Variants in *TLR6* Gene Influence Susceptibility to Tuberculosis in the Chinese Population

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Research article

Keywords: Tuberculosis, TLR6, Variant, Polymorphism, Genetic models

Posted Date: May 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-28365/v1>

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Abstract

BACKGROUND Tuberculosis (TB) is a common chronic infectious disease caused by *Mycobacteria tuberculosis*. Several researches revealed that *TLR6* play a crucial roles in the risk of TB.

METHODS The association between *TLR6* polymorphism and TB risk were evaluated by a case-control study. Total of 510 TB cases and 508 unrelated healthy controls were recruited. Subsequently, the Agena MassARRAY platform was conducted to genotype, and odds ratios (ORs) and 95% confidence intervals (CIs) were assessed the relationship between *TLR6* variants and TB risk.

RESULTS We found that rs6531668 of *TLR6* gene was significantly association with TB risk. Stratified analysis confirmed that rs6531668 was significant increased risk of TB in age > 41 years old. Interestingly, the G/C – C/C genotype of rs12642845 was significantly interacted with decreased risk of TB in age > 41 years. In males, rs3775073 G/A genotype and rs12642845 G/C genotype were correlated with decreased the risk of TB. Besides, we also observed that the CTA and TCG haplotypes were decreased TB risk.

CONCLUSIONS Our results shown that *TLR6* gene variants were related with TB risk among the Chinese population.

Instruction

Tuberculosis (TB) is a common chronic pulmonary contagious human disease, and remains a highly mortality around the world. It was reported that TB causes a serious public health issue, multiple socioeconomic burden in our world, especially in Asia [1]. In 2017, according to the WHO calculated, approximately 10.0 million people suffered from TB and 1.3 million people died (Global tuberculosis report). It is estimated that approximately 5 to 15% of the infected individuals develop clinical disease during their lifetimes [2]. Various factors affect TB infection, including environment, genetic, immunosuppressive treatment, lifestyle and aging [3–6]. Previous twin studies, genome-wide association studies (GWAS) indicated that host heredity factors was considered to play an crucial role in the sensibility to TB [7]. Furthermore, human and mouse experiments have confirmed various potential TB risk loci, such as genes involved in toll-like receptor (TLR) signaling [8].

Toll-like receptors (TLRs) family are consist of 10 proteins that play an important role in our innate immune system. In human, these receptors are primarily identified pathogen-associated molecular patterns (PAMPs) and activate signaling cascades that caused the human innate immune response, cytokines and formation of the adaptive immune response [9, 10]. Human genetic studies revealed that TLR pathway genes variants such as *TLR1*, *TLR2*, *TLR4* and *TLR9* have been confirmed with TB risk in different populations [11–13]. However, *TLR6*, a member of TLRs family. Less is known about the correlation between *TLR6* polymorphisms and the risk of TB, particularly in Chinese Han population [14].

Here, we performed a case-control study to investigate six SNPs of *TLR6* gene, including rs3775073, rs3796508, rs6531668, rs12644563, rs12640631, rs12642845. We verified the interaction of these SNPs with TB sensibility in a Chinese Han population from northwest China and our study are supposed to provide more evidence that can help elucidate TB pathogenesis among these individuals.

Materials And Methods

Subjects

The TB patients (n = 510) were recruited from Xi'an Chest Hospital, Shaanxi Province. According to positive sputum smear and some clinical signs, all of them were diagnosed by specialized doctors. TB patients including chronic inflammatory, HIV infection, primary immunodeficiency and other host immunity diseases were excluded. The healthy controls (n = 508) were matched to the TB patients by sex and age. In addition, we excluded healthy controls, who have TB history, autoimmune diseases and other chronic infections.

Genotyping

The blood samples (5 mL) were collected from each subject into a glass tube containing ethylenediaminetetraacetic acid (EDTA) for molecular analysis. Genomic DNA was extracted from whole blood samples by GoldMag whole blood genomic DNA kit (GoldMag, China). According to the specification, DNA purity was evaluated using NanoDrop 2000 platform (Thermo Fisher Scientific, USA). Base on the minor allele frequency > 0.05, six candidate SNPs of *TLR6* gene were choose from the 1000 Genomes Project data (<http://www.internationalgenome.org/>). The SNPs primers were designed by Agena Bioscience Assay Design Suite V2.0 software. Furthermore, the MassARRAY iPLEX platform (Agena, USA) was conducted to genotype SNPs. All data was analyzed using Agena Bioscience TYPER version 4.0 software as previously our described [15].

Statistical analysis

SPSS 20.0 software was performed statistical analysis. Hardy–Weinberg equilibrium (HWE) was evaluated by χ^2 test in healthy controls. We also compared allele and genotype frequencies using the χ^2 test among all subjects. The association between the *TLR6* polymorphism and the risk of TB was evaluated through odds ratios (ORs) and 95% confidence intervals (CIs) adjustment gender and age. Linkage disequilibrium (LD) between SNPs were performed using Haploview 4.2 software. For all statistical tests, $p < 0.05$ was considered statistically significant.

Results

The characteristics of the subjects were listed in Table 1. A total of 510 TB patients including 318 males and 192 females and 508 unrelated healthy controls involving 316 males and 192 females were employed. All participants were of Han ethnicity, and lived in or around the Xi'an city. The mean ages of TB cases and healthy controls were 41.90 ± 14.83 years old and 41.14 ± 18.42 years old, respectively. No significant differences between all individuals in age or gender proportion were observed.

Table 1
Demographic distribution of TB patients and Healthy controls

	Cases (n = 510) No. (%)	Controls (n = 508) No. (%)	p
Age, year (mean $\pm$ SD)	41.90 $\pm$ 14.83	41.14 $\pm$ 18.42	0.469
Gender			0.961
Male	318 (62.35)	316 (62.20)	
Female	192 (37.65)	192 (37.80)	

In our study, the detail information of these SNPs (the position, minor allele frequency (MAF) and HWE p value) were summarized in Table 2. We found that rs6531668 of *TLR6* gene was association with TB risk (OR = 1.28, 95% CI = 1.04–1.57, p = 0.023). Analysis of the genotype frequencies of *TLR6* in different genetic models, our results suggested that rs6531668 was correlated with increased the risk of TB in dominant model (OR = 1.30, 95% CI = 1.01–1.67, p = 0.046) and log-additive model (OR = 1.26, 95% CI = 1.03–1.55, p = 0.026). However, no significant association was identified between rs3775073, rs3796508, rs12644563, rs12640631, rs12642845 and TB risk.

In stratified analysis by age, the results confirmed that rs6531668 was increased TB risk in age > 41 years under the co-dominant model (OR = 1.75, 95% CI = 1.14–2.68, p = 0.010), the dominant model (OR = 1.77, 95% CI = 1.19–2.62, p = 0.005) and the log-additive model (OR = 1.51, 95% CI = 1.11–2.06, p = 0.005). Interestingly, we observed that the G/C – C/C genotype of rs12642845 was significantly interacted with decreased TB risk in age > 41 years old under the dominant model (OR = 0.67, 95% CI = 0.46–0.99, p = 0.042) (Table 4). When gender stratification was analyzed, the results confirmed that rs3775073 G/A genotype and rs12642845 G/C genotype were decreased TB risk in males (OR = 0.70, 95% CI = 0.50–0.98, p = 0.036; OR = 0.71, 95% CI = 0.51–0.99, p = 0.042, respectively). However, no association of rs3775073 and rs12642845 and TB risk were observed in females. The results were shown in Table 5.

We further performed LD and haplotype analyses of all SNPs in our study. Strong LD analysis displayed the existence of two blocks in *TLR6* SNPs (Fig. 1). LD was found between rs3775073 and rs6531688, among rs12640631 and rs12642845. Besides, we observed that the CTA and TCG haplotypes were associated with reduced risk of TB (OR = 0.74, 95% CI = 0.55–0.99, p = 0.043; OR = 0.47, 95% CI = 0.28–0.79, p = 0.004, respectively) (Table 6).

Moreover, we used Regulome DB and Haploreg v4.1 to determine the potential functional effect of these SNPs. The Regulome DB suggested that rs6531688 and rs3775073 were the binding site for the

transcription factor. The Regulome DB score was 1f and 2b. No data were shown the prediction functional of rs3796508 and rs12640631 (Supplementary Table 1).

Table 2
Basic characteristics and allele frequencies among TLR6 SNPs

SNP	Chr	Allele	MAF		HWE p-Value	OR (95% CI)	p ^a
			Case	Control			
rs3775073	4	A/G	0.31	0.33	0.163	0.89 (0.74–1.07)	0.205
rs3796508	4	A/G	0.04	0.05	0.639	0.72 (0.47–1.10)	0.130
rs6531668	4	A/G	0.25	0.20	0.276	1.28 (1.04–1.57)	0.023 [*]
rs12644563	4	C/T	0.04	0.05	0.148	0.72 (0.47–1.10)	0.130
rs12640631	4	C/T	0.08	0.07	0.340	1.14 (0.83–1.58)	0.425
rs12642845	4	C/G	0.21	0.24	0.272	0.87 (0.71–1.07)	0.188

Table 3
The association between six SNPs within the TLR6 gene and the risk of TB.

SNP	Model	Genotype	Cases	Controls	OR (95%CI)	p ^a
rs3775073	Co-dominant	G/G	245	219	1.00	
		G/A	216	240	0.80 (0.62–1.04)	0.090
		A/A	48	49	0.88 (0.57–1.36)	0.556
	Dominant	G/G	245	219	1.00	
		G/A – A/A	264	289	0.81 (0.63–1.04)	0.100
	Recessive	G/G – G/A	461	459	1.00	
		A/A	48	49	0.98 (0.64–1.49)	0.919
	Log-additive	–	–	–	0.88 (0.73–1.07)	0.191
rs3796508	Co-dominant	G/G	471	457	1.00	
		G/A	39	49	0.78 (0.50–1.21)	0.262
		A/A	0	2	–	–
	Dominant	G/G	471	457	1.00	
		G/A – A/A	39	51	0.75 (0.48–1.16)	0.190
	Recessive	G/G – G/A	510	506	1.00	
		A/A	0	2	–	–
	Log-additive	–	–	–	0.73 (0.48–1.11)	0.139
rs6531668	Co-dominant	G/G	294	326	1.00	
		G/A	175	157	1.24 (0.95–1.62)	0.118
		A/A	37	25	1.65 (0.97–2.81)	0.065
	Dominant	G/G	294	326	1.00	
		G/A – A/A	212	182	1.30 (1.01–1.67)	0.046*
	Recessive	G/G – G/A	469	483	1.00	
		A/A	37	25	1.53 (0.91–2.59)	0.110
	Log-additive	–	–	–	1.26 (1.03–1.55)	0.026*
rs12644563	Co-dominant	T/T	471	458	1.00	
		T/C	39	47	0.81 (0.52–1.27)	0.363

SNP	Model	Genotype	Cases	Controls	OR (95%CI)	p ^a	
rs12640631	Dominant	C/C	0	3	–	–	
		T/T	471	458	1.00		
		T/C–C/C	39	50	0.76 (0.49–1.18)	0.228	
	Recessive	T/T– T/C	510	505	1.00		
		C/C	0	3	–	–	
		Log–additive	–	–	–	0.73 (0.48–1.11)	0.144
	Co–dominant	T/T	430	437	1.00		
		T/C	75	67	1.15 (0.80–1.64)	0.453	
		C/C	5	4	1.26 (0.34–4.73)	0.733	
	rs12642845	Dominant	T/T	430	437	1.00	
T/C–C/C			80	71	1.15 (0.81–1.63)	0.423	
Recessive			T/T– T/C	505	504	1.00	
Co–dominant		C/C	5	4	1.24 (0.33–4.63)	0.753	
		Log–additive	–	–	–	1.14 (0.83–1.57)	0.417
		Co–dominant	G/G	318	289	1.00	
G/C			165	195	1.03 (0.58–1.82)	0.925	
C/C			27	24	0.77 (0.59–1.00)	0.050	
Dominant		G/G	318	289	1.00		
		G/C–CC	192	219	0.80 (0.62–1.03)	0.078	
	Recessive	G/G–G/C	483	484	1.00		
	Log–additive	C/C	27	24	1.13 (0.64–1.99)	0.665	
		–	–	–	0.87 (0.71–1.07)	0.192	

Table 4
Age stratification analysis of association between TLR6 and the risk of TB.

SNP	Model	Genotype	≤ 41	> 41		
			OR (95% CI)	p ^a	OR (95% CI)	p ^a
rs3775073	Co-dominant	G/G	1.00		1.00	
		G/A	0.76 (0.52–1.10)	0.141	0.80 (0.54–1.19)	0.275
		A/A	0.82 (0.43–1.57)	0.547	0.86 (0.45–1.63)	0.641
	Dominant	G/G	1.00		1.00	
		G/A – A/A	0.77 (0.54–1.09)	0.143	0.81 (0.56–1.18)	0.279
	Recessive	G/G – G/A	1.00		1.00	
		A/A	0.94 (0.51–1.76)	0.855	0.95 (0.52–1.76)	0.880
		–	0.84 (0.64–1.11)	0.221	0.88 (0.66–1.17)	0.377
	Log-additive	–				
rs3796508	Co-dominant	G/G	1.00		1.00	
		G/A	0.95 (0.49–1.85)	0.884	–	–
		A/A	–	–	–	–
	Dominant	G/G	1.00		1.00	
		G/A – A/A	0.92 (0.48–1.76)	0.792	0.60 (0.32–1.14)	0.118
	Recessive	G/G – G/A	1.00		1.00	
		A/A	–	–	–	–
		–	0.89 (0.47–1.66)	0.706	0.60 (0.32–1.14)	0.118
	Log-additive	–				
rs6531668	Co-dominant	G/G	1.00		1.00	
		G/A	1.10 (0.76–1.61)	0.613	1.75 (1.14–2.68)	0.010*

SNP	Model	Genotype	≤ 41	> 41		
			OR (95% CI)	p ^a	OR (95% CI)	p ^a
rs12644563	Dominant	A/A	1.73 (0.76–3.95)	0.194	1.83 (0.87–3.85)	0.111
		G/G	1.00		1.00	
		G/A – A/A	1.17 (0.81–1.67)	0.405	1.77 (1.19–2.62)	0.005*
	Recessive	G/G – G/A	1.00		1.00	
		A/A	1.67 (0.74–3.76)	0.219	1.53 (0.74–3.17)	0.256
	Log-additive	–	1.19 (0.88–1.61)	0.250	1.51 (1.11–2.06)	0.009*
	Co-dominant	T/T	1.00		1.00	
		T/C	1.00 (0.51–1.97)	0.998	–	–
		C/C	–	–	–	–
	Dominant	T/T	1.00		1.00	
rs12640631	Dominant	T/C–C/C	0.89 (0.46–1.73)	0.736	0.67 (0.36–1.26)	0.212
		T/T– T/C	1.00		1.00	
		C/C	–	–	–	–
	Recessive	T/T– T/C	1.00		1.00	
		C/C	–	–	–	–
	Log-additive	–	0.82 (0.44–1.51)	0.517	0.67 (0.36–1.26)	0.212
	Co-dominant	T/T	1.00		1.00	
		T/C	1.03 (0.61–1.74)	0.913	1.23 (0.73–2.07)	0.437
		C/C	0.73 (0.13–4.08)	0.719	–	–
	Dominant	T/T	1.00		1.00	
	Dominant	T/C–C/C	1.00 (0.60–1.67)	0.991	1.29 (0.77–2.16)	0.335
		T/T– T/C	1.00		1.00	
	Recessive	T/T– T/C	1.00		1.00	

SNP	Model	Genotype	≤ 41	> 41		
			OR (95% CI)	p ^a	OR (95% CI)	p ^a
rs12642845	Log-additive	C/C	0.73 (0.13–4.06)	0.716	–	–
		–	0.98 (0.62–1.55)	0.931	1.34 (0.81–2.2)	0.255
		G/G	1.00		1.00	
	Co-dominant	G/C	0.82 (0.56–1.19)	0.293	0.62 (0.42–0.93)	0.021*
		C/C	0.92 (0.40–2.12)	0.847	1.09 (0.46–2.56)	0.845
		G/G	1.00		1.00	
	Dominant	G/C–CC	0.83 (0.58–1.19)	0.310	0.67 (0.46–0.99)	0.042*
		G/G–G/C	1.00		1.00	
		C/C	1.00 (0.44–2.27)	0.992	1.30 (0.56–3.01)	0.541
	Recessive	–	0.88 (0.65–1.19)	0.392	0.79 (0.58–1.09)	0.152

Table 5
Gender stratification analysis of association between TLR6 and the risk of TB.

SNP	Model	Genotype	Males		Females	
			OR (95% CI)	p ^a	OR (95% CI)	p ^a
rs3775073	Co-dominant	G/G	1.00		1.00	
		G/A	0.70 (0.50–0.98)	0.036*	0.99 (0.66–1.51)	0.980
		A/A	0.91 (0.54–1.53)	0.712	0.80 (0.35–1.81)	0.589
	Dominant	G/G	1.00		1.00	
		G/A – A/A	0.74 (0.54–1.01)	0.059	0.97 (0.65–1.45)	0.872
	Recessive	G/G – G/A	1.00		1.00	
		A/A	1.08 (0.65–1.77)	0.776	0.80 (0.36–1.76)	0.579
	Log-additive	–	0.86 (0.68–1.09)	0.202	0.94 (0.68–1.31)	0.716
rs3796508	Co-dominant	G/G	1.00		1.00	
		G/A	0.86 (0.5–1.49)	0.594	0.66 (0.32–1.38)	0.272
		A/A	–	–	–	–
	Dominant	G/G	1.00		1.00	
		G/A – A/A	0.83 (0.48–1.44)	0.511	0.63 (0.30–1.30)	0.213
	Recessive	G/G – G/A	1.00		1.00	
		A/A	–	–	–	–
	Log-additive	–	0.81 (0.47–1.38)	0.438	0.61 (0.30–1.24)	0.174
rs6531668	Co-dominant	G/G	1.00		1.00	
		G/A	1.12 (0.80–1.58)	0.507	1.41 (0.92–2.18)	0.116

SNP	Model	Genotype	Males		Females	
			OR (95% CI)	p ^a	OR (95% CI)	p ^a
rs12644563	Dominant	A/A	1.57 (0.82–3.00)	0.173	1.76 (0.69–4.48)	0.237
		G/G	1.00		1.00	
		G/A – A/A	1.19 (0.86–1.64)	0.291	1.45 (0.96–2.20)	0.077
	Recessive	G/G – G/A	1.00		1.00	
		A/A	1.51 (0.80–2.85)	0.206	1.54 (0.61–3.88)	0.357
	Log-additive	–	1.19 (0.92–1.54)	0.179	1.37 (0.97–1.94)	0.071
	Co-dominant	T/T	1.00		1.00	
		T/C	0.89 (0.51–1.56)	0.693	0.70 (0.33–1.48)	0.351
		C/C	–	–	–	–
	rs12640631	Dominant	T/T	1.00		1.00
		T/C–C/C	0.83 (0.48–1.44)	0.513	0.67 (0.32–1.39)	0.278
Recessive		T/T– T/C	1.00		1.00	
		C/C	–	–	–	–
Log-additive		–	0.79 (0.47–1.33)	0.373	0.65 (0.32–1.31)	0.227
Co-dominant		T/T	1.00		1.00	
		T/C	1.18 (0.75–1.85)	0.479	1.11 (0.62–1.98)	0.722
	C/C	0.62 (0.10–3.78)	0.607	3.06 (0.31–2.73)	0.336	
	Dominant	T/T	1.00		1.00	
		T/C–C/C	1.14 (0.73–1.77)	0.566	1.18 (0.68–2.07)	0.557
	Recessive	T/T– T/C	1.00		1.00	

SNP	Model	Genotype	Males		Females	
			OR (95% CI)	p ^a	OR (95% CI)	p ^a
rs12642845	Log-additive	C/C	0.61 (0.10–3.70)	0.591	3.01 (0.31–2.25)	0.342
		–	1.09 (0.72–1.64)	0.686	1.23 (0.74–2.04)	0.431
		G/G	1.00		1.00	
	Co-dominant	G/C	0.71 (0.51–0.99)	0.042*	0.90 (0.59–1.38)	0.627
		C/C	1.34 (0.64–2.79)	0.439	0.70 (0.27–1.80)	0.455
		G/G	1.00		1.00	
	Dominant	G/C–CC	0.77 (0.56–1.05)	0.102	0.87 (0.58–1.32)	0.514
		G/G–G/C	1.00		1.00	
		C/C	1.52 (0.74–3.14)	0.257	0.73 (0.28–1.85)	0.501
	Recessive	–	0.88 (0.68–1.15)	0.350	0.87 (0.62–1.23)	0.428

Table 6
Haplotype analysis of TLR6 SNPs in association with the risk of TB.

Haplotype	Freq			
	Cases	Controls	OR (95% CI)	p ^a
TTA	0.87	0.88	0.87 (0.66–1.13)	0.284
CTA	0.74	0.91	0.74 (0.55–0.99)	0.043*
CCG	0.90	0.33	0.90 (0.74–1.09)	0.282
CTG	1.08	0.54	1.08 (0.90–1.28)	0.418
TTC	0.87	0.24	0.87 (0.71–1.07)	0.192
CCG	0.73	0.05	0.73 (0.48–1.11)	0.144
TCG	0.48	0.98	0.47 (0.28–0.79)	0.004*
TTG	0.93	0.31	0.93 (0.77–1.13)	0.479

Discussion

Numerous evidences suggested that host genetic variants confer enhanced TB risk, and several candidate genes have been demonstrated, such as the *CYP7A1* gene, Vitamin D receptor gene, the *CD14* gene and the TLRs family genes [16-19]. Nevertheless, the relationship between *TLR6* polymorphism and TB risk in Chinese population is poorly understand. In the present study, *TLR6* polymorphisms and TB susceptibility was investigated. Our results revealed that rs6531668 was significantly correlated with an increased the risk of TB. Next, stratified analyses discovered significant effect of rs6531668 and rs12642845 of *TLR6* on the risk of TB in age > 41 years, and rs3775073 G/A genotype and rs12642845 G/C genotype were decreased the TB risk in males.

During the past studies reported that the innate immune system can enables to recognize invading bacterial such as Mtb, and have a crucial role in host defense mechanism. In human, TLRs are thought to recognition of pathogens and influence the pathogenesis of the immune response [8, 20, 21]. Studies have been provided evidences that LTRs can recognize PAMPs of Mtb and initiate our innate immune response, ultimately culminating in antimicrobial host defense [22, 23]. Hence, the TLRs family genes have become biologically plausible candidate genes in studies of TB risk [24].

TLR6 is 2.3kb in length and located on chromosome 4. *TLR6* encodes a 796-amino acid type I transmembrane protein with a 21aa transmembrane domain, a 630aa extracellular leucine-rich repeat region and a 145aa intra-cellular Toll/IL-1R signaling domain [25]. *TLR6* belongs to *TLR2* subfamily, and forms heterodimers with *TLR2*, resulting in the recognition of Mtb [19]. Multiple studies confirmed that

TLR6 gene polymorphisms have been associated with TB risk [22, 23, 25]. In the study of Musse et al. due to *TLR6* variants were deficient in ability to mediate signal transduction, they found significant association between *TLR6* polymorphisms and increased TB sensibility in African Americans [26]. They et al. suggested that *TLR6* variants reduced NF- κ B signaling which led to an altered level of IL-6 production and thus protection against TB disease [25]. While Randhawa et al. reported that *TLR6* variants leads to increased IFN- γ production and thus resistance to TB disease [22]. Xu et al. was not confirmed that *TLR6* variants was related with the risk of TB in Chinese population [23]. However, our results demonstrated that *TLR6* variants (rs6531668, rs3775073, rs12642845) were significantly related with TB risk.

Furthermore, Regulome DB and Haploreg v4.1 suggested that rs6531688 and rs3775073 were the binding site for the transcription factor. Thus, further characterization is taken into account to investigate *in vivo* and *in vitro* at the molecular level.

In summary, our results confirmed that rs6531668, rs3775073 and rs12642845 of *TLR6* were significantly correlated with TB risk in Chinese population. Our work provided an evidence to estimate the relationship between *TLR6* polymorphism and TB susceptibility.

Abbreviations

CIs

confidence intervals

EDTA

ethylenediaminetetraacetic acid

GWAS

genome-wide association studies

HWE

Hardy–Weinberg equilibrium

LD

Linkage disequilibrium

MAF

minor allele frequency

ORs

odds ratios

PAMPs

pathogen-associated molecular patterns

TB

Tuberculosis

TLR

toll-like receptor

Declarations

Authors' contributions

GC designed the research; DC wrote the paper; WL analyzed the data; LQ collected the data; LY, DL and GZ performed research. All authors have read and. agreed with the final manuscript.

Funding

This study was supported by the Key Research and Development Program of Shaanxi (No. 2018SF-222).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study approved by the Ethical Committee of the Xi'an Chest Hospital, and the informed consent documents were signed by all participants.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

We are grateful to all participants for providing blood samples. We also appreciate the reviewers and editors for their efforts and patience.

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Figures

Figure 1

Haplotype block map for SNPs in the TLR6 gene. The LD between each pair of SNPs is standardized D' . The bright red corresponds to a very strong LD; white corresponds to no LD; and pink corresponds to intermediate LD.

Supplementary Files

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