCGTCTGTCCATAAAAAGGGC	GGGTTCCAGGTGGGGTC
rs6010620	ACGTTGGATGGCCTGTTTTCCCTTTTTGAG	ACGTTGGATGCTCTCAACATCTCAGCAACC	CAGATCATGCAAAGCAGG
rs6010621	ACGTTGGATGACCCATCCCTCCCCTCTGA	ACGTTGGATGAGCAGCAGAACAGCACCGAG	ACAGCACCGAGGAAAAG
rs4809324	ACGTTGGATGAGCCGTGTGCACAGATTCCAA	ACGTTGGATGGAGAAGTCAAGTGACATCAG	GTCAGAGGTCAATGGAAACA
rs2297441	ACGTTGGATGCTCAACTCCCACCACCAAG	ACGTTGGATGGTGTCCACTTTTAATCAGGG	GACAGGGCTCTCTAATAAA

**Abbreviations:** SNP, single-nucleotide polymorphism; UEP SEQ, unextended mini-sequencing primer.

overdominant) were used to assess the association between each genotype and the risk of COPD. The effects of the polymorphisms on the risk of COPD were expressed as odds ratios (ORs) with 95% confidence interval (CIs), which were calculated using unconditional logistic regression analysis after adjusting for age and gender.<sup>18</sup>

## Results

A total of 279 COPD cases (145 men and 134 women; mean age, 69.05±9.73 years) and 290 controls (148 men and 142 women; mean age, 56.13±14.05 years) were included in the study. The basic characteristics of the cases and controls are shown in Table 2. There were no significant differences in the gender distributions and smoking status between the case and control groups ( $P>0.05$ ).

The MAFs of the analyzed SNPs in the case and control groups are shown in Table 3. All SNPs were in Hardy–Weinberg equilibrium in the controls ( $P>0.05$ ). The MAFs of the SNPs in the control group were similar to those reported for the HapMap Asian population. No associations were observed between the alleles and COPD risk in an allele model.

The genotype frequencies of the *RTEL1* polymorphisms are shown in Table 4. Compared with the TT genotype, the CC frequency of rs4809324 polymorphism among cases was significantly different from controls (CC versus TT: OR =0.28; 95% CI =0.10–0.82;  $P=0.02$ ), which suggested that the rs4809324 polymorphism had a decreased effect on the risk of COPD.

Furthermore, we assumed that the minor allele of each SNP as a risk factor compared with the wild-type allele. Five genetic models (codominant, dominant, recessive, overdominant, and log-additive) were applied to analyze the

associations between the SNPs and risk of COPD using an unconditional logistic regression analysis with adjustments for age and gender. We found that the “C/C” genotype of rs4809324 was associated with a decreased risk of COPD based on the codominant model (OR =0.33; 95% CI =0.13–0.86;  $P=0.022$ ) and recessive model (OR =0.32; 95% CI =0.12–0.80;  $P=0.009$ ) (Table 5).

## Discussion

In this study, we investigated the associations between five selected *RTEL1* SNPs and risk of COPD in a Chinese Han population in Hainan. We found that rs4809324 is significantly associated with a decreased risk of COPD. Our results suggest that the polymorphisms of *RTEL1* may play an important role in the risk of COPD in the Chinese Han population.

Several studies have examined telomere length in the context of COPD. It has been demonstrated that COPD patients have short leukocyte telomeres, which are in turn associated with increased risk of COPD and cancer mortality.<sup>19,20</sup> The *RTEL1* gene is located on chromosome 20q13.3. *RTEL1* is an essential DNA helicase, which disassembles a variety of DNA secondary structures to facilitate its replication, repair, and recombination processes and helps to maintain telomere integrity.<sup>21</sup> Previous studies have shown overexpression of the *RTEL1* genomic locus in several cancers such as breast, lung, esophagus, gastric, and colorectal cancers.<sup>22–24</sup> Additionally, a mouse model demonstrated that *RTEL1* could support cell growth by participating in Wnt/b-catenin signaling,<sup>25</sup> which suggested that *RTEL1* may be considered as an oncogene. However, in the past decade, *RTEL1* variants have been identified to be associated with decreased risk of several brain cancers and age-related disease, including

**Table 2** Characteristics of cases and controls in this study

Variables	Case (N=279)	Control (N=290)	Total	P-value
Gender, number (%)				0.823 <sup>a</sup>
Male	145 (52)	148 (51)	293 (51.5)	
Female	134 (48)	142 (49)	276 (48.5)	
Smoking status				0.286 <sup>a</sup>
Smoker	93 (33.3)	85 (29.2)	178 (31.2)	
Nonsmoker	186 (66.7)	205 (70.8)	391 (68.8)	
Mean age ± SD	69.05±9.73	56.13±14.05		<0.001 <sup>b</sup>
FEV <sub>1</sub> % stage				
Mild (>80%)	21 (7.7)			
Moderate (50%–80%)	160 (57.4)			
Severe (30%–50%)	86 (30.8)			
Very severe (<30%)	12 (4.1)			

**Notes:** <sup>a</sup>P-value was calculated from Pearson's  $\chi^2$  tests. <sup>b</sup>P-value was calculated by Welch's *t*-tests.

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 second; SD, standard deviation.

**Table 3** Allele frequencies in cases and controls and odds ratio estimates for COPD

SNP ID	Gene	Band	Position	Role	Alleles A/B	P-value-HWE	MAF		P-value <sup>a</sup>	OR (95% CI)
							Case	Control		
rs6089953	<i>RTEL1</i>	20q13.33	62291008	Promoter	G/A	0.802	0.351	0.374	0.422	0.906 (0.711–1.154)
rs6010620	<i>RTEL1</i>	20q13.33	62309839	Intron	G/A	0.901	0.342	0.378	0.215	0.858 (0.673–1.093)
rs6010621	<i>RTEL1</i>	20q13.33	62310872	Intron	G/T	0.701	0.330	0.351	0.445	0.909 (0.711–1.162)
rs4809324	<i>RTEL1</i>	20q13.33	62318220	Intron	C/T	0.086	0.200	0.219	0.442	0.894 (0.671–1.190)
rs2297441	<i>RTEL1</i>	20q13.33	62327582	Intron	A/G	0.471	0.409	0.431	0.449	0.913 (0.721–1.156)

**Notes:** The position is based on the NCBI reference sequence NT\_011333.6. <sup>a</sup>P-values were calculated using two-sided  $\chi^2$  test.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; SNP, single-nucleotide polymorphism; Alleles A/B, Minor/major alleles; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium.

glioma,<sup>26</sup> astrocytoma,<sup>27</sup> glioblastomas,<sup>8</sup> and congenital dyskeratosis.<sup>28</sup> A mouse model further demonstrated that the *RTEL1-PCNA* interaction is critical for protecting cells against tumorigenesis.<sup>29</sup> These studies all suggested that *RTEL1* gene may function as a tumor-suppressor gene. In our study, we determined that *RTEL1* polymorphism is associated with decreased risk of COPD in the Chinese Han population, which supports for the tumor-suppressor role of *RTEL1* gene. Based on above studies and results, we speculated that overexpression or downregulation of *RTEL1* may both contribute to tumorigenesis.

In the present study, we investigated five SNPs in *RTEL1*, including rs6089953, rs6010620, rs6010621, rs4809324, and rs2297441. Among these SNPs, rs6010620, rs6010621, and rs4809324 were identified that have associations with distinct brain tumors in American and Chinese Han populations.<sup>7,30</sup> rs2297441 was found to be associated with Crohn's disease in Canadian children.<sup>31</sup> However, little information is found about rs6010621. In our study, we only found that rs4809324

is significantly associated with a decreased risk of COPD. As far as we know, we are the first to report the association between *RTEL1* polymorphisms rs4809324 and COPD risk, but the results identified here should be confirmed in further studies.

As is known, smoking is one of the most important risk factors of COPD. However, it is very interesting that the majority of our COPD group are lifelong nonsmokers who live in an area with little air pollution. It is also interesting that people who live in Hainan have longer life expectancy than those living in heavily polluted areas, yet a higher prevalence of COPD. Actually, Hainan is a major agricultural province in the People's Republic of China. The industry in Hainan is underdeveloped, so there is little air pollution in the area. So people who live in Hainan have longer life expectancy because of the good air quality. However, in the present study, >80% of the participants were indigenous farmers who lived in economically backward villages of Hainan. They lived in thatched huts that were made of

**Table 4** Genotypes frequencies of the SNPs and their associations with risk of COPD

SNP ID	Genotype	Genotype frequencies		Without adjustment		With adjustment	
		Case	Control	OR (95% CI)	P-value <sup>a</sup>	OR (95% CI)	P-value <sup>b</sup>
rs6089953	AA	117 (41.9%)	112 (38.6%)	1.00		1.00	
	AG	128 (45.9%)	139 (47.9%)	0.88 (0.62–1.26)	0.484	0.88 (0.59–1.32)	0.534
	GG	34 (12.2%)	39 (13.5%)	0.83 (0.49–1.42)	0.502	0.72 (0.39–1.33)	0.295
rs6010620	AA	118 (42.3%)	113 (39%)	1.00		1.00	
	AG	131 (46.9%)	135 (46.5%)	0.93 (0.65–1.32)	0.683	0.96 (0.64–1.44)	0.835
	GG	30 (10.8%)	42 (14.5%)	0.68 (0.40–1.17)	0.164	0.66 (0.36–1.23)	0.193
rs6010621	TT	123 (44.1%)	123 (42.6%)	1.00		1.00	
	TG	128 (45.9%)	129 (44.6%)	0.99 (0.70–1.41)	0.965	1.01 (0.68–1.50)	0.969
	GG	28 (10%)	37 (12.8%)	0.75 (0.44–1.31)	0.321	0.73 (0.38–1.37)	0.320
rs4809324	TT	171 (62.4%)	182 (63.2%)	1.00		1.00	
	TC	97 (35.4%)	88 (30.6%)	1.18 (0.83–1.68)	0.367	1.24 (0.83–1.85)	0.297
	CC	6 (2.2%)	18 (6.2%)	0.33 (0.13–0.86)	0.023*	0.28 (0.10–0.82)	0.020*
rs2297441	GG	96 (34.4%)	97 (33.6%)	1.00		1.00	
	GA	138 (49.5%)	135 (46.7%)	1.03 (0.71–1.49)	0.864	1.01 (0.66–1.54)	0.96
	AA	45 (16.1%)	57 (19.7%)	0.80 (0.49–1.30)	0.358	0.73 (0.42–1.27)	0.27

**Notes:** <sup>a</sup>P-values were calculated from unconditional logistic regression analysis. <sup>b</sup>P-values were calculated by unconditional logistic regression analysis with adjustments for age and gender. \*P $\leq$ 0.05 indicates statistical significance.

**Abbreviations:** SNP, single-nucleotide polymorphism; COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

**Table 5** Association between rs4809324 and risk of COPD in multiple inheritance models (adjusted by gender, age, and smoking status)

Model	Genotypes	Case	Control	Without adjustment				With adjustment			
				OR (95% CI)	P-value	AIC	BIC	OR (95% CI)	P-value	AIC	BIC
Codominant	T/T	171 (62.4%)	182 (63.2%)	1	0.022*	784.1	797.1	1	0.022*	632.7	658.7
	T/C	97 (35.4%)	88 (30.6%)	1.18 (0.83–1.68)				1.25 (0.83–1.88)			
	C/C	6 (2.2%)	18 (6.2%)	0.33 (0.13–0.86)				0.28 (0.10–0.85)			
Dominant	T/T	171 (62.4%)	182 (63.2%)	1	0.87	789.7	798.4	1	0.7	638.2	659.9
	T/C-C/C	103 (37.6%)	106 (36.8%)	1.03 (0.73–1.45)				1.08 (0.73–1.60)			
Recessive	T/T-T/C	268 (97.8%)	270 (93.8%)	1	0.009*	782.9	791.6	1	0.009*	631.9	653.6
	C/C	6 (2.2%)	18 (6.2%)	0.32 (0.12–0.80)				0.26 (0.09–0.78)			
Overdominant	T/T-C/C	177 (64.6%)	200 (69.4%)	1	0.2	788.1	796.8	1	0.15	636.3	658
	T/C	97 (35.4%)	88 (30.6%)	1.26 (0.88–1.78)				1.34 (0.90–2.01)			
Log-additive	–	–	–	0.89 (0.67–1.19)	0.44	789.1	797.8	0.91 (0.65–1.28)	0.6	638.1	659.7

**Note:** \*P-value  $\leq 0.05$  indicates statistical significance.

**Abbreviations:** OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; AIC, Akaike's Information criterion; BIC, Bayesian Information criterion.

some combustible materials including couch grass, timbo, and bamboo. Their kitchens are low and wet and with bad ventilation. Moreover, most of the indigenous farmers used straw and leaves for fuels. We suggested that these are the reasons contributing to the high prevalence of COPD.

Our study had several intrinsic limitations. For example, COPD is a heterogeneous disease, and tobacco consumption is an important risk factor for COPD. Because our study had a relatively small size, we did not conduct population stratification of smokers, so we could not explore the interactions between genetic polymorphisms and environmental factors in COPD patients. Therefore, the relationship between *RTEL1* polymorphisms and smoking status in COPD must be evaluated in future studies.

## Conclusion

Our present study provided evidence that SNPs in the *RTEL1* are associated with COPD in a Chinese Han population. It is possible that these variants are COPD risk factors, and these data can provide a theoretical foundation for other researchers to further study the association between the *RTEL1* gene and COPD risk in the Chinese Han or other populations.

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## Disclosure

The authors report no conflicts of interest in this work.

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