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Original Article

Association between IL-1 gene polymorphisms and tuberculosis susceptibility in the Chinese Tibetan population

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Abstract: Interleukin-1 (IL-1) gene is known to be implicated in tuberculosis (TB). The present case-control study was designed to investigate whether IL-1 polymorphisms associated with TB susceptibility in a Chinese Tibetan cohort. 300 Tibetan tuberculosis patients and 300 healthy controls were recruited for 12 single-nucleotide polymorphisms (SNPs) genotyping of IL-1 gene via Sequenom MassARRAY analysis. The odds ratio (OR) and 95% confidence interval (CI) were analyzed by unconditional logistic regression to evaluate the effect of polymorphisms on the risk of tuberculosis. Among genotyped SNPs, a significant high risk between TB and SNP rs3783550 G/T, rs3783546 G/C, rs2856838 A/G, rs1609682 G/T, rs3783521 A/G genotype within IL-1α as well as rs1143623 G/G genotype within IL-1β was found based on multiple model analysis. In addition, IL-1α SNPs mapped in a 10 kb LD block with D'>0.98, suggesting that a significant linkage disequilibrium presence among these SNPs, and "TCATG" haplotype of IL-1α SNPs with a 1.47-fold risk for TB was observed (P = 0.007). In conclusion, our data shed new light on how IL-1 SNPs may contribute to tuberculosis susceptibility in the Chinese Tibetan population.

Keywords: IL-1, tuberculosis, gene polymorphisms, Chinese Tibetan population

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis (Mtb), and remains a global emergency of morbidity and mortality especially in Asia and Africa [1, 2]. Approximately 2 million individuals die of TB and 9 million become infected annually based on the World Health Organization statistics [3]. The incidence of tuberculosis in China ranks as the top in the world [4], and the incidence of tuberculosis in Tibetans is high in China [5]. Conventional diagnosis of TB can be performed according to clinical manifestations, laboratory tests, and imaging studies.

The occurrence of TB at different rates among particular races, ethnicities, and families indicates a genetic predisposition to TB susceptibility [6]. Therefore, it is critical to understand if genetic variation is significantly related to more or less susceptibility to TB infection. Discovery of reliable genetic molecular markers are essential for early rapid diagnosis, improving therapeutic efficacy, and reducing drug toxicity. Several lines of evidence from genome-wide linkage studies and association-based candidate gene studies have defined a number of immune response genes for the development of active TB, including encoding pattern recognition receptors (TLR, CD14), C-type lectins, cytokines/chemokines, and their receptors (IFN-γ, TNF-α, IL-12, IL-10, MCP-1, MMP-1), major histocompatibility complex (MHC) molecules, vitamin D receptor (VDR), and proton-coupled divalent metal ion transporters (SLC11A1) [7, 8]. Genetic variations in these genes have a diverse influence on the susceptibility to or protection against TB among particular families, ethnicities, and races.

IL-1 gene cluster, as a type of immune response gene, is located in a 430-kb region of DNA on the long arm of human chromosome 2 and codes some of pro-inflammatory cytokines, which might play a role in various neuropatholo-

Table 1. Allele frequencies of candidates SNPs examined in IL-1 gene among cases and controls

SNP	Gene	Chr	Position	Allele	Minor allele frequency		HWE *P* value	OR (95% CI)	*P*[a]
					Case	Control			
rs3783550	IL-1α	2q13	113532885	T/G	0.410	0.333	0.7956	1.39 (1.10-1.76)	0.021*
rs3783546	IL-1α	2q13	113534830	C/G	0.420	0.332	0.8963	1.46 (1.15-1.85)	0.006*
rs2856838	IL-1α	2q13	113539972	A/G	0.297	0.240	0.6332	1.34 (1.03-1.73)	0.040*
rs1609682	IL-1α	2q13	113540205	T/G	0.410	0.334	0.7957	1.38 (1.09-1.75)	0.022*
rs3783521	IL-1α	2q13	113543577	G/A	0.430	0.333	0.7956	1.51 (1.19-1.91)	0.002*
rs2853550	IL-1β	2q13	113587121	A/G	0.090	0.092	0.2923	0.98 (0.66-1.45)	0.308
rs1143643	IL-1β	2q13	113588302	C/T	0.527	0.470	0.7276	1.26 (1.00-1.58)	0.128
rs3136558	IL-1β	2q13	113591275	G/A	0.372	0.379	0.8057	0.97 (0.77-1.22)	0.928
rs1143630	IL-1β	2q13	113591655	T/G	0.162	0.155	0.5060	1.05 (0.77-1.43)	0.936
rs1143627	IL-1β	2q13	113594387	G/A	0.561	0.465	0.0470	1.47 (1.17-1.85)	< 0.001*
rs16944	IL-1β	2q13	113594867	A/G	0.561	0.455	0.0803	1.53 (1.22-1.92)	< 0.001*
rs1143623	IL-1β	2q13	113595829	G/C	0.487	0.373	0.0359	1.59 (1.26-2.00)	< 0.001*

SNP: Single nucleotide polymorphism; OR = Odds ratio; 95% CI = 95% confidence interval; HWE: Hardy-Weinberg equilibrium; *$P < 0.05$ indicates statistical significance; [a]*P* values were calculated using Pearson Chi-square test/Fisher's exact test.

gies involved in neuron inflammation. The largest IL-1 family of interleukins consist of IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1RA). Among them, IL-1α and β are key players in the innate immune system, and also are endogenous pyrogens with similar activities to lipopolysaccharides (LPS), which are the major molecular components of the outer membrane of gram-negative bacteria [9, 10]. Several lines evidence supporting an association between IL-1 innate immune gene associated with TB pathogenesis [6, 11].

TB is a major public health problem among Tibetans, most of whom live in the Tibet Autonomous Region, and some groups reside in the Qinghai, Gansu, Sichuan, and Yunnan provinces of China. A study of genomic variations in Tibetan people suggested that a majority of the Tibetan gene pool may have diverged from that of the Han population around 3000 years ago [12]. To our best knowledge, there is no information between IL-1 gene polymorphisms and the susceptibility of tuberculosis in Chinese Tibetan population. Therefore, we performed this case-control study in order to overcome this limitation and provide useful information for TB treatment. A total of 12 SNPs were carefully selected for further genotyping based on 1000 Genomes Project (http://www.1000 genomes.org/) and dbSNP (https://www. ncbi.nlm.nih.gov/projects/SNP/) databases with MAFs>5% in Chinese Han population.

Materials and methods

Study participants

This case-control study was performed on 300 tuberculosis patients and 300 healthy individuals from Chinese Tibetan population. Tuberculosis cases were diagnosed according to the standard criteria of GB15987-1995 treated at the third Hospital of the Tibet Autonomous Region between September 2015 and July 2017. Control subjects without any clinical signs or tuberculosis history, and without any other severe diseases, were selected from normal Tibetans in physical examination. After signing the informed consent form, each subject was collected about 5 mL venous blood with EDTA and stored at -20°C until DNA extraction. This study was approved by the Clinical Research Ethics of Xizang Minzu University.

SNPs selection and genotyping

12 SNPs of the IL-1 gene were selected based on the databases of 1000 Genomes Project (http://www.1000genomes.org/) and dbSNP (https://www. ncbi.nlm.nih.gov/projects/SNP/) with MAFs>5% in Chinese Han population. Genomic DNA was extracted from peripheral blood samples by GoldMag-Mini Purification Kit (GoldMag Co. Ltd. Xi'an, People's Republic of China) [13], and measurement of DNA con-

Table 2. Relationship between IL-1 SNPs and tuberculosis risk under multiple models of analysis

SNP	Model	Genotype	Control	Case	OR (95% CI)	P^a
rs3783550	Codominant	G/G	132 (44.0%)	101 (33.8%)	1.00	0.020*
		G/T	136 (45.3%)	151 (50.5%)	1.45 (1.03-2.05)	
		T/T	32 (10.7%)	47 (15.7%)	1.92 (1.14-3.22)	
	Dominant	G/G	132 (44.0%)	101 (33.8%)	1.00	0.010*
		G/T+T/T	168 (56.0%)	198 (66.2%)	1.54(1.11-2.14)	
	Recessive	G/G+G/T	268 (89.3%)	252 (84.3%)	1.00	0.067
		T/T	32 (10.7%)	47 (15.7%)	1.56 (0.97-2.53)	
	Overdominant	G/G+T/T	164 (54.7%)	148 (49.5%)	1.00	0.210
		G/T	136 (45.3%)	151 (50.5%)	1.23 (0.89-1.70)	
	Log-additive	---	---	---	1.40 (1.10-1.79)	0.006*
rs3783546	Codominant	G/G	132 (44.3%)	95 (32.2%)	1.00	0.006*
		G/C	134 (45.0%)	152 (51.5%)	1.58 (1.11-2.24)	
		C/C	32 (10.7%)	48 (16.3%)	2.08 (1.24-3.5)	
	Dominant	G/G	132 (44.3%)	95 (32.2%)	1.00	0.002*
		G/C+C/C	166 (55.7%)	200 (67.8%)	1.67 (1.20-2.34)	
	Recessive	G/G+G/C	266 (89.3%)	247 (83.7%)	1.00	0.048*
		C/C	32 (10.7%)	48 (16.3%)	1.62 (1.00-2.61)	
	Overdominant	G/G+C/C	164 (55.0%)	143 (48.5%)	1.00	0.110
		G/C	134 (45.0%)	152 (51.5%)	1.30 (0.94-1.80)	
	Log-additive	---	---	---	1.48 (1.16-1.88)	0.001*
rs2856838	Codominant	G/G	170 (57.0%)	140 (46.7%)	1.00	0.039*
		A/G	113 (37.9%)	142 (47.3%)	1.53 (1.09-2.13)	
		A/A	15 (5.0%)	18 (6.0%)	1.46 (0.71-3.00)	
	Dominant	G/G	170 (57.0%)	140 (46.7%)	1.00	0.011*
		A/G+A/A	128 (43.0%)	160 (53.3%)	1.52 (1.10-2.10)	
	Recessive	G/G+A/G	283 (95.0%)	282 (94.0%)	1.00	0.600
		A/A	15 (5.0%)	18 (6.0%)	1.46 (0.71-3.00)	
	Overdominant	G/G+A/A	185 (62.1%)	158 (52.7%)	1.00	0.020*
		A/G	113 (37.9%)	142 (47.3%)	1.47 (1.06-2.04)	
	Log-additive	---	---	---	1.37 (1.05-1.80)	0.020*
rs1609682	Codominant	G/G	131 (44.0%)	101 (33.8%)	1.00	0.022*
		G/T	135 (45.3%)	151 (50.5%)	1.45 (1.02-2.06)	
		T/T	32 (10.7%)	47 (15.7%)	1.91 (1.13-3.20)	
	Dominant	G/G	131 (44.0%)	101 (33.8%)	1.00	0.011*
		G/T+T/T	167 (56.0%)	198 (66.2%)	1.54 (1.10-2.14)	
	Recessive	G/G+G/T	266 (89.3%)	252 (84.3%)	1.00	0.072
		T/T	32 (10.7%)	47 (15.7%)	1.55 (0.96-2.51)	
	Overdominant	G/G+T/T	163 (54.7%)	148 (49.5%)	1.00	0.200
		G/T	135 (45.3%)	151 (50.5%)	1.23 (0.89-1.70)	
	Log-additive	---	---	---	1.40 (1.10-1.78)	0.006*
rs3783521	Codominant	A/A	132 (44.0%)	89 (30.4%)	1.00	0.002*
		A/G	136 (45.3%)	156 (53.2%)	1.70 (1.19-2.42)	
		G/G	32 (10.7%)	48 (16.4%)	2.22 (1.32-3.75)	
	Dominant	A/A	132 (44.0%)	89 (30.4%)	1.00	< 0.001*
		A/G+G/G	168 (56.0%)	204 (69.6%)	1.80 (1.28-2.52)	
	Recessive	A/A+A/G	268 (89.3%)	245 (83.6%)	1.00	0.041
		G/G	32 (10.7%)	48 (16.4%)	1.64 (1.02-2.65)	
	Overdominant	A/A+G/G	164 (54.7%)	137 (46.8%)	1.00	0.054
		A/G	136 (45.3%)	156 (53.2%)	1.37 (0.99-1.9)	
	Log-additive	---	---	---	1.55 (1.21-1.97)	< 0.001*

rs2853550	Codominant	G/G	248 (82.9%)	254 (84.7%)	1.00	0.300
		A/G	47 (15.7%)	38 (12.7%)	0.79 (0.50-1.25)	
		A/A	4 (1.3%)	8 (2.7%)	1.95 (0.58-6.57)	
	Dominant	G/G	248 (82.9%)	254 (84.7%)	1.00	0.570
		A/G+A/A	51 (17.1%)	46 (15.3%)	0.88 (0.57-1.36)	
	Recessive	G/G+A/G	295 (98.7%)	292 (97.3%)	1.00	0.240
		A/A	4 (1.3%)	8 (2.7%)	2.02 (0.60-6.78)	
	Overdominant	G/G+A/A	252 (84.3%)	262 (87.3%)	1.00	0.280
		A/G	47 (15.7%)	38 (12.7%)	0.78 (0.49-1.23)	
	Log-additive	---	---	---	0.98 (0.68-1.42)	0.910
rs1143643	Codominant	T/T	82 (27.4%)	67 (22.6%)	1.00	0.130
		T/C	153 (51.2%)	146 (49.3%)	1.17 (0.79-1.73)	
		C/C	64 (21.4%)	83 (28.0%)	1.59 (1.00-2.51)	
	Dominant	T/T	82 (27.4%)	67 (22.6%)	1.00	0.180
		T/C+C/C	217 (72.6%)	229 (77.4%)	1.29 (0.89-1.87)	
	Recessive	T/T+T/C	235 (78.6%)	213 (72.0%)	1.00	0.060
		C/C	64 (21.4%)	83 (28.0%)	1.43 (0.98-2.08)	
	Overdominant	T/T+C/C	146 (48.8%)	150 (50.7%)	1.00	0.650
		T/C	153 (51.2%)	146 (49.3%)	0.93 (0.67-1.28)	
	Log-additive	---	---	---	1.26 (1.00-1.58)	0.048*
rs3136558	Codominant	A/A	116 (38.9%)	118 (39.3%)	1.00	0.930
		A/G	138 (46.3%)	141 (47.0%)	1.00 (0.71-1.42)	
		G/G	44 (14.8%)	41 (13.7%)	0.92 (0.56-1.51)	
	Dominant	A/A	116 (38.9%)	118 (39.3%)	1.00	0.920
		A/G+G/G	182 (61.1%)	182 (60.7%)	0.98 (0.71-1.37)	
	Recessive	A/A+A/G	254 (85.2%)	259 (86.3%)	1.00	0.700
		G/G	44 (14.8%)	41 (13.7%)	0.91 (0.58-1.45)	
	Overdominant	A/A+G/G	160 (53.7%)	159 (53.0%)	1.00	0.870
		A/G	138 (46.3%)	141 (47.0%)	1.03 (0.75-1.42)	
	Log-additive	---	---	---	0.97 (0.77-1.22)	0.790
rs1143630	Codominant	G/G	212 (70.7%)	208 (69.3%)	1.00	0.940
		G/T	83 (27.7%)	87 (29.0%)	1.07 (0.75-1.53)	
		T/T	5 (1.7%)	5 (1.7%)	1.02 (0.29-3.57)	
	Dominant	G/G	212 (70.7%)	208 (69.3%)	1.00	0.720
		G/T+T/T	88 (29.3%)	92 (30.7%)	1.07 (0.75-1.51)	
	Recessive	G/G+G/T	295 (98.3%)	295 (98.3%)	1.00	1.000
		T/T	5 (1.7%)	5 (1.7%)	1.00 (0.29-3.49)	
	Overdominant	G/G+T/T	217 (72.3%)	213 (71.0%)	1.00	0.720
		G/T	83 (27.7%)	87 (29.0%)	1.07 (0.75-1.52)	
	Log-additive	---	---	---	1.05 (0.77-1.45)	0.740
rs1143627	Codominant	G/G	55 (18.5%)	96 (32.3%)	1.00	5E-04*
		A/G	166 (55.9%)	141 (47.5%)	0.49 (0.33-0.73)	
		A/A	76 (25.6%)	60 (20.2%)	0.45 (0.28-0.73)	
	Dominant	G/G	55 (18.5%)	96 (32.3%)	1.00	1E-04*
		A/G+A/A	242 (81.5%)	201 (67.7%)	0.48 (0.33-0.7)	
	Recessive	G/G+A/G	221 (74.4%)	237 (79.8%)	1.00	0.120
		A/A	76 (25.6%)	60 (20.2%)	0.74 (0.50-1.08)	
	Overdominant	G/G+A/A	131 (44.1%)	156 (52.5%)	1.00	0.040*
		A/G	166 (55.9%)	141 (47.5%)	0.71 (0.52-0.99)	
	Log-additive	---	---	---	0.67 (0.53-0.85)	7E-04*

rs16944	Codominant	A/A	54 (18.0%)	95 (32.1%)	1.00	2E-04*
		A/G	165 (55.0%)	142 (48.0%)	0.49 (0.33-0.73)	
		G/G	81 (27.0%)	59 (19.9%)	0.41 (0.26-0.66)	
	Dominant	A/A	54 (18.0%)	95 (32.1%)	1.00	1E-04*
		A/G+G/G	246 (82.0%)	201 (67.9%)	0.46 (0.32-0.68)	
	Recessive	A/A+A/G	219 (73.0%)	237 (80.1%)	1.00	0.042*
		G/G	81 (27.0%)	59 (19.9%)	0.67 (0.46-0.99)	
	Overdominant	A/A+G/G	135 (45.0%)	154 (52.0%)	1.00	0.086
		A/G	165 (55.0%)	142 (48.0%)	0.75 (0.55-1.04)	
	Log-additive	---	---	---	0.64 (0.51-0.81)	2E-04*
rs1143623	Codominant	C/C	109 (36.3%)	80 (26.7%)	1.00	1E-04*
		G/C	158 (52.7%)	148 (49.3%)	1.28 (0.89-1.84)	
		G/G	33 (11.0%)	72 (24.0%)	2.97 (1.80-4.92)	
	Dominant	C/C	109 (36.3%)	80 (26.7%)	1.00	0.011*
		G/C+G/G	191 (63.7%)	220 (73.3%)	1.57 (1.11-2.22)	
	Recessive	C/C+G/C	267 (89.0%)	228 (76.0%)	1.00	< 1E-04*
		G/G	33 (11.0%)	72 (24.0%)	2.56 (1.63-4.00)	
	Overdominant	C/C+G/G	142 (47.3%)	152 (50.7%)	1.00	0.410
		G/C	158 (52.7%)	148 (49.3%)	0.88 (0.64-1.21)	
	Log-additive	---	---	---	1.63 (1.29-2.08)	< 1E-04*

SNPs: Single nucleotide polymorphisms; OR = odds ratio; 95% CI = 95% confidence interval; *P < 0.05 indicates statistical significance; [a]p values were calculated by unconditional logistic regression.

centration was performed by NanoDrop 2000 (Thermo Scientific, Waltham, MA, USA). Sequenom MassARRAY Assay Design 4.0 Software (Agena Bioscience Inc) was utilized to design a multiplexed SNP Mass EXTENDED assay [14]. SNP genotyping was carried out via the manufacturer's protocol on the Sequenom MassARRAY RS1000 platform. Data management and analysis were performed using the Sequenom Typer 4.0 Software (Agena Bioscience Inc).

Statistical analysis

Microsoft Excel and SPSS 19.0 Software (SPSS Inc, Chicago, IL, USA) were used for statistical analyses. Deviation from the Hardy-Weinberg equilibrium (HWE) for each SNP was tested to measure the distribution of the polymorphism using a Chi-square test [15, 16]. The *P* values obtained in our study were two-sided and *P*-value < 0.05 was considered significant. The odds ratio (OR) and 95% confidence interval (CI) were analyzed by unconditional logistic regression to evaluate the effect of polymorphisms on the risk of tuberculosis. Finally, software of haploview package (version 4.2) was adopted to evaluate the pairwise linkage disequilibrium (LD) among SNPs and the association between polymorphism loci and TB risk [17, 18].

Results

The IL-1 polymorphism was analyzed in 300 TB patients and 300 unrelated healthy controls. **Table 1** presented basic information for 12 genotyped SNPs with regard to their chromosomal position, allele, minor allele frequency, and HWE test results for all subjects. There was no deviation from Hardy-Weinberg equilibrium (HWE) for each SNP, suggesting good SNP genotyping quality. Almost all of SNPs except rs2853550, rs1143643, rs3136558, rs1143630 had strong association with TB risk (P < 0.05) based on allele frequencies Chi-square test.

Comparisons of the SNP genotypes and the risk of TB under the genetic model were listed in **Table 2**. Among genotyped SNPs, a positive association was found between significantly high TB risk and SNPs rs3783550 G/T (OR = 1.54; 95% CI = 1.11-2.54; P = 0.010), rs374-83546 G/C (OR = 1.67; 95% CI = 1.20-2.34; P = 0.002), rs2856838 A/G (OR = 1.52; 95% CI = 1.10-2.10; P = 0.011), rs1609682 G/T (OR = 1.54; 95% CI = 1.10-2.14; P = 0.011),

Table 3. Haplotype frequencies and their association with tuberculosis risk

Gene	SNPs	Haplotype	Frequency		OR (95% CI)	P^a
			Case	Control		
IL-1α	rs3783550	GGGGA	0.575	0.667	1.00	---
	rs3783546	TCATG	0.293	0.242	1.47 (1.11-1.94)	0.007*
	rs2856838	TCGTG	0.113	0.091	1.42 (0.97-2.08)	0.070
	rs1609682					
	rs3783521					
IL-1β	rs2853550	GT	0.474	0.530	1.00	---
	rs1143643	GC	0.436	0.378	1.30 (1.02-1.67)	0.034*
		AC	0.090	0.092	1.10 (0.75-1.62)	0.630
IL-1β	rs1143630	GAGG	0.432	0.537	1.00	---
	rs1143627	GGAG	0.324	0.220	1.86 (1.40-2.46)	< 0.0001*
	rs16944	TGAG	0.159	0.149	1.37 (0.96-1.95)	0.081
	rs1143623	GGAC	0.077	0.081	1.17 (0.76-1.80)	0.480

OR = odds ratio; 95% CI = 95% confidence interval; *P < 0.05 indicates statistical significance; [a]p value were calculated by unconditional logistic regression.

rs3783521 A/G (OR = 1.50; 95% CI = 1.28-2.52; P < 0.001) genotypes within IL-1α as well as rs1143623 G/G (OR = 2.56; 95% CI = 1.63-4.00; P < 1E-04) within IL-1β based on multiple models analysis.

The results for the association between the IL-1 haplotype and the risk of TB were listed in **Table 3**. Results revealed that five IL-1α SNPs (rs3783550, rs3783546, rs2856838, rs1609682, rs3783521) mapped in a 10 kb LD block with the D'>0.98 (**Figure 1A**), suggesting that a significant linkage disequilibrium presence among these SNPs. Furthermore, "TCATG" haplotype of IL-1α SNPs with a 1.47-fold risk for TB was observed (P = 0.007).

Discussion

Current evidence suggests that the IL-1 cytokine family is a complex self-regulating system, and its members have been proposed as candidate genes in inflammatory disorders. In the present study, we aimed to investigate whether the IL-1 polymorphism is related to susceptibility to TB in Chinese Tibetan population. Among analyzed 12 SNPs in our study, we found a positive association between higher TB risk and IL-1α polymorphism (rs3783550, rs3783546, rs2856838, rs1609682, rs3783521) as well as rs1143623 within IL-1β. Furthermore, "TCATG" haplotype of IL-1α SNPs with a 1.47-fold risk for TB was observed (P = 0.007), suggesting that these SNPs may contribute to tuberculosis susceptibility in Chinese Tibetan population.

IL-1α is a well-characterized gene that encodes the IL-1α protein of the interleukin 1 cytokine family, and is involved in a wide range of inflammatory activities and immune responses [19]. Encouraged by several lines of evidence supporting a potential link between IL-1α polymorphism and various diseases risk. SNP rs3783550 located within or near the interleukin IL-1α is suggested to be related to endometriosis in Japanese samples [19], higher probability of pre-eclampsia developing in a Brazilians [20], and preterm prelabor rupture of membranes [21]. Two other SNPs (rs3783546, rs2856838) were associated with a measure of processing speed for cognitive ability [22], chronic rhinosinusitis with and without nasal polyposis, and decreased risk of malaria infection in northern Uganda [23], respectively. IL-1β exerts its primary proinflammatory effects by stimulating the formation of its main effector, IL-6, which drives the inflammation cascade [24]. IL-1β SNP rs1143623 is within a promoter GATA transcription factor family binding site. A correlation between rs1143623 and triglyceride and interleukin 6 metabolism [25], pathogenesis of schizophrenia [26], and higher IL-13 plasma levels in adults living with HIV/AIDS [27] were found in several novel studies.

In this study, a significantly high risk of TB in the presence of SNP rs3783550, rs3783546, rs2856838, rs1609682, rs3783521 within IL-1α as well as rs1143623 within IL-1β was found. To the best of our knowledge, IL-1α rs1609682 and rs3783521 have not previously been associated with TB or other diseases. In this study, rs1609682 and rs3783521 are in tight linkage disequilibrium with rs3783550, rs3783546 and rs2856838 mapped in a 10 kb LD block with the D'>0.98, suggesting that they may have similar functionality involved in TB risk. Importantly, with

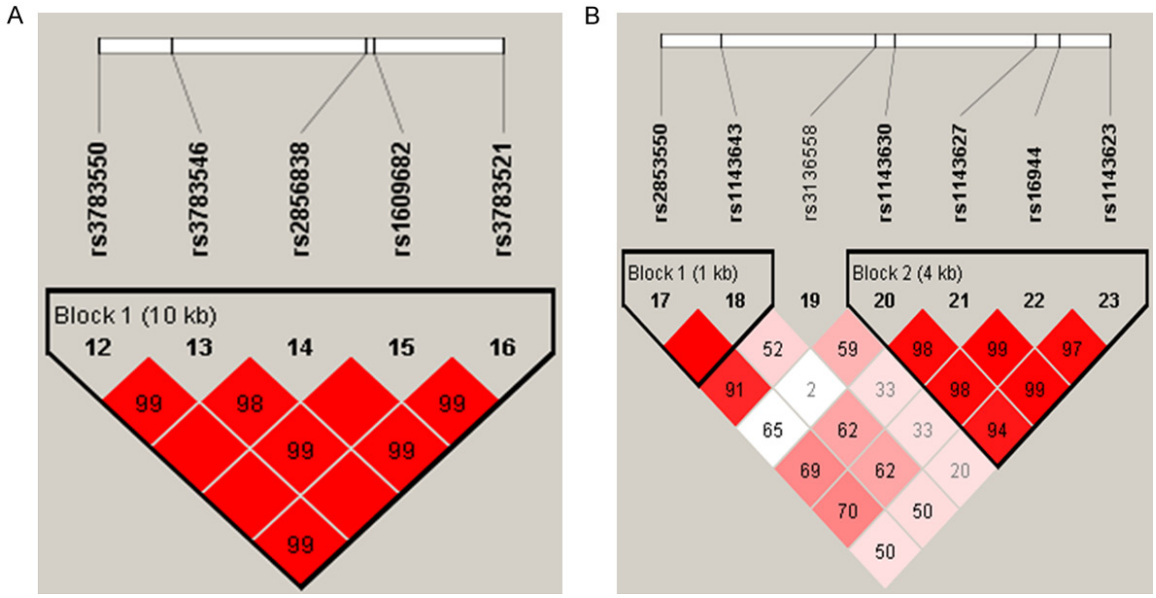

Figure 1. Haplotype block map for the SNPs in the IL-1 gene in our experiment. A. Hapotype block map for SNPs in the IL-1α gene. B. Hapotype block map for SNPs in the IL-1β gene.

regard to the mechanism how these SNPs effect on TB susceptibility, one possibility is that they are likely to represent a genuine disease susceptibility locus involved in regulating NLRP3 or NF-κB signaling pathway, which enhanced the LPS-induced expression of inflammatory [28, 29]. Alternatively, since IL-1α/β share common biological activities with the Toll/interleukin-1 receptor homology (TIR) domain, given their roles in inflammation response, it is not surprising to see specific polymorphisms of those loci contribute to the individual variability for TB susceptibility. However, these speculations need further investigation.

The results of this study also need to be considered in light of its limitations. Better support of our findings, requires replication in other samples. In addition, multiple testings are also considered. However, although we made many efforts to collect enough demographic and clinical information, there are still some unsatisfactory points.

In conclusion, IL-1 polymorphism, especially IL-1α variants, in our study were significantly associated with a higher risk of TB in the Chinese Tibetan population. Further investigation will be performed to determine how these relevant variants within IL-1 gene affect TB and determine the underlying mechanism via cell culture or knock-out mice models to provide a reliable theoretical basis for TB screening, early diagnosis and prognosis.

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Disclosure of conflict of interest

None.

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