Association between genetic variants in CD1A and CD1D genes and pulmonary tuberculosis in an Iranian population

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Abstract. Cluster of differentiation (CD)1 molecules are a highly conserved family of MCH-like transmembrane glycoproteins that bind lipid and glycolipid antigens and present a diverse range of microbial and self-glycolipids to antigen-specific T cells. The current study aimed to find out the impact of CD1A and CD1D polymorphisms on pulmonary tuberculosis (PTB). This case-control study encompassed 172 PTB patients and 180 healthy subjects. Genotyping of CD1A and CD1D variants was achieved using the polymerase chain reaction restriction fragment length polymorphism method. The results revealed that CD1A rs411089 variant significantly increased the risk of PTB in recessive model [odds ratio (OR)=2.71, 95% confidence interval (CI)=1.38-5.57, CC vs. TT+TC, P=0.005]. CD1D rs859009 polymorphism significantly reduced the risk of PTB in heterozygous codominant (OR=0.50, 95% CI=0.29-0.86, P=0.011, GC vs. GG) and dominant (OR=0.53, 95% CI=0.31-0.88, P=0.019, GC+CC vs. GG) inheritance model. The CD1A rs366316, CD1D rs973742 and CD1D rs859010 were not associated with the risk/protection from PTB (P>0.05). The results of the present study suggest that CD1A rs411089 and CD1D rs859009 but not CD1A rs366316, CD1D rs973742 and CD1D rs859010 polymorphisms are associated with PTB in a sample of the Iranian population. Further investigation with different ethnicities and larger sample sizes are necessary to certify the findings of the present study.

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Introduction

Mycobacterium tuberculosis (MTB) is respiratory tract infectious disease but can affect nearly all of the body, including the brain, the kidneys and the bones (1). Tuberculosis is still a major health problem and a leading cause of mortalities from infectious disease throughout the world (2). Based on a World Health Organization report 10.4 million new TB cases and 1.3 million fatalities occurred in 2016 globally (3). The prevalence of TB in Sistan and Baluchistan province is higher than other provinces of Iran. Whereas one-third of the world's population is infected with MTB, 5-10% of infected cases go on to develop active TB, which indicates that in addition to the environment host genetics factors may influence the risk of the disease (2,4,5).

Cluster of differentiation 1 (CD1) genes, mapped to human chromosome 1 (1q23.1), encoding five isoforms of the CD1 molecule, namely CD1a, CD1b, CD1c, CD1d and CD1e (6-9). CD1 is a family of glycoproteins which are expressed on antigen presenting cells (APCs) (10). They are belongs to major histocompatibility complex class I (MHC) and participate in presentation of lipid antigens to T cells (11) but unlike MHCs their expression is nearly identical in all humans (11). The CD1 family can be divided into three groups. Group 1 consists of CD1a, CD1b and CD1c that present lipid antigens to T-helper cells. CD1D belongs to group 2 and presents lipid antigens to natural killer T cells and group 3 that composed of CD1E (12).

It is clear that CD1 molecules participate in cell-mediated immune responses against MTB (13). Indeed, several kinds of mycobacterial lipids function as antigens in this system (11). CD1-restricted T cells identify MTB and react to mycobacterium cell wall lipid antigens (14). CD1 molecules, unlike classical MHC molecules, exhibit limited polymorphism (10,15) but, these few polymorphisms are demonstrated to be associated with susceptibility or resistance to certain diseases (12,14,16,17). Single nucleotide polymorphism (SNPs), the most common type of genetic variants can affect the expression and function of the gene (18,19). There is little data regarding the impact of CD1 gene polymorphisms and tuberculosis susceptibility (14). Seshadri *et al* (14) investigated the association between rs366316, rs2269714, rs411089 and rs389293 polymorphisms of CD1A gene and

risk of tuberculosis. They reported that rs411089 and rs366316 variants were significantly correlated with the development of tuberculosis. To the best of our knowledge, no study investigated the impact of CDID polymorphisms on tuberculosis susceptibility. The present study aimed to examine the association between CD1A (rs411089 and rs366316) and CD1D (rs973742, rs859009 and rs859010) polymorphisms and the risk of PTB in a sample of the southeast Iranian population.

Materials and methods

Patients. A total of 352 subjects including 172 clinically diagnosed patients with pulmonary tuberculosis (PTB) between 12 and 86 years of age (69 males and 103 females), and 180 unrelated healthy individuals ranging between 20 and 85 years of age (74 males and 106 females) were recruited in the study from May 2014 to March 2018. The cases were selected from PTB patients admitted to the University Affiliated Hospital (Bouali Hospital, Zahedan, Iran; referral center for TB). The diagnosis of PTB depended on clinical findings, radiological evidence, positive smear for MTB, culture and response to antituberculosis chemotherapy as described previously (20-23). The control individuals did not have a history of TB and inflammatory disease or other of chronic infectious disease; they were of the same ethnicity as patients and living in the same area as the patients with PTB (Southeast Iran). The local Ethics Committee of the Zahedan University of Medical Sciences (Zahedan, Iran) approved the project and written informed consent was taken from all participants. Blood samples (5 ml) were collected in Na-EDTA tubes from patients and healthy controls and stored at -20 until DNA extraction. Genomic DNA was extracted from whole blood by salting-out method as described previously (24).

Genotyping. Genotyping of CD1A and CD1D was achieved by polymerase chain reaction amplification-restriction fragment length polymorphism assays. The primers were synthesized by Metabion International AG (Erding, Germany) and the restriction enzyme were purchased from Fermentas; Thermo Fisher Scientific, Inc. (Waltham, MA, USA). Primer sequences restriction enzymes and length of the fragments are summarized in Table I. Amplification was achieved in a final volume of 20 μl containing 1 μl genomic DNA (~100 ng/ml), 1 μl each primer (10 μM) and 10 μl of 2X Prime Taq Premix (Genet Bio, Daejeon, Korea), and 7 μl ddH_2O. The PCR conditions were set as follows: 95˚C for 5 min, 30 cycles of 95˚C for 30 sec, 62˚C for CD1A rs411089, CD1D rs859009 and CD1D rs859010, 60˚C for CD1D rs973742, 65˚C for CD1A rs366316 and 72˚C for 30 sec and a final extension step of 72˚C for 5 min. Then, 10 μl of PCR product was digested with suitable restriction enzyme (Table II) and resolved on 2.5% agarose gel containing 0.5 μg/ml ethidium bromide and visualized under UV light. A total of ~10% of the random samples were regenotyped and the finding were confirmed as 100% concordant.

Statistical analysis. Analysis of the data was achieved by the statistical package SPSS 20 software (IBM Corp., Armonk, NY, USA). Association among variants and PTB risk was estimated by calculation the odds ratio (OR) and 95% confidence intervals (CI) from logistic regression analysis. The Bonferroni correction test was performed by multiplying P-values of logistic regression analysis by the number of SNPs examined for each gene.

Haplotype analysis was executed using SNPStats: A web tool for the analysis of association studies (25). P<0.05 was considered to indicate a statistically significant difference.

The observed genotype frequencies in the controls were examined for Hardy-Weinberg equilibrium (HWE) using the χ^2-test. The Bonferroni correction test was performed by multiplying P-values by the number of SNPs examined for each gene.

Results

Patients. The study participants include 172 patients with PTB (69 males and 103 females; mean age, 50.01±20.57 years) and 180 healthy individuals (74 males and 106 females; mean age, 49.92±15.10 years). There was no statistically significant difference between the groups regarding sex and age (P=0.486 and 0.572, respectively).

Association between the CD1A variants and PTB risk. The genotype and allelic frequencies of CD1A rs411089 and CD1A rs366316 gene polymorphisms in cases and controls are presented in Table II. The results demonstrated that the CC genotype of CD1A rs411089 polymorphism in recessive inheritance model increased the risk of PTB in comparison with TT+TC genotypes (OR=2.71, 95% CI=1.36-5.40, P=0.004). As presented in Table II there was no significant difference in genotype and allelic distribution of CD1A rs366316 gene polymorphisms between PTB patients and controls (P>0.05).

Association between the CD1D variants and PTB risk. Table III summarized the genotype and allele frequencies of CD1D rs973742, CD1D rs859009 and CD1D rs859010 polymorphisms in PTB patients and the control groups. The GC genotype as well as the GC+CC genotype of CD1D rs859009 polymorphism decreased the risk of PTB (OR=0.49, 95% CI=0.29-0.85, P=0.01 and OR=0.53, 95% CI=0.31-0.89, P=0.01, respectively). The allele frequency of CD1D rs859009 Polymorphism was not significantly different between the groups (P=0.22). The genotype and allele frequencies of CD1D rs973742 and CD1D rs859010 were not significantly different between two groups (χ^2=2.206, P=0.332 and χ^2=2.252, P=0.324, respectively). The results demonstrated that CD1D rs973742 and CD1D rs859010 variants were not associated with risk of/protection from PTB in codominant, dominant and recessive tested inheritance models (Table II). The results demonstrated that the rs366316, rs859010 polymorphisms but not rs411089, rs973742 and rs859009 polymorphisms were in present in HWE, Tables II and III).

Haplotypes analysis. Haplotypes analysis was achieved (Table IV) and the results demonstrated that haplotypes TGACA, TAACA, and TAAGA significantly decreased the risk of PTB in comparison with CAGGA (rs411089C/rs366316A/rs973742G/rs859009G/rs859010A).

Discussion

CD1 is a family of antigen presenting molecules that belongs to the MHC class I molecules but, unlike those that exist on

Table I. Primer sequences of polymerase chain reaction-restriction fragment length polymorphism for detection of CD1A and CD1D polymorphisms.

	Primer sequences (5'-3')	Restriction enzyme	Fragment (bp)
CD1A rs411089	F: TGTGTGTGGTTTCCCTAGCA	*Bse*GI	T allele: 297
	R: CGATCCAGGTGACATGGAAG		C allele: 205+92
CD1A rs366316	F: TGGGAAAATATTGAAAAGGACAG	*AlW*26I	G allele: 401
	R: ATTGGTCTTTGATTTCTGTTCCA		A allele: 254+147
CD1D rs973742	F: TGGGGAGTCTGCCATAATAGA	*Tai*I	A allele: 502
	R: TGCCCATTTATTATCTGAATGTTG		G allele: 273+229
CD1D rs859009	F: TGGCTGTCCAGGTACACACT	*Mwo*I	G allele 440
	R: GCAGTACATGTCTCTAGGTGGAA		C allele 338,102
CD1D rs859010	F: TGGCTGTCCAGGTACACACT	*ALw*26I	A allele 152, 271
	R: GCAGTACATGTCTCTAGGTGGAA		T allele 423

CD, cluster of differentiation; F, forward; R, reverse.

Table II. The genotypes and allele frequency distribution of CD1A polymorphism in pulmonary tuberculosis patients and control groups.

Polymorphism	Patients n (%)	Controls n (%)	OR (95% CI)	P-value	P^C	HWE (P-value)
CD1A rs411089						0.000
Codominant						
TT	21 (12.2)	20 (11.1)	1.00	-	-	
TC	121 (70.3)	147 (81.7)	0.78 (0.41-1.47)	0.503	-	
CC	30 (17.5)	13 (7.2)	2.20 (0.89-5.25)	0.118	-	
Dominant						
TT	21 (12.2)	20 (11.1)	1.00			
TC+CC	151 (87.8)	160 (88.9)	0.90 (0.48-1.69)	0.868	-	
Recessive						
TT+TC	142 (82.5)	167 (92.8)	1.00			
CC	30 (17.5)	13 (7.2)	2.71 (1.38-5.57)	0.005	0.010	
Alleles						
T	163 (47.4)	187 (51.9)	1.00			
C	181 (52.6)	173 (48.1)	1.20 (0.89-1.61)	0.221	-	
CD1A rs366316						0.079
Codominant						
AA	70 (40.7)	61 (33.9)	1.00			
AG	81 (47.1)	97 (53.9)	0.73 (0.46-1.14)	0.205	-	
GG	21 (12.2)	22 (12.2)	0.83 (0.42-1.66)	0.725		
Dominant						
AA	70 (40.7)	61 (33.9)	1.00			
AG+GG	102 (59.3)	119 (66.1)	0.74 (0.48-1.16)	0.225	-	
Recessive						
AA+AG	151 (47.8)	158 (87.8)	1.00			
GG	21 (12.2)	10 (12.2)	2.20 (1.05-4.62)	0.058	-	
Alleles						
A	221 (64.2)	219 (60.8)	1.00			
G	123 (35.8)	141 (39.2)	0.86 (0.64-1.17)	0.391	-	

The association was performed using logistic regression analysis. HWE was tested by χ^2 test. OR, odds ratio; CI, confidence interval; P^C, Bonferroni corrected P-value; HWE, Hardy-Weinberg equilibrium; CD, cluster of differentiation.

Table III. The genotypes and allele distribution of CD1D polymorphisms in pulmonary tuberculosis patients and control groups.

Polymorphism	Patients n (%)	Controls n (%)	OR (95% CI)	P-value	P^C	HWE (P-value)
CD1A rs973742						0.000
Codominant						
AA	61 (35.5)	67 (37.2)	1.00	-	-	
AG	93 (54.1)	102 (56.7)	1.00 (0.64-1.56)	0.999	-	
GG	18 (10.4)	11 (6.1)	1.80 (0.76-3.91)	0.217	-	
Dominant						
AA	61 (35.5)	67 (37.2)	1.00			
AG+GG	111 (64.5)	113 (62.8)	1.08 (0.69-1.68)	0.741	-	
Recessive						
AA+AG	154 (89.6)	169 (93.9)	1.00			
GG	18 (10.4)	11 (6.1)	1.80 (0.84-4.05)	0.175	-	
Alleles						
A	215 (62.5)	236 (65.6)	1.00	-	-	
G	129 (37.5)	124 (34.4)	1.14 (0.84-1.56)	0.432	-	
CD1D rs859009						0.000
Codominant						
GG	46 (26.7)	29 (16.1)	1.00	-	-	
GC	97 (56.4)	123 (68.3)	0.50 (0.29-0.86)	0.011	0.033	
CC	29 (16.9)	28 (15.6)	0.65 (0.32-1.31)	0.287	-	
Dominant						
GG	46 (26.7)	29 (16.1)	1.00	-	-	
GC+CC	126 (73.3)	151 (83.9)	0.53 (0.31-0.88)	0.019	0.057	
Recessive						
GG+GC	143 (83.1)	152 (84.4)	1.00	-	-	
CC	29 (16.9)	28 (15.6)	1.10 (0.63-1.92)	0.773	-	
Alleles						
G	189 (54.9)	181 (50.3)	1.00	-	-	
C	155 (45.1)	179 (49.7)	0.82 (0.61-1.11)	0.227	-	
CD1D rs859010						0.183
Codominant						
AA	89 (51.8)	105 (58.4)	1.00	-	-	
AT	73 (42.4)	69 (38.3)	1.25 (0.80-1.94)	0.322	-	
TT	10 (5.8)	6 (3.3)	1.97 (0.74-5.61)	0.297	-	
Dominant						
AA	89 (51.8)	105 (58.4)	1.00	-	-	
AT+TT	83 (48.2)	75 (41.6)	1.31 (0.86-1.98)	0.239	-	
Recessive						
AA+AT	154 (89.6)	169 (93.9)	1.00	-	-	
TT	18 (10.4)	11 (6.1)	1.80 (0.84-4.10)	0.175	-	
Alleles						
A	251 (72.9)	279 (77.5)	1.00			
T	93 (27.1)	81 (22.5)	1.28 (0.91-1.79)	0.190	-	

The association was performed using logistic regression analysis. HWE was tested by χ^2 test. OR, odds ratio; CI, confidence interval; P^C, Bonferroni corrected P-value; HWE, Hardy-Weinberg equilibrium.

all nucleated cells, the CD1 groups are expressed only on APCs, cortical thymocytes and dendritic cells (DC) (10,26). The human CD1 proteins present lipid antigens of MTB to T cells (27). Mounting evidence revealed a link between

Table IV. Haplotype association of CD1A (rs411089 and rs366316) and CD1D (rs973742, rs859009 and rs859010) variants with pulmonary tuberculosis risk.

rs411089	rs366316	rs973742	rs859009	rs859010	Cases (frequency)	Control (frequency)	OR (95% CI)	P-value
C	A	G	G	A	0.1133	0.1432	1.00	-
T	G	A	C	A	0.1522	0.1241	0.32 (0.13-0.75)	0.0092
C	A	A	C	A	0.0836	0.1096	1.22 (0.46-3.27)	0.69
T	A	A	G	T	0.0517	0.0804	0.86 (0.31-2.41)	0.78
C	A	A	G	T	0.0588	0.0632	0.97 (0.34-2.75)	0.96
C	A	G	C	A	0.0659	0.0598	0.47 (0.15-1.46)	0.19
T	G	G	C	A	0.0674	0.0587	0.79 (0.20-3.11)	0.74
T	A	A	C	A	0.0679	0.0419	0.14 (0.02-0.89)	0.038
T	G	A	G	T	0.0307	0.0409	0.75 (0.17-3.30)	0.7
T	A	A	G	A	0.0634	0.0407	0.12 (0.03-0.57)	0.0076
C	A	A	G	A	0.072	0.0378	0.99 (0.17-5.86)	1
T	G	A	G	A	NA	0.0296	1.16 (0.24-5.53)	0.85
C	G	A	C	A	NA	0.0283	0.99 (0.08-11.45)	0.99
T	G	A	C	T	0.0384	0.0189	0.91 (0.11-7.40)	0.93
C	G	A	G	A	0.0166	0.0186	0.40 (0.06-2.70)	0.35

Haplotype analysis was executed using SNPStats software. Each row represents separate polymorphisms. CD, cluster of differentiation.

CD1 polymorphisms and certain autoimmune and inflammatory diseases including inflammatory neuropathies (12), tuberculosis (14), cancer (28), multiple sclerosis (16,29), and Guillain-Barre syndromes (30). In the current study the possible association between CD1 and the risk pf PTB in a sample of a southeast Iranian population was investigated. The results of the present study indicated that CD1A rs411089 as well as CD1D rs859009 variant was significantly associated with the risk of PTB. The CC genotype of CD1A rs411089 polymorphism in recessive model increased the risk of PTB, while the GC genotype as well as GC+CC genotype of CD1D rs859009 polymorphism significantly decreased the risk of PTB.

To the best of the authors' knowledge, only one study has been performed on the impact of CD1 gene variants on the susceptibility to TB (14). Seshadri *et al* (14) in a case-population study genotyped rs366316, rs2269714, rs411089 and rs389293 in a discovery cohort of 352 cases and 382 controls. They identified that the rs366316 and rs411089 polymorphisms were significantly associated with the development of TB. In a next step they genotyped rs366316 and rs411089 in a validation cohort of 339 cases and 376 controls and another time discovered a significant association between rs411089 and TB, however they did not find any association between rs366316 and TB (14). In agreement with the results of the present study they demonstrated that the minor homozygous genotype of rs411089 was associated with an increased risk of TB in a recessive model (14). It seems that the minor homozygous genotype of rs411089 accompanied with a functional CD1A-deficiency and this polymorphism cause a low CD1A expression level. Sieling *et al* (31) demonstrated an increased expression of CD1 proteins (CD1A, CD1B and CD1C) at the site of tuberculoid leprosy lesions. Buettner *et al* (32) detected DCs in bronchoalveolar lavage specimens of tuberculosis patients with strongly upregulated of CD1A, CD83 and CCR7. Roura-Mir *et al* (33) have identified that MTB or its cell wall lipids caused increased expression level of CD1A, CD1B and CD1C but not CD1D. CD1A-deficient cells failed to present mycobacterium peptides to T cells. Behar *et al* (34) demonstrated that CD1D-deficient mice were not significantly different in their susceptibility to infection compared with control mice. This information demonstrates the use of a population genetics study to understanding the role of CD1 antigen-presenting molecules in human disease.

It has been reported that the rs366316 variant which is located in the in the promoter region is strongly associated with low CD1a surface expression (18). The rs411089, an intronic variant, is strongly linked to rs858998 and may regulate transcription independently of rs366316 (14). rs973742 is located 4-kb downstream from the CD1D gene and the functional role of this variant is unknown (35). The impact of intronic rs859009 and rs859010 polymorphisms on CD1D expression has not been recognized.

There is no clear explanation for the departure from HWE in the study population regarding rs411089, rs973742 and rs859009 polymorphisms. It may be owing to a small sample size, genetic drift or consanguineous marriages, which is common in this region of the country.

A limitation of this study is that there is no data regarding smoking, diabetes mellitus, socioeconomic status and other risk factor for PTB.

In conclusion, the results of the present study revealed that CD1A (rs411089) and CD1D (rs859009) polymorphisms protect against PTB in a sample of the Iranian population. More well-designed studies in diverse ethnicities are necessary to verify the present results.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

MT, MH conceived and designed the study; HD, FB and GB performed the experiments and analyzed the data; MN performed data collection. All authors contributed to the writing of the manuscript and reviewed and approved the final manuscript.

Ethics approval and consent to participate

The local Ethics Committee of the Zahedan University of Medical Sciences approved the project and written informed consent was taken from all participants.

Patient consent for publication

Not applicable.

Conflict of interest

The authors declare no conflict of interest. The abstract of the present study was previously presented at a conference (https://www.nature.com/articles/s41431-018-0248-6).

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