

Association of Mannose-Binding Lectin 2 Gene Polymorphism with Tuberculosis Based on *Mycobacterium tuberculosis* Lineages

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Purpose: Polymorphisms in *MBL2* may contribute to the susceptibility to tuberculosis. The aim of the present study was to determine the associations of the polymorphisms of five loci (rs1800450, rs1800451, rs7096206, rs7095891, and rs11003125) in the *MBL2* gene with susceptibility to tuberculosis and specific lineages of *Mycobacterium tuberculosis* causing tuberculosis in the Uyghur population of Xinjiang, China.

Methods: From January 2019 to January 2020, we enrolled 170 Uyghur tuberculosis patients as the case group and 147 Uyghur staff with no clinical symptoms as the control group from four designated tuberculosis hospitals in southern Xinjiang, China. The polymorphisms of five loci in *MBL2* of human were detected by sequencing. Whole-genome sequencing was applied in 68 *M. tuberculosis* isolates from the case group and the data were used to perform genealogy analysis.

Results: The distributions of allele and genotype frequencies of five loci in *MBL2* varied little between the case and control groups and varied little among the groups, including those infected with different lineages of *M. tuberculosis* and the control (except those of rs11003125), the *P* values were all >0.05. The distribution of alleles of rs11003125 was statistically different between patients infected with lineages 3 and 4 *M. tuberculosis* ($\chi^2=7.037$, $P=0.008$). The C allele and CC genotype of rs11003125 were found to be protective factors against lineage 4 infection when compared to lineage 3 (ORs were 0.190 and 0.158, respectively; 95% confidence intervals were 0.053–0.690 and 0.025–0.999, respectively).

Conclusion: Our results suggested that human's susceptibility to tuberculosis is affected both by the host genetic polymorphisms and the lineage of the *M. tuberculosis* that people were exposed to. However, due to the limitation of the sample size in the present study, larger sample size and more rigorous design should be guaranteed in future studies.

Keywords: mannose-binding lectin 2 gene, polymorphism, tuberculosis, *Mycobacterium tuberculosis*, lineage

Introduction

Tuberculosis is a serious public health problem, and the global COVID-19 pandemic since 2020 may reverse progress in reducing the global tuberculosis burden, allowing for more than 1 million additional tuberculosis cases per year during 2020–2025.¹ The World Health Organization (WHO) estimates that the number of new tuberculosis patients in China was 833,000 in 2019, ranking third among the top thirty countries with high tuberculosis burden globally.¹ About a quarter of the world's population are latently infected with *Mycobacterium tuberculosis*. However, their lifetime risk of reactivation is about 5–10%,¹ suggesting that the individual differences in susceptibility to tuberculosis are universal. Another fact far back in 1930 in Germany, noted as the Ramp van Lübeck disaster, also provided clues: among 250

newborns vaccinated with the vaccine contaminated with the virulent *M. tuberculosis*, 77 died, 127 cases showed tuberculosis symptoms, while the other 47 had no manifestations of *M. tuberculosis* infection.²⁻⁴

In recent years, genes related to tuberculosis susceptibility have been reported continuously through genome-wide association studies (GWAS) and hot single nucleotide polymorphism (SNP) correlation studies.⁵⁻⁷ The human mannose-binding lectin 2 gene (*MBL2*) is located on chromosome 10q21.1. The *MBL2* gene encodes a liver-derived glycoprotein named mannose-binding lectin (MBL), which exists in the serum as a multimeric protein and acts as an important anti-infective factor in the innate immune system. MBL is a member of the Ca²⁺ dependent C-type lectin superfamily,⁸ which is involved in the detection of pathogens by recognizing the conserved structures known as pathogen associated molecular patterns (PAMPs) and subsequently promotes the activation of innate immunity.⁹ For the characteristics that MBL can recognize PAMPs on the surface of pathogens, it is also considered to be a pattern recognition receptor (PRRs).⁸ MBL attached to the surface of the pathogen can activate the MBL-related serine proteases MASP-1 and MASP-2, which will trigger the proteolytic cascade reaction and induce the activation of the complement system.^{8,10} Several single nucleotide polymorphisms (SNPs) on the *MBL2* gene associated with serum MBL levels and function have been reported, including rs7096206, rs7095891 and rs11003125 in the upstream region, and sites rs5030737, rs1800450 and rs1800451 in the exon 1 region.^{11,12} As knowledge on the *MBL2* immune defense activity and the immunological mechanism against *M. tuberculosis* is growing, a number of studies were conducted to find hints on the *MBL2* gene polymorphisms to clarify the mechanisms of people's susceptibility to tuberculosis. However, consistency in conclusions was lacking across different groups in terms of race, age and gender.^{6,13,14}

Liu et al performed whole-genome sequencing (WGS) on a large number of individual colonies from 18 patients to characterize the genetic diversity of the *M. tuberculosis* population at the onset of the disease and reconstruct the evolution of *M. tuberculosis* within the host, and they found that mutagenesis of *M. tuberculosis* in vivo is modulated by the host environment.¹⁵ Omae et al performed a *M. tuberculosis* lineage-based GWAS with CD53 gene and found that two SNPs (rs1418425 and rs1494320) are risk factors for the old age tuberculosis onset infected with strains of non-Beijing genotype, and they speculated that the genetic risk of host susceptibility is related to the genotypes of infected strains.¹⁶ Therefore, the interactions between the genetic systems of humans and *M. tuberculosis* should be taken into account in discovering the mechanisms of host susceptibility to tuberculosis. The various lineages of *M. tuberculosis* defined by molecular epidemiology tools like WGS showed genetic distance may pose different stress on the human immune system. In the present study, we will explore the polymorphisms of rs1800450, rs1800451, rs7096206, rs7095891 and rs11003125 in the *MBL2* gene among the Uyghur population with tuberculosis or not, as well as among people infected with different lineages of *M. tuberculosis* defined by WGS from Xinjiang, China, in order to determine their impact on the susceptibility to tuberculosis.

Methods

The Sources of Subjects

The Case Group

A total of 170 Uyghur tuberculosis patients were enrolled from the Eighth Affiliated Hospital of Xinjiang Medical University, Kashgar Pulmonary Hospital, Kuqa County Infectious Disease Hospital and Wushi County People's Hospital from January 2019 to January 2020. The inclusion criteria for the case group are as follows: 1) comply with the diagnostic criteria for tuberculosis in the industry standard "WS 288-2017 Diagnosis for pulmonary tuberculosis" issued by the National Health and Family Planning Commission of the People's Republic of China;¹⁷ and 2) both parents of the patients are Uyghur. We excluded the patients with severe damage to organs such as the heart, liver and kidney (primary disease), endocrine system diseases (such as hyperthyroidism, Cushing syndrome, etc.), malignant tumors, hematological diseases, mental diseases and pregnancy.

The Control Group

The control group consisted of 147 Uyghur staff in the Eighth Affiliated Hospital of Xinjiang Medical University with no clinical symptoms. The inclusion criteria for the control group are as follows: 1) they were confirmed to have a negative

TSPOT.TB through participating in annual physical examination; and 2) both parents of the controls are Uyghur. The exclusion criteria are the same as those of the case group.

Collection of Specimens and DNA Preparation

After all participants signed the informed consent form and joined the group, 5 mL of venous blood from each participant were collected in EDTA anticoagulant tubes. The nucleic acid extraction kit (magnetic bead method) and AU1001-96 automatic nucleic acid extractor provided by China Wuxi Biotech Biotechnology Co., Ltd were then used to extract DNA. A total of 68 clinical isolates of *M. tuberculosis* in the case group were collected, and their genomic DNA was extracted through the cetyltrimethylammonium bromide (CTAB) method.¹⁸ The quantity and quality of the obtained DNA samples were analyzed spectrophotometrically (NanoDrop 2000, Thermo Scientific, MA, USA).

Polymorphisms of Five SNPs in MBL2

A total of five SNPs in *MBL2* were analyzed in the present study (Table 1). According to the NCBI dbSNP database, rs1800450 and rs1800451, rs7096206 and rs7095891 in *MBL2* are adjacent to each other, respectively. So, we totally designed three pairs of primers to sequence all of the five SNPs. The primers were designed by Oligo 6.0 software and synthesized by Beijing Tianyi Huiyuan Biotechnology Co., Ltd, Beijing, China. The total volume of the PCR reaction was 25 μ L, including 12.5 μ L PCR mixture, 1 μ L DNA, 10 ng upstream primer, 10 ng downstream primer and 9.5 μ L ddH₂O. PCR conditions were 95 °C for 3 min, followed by 35 cycles of 95 °C for 30 s, 62.0 °C (rs1800450 and rs1800451) or 61.4 °C (rs7096206 and rs7095891) or 53.9 °C (rs11003125) for 30 s, and 72 °C for 30 s, and finally extension at 72 °C for 7 min (Table 1). All samples were amplified and the PCR products were sent to Beijing Tianyi Huiyuan Biotechnology Co., Ltd, Beijing, China for sequencing on an ABI 3730xl DNA Sequencer (Applied Biosystems, Foster City, CA, USA).

Whole-Genome Sequencing and Genetic Lineage Analysis of *M. tuberculosis* Isolates

DNA libraries were prepared with genomic DNA using kits as instructed by the manufacturer. DNA libraries were then selected to perform cluster growth and 150 bp paired-end sequencing on DNB SEQ-2000 instrument (Beijing Genomics Institute, China). Following the quality control process, Snippy software (<https://github.com/tseemann/snippy>, version: 4.6.0) was used to analyze all of the genome sequence data that met the quantity control criteria. The *M. tuberculosis* H37Rv genome sequence (NC_000962.3) was used as the reference to identify the core SNPs and the SNPs located in the PE/PPE/PGRS gene regions were filtered out. The lineage information was determined by TB-Profler (<https://github.com/jodyphelan/TBProfler>, version 4.0.3). Then the core SNPs were used for building the phylogeny tree using the FastTree software (<http://www.microbesonline.org/fasttree/>) and then the lineage information was used for annotating the phylogeny tree by iTOL.¹⁹

Statistical Analysis

A nearest neighbor 1:1 matching ratio with propensity scores that fell within a caliper of 0.10 was used to generate the matched group to balance potentially confounding baseline characteristics. Univariate regression analysis and multi-variable logistic regression model were then used to study the relationships between alleles or genotypes of *MBL2* gene

Table 1 Primer Information for the Five Loci of the *MBL2* Gene

SNP_ID	F/R	Base Sequence	Fragment Size (bp)	Annealing Temperature (°C)
rs1800450/ rs1800451	F R	TCAAATAGGACATCAGTCTC GCAGTGTCAACAAGGAATGTT	448	62
rs7096206/ rs7095891	F R	AGGAGAAGGAGAGGGAGTGA TGGGATTCAGGTGGCAGATG	474	61.4
rs11003125	F R	GAATCCCATCTTTGTATCTG AGGCTGCTGAGGTTCTTAG	421	53.9

and tuberculosis status or lineages of *M. tuberculosis* infection as applicable. All analyses were performed by SPSS 25.0 (SPSS Inc., Chicago, IL, USA). The statistical significance was established at $P \leq 0.05$.

Results

Hardy–Weinberg Equilibrium Test

According to previous literature reports, if gene polymorphisms are linked to disease susceptibility, the case group may not be in accordance with the Hardy–Weinberg equilibrium.²⁰ It is recommended that the Hardy–Weinberg equilibrium test be performed only in the control group.

Goodness-of-fit test using a chi-square discrepancy measure was employed to compare the distribution of the actual frequency and the theoretical frequency of objective loci to observe the fitting degree. The results demonstrated that the control group's genetic inheritance followed the Hardy–Weinberg equilibrium ($P > 0.05$) (Table 2), implying that the control group is representative of the research population.

Association Analysis of *MBL2* Gene Polymorphisms and Susceptibility to tuberculosis Univariate Regression Analysis on the Associations Between the Alleles or Genotypes of Five Loci and Susceptibility to Tuberculosis

For the whole subjects, it was found that the differences in gender and age between the two groups were statistically significant (both P values < 0.05). In addition, none of the alleles or genotypes of the five loci were statistically associated with susceptibility to tuberculosis (Supplementary Table 1).

We used PS with nearest neighbor 1:1 matching to control the effect attributed to age and gender between the two groups, and 103 subjects were included in each group after matching. Among these subjects, the SMD values of each covariate (age and gender) were less than 0.10, indicating a good balance between the groups and good propensity score matching. None of the alleles or genotypes of the five loci were found to statistically associated with susceptibility to tuberculosis, too (Supplementary Table 1).

Multivariable Logistic Regression Analysis

For the whole subjects, age, gender, rs1800451 and rs11003125 genotypes were found with $P < 0.20$ in the univariate regression analysis and were included in the multivariable logistic regression model for further analysis. The results

Table 2 Distributions of the *MBL2* Genotypes and HWE Testing in the Control Group

SNP	Genotyping Rate* (%)	Genotype	Controls (n=147)		χ^2	P
			Actual Frequency	Theoretical Frequency		
rs1800450	99.7	CC	98	100	0.820	0.664
		CT	46	43		
		TT	3	5		
rs1800451	99.7	CC	143	29	0.000	1.000
		CT	4	98		
		TT	0	46		
rs7096206	96.8	GG	6	3	1.045	0.593
		GC	37	40		
		CC	98	96		
rs7095891	96.8	GG	106	103	4.189	0.123
		GA	29	35		
		AA	6	3		
rs11003125	97.5	GG	39	42	1.131	0.568
		GC	75	69		
		CC	25	28		

Note: *The rate of the available genotyping samples to total samples.

Table 3 Association of *MBL2* Gene Polymorphisms with Different Lineages of *M. tuberculosis* Infection

Factor	Lineage 2 (n%)	Lineage 3 (n%)	Lineage 4 (n%)	Other Lineages (n%)	χ^2	P ^a
Age						
<45	12 (35.3)	2 (25.0)	6 (27.3)	1 (25.0)	0.642	0.887
≥45	22 (64.7)	6 (75.0)	16 (72.7)	3 (75.0)		
Gender						
Male	18 (52.9)	4 (50.0)	9 (40.9)	1 (25.0)	1.660	0.646
Female	16 (47.1)	4 (50.0)	13 (59.1)	3 (75.0)		
rs1800450						
CC	25 (75.8)	6 (75.0)	16 (72.7)	4 (100.0)	2.326	0.508
CT	8 (24.2)	2 (25.0)	6 (27.3)	0 (0.0)		
C	58 (87.9)	14 (87.5)	38 (86.4)	8 (100.0)	2.157	0.540
T	8 (12.1)	2 (12.5)	6 (13.6)	0 (0.0)		
rs7096206						
GG	1 (3.0)	0 (0.0)	0 (0.0)	1 (25.0)	8.402	0.210
GC	14 (42.4)	1 (12.5)	5 (25.0)	1 (25.0)		
CC	18 (54.5)	7 (87.5)	15 (75.0)	2 (50.0)	5.966	0.113
G	16 (24.2)	1 (6.3)	5 (12.5)	3 (37.5)		
C	50 (75.8)	15 (93.7)	35 (87.5)	5 (62.5)		
rs7095891						
GG	27 (81.8)	5 (62.5)	12 (60.0)	3 (75.0)	4.529	0.606
GA	5 (15.2)	3 (37.5)	7 (35.0)	1 (25.0)		
AA	1 (3.0)	0 (0.0)	1 (5.0)	0 (0.0)	2.858	0.414
G	59 (89.4)	13 (81.3)	31 (77.5)	7 (87.5)		
A	7 (10.6)	3 (18.7)	9 (22.5)	1 (12.5)		
rs11003125						
GG	9 (26.5)	0 (0.0)	9 (40.9)	1 (25.0)	8.834	0.183
GC	15 (44.1)	4 (50.0)	10 (45.5)	2 (50.0)		
CC	10 (29.4)	4 (50.0)	3 (13.6)	1 (25.0)	7.530	0.057
G	33 (48.5)	4 (25.0)	28 (63.6)	4 (50.0)		
C	35 (51.5)	12 (75.0)	16 (36.4)	4 (50.0)		

Notes: Because rs1800451 only appeared in the CC genotype in each group, it was excluded from the analysis. ^aAcquired by Likelihood ratio chi-square test.

Table 4 Distributions of the Alleles of rs11003125 in *MBL2* Gene Between Patients Infected with Lineages 3 and 4 of *M. tuberculosis*

SNP	Allele	Lineage 3 (n%)	Lineage 4* (n%)	χ^2	P	OR (95% CI)
rs11003125	G	4 (25.0)	28 (63.6)	7.037	0.008	1 0.190 (0.053–0.690)
	C	12 (75.0)	16 (36.4)			

Note: *Lineage 4 was used as indicator; while lineage 3 was used as control.

Table 5 Univariate Regression Analysis of rs11003125 Polymorphisms and Lineages 4 of *M. tuberculosis* Infection

SNP	Genotype	Lineage 3 (n%)	Lineage 4* (n%)	P	OR (95% CI)
rs11003125	GC/GG	4 (50.0)	19 (86.4)	0.05	1 0.158 (0.025–0.999)
	CC	4 (50.0)	3 (13.6)		

Note: *Lineage 4 was used as indicator, while lineage 3 was used as control.

Considering the number of four groups of *M. tuberculosis* was insufficient, we classified *M. tuberculosis* into lineage 2- and non-lineage 2-infected groups. And then compared the differences in the distribution of *MBL2* gene polymorphisms among these two groups and the control group. The results showed that none of the alleles or genotypes of the four loci were statistically associated with specific lineages of *M. tuberculosis* infection ([Supplementary Table 3](#)).

Discussion

Previous researches have indicated that comprehending the co-evolution of pathogen and host faces many different constraints, and has advised that reciprocal polymorphisms in genes involved in the host–pathogen interaction be identified at the molecular level.^{21–23} By understanding the genetic architecture of coevolution, we can use population genetic models to predict such events as the expected temporal dynamics of allele frequencies, the likelihood of new mutations arising, and the spread of new variants.²⁴ In the present study, we explore the association of the polymorphisms in rs1800450, rs1800451, rs7096206, rs7095891 and rs11003125 of the *MBL2* gene with susceptibility to tuberculosis and their potential interactions with infected *M. tuberculosis* lineages in the Uyghur population of Xinjiang, China. When merely population genetic factors were considered, however, no significant association was discovered. This is the first report on the association between genetic polymorphisms and the lineages of *M. tuberculosis* infection in the population of China.

The MBL pathway identifies the peptidoglycan of Gram-positive bacteria through the C-type lectin domain and regulates the release of cytokines and chemokines, making it a key component of the innate immune system in pathogen identification.²⁵ In one study, serum MBL deficiency rates were consistent regardless of the severities of tuberculosis patients, implying that MBL deficiency may predispose patients to *M. tuberculosis* infection.²⁶ Nevertheless, other researchers have suggested that MBL deficiency may protect patients from tuberculosis infection by restricting pathogen entry into host cells.²⁷ Although the mechanism of *MBL2* gene mutation regulating the progression of tuberculosis is not clear, there is no doubt that *MBL2* gene plays a significant part in tuberculosis pathogenesis.

In the present study, 170 Uyghur tuberculosis patients and 147 healthy controls were selected to explore the polymorphisms of *MBL2* associated with susceptibility to tuberculosis. The results showed that the frequency distributions of alleles and genotypes of rs1800450, rs1800451, rs7096206, rs7095891 and rs11003125 in patients were not statistically different from those of the control group, which was inconsistent with the previously reported results.^{13,14,28,29} Several studies have been conducted among the Chinese Han population.^{13,28,29} The rs7096206-GC genotype and the rs7095891-GA genotype were revealed to be risk factors for the progression of spinal tuberculosis by Zheng et al.¹³ Chen et al discovered that the risk of tuberculosis is higher with the GC genotype than with the CC genotype of rs7096206 after eliminating various confounding factors.²⁹ Guo et al discovered that the YA/YA haplotype was associated with a high serum MBL level, suggesting that it was a key predictor of serum MBL level and could be a protective factor for tuberculosis susceptibility.²⁸ The CC genotype and C allele of rs11003125 were shown to be strongly related with tuberculosis susceptibility (risk factors) in an Iranian population, but the G allele may be a protective factor.¹⁴ The variations between the studies could be due to the diversity of geographic origins, although further research is needed to establish this.

According to the National Survey of Drug-Resistant Tuberculosis database from 2007, lineages 1, 2, 3, and 4 of *M. tuberculosis* isolates were the most prevalent in China.³⁰ Lineage 2 accounted for 50% of all lineages identified using whole-genome sequencing (WGS) in our study, which is lower than the national average of 75% mentioned above.³⁰ Lineage 2 (or East Asian lineage), which is prevalent in East Asian countries, has attracted interest due to its hypervirulence in laboratory models.^{31,32} In the present study, we divided *M. tuberculosis* into lineage 2- and non-lineage 2-infected groups for analysis. However, none of the alleles or genotypes of the four loci were observed to statistically associate with lineage 2. Analysis among the four major lineages of isolates, the C allele and the CC genotype of rs11003125 were found to be protective factors in lineage 4 infection by using lineage 3 infection as control, which provides clues for tuberculosis control where lineage 3 and 4 of *M. tuberculosis* were prevalent and suggested that the host's susceptibility to tuberculosis differs depending on the lineages of *M. tuberculosis* challenges they face. Wang et al infected human macrophages and dendritic cells with *M. tuberculosis* clinical isolates from various mycobacterial families and found that Beijing strains elicited fewer cytokines than other *M. tuberculosis* strains, indicating that Beijing strains have a different ability to elicit innate and adaptive immune responses than other *M. tuberculosis* strains.³³ Various *M. tuberculosis* strains have varied pro-inflammatory cytokine profiles, which could explain how biological factors play a role in disease transmission.³⁴ Müller et al compared two geographically distinct cohorts (the South African population of 947 participants and the Ghanaian population of 3311 participants) and discovered that 32 SNPs

were statistically significantly associated with risk of infection with various *M. tuberculosis* strains in the Ghanaian cohort, whilst no correlation was found in the South African cohort.³⁵

In the present study, we observed that rs11003125 exhibited a lineage-dependent association in the Uyghur population. These findings imply that combining the pathogen and host genetic nature would assist in the identification of consistent genetic risk factors of tuberculosis in different populations and then contribute to long-term tuberculosis control. MBL is a PRR and has ability of inducing different inflammatory responses to different *M. tuberculosis* lineages, and potential interaction between *MBL2* function and lineages appears to be a viable prospect. One limitation of the present study is that the sample sizes of the host subjects and the patients with *M. tuberculosis* were small, so larger sample size and more rigorous design should be guaranteed in future studies.

Conclusion

We found that the C allele and CC genotype of rs11003125 were protective factors in the Uyghur population against lineage 4 of *M. tuberculosis* infection by using lineage 3 infection as control, which provides clues for tuberculosis control where lineage 3 and 4 of *M. tuberculosis* were prevalent and suggests that human's susceptibility to tuberculosis is affected both by the host genetic polymorphisms and the lineages of the *M. tuberculosis* that people are exposed to.

Abbreviations

CI, confidence interval; CTAB, cetyltrimethylammonium bromide; EDTA, ethylene diamine tetraacetic acid; GWAS, genome-wide association studies; HWE, Hardy–Weinberg equilibrium; *MBL2*, mannose-binding lectin 2; *M. tuberculosis*, *Mycobacterium tuberculosis*; PAMPs, pathogen associated molecular patterns; PRRs, pattern recognition receptors; PSM, propensity score matching; SNPs, single nucleotide polymorphisms; WGS, whole-genome sequencing; WHO, World Health Organization.

Data Sharing Statement

Data can be made available through contact with the corresponding author.

Ethics Approval and Informed Consent

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of the Eighth Affiliated Hospital of Xinjiang Medical University (XJMU8HEC-20161215). Written informed consent was obtained from individuals.

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Disclosure

The authors report no conflicts of interest in this work.

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