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Original Article

MBL2 rs7095891 G > A polymorphism was associated with an increased risk of tuberculosis in the Chinese Uygur population

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Abstract: Introduction: Tuberculosis (TB) is a foremost infectious disease in most parts of the world. Globally, tuberculosis is the second-leading cause of infectious diseases. This has become a significant world-wide social and public health issue, and one of the major diseases in China. In addition to environmental risk factors, genetic factors may play an important role in the development of tuberculosis. Methods: We conducted a case-control study to evaluate the genetic effects of functional single nucleotide polymorphisms (SNPs): MBL2 rs1800450 C > T, MBL2 rs7095891 G > A and MBL2 rs7096206 C > G, and their influences on the development of tuberculosis. A total of 231 tuberculosis cases and 240 controls were included in this study. Genotypes were determined using a custom-designed 48-Plex SNPscanTM kit. Results: The MBL2 rs7095891 G > A polymorphism was associated with an increased risk of TB. However, there were no significant links with the other two SNPs. In any subgroup, there was no relvant risk of TB associated with MBL2 rs7095891 G > A polymorphism. Conclusion: These findings suggest that functional polymorphism MBL2 rs7095891 G > A may be positively correlated with susceptibility to tuberculosis. These findings may be somewhat limited by sample size. A further study with more focus on different regions, ethnic groups and larger sample sizes is therefore suggested.

Keywords: MBL2 rs7095891, MBL2 rs1800450, MBL2 rs7096206, tuberculosis, Uygur

Introduction

Tuberculosis (TB) is a foremost infectious disease in most parts of the world. Globally, tuberculosis is the second-leading cause of infectious diseases [1]. This has become a significant social and public health issue world-wide, and it has also become one of the major diseases in China [2]. It has been expressed that tuberculosis has a high incidence throughout all regions of the country, especially in agriculture and animal husbandry areas, and showed significant regional differences [3-5]. Therefore, the number of tuberculosis in the Xinjiang Uyghur Autonomous region is high, particularly in the Uyghur population [6].

It has been confirmed that some environmental risk factors, such as smoking and drinking are independent risk factors for tuberculosis [7]. Nevertheless, only 10% of those infected with *Mycobacterium tuberculosis* develop a TB activity period during their lifetime. This prompts that individual divergences, such as genetic factors may lead to susceptibility to tuberculosis [8]. The susceptibility genes associated with the tuberculosis include natural resistance-associated macrophage protein 1 (Nramp1 or Slc11a1), vitamin D receptor (VDR), HLA DR2, and mannose binding lectin (MBL) [8, 9]. The present study focuses on whether MBL polymorphism was associated with the susceptibility to tuberculosis.

Mannose binding lectin (MBL), an acute-phase serum protein of the collecting family, plays a decisive role in regulating the host's innate immune function [10]. Once microorganisms invade the body, MBL initiates the complement activation pathway by binding to bacterial man-

nose residues and serine proteases to facilitate opsonization, phagocytosis or lysis of microorganisms [10-12].

Some studies showed that MBL2 located on chromosome 10 is the encoding gene of MBL. MBL2 polymorphism has been declared to affect the serum level of MBL. This protein exerts multiple effects in the serum [13, 14]. MBL2 can increase the body's ability to combat pathogens, stimulate the activation of complement and intervene in immunity and promote cell phagocytosis. After MBL2 binds to the invading pathogen, it can also activate the hydrolyzed protein cascade in conjunction with serine proteases 1 and 2 (MASP-1 and MASP-2) to constitute a membrane attack complex, and then unlock the lectin pathway and exert human immune effects. It has been verified that the MBL2 gene is closely related to various infectious diseases, such as respiratory infection [15, 16]. Nevertheless, a consistent conclusion hasn't been reached on whether MBL2 polymorphism can confer resistance or susceptibility to pulmonary TB [17].

Many scholars have found that the MBL2 polymorphism is involved in the occurrence and development of tuberculosis with some differences between races and ethnic groups. Interstingly, there may be significant ethnic differences between MBL2 polymorphisms and tuberculosis susceptibility. However, no study has reported the association between tuberculosis patients and MBL polymorphisms in the Xinjiang Uygur ethnic group. Therefore, we chose Xinjiang Uygur tuberculosis patients as case subjects. The purpose is to evaluate the association between MBL rs1800450 C > T, MBL rs7095891 G > A and, MBL rs7096206 C > G genotypes and susceptibility to tuberculosis in the Xinjiang Uygur population, Northwest of China, in order to evaluate their possible influence on disease attack.

Materials and methods

Ethical approval of the study protocol

This hospital-based case-control study was approved by the Review Board of Kashgar Pulmonary Hospital (Xinjiang, China). All subjects provided written informed consent to be included in this study.

Study subjects

Two hundred and thirty one Uygur subjects with tuberculosis were consecutively enrolled from Kashgar in Xinjiang Uygur Autonomous Region of China between October 2012 and November 2013. All cases of tuberculosis were diagnosed by pulmonary tuberculosis, with diagnostic criteria: sputum smear or culture-positive diagnosis, chest X-ray shows signs of tuberculosis and clinical manifestations.

The exclusion criteria were patients who had complications, such as diabetes, asthma, chronic obstructive pulmonary disease (COPD), lung cancer, etc. and the patients who infected with hepatitis virus, AIDS, cancer patients, long-term use of hormone drugs and organ transplants, which lead to immunocompromised persons, and no family history of genetic disease.

And 240 individuals with age and gender-fitted controls and without an inquired history of the disease and no symptoms of tuberculosis from the hospital as referred to the above during the same period.

Trained interviewers using a standardized clinical-epidemiological questionnaire to collect the information including demographic data (e.g. age and sex) and related risk factors (e.g. tobacco smoking and alcohol consumption). After the interview, 2-mL samples of venous blood were harvested from each patient. Smokers were described as people who smoked one cigarette per day for > 1 year. Alcohol users were described as individual who consumed ≥ 3 alcoholic drinks a week for > 6 months.

Isolation of DNA and genotyping of MBL by a custom-by-design 48-Plex SNPscanTM Kit

Blood samples from patients were harvested by vacutainer tubes containing ethylenediamine tetra-acetic acid (EDTA). Genomic DNA was separated from whole blood with the QIAamp DNA Blood Mini Kit (Tianhao, Shanghai, China). Sample DNA (10 ng) was amplified by PCR according to the manufacturer's recommendations. SNP genotyping work was performed using a custom-by-design 48-Plex SNPscanTM Kit (Genesky Biotechnologies Inc., Shanghai, China) as previously described. This kit was developed according to patent SNP

Table 1. Distribution of selected demographic variables and risk factors in TB cases and controls

Variable	Cases (n = 231)		Controls (n = 240)		*P**
	n	%	n	%	
Age (years)					0.000
< 60	128	55.4	180	75	
≥ 60	103	44.6	60	25	
Sex					0.968
Male	114	49.4	118	49.2	
Female	117	50.6	122	50.8	
Tobacco use					0.031
Never	199	86.1	217	92.3	
Ever	32	13.9	23	7.7	
Alcohol use					0.106
Never	211	91.3	208	86.7	
Ever	20	8.7	32	13.3	

*Two-sided X^2 test.

genotyping technology by Genesky Biotechnologies Inc., which was built on double ligation and multiplex fluorescence PCR. In this study, the SNPs we selected were rs1800450, rs7095891 and rs7096206. For quality control, repeated analyses were done for 4% of randomly selected samples with high DNA quality.

Statistical analyses

The chi-square test (X^2) was used to evaluate the differences in the distribution of demographic traits, selected variables, and genotypes of the rs1800450 C > T, rs7095891 G > A and rs7096206 C > G between the two queues.

The ORs and their 95% CIs calculated by logistic regression analyses were forecasted the associations between rs1800450 C > T, rs7095891 G > A and rs7096206 C > G genotypes, and the risk of tuberculosis. The adjusted ORs were calculated when adjusting for age, sex, smoking and drinking modes. A goodness-of-fit X^2 test was computed to assess the Hardy-Weinberg equilibrium (HWE) in the tested genotype frequencies and the control genotype frequency. All statistical analyses were conducted using SPSS 17.0 software.

Results

Characteristics of the study population

Table 1 summarizes the demographic characteristics of the study. There were no significant differences in terms of sex ratio ($P > 0.05$) between the two groups. It suggested that the selected groups were exactly matched for sex ($P = 0.968$), as showed by the chi-square test. However, **Table 1** shows that there was a key difference in the age distribution between cases and controls ($P = 0.000$) indicating the ages between the two groups were not completely matched. As showed in **Table 1**, there were no significant differences in alcohol consumption between cases and controls ($P = 0.106$), but the prevalence of smoking among tuberculosis patients was significantly higher than that of the control group ($P = 0.031$). The primary information for the three genotype SNPs is displayed in **Table 2**. The genotypes of the three SNPs were successful, the value of which was 98.632% in all 471 samples. Concordance rates of repeated analyses with random and double-blinded methods turned 100%. The Hardy-Weinberg balance test showed that the MBL rs1800450, rs7095891 and rs7096206 loci of the Uygur nationality have good population representativeness and can be further studied.

Associations between three polymorphisms and risk of TB

Table 3 shows the genotype distributions of MBL2 rs1800450 C > T, MBL2 rs7095891 G > A and MBL2 rs7096206 C > G in cases and controls. In single locus analyses, the genotype frequencies of MBL2 rs7095891 G > A were 65.4% (GG), 31.2% (GA) and 3.5% (AA) in the cases while they were 74.6% (GG), 20.8% (GA) and 4.6% (AA), respectively in the controls, and no statistical significance was found in the single locus analyses. When the MBL2 rs7095891 GG homozygote genotype was used as the reference group, the GA genotype was associated with a significantly increased risk for TB (GA vs. GG: OR = 1.707, 95% CI = 1.121-2.600, $P = 0.013$). However, the AA genotype was not associated with TB risk (AA vs. GG: OR 0.862, 95% CI 0.338-2.198, $P = 0.756$). In the recessive model, when the MBL2 rs7095891 GG/GA genotypes were used as the reference group, the AA homozygote genotype was not associated with the risk of TB (OR 0.747, 95% CI 0.295-1.891, $P = 0.538$). While in the dominant model, a significantly increas-

Table 2. Primary information of the three genotyped SNPs

Genotyped SNPs	chr	Location	Test for HWE[a] (*P* Value)	MAF[b] in our controls n = 392		MAF (Hapmap-HCB)		MAF (Hapmap-CEU)		Genotyping value (%)
MBL2 rs1800450 C > T	10	exon1	0.008	0.126	T	0.132	T	0.150	T	98.632
MBL2 rs7095891 G > A	10	5'FLANKING	0.577	0.191	A	0.154	A	0.204	A	98.632
MBL2 rs7096206 C > G	10	5'FLANKING	0.764	0.160	G	0.147	G	0.217	G	98.632

[a]HWE: Hardy-Weinberg equilibrium; [b]MAF: minor allele frequency.

Table 3. Logistic regression analyses of the association between *MBL2* polymorphisms and the risk of TB

Genotype	Cases (n = 231)		Controls (n = 240)		Crude OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*
	n	%	n	%				
rs1800450 C > T								
CC	176	76.2	181	75.4	1		1	
CT	48	20.8	54	22.5	0.914 (0.588-1.420)	0.69	0.834 (0.529-1.316)	0.436
TT	7	3	5	2	1.440 (0.449-4.622)	0.54	1.614 (0.484-5.384)	0.436
CT+TT	55	23.8	59	24.6	0.959 (0.629-1.462)	0.845	0.895 (0.579-1.383)	0.616
CC+CT	224	97	235	98	1		1	
TT	7	3	5	2	1.469 (0.459-4.695)	0.571	1.676 (0.505-5.567)	0.399
rs7095891 G > A								
GG	151	65.4	179	74.6	1		1	
GA	72	31.2	50	20.8	**1.707 (1.121-2.600)**	**0.013**	**1.575 (1.019-2.434)**	**0.041**
AA	8	3.5	11	4.6	0.862 (0.338-2.198)	0.756	0.830 (0.316-2.181)	0.706
GA+AA	80	34.6	61	25.4	**1.555 (1.045-2.313)**	**0.03**	1.442 (0.955-2.176)	0.081
GG+GA	223	96.5	229	95.4		1	1	
AA	8	3.5	11	4.6	0.747 (0.295-1.891)	0.538	0.733 (0.280-1.914)	0.525
rs7096206 C > G								
CC	166	71.9	156	65			1	
CG	56	24.2	77	32.1	0.683 (0.455-1.028)	0.067	0.731 (0.480-1.111)	0.142
GG	9	3.9	7	3	1.208 (0.439-3.323)	0.714	1.248 (0.444-3.513)	0.674
CG+GG	65	28.1	84	35	0.727 (0.492-1.075)	0.11	0.775 (0.518-1.158)	0.213
CC+CG	222	96.1	233	97.1			1	
GG	9	3.9	7	3	1.349 (0.494-3.685)	0.559	1.371 (0.490-3.832)	0.548

[a]Adjusted for age, sex, smoking and drinking status; Bold values are statistically significant ($P < 0.05$).

ed risk of TB was found between the MBL2 rs7095891 GA/AA variants and TB (OR 1.555 95% CI 1.045-2.313, $P = 0.03$) (**Table 3**). After adjusting for age, gender, smoking and drinking, the heterozygous comparison and dominant models were observed in increased risk of TB on the critical statistics (GG vs. GA: adjusted OR 1.575, 95% CI 1.019-2.434, $P = 0.041$) (**Table 3**).

Likewise, neither the MBL2 rs1800450 C > T nor the MBL2 rs7096206 C > G polymorphisms were found a statistical difference in the genotype distribution between the two groups. Furthermore, no associations between these SNPs and the risk of TB were declared by Logistic regression analyses (**Table 3**).

Stratification analyses of MBL2 rs7095891 G > A polymorphisms and risk of TB

Stratification analyses was applied to investigate the impact of MBL2 rs7095891 G > A genotype on TB risk in different age, gender, smoking, and alcohol status (**Table 4**). In any subgroup, there was no significant risk of TB associated with MBL2 rs7095891 G > A polymorphism (**Table 4**).

Discussion

This case-control study investigated MBL2 rs1800450 C > T, MBL2 rs7095891 G > A and MBL2 rs7096206 C > G association with the risk of tuberculosis in a high-risk Chinese Uygur

Table 4. Stratified analyses between MBL2: rs7095891 G > A polymorphism and TB risk by sex, age, smoking status and alcohol consumption

Variable	MBLrs7095891 G > A (case/control)				Adjusted OR[a] (95% CI); P			
	GG	GA	AA	GA+AA	GG	GA	AA	GA+AA	AA vs. (GA+GG)
Sex									
Male	72/87	38/27	4/4	42/31	1	1.594 (0.874-2.908)	1.138 (0.267-4.848)	1.535 (0.863-2.733)	0.986 (0.233-4.174)
						0.128	0.862	0.145	0.985
Female	79/92	34/23	4/7	38/30	1	1.730 (0.897-3.335)	0.588 (0.148-2.335)	1.454 (0.789-2.679)	0.514 (0.131-2.019)
						0.102	0.451	0.23	0.34
Age (years)									
< 60	86/136	39/34	3/10	42/44	1	1.688 (0.976-2.921)	0.437 (0.113-1.685)	1.404 (0.837-2.353)	0.380 (0.099-1.459)
						0.061	0.229	0.198	0.159
≥ 60	65/43	33/16	5/1	38/17	1	1.495 (0.671-3.331)	3.029 (0.309-29.697)	1.596 (0.732-3.479)	2.608 (0.275-24.700)
						0.325	0.341	0.24	0.403
Tobacco use									
Never	136/165	56/43	7/9	63/52	1	1.518 (0.941-2.450)	0.992 (0.342-2.871)	1.431 (0.911-2.247)	0.895 (0.311-2.576)
						0.087	0.987	0.12	0.837
Ever	15/14	16/7	1/2	17/9	1	3.246 (0.872-12.090)	0.554 (0.039-7.796)	2.528 (0.748-8.546)	0.348 (0.027-4.486)
						0.079		0.135	0.418
Alcohol use									
Never	140/154	64/44	7/10	71/54	1	1.438 (0.901-2.296)	0.722 (0.256-2.032)	1.308 (0.840-2.035)	0.651 (0.233-1.822)
						0.128	0.537	0.234	0.414
Ever	11/25	8/6	1/1	9/7	1	2.605 (0.570-11.898)	2.061 (0.112-38.085)	2.504 (0.602-10.411)	1.545 (0.087-27.358)
						0.217	0.627	0.207	0.767

[a]Adjusted for age, sex, smoking status and alcohol consumption (besides stratified factors accordingly) in a logistic regression model.

population. The results showed that the MBL2 rs7095891 G > A genotype raised the likelihood of tuberculosis, and the results were statistically significant ($P < 0.05$). The MBL2 rs1800450 C > T and MBL2 rs7096206 C > G may not be linked to TB susceptibility in the Uygur population in Xinjiang area.

Lectin pathway is a very important part of the three complement activation pathways. The mannose binding lectin (MBL) gene plays a leading role and participates in the activation of pathogenic microbes and conditioning functions, especially in the process of preventing infectious diseases. The abnormal MBL gene can reduce the level of related proteins in the serum and affect the occurrence and development of infectious diseases [10].

Mannose binding lectin gene is mainly associated with the pathogenesis of pulmonary tuberculosis. The most studied MBL genes are: rs5030737, rs1800450, rs1800451, rs1100-3125, rs7096206 and rs7095891. To date, research clues have studied the tendentious contribution of the MBL gene polymorphism in different diseases, such as respiratory infection [18], neonatal sepsis [19], diabetes [20], autoimmune diseases [21] and cardiovascular diseases [22]. However, no positive correlation has been found between MBL2 rs7095891 G > A and TB so far. We found that MBL2 rs-7095891 GA variant heterozygote rather than MBL2 rs7095891 AA homozygote was associated with TB risk. Whether smoking and drinking are factors in inducing the development of tuberculosis is also a controversial issue [24]. Ghufron's experimental study also proves that the amount of smoking, and the duration of smoking are related to the occurrence of tuberculosis. Salmaso and others have found that the number of people who drink a lot of alcohol daily in TB patients is more susceptible than that of the general population, which suggests that drinking is also a major factor in tuberculosis [25]. MBL2 rs7095891 G > A polymorphism was not associated with risk of TB among smoking or non-smoking subgroups and drinkers or non-drinkers. This may be explained by a relatively small sample size as we do not get a large enough number of GG genotypes and GA genotype subgroups.

There was no statistically significant association between the other 2 SNPs and the risk of tuberculosis in our study population. These

findings are inconsistent with previous research. It has been found that the rs1800450 locus in the Ningxia Hui population is associated with susceptibility to tuberculosis in the homozygous recessive infection model. However, no correlation was noted in this study. This may be explained by the difference in the frequency of race, population and geographical distribution of gene polymorphisms.

In conclusion, the reasons for previous research discrepancies may be due to: (1) the sample size; (2) the inclusion and exclusion criteria of samples; (3) ethnic and regional differences of the population; and (4) immune factors. In addition to MBL, there are many immune factors, such as vitamin D receptor (VDR), tumor necrosis factor (TNF), monotypic chemical attractor -1 (MCP-1), MASP-2 and many other related factors. Therefore, different regions, ethnic groups and larger sample size studies still have to be carried out to verify our findings.

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Disclosure of conflict of interest

None.

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