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Original Article

Association between *TAP2* and *SEC14L2* polymorphisms and pulmonary tuberculosis risk in the Tibetan Chinese population

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Abstract: Aim: Pulmonary tuberculosis (PTB) is an infectious disease with a high incidence worldwide. Previous genome-wide association studies have identified multiple susceptibility loci for pulmonary tuberculosis (PTB); however, validation of these findings is still needed. Methods: For this study, we recruited 300 subjects with PTB and 300 healthy subjects from a Tibetan population living in near or in Xi'an, China. Association analyses of single-nucleotide polymorphisms (SNPs) in *TAP2* and *SEC14L2* were performed with SPSS Statistics (version 17.0), SNPStats, Haploview (version 4.2), and SHEsis software. Results: We found a correction between one SNP (rs1061660) and PTB based on Chi-square or Fisher's exact tests. In the allelic model analysis, the SNPs rs1061660 in *SEC14L2* gene increased PTB 1.32-fold risk (OR = 1.32, CI = 1.05-1.66, *P* = 0.017). In the genetic model analysis, the rs3819721 in *TAP2* gene was associated with increased 1.65-fold risk in the co-dominant model and 1.67-fold risk in the over-dominant model, respectively. For the rs1061660 in *SEC14L2* gene, we found it was associated with a 1.49-fold increase the risk of PTB in the dominant model and a 1.37-fold increase the risk of PTB in the log-additive model, respectively. Conclusion: We found that two SNPs are associated with increased PTB risk in the Chinese Tibetan population.

Keywords: PTB, *TAP2, SEC14L2*, genetic polymorphisms, Tibetan population

Introduction

Pulmonary tuberculosis (PTB), as one of the most communicable diseases in humans, is caused by various strains of mycobacteria frequently Mycobacterium tuberculosis [1, 2]. According to the World Health Organization (WHO) report, most of the estimated number of TB cases occurred in Asia (55%) and Africa (30%). PTB with 8 million new cases and 1.5 million deaths worldwide annually remains as a major global health problem [3]. The number of PTB patients in China is the second largest in the world, and China is ranked on a list of 22 high-burden countries. Though one third of human infected with Mycobacterium tuberculosis, only 10% of the infected persons develop the clinical disease [4]. Correlative evidence indicates that in addition to the environment, genetic factors play an important role in susceptibility to PTB [5-7].

Previous studies have identified genes that confer disease susceptibility by regulating the immune response [8, 9]. We expect that identification of host genetic factors for PTB susceptibility might play a key role in PTB control worldwide. Genetic research has provided insight into tuberculosis, including the pathological and cytological bases of PTB. Several genes that influence PTB risk have been identified, including *CCL2* [10], *MIF* [11], *CD14* [12], *TNF* [13], *IL18* [14], Vitamin D receptor gene [15], *P2X7R [16]*, *SP110* and *PMP22* [17]. Most of genes contribute in immune response and their genetic polymorphisms may associate with PTB. Many studies showed that *TAP2* and *SEC14L2* gene are considered to be associated with a number of immune diseases, viral infection diseases, and even cancer [2, 18-20]. Tuberculosis, as a kind of immune disease, its susceptibility may be associated with *TAP2* and *SEC14L2* gene.

Table 1. General characteristics the of this study population

Variable	Cases (n = 300)	%	Controls (n = 300)	%	*P*-value
Sex					< 0.001
Male	167	55.7%	238	79.3%	
Female	133	44.3%	61	20.3%	
Age, yr (mean ± SD)	37.7±15.3		22.8±1.6		< 0.001

Although genome-wide association studies (GWAS) found that some sites have relationships with PTB, but studies about the loci of *TAP2* and *SEC14L2* genes have little reported. Thus, in this study, we conducted a comprehensive association analysis between PTB and 6 susceptible SNPs in the *TAP2* and *SEC14L2* genes, to further clarify their potential roles in disease and reveal the association between common SNPs and PTB risk in the Tibetan Chinese population.

Materials and methods

Ethics statement

Our present study strictly observed the principles of the Declaration of Helsinki of the World Medical Association and was approved by the Ethics Committee of Tangdu Hospital affiliated with The Fourth Military Medical University in Xi'an. Informed consent forms were signed by all participants.

Study participants

Between October 2014 and September 2016, we selected 600 individuals in Tangdu Hospital and Xi'an Tuberculosis and Thoracic Tumor Hospital, including 300 PTB patients and 300 healthy controls. All PTB patients were ethnic of Tibetan and were newly diagnosed with consistent chest radiography and a positive sputum smear. Patients with human immunodeficiency virus (HIV), diabetes mellitus, or other tuberculosis diseases or who used immunosuppressive drugs were excluded. Individuals in the control group had no PTB history and no evidence of PTB in chest radiography or a positive sputum smear. We recruited subjects without consideration of age and gender.

SNP selection

We selected 6 SNPs with a minor allele frequency (MAF) above 5% in the HapMap Chinese Tibetan population. We selected these SNPs on the basis of their allele frequencies, location, and disease relevance through public HapMap databases (http://www.Hapmap.org/index.html.en).

Genotyping

Genomic DNA was extracted from peripheral blood samples using a genomic DNA purification kit (GoldMag, Xi'an, China). We used spectrometry (DU530 UV/VIS spectrophotometer, Beckman Instruments, Fullerton, CA) to measure the DNA concentration. The primers for amplification and extension reactions were designed with Sequenom MassARRAY Assay Design 3.0 Software (Sequenom, San Diego, CA) [21]. We used Sequenom MassARRAY RS1000 to perform the SNP genotyping with the agreement of the manufacturer [21], and we used Sequenom Typer 4.0 software for data management and analysis [21, 22].

Statistical analysis

Microsoft Excel (Microsoft, Redmond, WA) and SPSS Statistics (version 17.0, SPSS, Chicago, IL) were used for statistical analyses. All *p*-values were two-tailed, and $P \leq 0.05$ was considered to be statistically significant. SNP genotype frequencies in the case and control groups were calculated by Chi-square Test, and the Hardy-Weinberg equilibrium (HWE) was used to check the genotype frequency of the control group. Unconditional logistic regression analysis was used to examine the odds ratios (ORs) and 95% confidence intervals (CIs) in order to assess the association between SNPs and PTB [23]. Three models (dominant, recessive, log-additive) were used to test the association between SNPs and PTB [24]. Furthermore, Haploview (version 4.2, Broad Institute, Cambridge, MA) and SHEsis software (http://www.nhgg.org/analysis/) were used for checking the linkage disequilibrium structure.

Results

Characteristics of the participants

This study involved 600 subjects, including 300 patients (167 males and 133 females; age at diagnosis: 37.7±15.3 years) and 300 healthy controls (238 males, 61 females and 1 other; age: 22.8±1.6 years). There were statistical dif-

Table 2. Allele frequencies in cases and controls and odds ratio estimates for PTB risk

SNP	Gene (s)	Locus	Alleles A/B	MAF		HWE *p* value	OR	95% CI	*p*-value
				Case	Control				
rs13501	TAP2	6p21.32	A/G	0.265	0.258	0.652	1.039	0.803-1.345	0.768
rs241447	TAP2	6p21.32	A/G	0.258	0.255	0.543	1.018	0.785-1.319	0.895
rs183585	TAP2	6p21.32	C/T	0.265	0.265	0.768	1.002	0.774-1.296	0.99
rs3819721	TAP2	6p21.32	A/G	0.233	0.192	1	1.284	0.972-1.684	0.078
rs1010324	SEC14L2	22q12.2	A/G	0.283	0.257	0.881	1.145	0.887-1.478	0.298
rs1061660	SEC14L2	22q12.2	C/T	0.475	0.407	0.122	1.32	1.05-1.659	0.017*

SNP: single-nucleotide polymorphism; MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium; OR: odds ratio; CI: confidence interval. *$P < 0.05$ indicates statistical significance.

Table 3. Single SNP association with PTB (logistic regression, crude)

SNP	Model	Genotype	Control	Case	OR (95% CI)	*P*-value	AIC	BIC
rs3819721	Codominant	G/G	196 (65.3%)	176 (58.7%)	1	0.21	834.6	847.8
		A/G	93 (31%)	108 (36%)	1.29 (0.92-1.82)			
		A/A	11 (3.7%)	16 (5.3%)	1.62 (0.73-3.58)			
	Dominant	G/G	196 (65.3%)	176 (58.7%)	1	0.092	832.9	841.7
		A/G-A/A	104 (34.7%)	124 (41.3%)	1.33 (0.95-1.85)			
	Recessive	G/G-A/G	289 (96.3%)	284 (94.7%)	1	0.32	834.8	843.6
		A/A	11 (3.7%)	16 (5.3%)	1.48 (0.68-3.24)			
	Overdominant	G/G-A/A	207 (69%)	192 (64%)	1	0.19	834.1	842.9
		A/G	93 (31%)	108 (36%)	1.25 (0.89-1.76)			
	Log-additive	---	---	---	1.28 (0.97-1.70)	0.077	832.7	841.4
rs1061660	Codominant	C/C	112 (37.3%)	80 (26.7%)	1	0.02*	829.9	843.1
		C/T	132 (44%)	155 (51.7%)	1.64 (1.14-2.38)			
		T/T	56 (18.7%)	65 (21.7%)	1.63 (1.03-2.57)			
	Dominant	C/C	112 (37.3%)	80 (26.7%)	1	0.005*	827.9	836.7
		C/T-T/T	188 (62.7%)	220 (73.3%)	1.64 (1.16-2.32)			
	Recessive	C/C-C/T	244 (81.3%)	235 (78.3%)	1	0.36	834.9	843.7
		T/T	56 (18.7%)	65 (21.7%)	1.21 (0.81-1.80)			
	Overdominant	C/C-T/T	168 (56%)	145 (48.3%)	1	0.06	832.2	841
		C/T	132 (44%)	155 (51.7%)	1.36 (0.99-1.88)			
	Log-additive	---	---	---	1.31 (1.05-1.64)	0.019*	830.2	839

Abbreviations: OR, odds ratio; CI, confidence interval. *$P < 0.05$ indicates statistical significance.

ferences in age and sex distribution between the case and control groups (**Table 1**).

SNPs and the risk of PTB

Table 2 shows the basic information of candidate SNPs in our study, such as MAF, OR, 95% CI, position, HWE, chromosome position, alleles and the *p*-value of alleles. We used the chi-squared test to assess the influence of gene polymorphism of risk in the allele model, and found that rs1061660 was significantly associated with an increased risk of pulmonary tuberculosis (rs1061660, OR = 1.32, 95% CI = 1.05-1.659, *P* = 0.017). However, the other five SNPs (rs13501, rs241447, rs183585, rs3819721, rs1010324) had no significant association with PTB risk.

Associations between genotype frequencies and PTB

As shown in **Table 3**, we found the genotype "C/T" of rs1061660 in *SEC14L2* was associated with a 1.49-fold increase the risk of PTB in the co-dominant model (OR = 1.64, 95% CI = 1.14-2.38, *P* = 0.02), 1.14-fold increase the risk of PTB in the dominant model (OR = 1.14,

Table 4. Single SNP association with PTB (logistic regression, adjusted by sex, age)

SNP	Model	Genotype	Control	Case	OR (95% CI)	*P*-value	AIC	BIC
rs3819721	Codominant	G/G	196 (65.3%)	176 (58.7%)	1	0.0069*	538.3	564.7
		A/G	93 (31%)	108 (36%)	1.65 (1.05-2.59)			
		A/A	11 (3.7%)	16 (5.3%)	0.78 (0.25-2.40)			
	Dominant	G/G	196 (65.3%)	176 (58.7%)	1	0.056	538	560
		A/G-A/A	104 (34.7%)	124 (41.3%)	1.53 (0.99-2.37)			
	Recessive	G/G-A/G	289 (96.3%)	284 (94.7%)	1	0.45	541.1	563.1
		A/A	11 (3.7%)	16 (5.3%)	0.65 (0.22-1.98)			
	Overdominant	G/G-A/A	207 (69%)	192 (64%)	1	0.023*	536.5	558.5
		A/G	93 (31%)	108 (36%)	1.67 (1.07-2.62)			
	Log-additive	---	---	---	1.30 (0.90-1.88)	0.17	539.8	561.7
rs1061660	Codominant	C/C	112 (37.3%)	80 (26.7%)	1	0.058	538	564.3
		C/T	132 (44%)	155 (51.7%)	1.72 (1.06-2.79)			
		T/T	56 (18.7%)	65 (21.7%)	1.77 (0.96-3.29)			
	Dominant	C/C	112 (37.3%)	80 (26.7%)	1	0.017*	536	558
		C/T-T/T	188 (62.7%)	220 (73.3%)	1.74 (1.10-2.75)			
	Recessive	C/C-C/T	244 (81.3%)	235 (78.3%)	1	0.38	540.9	562.9
		T/T	56 (18.7%)	65 (21.7%)	1.28 (0.74-2.19)			
	Overdominant	C/C-T/T	168 (56%)	145 (48.3%)	1	0.12	539.2	561.2
		C/T	132 (44%)	155 (51.7%)	1.40 (0.92-2.13)			
	Log-additive	---	---	---	1.37 (1.02-1.86)	0.038*	537.3	559.3

Abbreviations: OR, odds ratio; CI, confidence interval. *$P < 0.05$ indicates statistical significance.

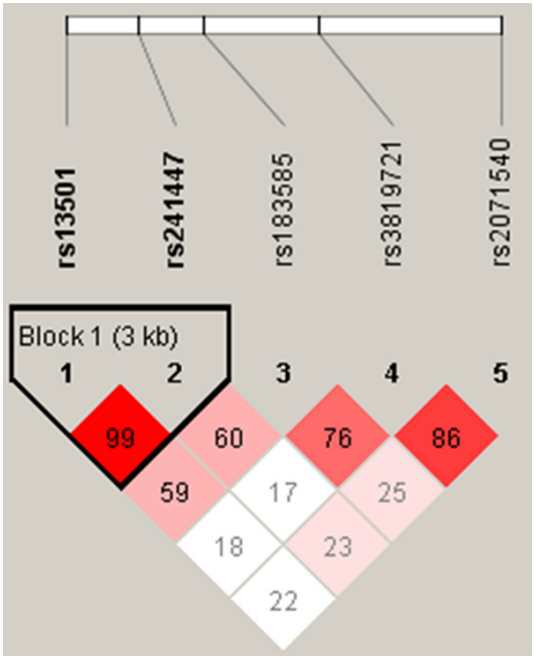

Figure 1. Linkage disequilibrium (LD) plots containing four SNPs from *TAP2* gene.

95% CI = 1.16-2.23, *P* = 0.005) and 1.31-fold increase the risk of PTB in the Log-additive model (OR = 1.31, 95% CI = 1.05-1.64, *P* = 0.019), respectively. However, when adjusted by sex and age (**Table 4**), the rs3819721 in *TAP2* was associated with increased 1.67-fold risk of PTB in the over-dominant model (OR = 1.67, 95% CI = 1.07-2.62, *P* = 0.023). For rs1061660 in *SEC14L2*, we found it was associated with increased 1.49-fold risk of PTB in the dominant model (OR = 1.74, 95% CI = 1.10-2.75, *P* = 0.017) and a 1.37-fold increase the risk of PTB in the log-additive model (OR = 1.02, 95% CI = 1.01-1.86, *P* = 0.038), respectively.

Associations between haplotype analyses and PTB risk

LD and haplotype analyses of the SNPs in the case and control samples were further studied. In order to assess the association between haplotypes and PTB risk, a Wald test was performed using an unconditional multivariate regression analysis. Although some candidate SNPs have showed strong linkage, but no positive result were observed (**Figure 1**). The result for the haplotype was not found to be associated with a risk of PTB, because the *P* value has no statistical difference (**Table 5**).

Table 5. Haplotype analysis results in this study

Haplotypes				Crude analysis		Adjusted by Gender and Age	
	rs13501	rs241447	Freq	OR (95% CI)	*P*-value	OR (95% CI)	P^a-value
1	G	T	0.7375	1	---	1	---
2	A	C	0.255	1.02 (0.79-1.33)	0.86	1.03 (0.73-1.45)	0.88
Rare	*	*	0.0075	1.80 (0.49-6.52)	0.37	5.23 (0.90-30.24)	0.065

Abbreviations: CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism. P^a: Adjusted by gender and age.

Discussion

In this study, we investigated the association between *TAP2* and *SEC14L2* polymorphisms and PTB risk in a Tibetan Chinese population. We found two SNPs were significantly increased the PTB risk. Previous PTB studies investigated the function of host genetic factors and immunoreaction in M. tuberculosis infection [25]. In humans, macrophages are the main host cells for the intracellular replication pathway of *M. tuberculosis*. Macrophages also serve as the antigen-presenting cells during the reactivation of lymphocytes, and they function as a vital killer of mycobacteria [26]. In vivo and in vitro studies show that M. tuberculosis infection causes apoptosis in monocytes and macrophages [27]. and we previously found that apoptosis of these two cell types is a protective factor in human tuberculosis [28].

TAP2 gene, located in chromosome 6p21.32, plays an important role in antigen presentation on MHC class 1 molecule [29]. *TAP2* gene polymorphisms can influence the antigen peptide selection and transport process and modify immune response regulation [30]. Polymorphic residues in *TAP2* genes were identified which modify specificity of substrate transport [31]. Consequently, these genes are considered as candidate genes for susceptibility to a number of immune diseases, viral infection diseases, and even cancer [30, 32-34]. Study has reported the associations between polymorphisms of *TAP* genes and susceptibility to PTB in a sample of Iranian [35]. In present study, we focused on the association of *TAP2* gene polymorphisms with PTB susceptibility in a cohort of Tibetan Chinese population. We found a significant association between *TAP2* rs3819721 A/G variant and PTB.

SEC14L2, as an immunohistochemical related-protein, regulating the immune response and mediate inflammatory cells, which is associated with immune disease and cancer, for example, *SEC14L2* can promote the hepatitis C virus (HCV) [36] and prostate cancer [37]. *SEC14L2*, also known as c22orf6, supernatant protein factor 1 (*SPF1*), or tocopherol-associated protein 1 (*TAP1*), is a cytosolic lipid-binding protein family member [38, 39], which is ubiquitously expressed in human tissues [40]. Study shows that *TAP/SEC14L2* had a high expression in normal/benign breast, prostate, and liver tissues as compared to lung, colon, and kidney [20]. In our case-control study, we found that rs1061660, as the intronic SNP within the gene *SEC14L2*, were markedly associated with PTB risk according to both genotype and allele association analysis in a Tibetan Chinese population.

To our knowledge, our study is the first to investigate the association between polymorphic SNPs of *TAP2* and *SEC14L2* gene and PTB risk in a Tibetan Chinese population, which may provide new data to facilitate earlier diagnosis and promote early prevention and shed light on the new candidate genes and new ideas for the study of subsequent occurrence mechanism of PTB. Therefore, more studies should investigate these SNPs using more clinical data with bigger samples. In conclusion, our results show that *TAP2* polymorphisms rs3819721 and *SEC14L2* polymorphisms rs1061660 are associated with increased PTB risk in the Tibetan population.

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Disclosure of conflict of interest

None.

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