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ORIGINAL RESEARCH

Transporter Associated with Antigen Processing 1 Gene Polymorphisms Increase the Susceptibility to Tuberculosis

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Purpose: Tuberculosis (TB) is known to result from a complex interaction between the host immune response and *Mycobacterium* infection. The transporter associated with antigen processing (TAP) plays an important role in the processing and presentation pathways for the *Mycobacterium tuberculosis* (*M. tb*) antigen. To investigate the possible association of the *TAP1* and *TAP2* genes with TB.

Patients and Methods: A total of 449 TB patients and 435 control subjects were included in this study, and single nucleotide polymorphisms (SNPs) in the *TAP* gene, as well as *TAP1* and *TAP2* alleles, were genotyped.

Results: *TAP* gene association analysis of TB diseases showed that rs41551515-T in the *TAP1* gene was significantly associated with susceptibility to TB (*P*=7.96E-04, OR=4.124, 95% CI: 1.683–10.102), especially pulmonary TB (PTB, *P*=6.84E-04, OR=4.350, 95% CI: 1.727–10.945), and the combination of rs1057141-T-rs1135216-C in the *TAP1* gene significantly increased the risk of TB susceptibility (*P*=5.51E-05, OR=10.899, 95% CI: 2.555–46.493). Five novel *TAP1* alleles were detected in Yunnan Han people, and the allele frequency of *TAP1*unknown_3* (rs41555220-rs41549617-rs1057141-rs1135216-rs1057149-rs41551515: C-A-T-C-C-T) was notably increased in all TB patients, including in the PTB and EPTB subgroups, and was significantly associated with the risk of susceptibility to TB. However, no association between the *TAP2* gene and TB was found in this study.

Conclusion: Host genetic variants of rs41551515-T and the combination rs1057141-T-rs1135216-C, as well as *TAP1*unknown_3* may play a critical role in susceptibility to TB disease.

Keywords: tuberculosis, association, *TAP* gene, polymorphism, novel allele

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*M. tb*) and is still a major health problem worldwide.[1] Approximately two billion people worldwide are infected with *M. tb*, with 10 million new cases of active tuberculosis (TB) and 1.7 million death each year.[2] Only 10% of infections finally develop into clinical TB, and most infected people carry the bacteria without overt symptoms.[3,4] That is, host genetic factors contribute significantly to this interindividual variability,[5] and recent twin studies[6] and genome-wide association studies (GWASs)[6–9] have shown evidence of the influence of host genetics on susceptibility to TB. In recent years, association studies on TB susceptibility with host genes have found many genes and pathways as candidate genes that play a role in TB susceptibility risk. These

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genes participate in immune responses and include the human leukocyte antigen (HLA),[10,11] chemokine (C–C motif) ligand-2 (CCL2)[12] and its receptor chemokine receptor 5 (CCR5),[13] solute carrier protein 11A1 (SLC11A1),[14] interleukin (IL)-8, IL-10,[15] toll-like receptor (TLR),[16] and nucleotide-binding oligomerization domain-containing protein 2 (NOD 2) genes.[17]

M. tuberculosis infection elicits CD8+ T cell responses in both people and in experimental animals. CD8+ T cells are recruited to lung during *M. tb* infection and are found in the granulomas of infected people. It was reported that infection people generate CD8+ T cells and those CD8+ T cells express effector function that can suppress bacterial growth. Additionally, studies have found that mycobacterial antigens such as culture filtrate protein-10 (CFP10) do enter the class I MHC pathway, and CFP10-specific CD8+ T cells clones recognize infected cells and potentially act as effector cells to eliminate *M. tb*.[18] A mouse TB infection model showed that host $CD8^+$ T cells play a protective role against TB infection and that mice deficient in major histocompatibility complex (MHC)-I expression are more susceptible to TB.[19] Studies have revealed that *M. tb* antigens can be processed and presented by cytosolic and vacuolar pathways, as well as by the *M. tb* phagosome.[20,21] *M. tb* antigen processing and presentation via these pathways are dependent on TAP.[20,21] The transporter associated with antigen processing (TAP) transports the peptide fragments into the endoplasmic reticulum (ER) to bind MHC-I molecules and then loads the MHC-I-peptide complex through the ER-Golgi or back to the phagosome, which is called the cytosolic pathway.[22] For some antigens, processing can occur through the vacuolar pathway, in which antigens are degraded by vacuolar proteases within endocytic compartments in a TAP-dependent way.[22] *M. tb* remains in phagosomal compartments and can act as an organelle capable of loading MHC-I with the *M. tb* antigen itself, called the phagosome pathway.[23] Therefore, not only HLA-I but also TAP is important in the processing and presentation pathways for the *M. tb* antigen.

SNPs located in the key region of the *TAP1* and *TAP2* genes can influence the function of TAP molecules and consequently affect the disease susceptibility risk. Colonna et al demonstrated that allele variants in TAP could influence the selection of peptides delivered to MHC-I molecules and are involved in susceptibility to MHC-associated diseases, such as ankylosing spondylitis, insulin-dependent diabetes mellitus, and celiac disease.[24] Quadri and Singal investigated whether *TAP* polymorphisms influence peptide substrate specificity in human B-lymphoblastoid and tumor cell lines.[25] Some studies have shown that *TAP* gene polymorphisms are associated with TB in some populations.[26–31]

In the present study, we analyzed the association between TB and *TAP* gene polymorphisms in a Han population in China. Previous studies revealed that the genetic effect could be affected by age, sex and family income. Considering the distribution of the factors, we performed the analysis by adjusting for potential factors, such as age and sex, and consequently measured the association by stratification.

Materials and Methods

Ethical Issues

The present study was reviewed and approved by the Institutional Review Board and Biosecurity Committee of the Third People's Hospital of Kunming (Kunming, China). All the experimental protocols used in this study were in accordance with the approved guidelines and principles according to the Declaration of Helsinki and its later amendments or comparable ethical standards of 1975.[32] All participants provided written informed consent.

Subjects

A total of 449 TB patients and 435 healthy controls were enrolled in the Third People's Hospital of Kunming from 2018 to 2019. All subjects were Han Chinese individuals in Yunnan Province (Southwest China).

Diagnoses of TB were based on clinical symptoms, radiological evidence, and bacteriological investigations according to the clinical case definition guidelines for TB issued by the World Health Organization (WHO),[33] the Diagnosis for Pulmonary Tuberculosis (WS 288–2017)[34] and the Classification of Tuberculosis (WS 196–2017)[35] from the Health Industry Standard of the People's Republic of China. All the TB patients were *M. tuberculosis* positive confirmed by sputum smear culture bacteriological assessment. And, tuberculosis skin test (TST) and interferon-γ release assay (IGRA) are also positive. Clinical symptoms such as cough, fever and weight loss over weeks and chest

X-ray test were recorded for each patients. The TB patients were stratified into pulmonary TB (PTB), extrapulmonary TB (EPTB, which was defined as TB which was defined as TB influencing extrapulmonary sites such as lymph nodes, abdomen, urinary tract, skin, joints, bones, and meninges, exclusively or in combination with pulmonary TB) according to the pathological site. The control group was healthy individuals who were negative TST and had negative history for TB disease and were without any acute or chronic pulmonary disorder, or any bacterial or viral infection or other immune mediated disorders.

Selection and Genotyping of SNPs

TAP1 alleles were defined by six SNPs (rs41555220, rs41549617, rs1057141, rs1135216, rs1057149, and rs41551515) in the *TAP1* gene, and *TAP2* alleles were defined by three SNPs (rs1042116, rs2228396, and rs4148876) in the *TAP2* gene (Supplementary Tables 1 and 2) according to the *TAP1* and *TAP2* allele typing pattern diagram that was designed based on the IPD-IMGT/HLA database (http://hla.alleles.org)[36] by the HLA Nomenclature Committee of the World Health Organization requirement.

SNP genotyping was performed by using the Custom TaqMan SNP Genotyping assay (TaqMan Applied Biosystems, Foster City, CA, USA), and the TaqMan probes for each SNP are listed in Supplementary Table 1. The TaqMan probe information and genotyping assay were obtained from the Applied Biosystems website (http://www.thermofisher.com/cn/zh/home/life-science/pcr/real-time-pcr/real-time-pcr-assays.html). The PCR reaction was performed in 384-well plates using QuantStudio 6 Flex Fast Real-Time PCR System (Thermo Fisher, Foster City, USA) according to the manufacturer's instructions. A 5-μL reaction system consisting of 2.5-μL 2× TaqMan Master Mix, 0.125-μL 40× SNP Genotyping Assay (specific for each polymorphism site and compromised Primer and TaqMan Probe mix which labeled FAM and VIC dye), 1 to 10 ng of purified genomic DNA sample per plate well, and added distilled water to make up the volume to 5-μL. In addition, positive and negative controls were included in each experiment to identify the accuracy of SNP genotyping. Real-tme PCR cycle conditions is: 95°C predenaturation for 10 min, 92°C for 10s, and 60°C for 1 min and repeated in 40 cycles. The Applied Biosystems TaqMan Genotyper Software to automatically determines sample genotypes and displays data. Directed sequencing was performed to verify the genotyping results.

Statistical Analysis

Sample size estimation and statistical power analysis were performed using Power and Sample Size Calculations (v.3.1.2).[37] The genotype and allele frequency, as well as Hardy-Weinberg equilibrium (HWE), for each SNP were calculated by PLINK software (version 1.9; Harvard & MIT http://pngu.mgh.harvard.edu/~purcell/plink/).[38] The distributions of alleles and genotypes in the case and control groups were compared by the χ^2 test, and risks were estimated using odds ratios (ORs) with 95% confidence intervals (95% CIs) by PLINK. The frequency of *TAP1* and *TAP2* alleles and genotypes and haplotypes were determined using Pypop software.[39,40] Frequency comparisons in the case and control groups were performed by the χ^2-test, and the 95% CIs were calculated. The significance threshold was set at $P<0.05$. *Bonferroni* correction was applied for multiple comparisons among alleles and genotypes, and the *P* value was adjusted to 0.05/n.

Results

Characteristics of Participants

A total of 449 TB patients, including 324 PTB patients and 125 EPTB patients, and 435 healthy controls were enrolled in this study. The average age of the TB group and the control group were 43.71±15.99 and 45.32±8.99, respectively. There was no difference in the distribution of age or sex between the TB and control groups ($P>0.05$). The PTB group included 145 infiltration, 161 secondary, and 18 cavity patients; the EPTB group included 13 lymph node, 31 genitourinary tract, 24 bone and joint, 5 cutaneous, 14 celiac, 8 meningitis, 2 peritoneal, 1 pleuritis, 17 multisite concurrent and 10 other patients. The basic characteristics of the subjects in this study were shown in our previous publication.[41]

Differences in the Allele and Genotype Distributions of SNPs in the TAP1 and TAP2 Genes Between TB Patients and Controls

Hardy-Weinberg equilibrium (HWE) tests were performed for each SNP in the *TAP1* and *TAP2* genes, and all SNPs exhibited HWE in the TB and control groups ($P>0.05$). There was no polymorphism in site rs41555220, and all subjects had a C allele in this SNP. The allele and genotype frequencies of eight other SNPs in the *TAP1* and *TAP2* genes were compared between the TB patient and control groups, and there were significant frequency differences in both alleles ($P=7.96E-04$, OR=4.124, 95% CI: 1.683–10.102) and genotypes ($P=7.13E-04$) at rs41551515 between TB patients and controls after *Bonferroni* correction (Table 1). An allele frequency difference was also found for rs41549617 ($P=0.034$, OR=2.144, 95% CI: 1.044–4.405), and genotype frequency differences were found for rs41549617 ($P=0.031$) and rs1057141 ($P=0.039$), but the significance disappeared after *Bonferroni* correction. We also performed inheritance analysis for the SNPs rs1057141, rs1135216, rs2228396, and rs4148876, but no significant difference of association with TB were found. In addition, the rs1057141 and rs1135216 combination was analyzed based on a previous report on the functional influence of *TAP1* variants, and the results showed there is significant gene interactions between rs1057141 and rs1135216 ($P=0.019$), and these two SNPs were also in Linkage Disequilibrium ($D'=0.89$). The combination of rs1057141-T-rs1135216-C significantly increased the risk of susceptibility to TB ($P=5.51E-05$, OR=10.899, 95% CI: 2.555–46.493, Table 2).

Comparison of the Allele and Genotype Frequencies of TAP1 and TAP2 in the TB Patient and Control Groups

TAP alleles were defined according to the IPD-IMGT/HLA database (Supplementary Table 2). *TAP1*01:01* and *TAP2*01:01* were the major alleles in Yunnan Han people; the frequency of *TAP1*01:01* was 75.86% in controls and 77.39% in TB patients, and the frequency of *TAP2*01:01* was 80.00% in controls and 79.18% in TB patients (Table 3). We found several novel *TAP1* alleles in this study (Table 3) and named them *TAP1*unknown_1* (rs41555220-rs41549617-rs1057141-rs1135216-rs1057149-rs41551515: C-G-T-C-C-C), *TAP1*unknown_2* (rs41555220-rs41549617-rs1057141-rs1135216-rs1057149-rs41551515: C-A-C-C-C-C), *TAP1*unknown_3* (rs41555220-rs41549617-rs1057141-rs1135216-rs1057149-rs41551515: C-A-T-C-C-T), *TAP1*unknown_4* (rs41555220-rs41549617-rs1057141-rs1135216-rs1057149-rs41551515: C-A-T-T-C-C), and *TAP1*unknown_5* (rs41555220-rs41549617-rs1057141-rs1135216-rs1057149-rs41551515: C-G-T-C-C-T). The comparison results showed that the frequency of *TAP1*unknown_3* was much higher in the TB patient group than in the control group (2.2% vs 0.1%, $P=4.16E-05$), and this *TAP1* allele obviously increased the risk of TB (OR=19.795, 95% CI: 2.651–147.824). The frequency of *TAP1*01:01/TAP1*unknown_3* heterozygosity was notably higher in the TB patient group than in the control group (Table 4, 4.4% vs 0.2%, $P=3.73E-05$), and this heterozygosity also significantly increased the risk of TB susceptibility (OR=20.233, 95% CI: 2.703–151.434). The frequency of *TAP2*01:02/TAP2*01:03* also showed an increase in TB susceptibility (Table 4, $P=0.008$, OR=3.982, 95% CI: 1.320–12.006), but the significance was weak after *Bonferroni* correction (the significance threshold was $P<0.001923$). We also analyzed the haplotypes constructed by *TAP1* and *TAP2* alleles, and only the haplotypes with frequencies over 0.01 were compared and are listed in Supplementary Table 3. The results showed that haplotype *TAP1*unknown_3-TAP2*01:02* had a significantly higher frequency in the TB patient group and increased the risk of TB by 17-fold ($P=1.17E-04$, OR=17.775, 95% CI: 2.367–133.444).

Stratification Analysis of the Association Between TB and TAP Gene Variants

We stratified the TB patients into pulmonary TB (PTB) and extrapulmonary TB (EPTB) subgroups according to the site of TB infection, and then compared the allele and genotype frequencies of SNPs in the *TAP1* and *TAP2* genes as well as the allele and genotype frequencies of the *TAP1* and *TAP2* variants between the TB subgroups and the control groups. The results are listed in Table 5 and Supplementary Tables 4–8. The frequency of rs41551515-T was significantly higher in the PTB ($P=6.84E-04$, OR=4.350, 95% CI: 1.727–10.954) subgroups than in the control group and was also slightly higher in the EPTB subgroup ($P=0.021$, OR=3.541, 95% CI: 1.132–11.077) than in the control group. In addition, the

Table 1 Comparison of Allele and Genotype Frequency Between TB Patients and Controls

Gene	Comparison		Control	TB	*P*	OR (95% CI)
			n (Freq.)	n (Freq.)		
TAP1	**rs41549617**					
	Allele	G	859(0.987)	874(0.973)		Ref.
		A	11(0.013)	24(0.027)	0.034	2.144(1.044–4.405)
	Genotype	GG	424(0.975)	425(0.947)	0.031	
		GA	11(0.025)	24(0.053)		
		AA	0(0.000)	0(0.000)		
	rs1057141					
	Allele	T	664(0.763)	717(0.798)		Ref.
		C	206(0.237)	181(0.202)	0.073	0.814(0.649–1.020)
	Genotype	TT	250(0.575)	292(0.650)	0.039	
		TC	164(0.377)	133(0.296)		
		CC	21(0.048)	24(0.053)		
	DOM	TT	250(0.575)	292(0.650)		Ref.
		CT+CC	185(0.425)	157(0.350)	0.021	0.727(0.554–0.953)
	REC	TT+TC	414(0.952)	425(0.947)		Ref.
		CC	21(0.048)	24(0.053)	0.726	1.113(0.610–2.031)
	rs1135216					
	Allele	T	718(0.825)	744(0.829)		Ref.
		C	152(0.175)	154(0.171)	0.858	0.978(0.764–1.251)
	Genotype	TT	297(0.683)	305(0.679)	0.625	
		TC	124(0.285)	134(0.298)		
		CC	14(0.032)	10(0.022)		
	DOM	TT	297(0.683)	305(0.679)		
		CT+CC	138(0.317)	144(0.321)	0.912	1.0156(0.766–1.348)
	REC	TT+TC	421(0.968)	439(0.978)		
		CC	14(0.032)	10(0.022)	0.365	0.685(0.301–1.559)
	rs1057149					
	Allele	C	867(0.997)	898(1.000)		Ref.
		T	3(0.003)	0(0.000)	0.078	0.321(0.033–3.097)
	Genotype	CC	432(0.993)	449(1.000)	0.077	
		CT	3(0.007)	0(0.000)		
		TT	0(0.000)	0(0.000)		
	rs41551515					
	Allele	C	864(0.993)	873(0.972)		Ref.
		T	6(0.007)	25(0.028)	**7.96E-04**	4.124(1.683–10.102)
	Genotype	CC	429(0.986)	424(0.944)	**7.13E-04**	
		CT	6(0.014)	25(0.056)		
		TT	0(0.000)	0(0.000)		
TAP2	**rs1042116**					
	Allele	G	852(0.979)	887(0.988)		Ref.
		A	18(0.021)	11(0.012)	0.162	0.587(0.276–1.250)
	Genotype	GG	417(0.959)	438(0.976)	0.158	
		GA	18(0.041)	11(0.024)		
		AA	0(0.000)	0(0.000)		

(*Continued*)

Table 1 (Continued).

Gene	Comparison		Control	TB	*P*	OR (95% CI)
			n (Freq.)	n (Freq.)		
	rs2228396					
	Allele	C	762(0.876)	775(0.863)		Ref.
		T	108(0.124)	123(0.137)	0.423	1.120(0.849–1.477)
	Genotype	CC	336(0.772)	339(0.755)	0.676	
		CT	90(0.207)	97(0.216)		
		TT	9(0.021)	13(0.029)		
	DOM	CC	336(0.772)	339(0.755)		
		TC+TT	99(0.228)	110(0.245)	0.543	1.101(0.807–1.502)
	REC	CC+CT	426(0.979)	436(0.971)		
		TT	9(0.021)	13(0.029)	0.430	1.411(0.597–3.336)
	rs4148876					
	Allele	G	822(0.945)	845(0.941)		Ref.
		A	48(0.055)	53(0.059)	0.727	1.074(0.718–1.606)
	Genotype	GG	389(0.894)	397(0.884)	0.701	
		GA	44(0.101)	51(0.114)		
		AA	2(0.005)	1(0.002)		
	DOM	GG	389(0.894)	397(0.884)		
		AA+AG	46(0.106)	52(0.116)	0.634	1.108(0.727–1.687)
	REC	AG+GG	433(0.995)	448(0.998)		
		AA	2(0.005)	1(0.002)	0.545	0.483(0.044–5.349)

Notes: There are only two genotype for rs41549617, rs1057149, rs41551515, and rs1042116, so inheritance analysis were not performed for these four SNPs. After Bonferroni correction, the significance threshold is *P* <0.00625. And the *P*-value lower than the significance threshold is marked in bold.
Abbreviation: DOM, dominant model; REC, recessive model.

frequency of rs41549617-A was higher in the PTB subgroup (*P*=0.021, OR=2.359, 95% CI: 1.115–4.992), whereas the rs1057141-C allele frequency was lower in the PTB subgroup (*P*=0.023, OR=0.748, 95% CI: 0.581–0.961); however, the significance disappeared after *Bonferroni* correction. The combination of rs1057141-T-rs1135216-C increased the risk of susceptibility to PTB and EPTB (Table 5). The allele *TAP1*unknown_3* showed a frequency increase in the PTB and EPTB subgroups compared with the control group and increased the risk of susceptibility to all clinical stratifications of TB diseases (Table 5). The genotype *TAP1*01:01/TAP1*unknown_3* increased the risk of susceptibility to PTB and EPTB (Table 5). We also compared the *TAP1-TAP2* haplotype frequencies in the clinical stratification subgroups (Supplementary Table 8) and found that the *TAP1*unknown_3-TAP2*01:02 haplotype* was associated with increased susceptibility to PTB and EPTB (Table 5).

Table 2 Analysis of rs1057141 and rs1135216 Combination Effects

rs1057141-rs1135216	Control Num. (Freq)	TB Num. (Freq)	*P*	Odds Ratio (95% CI)
T-T	662 (0.761)	695(0.773)	0.516	1.075 (0.862–1.341)
C-C	2.14(0.002)	132(0.146)	0.144	0.827 (0.640–1.067)
C-T	56.14(0.065)	49(0.054)	0.383	0.838 (0.565–1.245)
T-C	149.86(0.172)	22(0.024)	**5.51E-05**	10.899 (2.555–46.493)

Notes: There is significant gene interactions between rs1057141 and rs1135216 (*P*=0.019), these two SNP were also in Linkage Disequilibrium (*D'*=0.89). After Bonferroni correction, the significance threshold is *P* <0.00625. And the *P*-value lower than the significance threshold is marked in bold.

Table 3 The Distribution of *TAP* Allele in TB and Control Group

TAP Allele	Co (2n=870)	TB (2n=898)	*P*	OR (95% CI)
*TAP1*01:01*	660(0.759)	695(0.774)	0.447	1.089(0.874–1.358)
*TAP1*02:01:01*	139(0.160)	128(0.143)	0.316	0.875(0.675–1.136)
*TAP1*03:01*	56(0.064)	49(0.055)	0.383	0.839(0.565–1.246)
*TAP1*04:01*	3(0.003)	0(0.000)	0.078	0.321(0.033–3.097)
*TAP1*05:01*	5(0.006)	4(0.004)	0.703	0.774(0.207–2.892)
*TAP1*unknown_1*	1(0.001)	1(0.001)	0.982	0.969(0.060–15.514)
*TAP1*unknown_2*	3(0.003)	0(0.000)	0.078	0.321(0.033–3.097)
*TAP1*unknown_3*	1(0.001)	20(0.022)	**4.16E-05**	19.795(2.651–147.824)
*TAP1*unknown_4*	2(0.002)	0(0.000)	0.151	0.483(0.044–5.334)
*TAP1*unknown_5*	0(0.000)	1(0.001)	0.325	0.971(0.061–15.549)
*TAP2*01:01*	696(0.800)	711(0.792)	0.667	0.951(0.754–1.198)
*TAP2*01:02*	108(0.124)	123(0.137)	0.423	1.120(0.849–1.477)
*TAP2*01:03*	48(0.055)	53(0.059)	0.727	1.074(0.718–1.606)
*TAP2*02:01*	18(0.021)	11(0.012)	0.162	0.587(0.276–1.250)

Notes: After Bonferroni correction, the significance threshold is *P* <0.00357. And the *P*-value lower than the significance threshold is marked in bold.
Abbreviation: Co- control

Table 4 The Distribution of *TAP* Genotype in TB and Control Group

TAP1 Common Genotypes	Co (n=435)	TB (n=449)	*P*	OR (95% CI)
*TAP1*01:01/TAP1*01:01*	246(0.565)	270(0.601)	0.280	1.159(0.887–1.515)
*TAP1*01:01/TAP1*02:01:01*	110(0.252)	103(0.229)	0.415	0.880(0.646–1.197)
*TAP1*01:01/TAP1*03:01*	46(0.105)	30(0.066)	0.039	0.605(0.375–0.979)
*TAP1*01:01/TAP1*04:01*	2(0.004)	0(0.000)	0.150	0.481(0.043–5.325)
*TAP1*01:01/TAP1*05:01*	4(0.009)	0(0.000)	0.042	0.239(0.027–2.151)
*TAP1*01:01/TAP1*unknown_1*	1(0.002)	1(0.002)	0.982	0.969(0.060–15.537)
*TAP1*01:01/TAP1*unknown_2*	2(0.004)	0(0.000)	0.150	0.481(0.043–5.325)
*TAP1*01:01/TAP1*unknown_3*	1(0.002)	20(0.044)	**3.73E-05**	20.233(2.703–151.434)
*TAP1*01:01/TAP1*unknown_4*	2(0.004)	0(0.000)	0.150	0.481(0.043–5.325)
*TAP1*01:01/TAP1*unknown_5*	0(0.000)	1(0.002)	0.325	0.973(0.061–15.609)
*TAP1*02:01:01/TAP1*02:01:01*	11(0.025)	8(0.017)	0.444	0.699(0.279–1.755)
*TAP1*02:01:01/TAP1*03:01*	4(0.009)	7(0.015)	0.391	1.706(0.496–5.871)
*TAP1*02:01:01/TAP1*04:01*	1(0.002)	0(0.000)	0.309	0.964(0.060–15.468)
*TAP1*02:01:01/TAP1*05:01*	1(0.002)	2(0.004)	0.304	1.942(0.175–21.494)
*TAP1*02:01:01/TAP1*unknown_2*	1(0.002)	0(0.000)	0.309	0.964(0.060–15.468)
*TAP1*03:01/TAP1*03:01*	3(0.006)	5(0.011)	0.506	1.622(0.385–6.827)
*TAP1*03:01/TAP1*05:01*	0(0.000)	2(0.004)	0.163	1.951(0.176–21.593)
***TAP2* Common genotypes**				
*TAP2*01:01/TAP2*01:01*	278(0.639)	294(0.654)	0.625	1.071(0.813–1.412)
*TAP2*01:01/TAP2*01:02*	84(0.193)	80(0.178)	0.568	0.906(0.645–1.272)
*TAP2*01:01/TAP2*01:03*	40(0.091)	34(0.075)	0.384	0.809(0.502–1.304)
*TAP2*01:01/TAP2*02:01*	16(0.036)	9(0.020)	0.133	0.536(0.234–1.225)
*TAP2*01:02/TAP2*01:02*	9(0.020)	13(0.028)	0.430	1.411(0.597–3.336)
*TAP2*01:02/TAP2*01:03*	4(0.009)	16(0.035)	**0.008**	3.982(1.320–12.006)
*TAP2*01:02/TAP2*02:01*	2(0.004)	1(0.002)	0.545	0.483(0.044–5.349)
*TAP2*01:03/TAP2*01:03*	2(0.004)	1(0.002)	0.545	0.483(0.044–5.349)
*TAP2*01:03/TAP2*02:01*	0(0.000)	1(0.002)	0.325	0.973(0.061–15.609)

Notes: After Bonferroni correction, the significance threshold is *P* <0.001923. And the *P*-value lower than the significance threshold is marked in bold.
Abbreviation: Co- control

Table 5 Significantly Difference of Pairwise Comparison Between Stratified Group and Control

Comparison			Co (n=870) n (Freq.)	PTB (n=324)		EPTB (n=125)	
				n (Freq.)	*P* OR (95% CI)	n (Freq.)	*P* OR (95% CI)
rs41551515	Allele	C	864(0.993)	629(0.971)	6.84E-04	244(0.976)	0.021
		T	6(0.007)	19(0.029)	4.350(1.727–10.954)	6(0.024)	3.541(1.132–11.077)
	Genotype	CC	429(0.986)	305(0.941)	6.21E-04	119(0.952)	0.019
		CT	6(0.014)	19(0.059)		6(0.048)	
		TT	0(0.000)	0(0.000)		0(0.000)	
rs1057141-rs1135216 combination		T-C	2(0.002)	16(0.024)	6.70E-05 10.987 (2.517–47.957)	6(0.024)	3.29E-04 10.672 (2.14–53.21)
*TAP1*unknown_3*			1(0.001)	15(0.023)	3.31E-05 20.592(2.713–156.302)	5(0.020)	3.19E-04 11.735(2.062–152.516)
*TAP1*01:01/TAP1*03:01*			46(0.105)	14(0.043)	0.001 0.364(0.197–0.673)	16(0.128)	0.485 1.241(0.676–2.278)
*TAP1*01:01/TAP1*unknown_3*			1(0.002)	15(0.046)	2.99E-05 21.068(2.768–160.338)	5(0.040)	3.08E-04 18.083(2.093–156.266)
*TAP2*01:02/TAP2*01:03*			4(0.009)	12(0.037)	0.008 4.144(1.324–12.970)	4(0.032)	0.058 3.562(0.878–14.452)
*TAP1*unknown_3-TAP2*01:02*			1(0.001)	14(0.021)	6.74E-05 19.189 (2.516–146.309)	4(0.016)	0.001 14.130 (1.572–127.004)

Notes: Only the comparison with significance was showed in this table. After Bonferroni correction, for SNP allele comparison, the significance threshold is $P < 0.00625$ (0.05/8); for the *TAP* allele comparison, the significance threshold is $P < 0.00357$ (0.05/14); for the *TAP* genotype comparison, the significance threshold is $P < 0.001923$ (0.05/26); and for the *TAP1-TAP2* haplotype comparison, the significance threshold is $P < 0.005$ (0.05/10).
Abbreviations: Co, control; PTB, pulmonary TB; EPTB, extrapulmonary TB.

Discussion

TB remains a significant global public health burden. It was estimated that approximately one-third of the world's population is infected with *M. tuberculosis*, but most infections do not usually lead to active disease. After exposure to *M. tb*, only a small portion of people develop primary extrapulmonary TB, whereas approximately 90% of people develop latent TB infection (LTBI). Most patients with LTBI will remain healthy throughout their lifetime without clinical disease, and the remaining patients develop clinical TB later in life, called reactivation TB.[1] The host cellular immune response is essential for controlling *M. tb* infection and preventing the development of active TB.[23] In the process of immune surveillance through the granule exocytosis pathway, $CD8^+$ T cells react to *M. tb*-containing cells.[42] De Libero et al demonstrated that *M. tb*-specific $CD8^+$ T-cell lines could inhibit *M. tb* growth in vitro.[43] *M. tb* antigens are processed and presented via cytosolic, vacuolar and *M. tb* phagosome pathways, and all of these pathways are TAP-dependent.[20,21] Mice with a disruption in the TAP molecule, which is required for generating the MHC-I-peptide complex, are thus deficient in MHC class I molecules and $CD8^+$ T cells and are quite susceptible to *M. tb* infection.[19,44,45] Thus, TAP plays a critical role in *M. tb* antigen processing and presentation.

In the present study, SNPs located in key regions of the *TAP1* and *TAP2* genes were detected, and we analyzed the differences in SNP allele and genotype frequencies, as well as the *TAP* alleles and genotypes according to the definition of the IPD-IMGT/HLA database, between TB patients and the control group and between the TB clinical stratified subgroups and the control group to analyze their association with TB. We found that the frequency of the rs41551515-T allele was significantly higher in the TB group and PTB than in the control group. rs41551515 (C>T) in the *TAP1* gene is a synonymous variant. The frequency of rs41551515-T in different populations of the world is 0–3% according to the 1000 Genomes Project, and the frequency of rs41551515-T in Han Chinese in the Beijing population is 1%. In our Yunnan Han population, the frequency of the rs41551515-T allele was 0.7% in the control group but increased to 2.8% in TB patients. According to the GTEx database (https://www.gtexportal.org/home/snp/rs41551515), rs41551515-A is associated with a decline in TAP expression. We also detected the possible function of rs41551515 using HaploReg v4.1 and found that rs41551515 is a binding site of Ets, Pax-6 and GR, and nucleotide substitution in this region could

change motif binding and then affect the expression of TAP. In addition, studies have found that the nucleotide substitution of rs41551515 could also influence the chromatin states in T cells (resources from HaploReg v4 online tools, https://pubs.broadinstitute.org/mammals/haploreg/detail_v4.1.php?query=&id=rs41551515). Therefore, the rs41551515 variant might affect the function of TAP1 and influence the clearance of *M. tb*. Therefore, people carrying rs41551515-T might be susceptible to TB. Except for rs41551515, none of these SNPs in the *TAP1* and *TAP2* genes were associated with TB after *Bonferroni* correction. Most studies on the association between TB and the *TAP* gene have concentrated on the rs1057141 and rs1135216 variants, which are considered to influence the function of TAP binding to antigen peptides. Sunder et al found that individuals with the TAP1 (637) rs1135216-CT genotype were more likely to develop TB and HIV coinfection.[26] Wang et al reported that rs1135216-C was significantly associated with the risk of TB in Li people in China.[27] Roh et al reported that *TAP1* rs1057141 and rs1135216 SNPs were associated with susceptibility to active TB.[28] Naderi et al reported that the rs1135216-C allele was associated with an increased risk of PTB (P<0.001, OR=2.65, 95% CI=1.784–3.969). The *TAP2* rs241447 TC and TC+CC genotypes decreased the risk of PTB (P<0.001, OR=0.41, 95% CI: 0.26–0.65; OR=0.54, 95% CI: 0.35–0.85, respectively), but no significant association was found between *TAP1* (rs1057141) and *TAP2* (rs2228396, rs67511411, rs141555015) variants and PTB.[29] Cazarez-Navarro et al found that rs1135216-C allele carriers were susceptible to LTBI.[31] Zhang et al found that rs1057141 significantly increased PTB risk (OR = 0.17, 95% CI 0.04–0.79) among people aged over 60 years, while rs1135216 was significantly associated with susceptibility to PTB in people younger than 60 years.[30] rs1135216 was also found to be associated with other diseases, such as primary dengue hemorrhagic fever and dengue shock syndrome,[46] hypersensitivity pneumonitis in the Mexican population,[47] and hypertension[48] and leprosy in the Indian population.[49] In our study, the frequency of rs1057141-C was slightly higher in the control group than in the TB group and PTB subgroup (P=0.039 and P=0.023, respectively), which slightly reduced the risk of TB in the Yunnan Han population. We performed gene–interaction analysis between rs1057141 and rs1135216 using SHEsis, and found there is significant gene interaction of these two SNPs (P=0.019). Then, we analyzed differences in the rs1057141–rs1135216 combination between TB patients and controls, as well as between clinical subgroups and controls, and found that the frequency of rs1057141-T-rs1135216-C was significantly higher in all TB subgroups and obviously increased the risk of susceptibility to TB disease. Previous studies have found that rs1057141 (TAP1 codon 333) was located in the hydrophobic transmembrane domain and rs1135216 (TAP1 codon 637) was located in the ATP-binding site, and these two SNP combinations could influence the binding of TAP1 and antigen peptide and subsequently affect antigen processing.[24,25] Stephen et al previously reported different haplotypes of rs1135216-rs1057141: *TAP1A* (rs1057141-T-rs1135216-T), *TAP1B* (rs1057141-C-rs1135216-C) and *TAP1C* (rs1057141-C-rs1135216-T) in different human cell lines, and none of the cell lines detected carried the haplotype rs1057141-T-rs1135216-C.[50] Shafat et al indicated that *TAP1A* (rs1057141-A-rs1135216-A) and *TAP1C* (rs1057141-G-rs1135216-A) favored the efficient transport of peptides with a basic C-terminus, and *TAP1B* (rs1057141-C-rs1135216-C) translocated peptides regardless of their differences in C-terminal amino acid residues. Therefore, how the rs1057141-T-rs1135216-C haplotype influences TAP1 binding with the peptide will be interesting research in the future owing to its notable risk association with TB.

In this study, we found five novel *TAP1* alleles and named them *TAP1*unknown_1, TAP1*unknown_2, TAP1*unknown_3, TAP1*unknown_4* and *TAP1*unknown_5*. We found that the novel allele *TAP1*unknown_3* notably increased the risk of susceptibility to TB. The frequency of the *TAP1*unknown_3* allele was notably increased in all TB patients, including in the PTB and EPTB subgroups, and this allele was significantly associated with the risk of susceptibility to TB. The heterozygosity *TAP1*01:01/TAP1*unknown_3* has a significant higher frequency in all TB subgroups. And the haplotype *TAP1*unknown_3-TAP2*01:02* also has a higher frequency in all TB patients. This novel allele combined most of the risk SNP alleles, such as rs41549617-A, rs1057141-T-rs1135216-C and rs41551515-T, which might be the reason why *TAP1*unknown_3* showed such notable risk of susceptibility to TB. In addition, *TAP1*unknown_3* combined with *TAP2*01:02* significantly increased the risk of all TB diseases. In this study, no *TAP2* allele was found to be associated with TB. Gomez et al observed a trend between *TAP2*02:01* and TB disease in Colombians,[51] and Rajalingam also found that *TAP2*02:01* was associated with susceptibility to tuberculoid leprosy and pulmonary tuberculosis in North India.[52] Quadri and Singal indicated that *TAP2* gene variants did not influence antigen peptide transport.[25] Although *TAP2* was not obviously associated with TB, antigen peptide transport into the ER

progresses through TAP1 and TAP2 heterodimers, and the variant combination may influence the TAP1 and TAP2 complex and the progression of antigen transportation. And SNP combination might be an interesting direction to study the TAP functional variation.

There is also some limitations affecting the association of TAP genes with TB in current study. Although the sample size has enough power to calculate the statistical significance, larger sample size and multiple center study is need to give a more powerful association. Moreover, further study on the mechanism of TAP gene mutation influence the tuberculosis infection is also needed in the future.

Conclusion

In conclusion, this study highlights the role of *TAP* gene polymorphisms in TB. Host genetic variants of rs41551515-T and the combination rs1135216-T-rs1135216-C in the *TAP1* gene, as well as *TAP1*unknown_3* are significantly increased the risk of TB susceptibility. And SNP combination showed a significantly influence on TAP function.

Data Sharing Statement

All the genotyping data of SNPs in TAP1 and TAP2 gene in this study have been deposited in the Figshare database named "Genotypes of SNPs in TAP gene of TB patients and controls" (DOI: https://figshare.com/s/a36d0cda19bc08f17f5e).

Ethics Approval and Informed Consent

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board and Biosecurity Committee of the Third People's Hospital of Kunming (Kunming, China) (approval number is 2018030720, Date March 07, 2018). And Informed consent was obtained from all individual participants included in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. And all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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