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Association of TAP1 and TAP2 Gene Polymorphisms with Susceptibility to Pulmonary Tuberculosis

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ABSTRACT

TAP1 and TAP2 genes encode heterodimeric molecule involved in endogenous antigen processing. The present study was undertaken to find out the possible association between TAP1 and TAP2 polymorphisms and risk of pulmonary tuberculosis (PTB) in a sample of Iranian population. Polymorphisms of TAP1 (rs1057141, rs1135216) and TAP2 (rs2228396, rs241447, rs67511411, rs141555015) were determined in 173 PTB patients and 164 healthy subjects. Our findings showed that rs1135216 AG, GG and AG+GG genotypes increased the risk of PTB in comparison with AA (OR=2.36, 95%CI=1.47-3.79, p<0.001; OR=19.13, 95%CI=2.47-148.2, p<0.001 and OR=2.77, 95%CI=1.74-4.39, p<0.001, respectively).

The rs1135216 G allele was associated with increased risk of PTB (OR=2.65, 95%CI=1.784-3.969, p<0.001). TAP2 rs241447 AG and AG+GG genotypes decreased the risk of PTB (OR=0.41, 95%CI=0.26-0.65, p<0.001; OR=0.54, 95%CI=0.35-0.85, respectively).

No significant association was found between TAP1 (rs1057141), TAP2 (rs2228396, rs67511411, rs141555015) variants and PTB.

In conclusion, our findings proposed that TAP gene polymorphisms might be associated with PTB susceptibility among patients in Zahedan, southeast Iran.

Keywords: Polymorphism; TAP1; TAP2; Tuberculosis

INTRODUCTION

Tuberculosis (TB) is one of the most important global public health problem and remains a major cause of morbidity and mortality worldwide particularly in Asia and Africa.[1, 2] According to the annual report on global control of TB from WHO, approximately 8.6 million new cases occurred in 2012.[3] It has been

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expected that one-third of population is infected with TB, though 10% of infected cases will develop clinical disease during their lifetime.[3] TB is a complex disease and it is not well verified why some infected persons develop active disease while others do not.

Various factors contribute to the risk and development of TB including environmental factors, host-pathogen interactions and genetic factors.[4] Up to the present time, many studies have shown the evidence of association between host genetic polymorphisms and TB susceptibility, including chemokine (CC-motif) ligand-2 (CCL2)[5], macrophage migration inhibitory factor (MIF)[6],toll-like receptor 2 (TLR2)[7], immunity-related GTPase family M protein (IRGM)[8], tumor necrosis factor (TNF)[9], CD14[10], TIRAP[7], cluster of differentiation 209 (CD209)[11], natural resistance-associated macrophage protein 1 (NRAMP1)[12], interleukin 18 (IL-18)[13], and CD209 ligand (CD209L).[14] Most of these genes contribute in immune response and their polymorphisms may lead to increase genetic susceptibility to TB. TAP1 and TAP2 genes maps to chromosome 6p21.32 within the MHC. They encode two subunits to compose a heterodimeric molecule, which actively transports antigenic peptide fragments from the cytosol into the lumen of the endoplasmic reticulum (ER) under an ATP-dependent manner.[15-17] It is imaginable that TAP gene polymorphisms can influence the antigen peptide selection and transport process and modify immune response regulation.[18] Several polymorphisms of the TAP gene have been detected and are considered to be associated with a number of immune diseases, viral infection diseases, and even cancer.[19-23]

There are only few studies investigated the impact of TAP polymorphisms on TB.[24-26] The aim of this study was to investigate the possible associations between polymorphisms of TAP genes and susceptibility to PTB in a sample of Iranian population.

MATERIALS AND METHODS

This case-control study was done on 174 PTB patients and 163 healthy subjects. The cases were selected from PTB patients admitted to a university-affiliated hospital (Bou-Ali Hospital, Zahedan, referral center for TB). The diagnosis of PTB was based on clinical symptoms, radiological evidence, and bacteriological investigations such as sputum Acid Fast Bacillus (AFB) smear positivity, culture and response to antituberculosis chemotherapy.[6,27,28]

The control subjects were unrelated adults selected through the population without recent sign, symptom or history of TB and they were living in the same region as the patients with PTB (Zahedan, southeast Iran). The cases and controls had no HIV infection, autoimmune diseases and cancer which affecting host immunity.

The local ethics committee of the Zahedan University of Medical Sciences approved the project, and informed consent was obtained from all individual participants included in the study. Whole blood samples were collected from all subjects and genomic DNA was extracted by the salting out method.

The genotyping of TAP1 (rs1057141, rs1135216) and TAP2 (rs2228396, rs241447) polymorphisms were done by tetra amplification refractory mutation system–polymerase chain reaction (T-ARMS-PCR) as described previously.[29,30] TAP2 rs67511411 and rs141555015 variants were genotyped by PCR methods. The primer sequences with respective annealing temperatures and their product sizes were shown in table 1.

In each 0.20 ml PCR reaction, 1 μL of genomic DNA (~100 ng/ml), 1 μL of each primers and 10 μL of 2X Prime Taq Premix (Genet Bio, Korea) and the appropriate amount of ddH2O were added.

The PCR cycling conditions for SNPs were the initial denaturation at 95°C for 5 min followed by 30 cycles for 30 s at 95°C and annealing temperature (table 1) for 30 s, and extension at 72 °C for 30 s, with a final extension of 72 °C for 10 min. The PCR products were verified onto 2.5 % agarose gels containing 0.5 μg/ml ethidium bromide and observed under UV light.

Statistical Analysis

Analysis of the data was done using the SPSS 18.0 software. Independent sample t-test for continuous data and $\chi 2$ test for categorical data were used. The associations between genotypes and PTB were calculated by computing the odds ratio (OR) and 95% confidence intervals (95% CI) from logistic regression analyses. *p*-value less than 0.05 were considered statistically significant.

Table 1. Primers sequences used for detection of TAP1 and TAP2 gene polymorphisms.

Gene polymorphism	Primers	Sequence (5`->3`)	Product size (bp)	Anneling temperature (°C)
TAP1 rs1057141 A/G (Ile333val)	FO	CCCTGCACTGAGATTTGCAGACCTCTGGAG	Control 533	63
	RO	ACCTGGGAACATGGACCACAGGGACAGGGT	G allele (val) 351	
	FI (A allele)	GATCAGTGTCCCTCACCATGGTCACCCGGA	A allele (Ile) 241	
	RI (G allele)	GGGCAGAAGGAAAAGCAGAGGCAGGGTCAC		
TAP1 rs1135216 A/G (Asp637Gly)	FO	CATCTTCCCAGAATCTCCCCTATCCAGCTA	Control 429	65
	RO	TGGGGAGGCATCCAATGGAACTGGATTTGG	A allele (Asp) 307	
	FI (A allele)	CATCTTGGCCCTTTGCTCTGCAGAGGTACA	G allele (Gly) 180	
	RI (G allele)	ACCCCCTGACAGCTGGCTCCCAGCCTCCC		
TAP2 rs2228396 G/A (Thr565Ala)	FO	CTCACAGTATGAACACTGCTACCTGCACAG	Control 400	64
	RO	GGAGCAAGCTTACAATTTGTAGAAGATACC	G allele (Ala) 298	
	FI (A allele)	TGTTCTCCGGTTCTGTGAGGAACAACAGTA	A allele (Thr) 161	
	RI (G allele)	ATCATCTTCGCAGCTCTGCAGCCCATAAAC		
TAP2 rs241447 G/A (Ala665Thr)	FO	TTGGGGAATGGAATCCGGTGGTGTGAGGGC	Control 408	68
	RO	TCAGCCGCTGCTGCACCAGGCGGGAATAGA	G allele (Ala) 326	
	FI (A allele)	CAGTGCTGGTGATTGCTCACAGGCTGCAAA	A allele (Thr) 141	
	RI (G allele)	CACCAGGATCTGGTGGGCGCGCTGAACTAC		
TAP2 rs67511411 (177bp Ins/Del)	F	CCATATGCAAAGGCACAAAGGT	Ins allele 400	60
	R	TCAATTATATTGCATCTTGGGTCC	Del allele 223	
TAP2 rs141555015 (18-bp I/D)	F	GCAATGAGTCTCACTCGCCT	Ins allele 196	65
	R	GTAGGCTCAGAGCTTGAAGTAGT	Del allele 178	

RESULTS

This case-control study was done on 173 PTB (64 males, 109 females; ages 50.1±20.6 years) patients and 164 healthy subjects (70 males and 94 females; ages 47.5±15.3 years).

There was no significant difference between the groups concerning sex and age (p=0.317 and p=0.191, respectively). Genotypes and allele frequencies of TAP1 (rs1057141, rs1135216) and TAP2 (rs2228396, rs241447, rs67511411, rs141555015) polymorphisms are shown in table 2.

The results showed an association between TAP1 rs1135216 A/G polymorphism and PTB risk. The AG, GG and AG+GG genotypes increased the risk of PTB in comparison with AA (OR=2.36, 95%CI=1.47-3.79, p<0.001; OR=19.13, 95%CI=2.47-148.2, p<0.001 and OR=2.77, 95%CI=1.74-4.39, p<0.001, respectively). The G allele of TAP1 rs1135216 contributes to an increased risk to PTB compared to A allele (OR=2.65, 95%CI=1.784-3.969, p<0.001).

An association between TAP2 rs241447 A/G variant and PTB was found. The AG and AG+GG genotypes decreased the risk of PTB compared to AA (OR=0.41, 95%CI=0.26-0.65, p<0.001 and OR=0.54, 95%CI= 0.35-0.85, respectively). No significant association was found between TAP1 (rs1057141), TAP2 (rs2228396, rs67511411, rs141555015) variants and PTB.

DISCUSSION

TAP1 and TAP2 proteins play an important role in antigen presentation on MHC class 1 molecule.[31] Variants in TAP genes might lead to the modification in peptide translocation.[19] Polymorphic residues in TAP1 and TAP2 genes were identified which modify specificity of substrate transport.[30] Consequently, these genes are considered as candidate genes for susceptibility to disease.[18,24,29,32]

Table 2. Frequency distribution of TAP1 and TAP2 gene polymorphisms in PTB and controls.

Gene polymorphism	PTB n (%)	Controls n (%)	OR (95% CI)	*p* value
TAP1 rs1057141 A/G (Ile393val)				
AA	94 (54.3)	84 (51.2)	1.00	-
AG	77 (44.5)	75 (45.7)	0.92 (0.59-1.42)	0.740
GG	2 (1.2)	5 (3.0)	0.36 (0.07-1.89)	0.264
Allele				
A	265 (76.5)	243 (74.1)	1.00	-
G	81 (23.5)	85 (25.9)	0.87 (0.62-1.24)	0.475
TAP1 rs1135216 A/G (Asp637Gly)				
AA	90 (52.0)	123 (75.0)	1.0	-
AG	69 (39.9)	40 (24.4)	2.36 (1.47-3.79)	<0.001
GG	14 (8.1)	1 (0.6)	19.13 (2.47-148.2)	<0.001
AG+GG	83 (48.0)	41 (25.0)	2.77 (1.74-4.39)	<0.0001
Allele				
A	249 (72.0)	286 (87.2)	1.00	-
G	97 (28.0)	42 (12.8)	2.65 (1.78-3.96)	<0.0001
TAP2 rs2228396 G/A (Thr565Ala)				
GG	156 (90.2)	149 (90.9)	1.00	-
GA	17 (9.8)	15 (9.1)	1.08 (1.78-3.96)	0.855
AA	0 (0.0)	0 (0.0)	-	-
Allele				
G	329 (95.1)	313 (95.4)	1.00	-
A	17 (4.9)	15 (4.6)	1.08 (0.53-2.20)	0.858
TAP2 rs241447 G/A (Ala665Thr)				
AA	76 (44.0)	49 (29.9)	1.00	-
AG	71 (41.0)	112 (68.3)	0.41 (0.26-0.65)	<0.001
GG	26 (15.0)	3 (1.8)	1.29 (0.61-2.75)	0.573
AG+GG	97 (55.0)	115 (70.1)	0.54 (0.35-0.85)	<0.001
Allele				
A	223 (64.5)	210 (64.0)	1.00	-
G	123 (35.5)	118 (36.0)	0.98 (0.72-1.35)	0.936
TAP2 rs67511411 (177bp I/D)				
II	81 (46.8)	87 (53.0)	1.00	-
ID	78 (45.1)	63 (38.4)	1.33 (0.85-2.08)	0.253
DD	14 (8.1)	14 (8.6)	1.07 (0.48-2.39)	0.987
Allele				
I	240 (69.4)	237 (72.2)	1.00	-
D	106 (30.6)	91 (27.8)	1.15 (0.82-1.60)	0.446
TAP2 rs141555015 (18-bp I/D)				
II	173 (100)	164 (100)	-	-
ID	0 (0)	0 (0)	-	-
DD	0 (0)	0 (0)	-	-
Allele				
I	246 (100)	328 (100)	-	-
D	0 (0)	0 (0)	-	-

In the present study, we focused on the association of TAP1 and TAP2 gene polymorphisms with PTB susceptibility in a cohort of Iranian population. We found a significant association between TAP1 rs1135216 A/G variant and PTB. The homozygote GG and heterozygote AG increased the risk of PTB in comparison with homozygote AA genotype.

The TAP1 rs1135216 G allele was associated with increased risk of PTB. The results showed that TAP2 rs241447 polymorphism decreased the risk of PTB. The frequency distribution of AG as well as AG+GG genotypes was significantly lower in PTB than controls. No statistical significant associations were found at polymorphic sites of TAP1 (rs1057141) and TAP2 (rs2228396, rs241447, rs67511411) genes to the risk of PTB.

Wang et al[33] investigated the impact of rs1135216 A/G and rs1057141 A/G polymorphisms of TAP1 gene with TB susceptibility in Li Population in China and found that these variants increased the risk of TB. Rajalingam et al[24] reported a statistical association between alleles in TAP2 region with PTB and tuberculoid leprosy susceptibility in the North India populations.

In a study carried out in a Northwestern Colombian population failed to find any association of TAP1 gene with TB disease.[25]

Sunder et al[29] demonstrated that the rs1057141 GG genotype of TAP1 and rs1135216 GA genotype of TAP1 gene were positively associated with HIV-TB co-infection and these genotypes may act as a risk factor for developing TB co-infection in HIV-positive individuals. It has been shown that TAP-deficient mice displayed an increased susceptibility to TB that was manifested by a decreased survival after infection, a greater bacterial burden, and more severe tissue pathology.[34]

Soundravally et al[35] reported that TAP2 Val379Ile increased the risk of dengue hemorrhagic fever cases (DHF) compared to control subjects. Significantly high proportion of DHF was found to have TAP2 665 Thr/Ala genotypes (30.7%) in comparison with dengue fever DF (13.3%) cases which indicted that this variant is a risk factor for development of DHF. It has been shown that TAP1 637 Asp/Gly polymorphism decreased the risk of dengue shock syndrome (DSS).[36]

TAP plays an essential role in a cellular immune response against Hepatitis B virus (HBV). Xu et al[26] showed that TAP1 Asp637Gly, and TAP2 Arg651Cys variants increase the risk of HBV infection. It has been proposed that TAP variants play a key role in different outcomes of persistent HBV infection.[37]

The discrepancy between our results and those reported findings may be due to the phenotype definition both in cases and controls, population genetic factors, and even potential global differences in M. tuberculosis strain.[38]

In summary, our findings suggest a risk association of TAP1 rs1135216 A/G polymorphism and PTB, while TAP2 rs241447 A/G variant decreased the risk of PTB in this case-control study in a sample of Iranian population. Larger studies with different ethnicities are needed to validate our findings.

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