Genetic polymorphisms of MBL2 and tuberculosis susceptibility: a meta-analysis of 22 case-control studies

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Abstract

Introduction: The association of mannose-binding lectin gene (MBL2) polymorphisms with tuberculosis susceptibility was inconclusive. In this study, a meta-analysis of 22 case-control studies was carried out to assess the effect of MBL2 polymorphisms on tuberculosis risk.

Material and methods: A search was performed in Embase, PubMed and Web of Science up to Sep 30, 2015. Odds ratio (OR) and 95% confidence interval (95% CI) were used to assess the association. Statistical analyses were performed using STATA 12.0 software.

Results: rs1800451 was associated with a decreased tuberculosis risk in the allele model (C vs. A: OR = 0.93, 95% CI: 0.86–1.00, p = 0.050). In analyses stratified by ethnicity, rs7096206 (C/G: OR = 1.31, 95% CI: 1.10–1.57, p = 0.003; GG vs. GC + CC: OR = 0.69, 95% CI: 0.56–0.85, p < 0.001) and A/O (O/A: OR = 1.34, 95% CI: 1.10–1.64, p = 0.004) were associated with tuberculosis risk in Asians, A/O (AA vs. AO + OO: OR = 0.71, 95% CI: 0.51–0.99, p = 0.043) and rs1800451 (AC vs. AA + CC: OR = 2.70, 95% CI: 1.27–5.74, p = 0.010) were associated with tuberculosis risk in Americans, and rs1800451 (CA/A: OR = 0.92, 95% CI: 0.86–0.99, p = 0.035) was associated with tuberculosis risk in Africans. Additionally, rs1800450 (B/A: OR = 0.42, 95% CI: 0.25–0.72, p = 0.001) was associated with tuberculosis risk in Europeans.

Conclusions: The MBL2 rs1800451 polymorphism is associated with decreased TB risk in the general population, and A/O, rs7096206, rs1800450 and rs1800451 are likely to be associated with the risk for some specific ethnic groups.

Key words: tuberculosis; gene polymorphism; susceptibility.

Introduction

Mycobacterium tuberculosis (TB) is one of the most common infectious diseases and ranks as the leading cause of mortality worldwide, with approximately 9 million new cases and 1.5 million deaths globally in 2013. According to the latest World Health Organization (WHO) report, the greatest burden of disease falls in developing countries, with approximately 56% of new cases occurring in the South-East Asia and Western Pacific regions [1]. It is well known that the outcome of infection with M. tuberculosis may be influenced by many factors, such as smoking history, physical condition, environmental and host genetic factors [2]. Recently, there have been vari-
ous studies reporting that host genetic factors may play an important role in TB susceptibility, which includes single nucleotide polymorphisms (SNPs) as a major factor. Multiple candidate genes have been investigated to determine the relationship between SNPs and TB risk, including TIRAP [3], VDR [4], P2X7 [5], and MBL2 [6].

The MBL2 gene codes for the complement factor mannose binding lectin (MBL), which can bind through multiple lectin domains to the carbohydrate moieties present in a wide variety of bacteria, viruses and fungi. Upon binding, MBL-associated serine proteases (MASPs) are activated to initiate the lectin pathway of the complement system, opsonizing and facilitating phagocytosis of micro-organisms by macrophages [7]. MBL2 deficiency may be advantageous in resistance against mycobacteria by reducing opsonization. MBL2 also plays a role in the regulation of inflammatory cytokines released by monocytes and enhances toll-like receptor (TLR) 2 and TLR6 signaling in response to microbial infection, and hence may affect the inflammation severity or disease progression [8].

Previous studies have suggested that certain SNPs within the promoter region and structural region of the MBL2 gene affect the formation of MBL multimer and serum MBL concentration [9]. The reduction of MBL multimer results in impaired binding with the ligand and the increased likelihood of being degraded by metalloproteinase. Three SNPs (rs1800450, rs5030737 and rs1800451) in exon 1 of the MBL2 gene give rise to amino acid substitutions, which disrupt the collagenous structure and the formation of functional oligomers. These three SNPs, collectively designated as "AO" polymorphisms, while the wild-type allele is described as allele "A" and the mutant allele as "O", indicate the presence of one or more mutant alleles in either rs1800450, rs5030737 or rs1800451. The heterogeneous-type A/O correlates with low MBL levels in the serum and the homologous-type O/O with almost undetectable MBL levels. The other SNPs, rs11003125, rs7096206, and rs7095891, also have been found in the promoter and 5 untranslated region, and the X variant shows negatively regulated transcriptional activity and results in reduced serum MBL levels [10]. Studies have evaluated the relationship of these polymorphisms with TB risk in black people, Asians, and Caucasians. However, the results obtained are controversial. Considering the critical role of the MBL2 gene in the pathogenesis of tuberculosis and the fact that a small sample size may lack the power to provide comprehensive conclusions, we performed a meta-analysis to investigate the association between MBL2 gene polymorphisms and TB risk.

Material and methods

Literature search

A systematic search was conducted using the databases of the US National Institutes of Health (PubMed), Web of Science and Embase databases, with the following combination of search terms: ‘Mycobacterium tuberculosis’ OR ‘tuberculosis’ AND ‘polymorphism’ OR ‘variant’ OR ‘genotype’ OR ‘allele’ OR ‘mutation’ OR single nucleotide polymorphism AND ‘MBL’ OR ‘mannose-binding lectin’ OR ‘mannose-binding protein’. To identify additional eligible articles, the relevant published articles and review articles were also identified by hand searching. The search in these databases was limited to articles relating to humans, covering all relevant English and Chinese language publications published up to March 2016.

The studies identified in our meta-analysis met all of the following criteria: (1) studies had to assess the association between MBL2 polymorphisms rs5030737, rs1800450, rs1800451, A/O, rs11003125, rs7096206, rs7095891 and tuberculosis risk; (2) unrelated case-control studies or cohort design, and studies included available genotype frequencies to calculate odds ratio (OR) and 95% confidence interval (CI); (3) independent studies using original data. Studies were excluded for the following criteria: (1) studies not providing genotype distribution or allele frequency data; (2) reviews or case reports, case studies without control subjects; (3) duplicated previous publications.

Data extraction

Two investigators (CY and WXJ) independently performed the required data extraction, and then conducted group discussion to resolve the disagreements. The following data were extracted from each study: publication year, name of first author, country, ethnicity, genotyping method, method of diagnosis of cases, tuberculosis type, number of cases and controls, numbers and mean age of cases and controls, genotypic and allele frequencies for cases and controls, and HIV status of cases and controls.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was assessed among the control population for each study using the Hardy-Weinberg Equilibrium Online Calculator (http://www.changbioscience.com/genetics/hardy.html). A p-value of > 0.05 was considered to meet HWE.

All statistical analyses were performed using Stata statistical software 12.0 (Stata Corporation,
College Station, TX, USA), with two-sided \(p\)-values. The OR and its corresponding 95% CI were calculated to assess the strength of association between MBL2 polymorphism and the TB risk. The pair-wise differences were analyzed to indicate the best genetic models as suggested by Thakkinstian et al. [11]. Data were then pooled using the best model. Ethnicity was adopted to carry out the stratified analysis, when data were available.

The significance of pooled ORs was measured by the \(Z\)-test \((p < 0.05\) was considered statistically significant). The heterogeneity assumption was tested by the \(\chi^2\)-based Q-statistic and Higgins’ \(I^2\) test. If \(p < 0.10\), the heterogeneity was considered statistically significant, and then the RE model was used. The heterogeneity was considered significant if \(I^2 > 50\%\), then ORs were pooled according to the random effect model (Mantel-Haenszel method) [12]. Otherwise the fixed effect model was used (DerSimonian-Laird method) [13]. Meta-regression was performed to detect the source of heterogeneity. Publication bias was evaluated by examining the Beggs’s funnel plots and Egger’s linear regression test [14, 15].

**Results**

**Characteristics of studies**

Our initial search identified 250 articles according to the search terms (PubMed: 56; Embase: 89; Web of Science: 105). One hundred and thirty-two abstracts were retrieved for more detailed evaluation after removing duplicates. Thirty-four articles addressing the association of MBL2 polymorphisms and TB were identified. After reviewing the full text, 12 articles were excluded (1 was excluded due to not being on MBL2 polymorphism; 1 was excluded due to not being on tuberculosis; 10 were excluded due to not providing genotype distribution). Finally, a total of 22 case-control studies that consisted of a total of 7056 tuberculosis patients and 7764 control subjects were included in this meta-analysis [16–37]. Figure 1 provides the detailed screening process. Among them, 9 were performed in an Asian population, 2 were performed in an American population, 6 were performed in a European population, and 5 were performed in an African population. The study of Soborg et al. 2003 has mixed data with 59 Europeans, 26 Asians, 17 Africans, and 7 Inuit, so it is not included in the subgroup analysis. The characteristics of each included study are listed in Table I.

**Quantitative data synthesis**

**MBL2 rs7096206 polymorphism**

Six case-control studies (3154 cases and 3441 controls) on the relationship between the rs7096206 polymorphism and the risk of TB were included in the meta-analysis. For rs7096206, the estimated OR1 (CC vs. GG), OR2 (GC vs. GG) and OR3 (CC vs. GC) were 0.964 (95% CI: 0.689–1.347), 1.290 (95% CI: 1.004–1.657) and 0.828 (95% CI: 0.587–1.168) (Table II). Thus, we mainly pooled the OR for allele comparison and the recessive genetic model in the subgroup analysis by ethnicity (Table III). The pooled examination showed no significant association between rs7096206 polymorphism and the risk of tuberculosis (C/G: OR = 1.15, 95% CI: 0.97–1.36, \(p = 0.100\), \(p^* = 0.061\); GG vs. GC + CC: OR = 0.80, 95% CI: 0.64–1.01, \(p = 0.058\), \(p^* = 0.010\)) (Table III). The results of subgroup analysis based on ethnicity indicated that the rs7096206 C allele increased susceptibility to tuberculosis risk in Asian populations, but not in American and African populations (C/G: OR = 1.31, 95% CI: 1.10–1.57, \(p = 0.003\), \(p^* = 0.634\); GC vs. GG + CC: OR = 0.69, 95% CI: 0.56–0.85, \(p < 0.001\), \(p^* = 0.381\)) (Table III). For the subgroup analysis by the genotyping methods, the recessive genetic model (GG vs. GC + CC: OR = 0.76, 95% CI: 0.59–0.96, \(p = 0.022\), \(p^* = 0.152\)) remained statistically significant in polymerase chain reaction sequence-specific primer (PCR-SSP) studies (Table III).

**Table I. Articles included in this meta-analysis (n = 22)**

| Article | Study Design | Population | Genotyping Method | Ethnicity |
|---------|-------------|------------|-------------------|-----------|
| Soborg et al. 2003 | Clinic | Mixed | PCR-SSP | European, Asian, African, Inuit |

**Figure 1. Flowchart for study selection**
| Year | First author | Country | Ethnicity | Study design | Tuberculosis | Samples (n) | Age, years mean ± SD or mean (range) | Diagnosis method | Genotyping method | Controls source | HIV status | SNPs |
|------|--------------|---------|-----------|--------------|--------------|-------------|-------------------------------------|-----------------|-----------------|----------------|------------|------|
| 2015 | Chen         | China   | Chinese Han | HB          | Pulmonary tuberculosis | 503 | 419 | > 19 years Matched | Confirmed with the TB diagnosis criteria | PCR-SSP | Healthy persons | Not available | rs7096206 |
| 2014 | Chen         | China   | Chinese Han | HB          | Pulmonary tuberculosis | 205 | 216 | > 19 years Matched | Confirmed with the TB diagnosis criteria | PCR-SSP | Healthy persons | Not available | rs7096206 |
| 2014 | Garcia-Gasalla | Spain   | Spanish | PB          | Pulmonary tuberculosis (58) extra-pulmonary or military TB (21) | 76 | 106 | 45 (18–84) 45 (18–94) | Clinically, radiologically diagnosed and culture | PCR-SSP | Household contacted | Case: positive: 33%; Control: positive: 2.5% | rs7096206 rs1800450 rs5030737 rs1800451 rs11003125 rs7096891 |
| 2013 | da Cruz      | Brazil  | Brazilian | PB          | Pulmonary tuberculosis (119) and extra-pulmonary tuberculosis (36) | 155 | 148 | 29.8 ±16.14 25 ±2.42 | Clinical symptoms, radiographic findings, bacteriological confirmation (culture, smear and/or polymerase chain reaction) | Sequencing | Healthy persons | Negative | rs11003125 rs7096206 rs1800450 rs5030737 rs1800451 |
| 2013 | Araujo       | Brazil  | Brazilian | HB          | Pulmonary tuberculosis (133) and extra-pulmonary tuberculosis (34) | 167 | 159 | \ | AFB smear and culture, X-rays and positive biopsy for M. tuberculosis | PCR-RFLP | Contacted workers | Negative | rs1800450 rs5030737 rs1800451 |
| 2011 | Singla       | India   | North Indian | HB          | Pulmonary tuberculosis (286) and extra-pulmonary tuberculosis (71) | 357 | 392 | 33.1 ±15.42 36.4 ±14.88 | Respiratory symptoms, sputum smear or culture, chest radiographs | PCR-RFLP | Healthy persons, contacted workers | Negative | rs1800450 |
| 2011 | Thye         | Ghana   | Akan, Ga-Adangbe, Ewe | PB          | Pulmonary tuberculosis | 2010 | 2346 | \ | X-rays, clinical symptoms, and AFB smear and culture | Pyrosequencing, dynamic allele-specific hybridization with FRET | Contacted healthy persons | Negative | rs11003125 rs7096206 rs7095891 rs1800451 |
| 2011 | de Wit       | South Africa | South African Coloureds | PB          | Pulmonary tuberculosis | 505 | 318 | 31 30 | Culture-proven | PCR-RFLP | Healthy persons | Negative | rs5030737 rs1800450 rs1800451 |
| Year | First author | Country | Ethnicity | Study design | Tuberculosis | Samples (n) | Age, years mean ± SD or mean (range) | Diagnosis method | Genotyping method | Controls source | HIV status | SNPs |
|------|--------------|---------|-----------|--------------|--------------|-------------|--------------------------------------|-----------------|-----------------|----------------|------------|------|
| 2011 | Li Y         | China   | Chinese Han | PB           | Pulmonary tuberculosis | 231 / 226 | 39.2 (23–75) / 36.8 (25–72) | Confirmed with the TB diagnosis criteria | PCR-SSP | Healthy persons | Negative | rs11003125, rs7095891, rs1800450 |
| 2009 | Capparelli   | Italy   | Italian   | PB           | Pulmonary tuberculosis | 277 / 288 | 47 ±17 / 40 ±17 | Chest radiography and sputum smears | PCR-sequencing | Household contacted | Negative | rs11003125, rs7096206, rs7095891 |
| 2008 | Cosar        | Turkish | Turkish   | PB           | Pulmonary tuberculosis (27) and extra-pulmonary tuberculosis (17) | 44 / 99 | 7.02 ±4.5 / 7.38 ±4.07 | Culture, clinical and radiological findings | PCR-RFLP | Healthy persons | Negative | rs1800450 |
| 2007 | Alagarasu    | India   | Dravidian | PB           | Pulmonary tuberculosis (226) and extra-pulmonary tuberculosis (31) | 257 / 297 | 35.37 ±10.8 / 32.87 ±8.76 | Clinical, radiographic, bacteriological findings, AFB smear | PCR-sequencing | Healthy persons | Cases: positive (109); negative (148) / Controls: positive (151); negative (146) | rs5030737, rs1800450, rs1800451 |
| 2007 | Soborg       | Tanzania | Tanzania  | HB           | Pulmonary tuberculosis | 443 / 426 | 35 (15–73) / 34 (14–85) | Culture positive | PCR-SSP | Culture negative | Cases: Positive (44%); controls: positive (18%) | rs5030737, rs1800450, rs1800451, rs7096206 |
| 2006 | Liu W        | China   | Chinese Han | PB           | Pulmonary tuberculosis | 152 / 293 | 25.69 ±7.98 / 27.40 ±8.62 | Confirmed with the TB diagnosis criteria | PCR-SSP | PCR-SSOP | Healthy persons | Negative | rs1800450, rs7096206, rs11003125, rs7095891 |
| 2006 | Selvaraj     | India   | Indian    | HB           | Pulmonary tuberculosis | 58 / 48 | 29.93 ±1.5 / 27.48 ±0.95 | Clinical, radiographic, AFB smear and culture | PCR-SSOP | Healthy persons | Negative | rs5030737, rs1800450, rs1800451 |
| Year | First author | Country | Ethnicity | Study design | Tuberculosis | Samples (n) | Age, years mean ± SD or mean (range) | Diagnosis method | Genotyping method | Controls source | HIV status | SNPs |
|------|--------------|---------|-----------|--------------|--------------|-------------|-------------------------------------|----------------|----------------|----------------|------------|------|
| 2006 | Garcia-Laorden | Spain | Spanish | PB | Pulmonary tuberculosis | 233/344 | (27–47); (6–3 y) | Culture and microscopy | PCR-RFLP, PCR-SSP | Healthy persons and household contacted | Cases: positive (106) | rs5030737, rs1800450, rs1800451 |
| 2004 | Fitness | Malawi | Malawian | PB | Pulmonary tuberculosis | 322/546 | (25–45) | Culture, smear, or histology | PCR-RFLP | Healthy persons | Cases: positive (154) | rs1800451 |
| 2003 | Soborg | Tanzania | 59 whites, 26 Asians, 17 Africans, and 7 Inuits | PB | Pulmonary tuberculosis | 109/250 | (27–47); (6 m–3 y) | Culture positive or microscopy | PCR-SSP | Healthy persons | Negative | rs5030737, rs1800450, rs1800451 |
| 2003 | Ozbas-Gerceker | Turkey | Turkish | PB | Pulmonary tuberculosis | 118/100 | (25–45) | Not available | PCR-RFLP | Healthy persons | Negative | rs1800450 |
| 2000 | Selvaraj | India | Indian (Dravidian) | PB | Pulmonary tuberculosis | 67/44 | 37.1 ±1.7 | Smear and culture | PCR-RFLP | Healthy persons (35); House contacted (32) | Not available | rs5030737, rs1800450, rs1800451 |
| 1999 | Selvaraj | India | Indian (Dravidian) | PB | Pulmonary tuberculosis | 202/109 | 40.3 ±0.9 | Smear and culture | PCR-SSOP | Healthy persons (62); House contacted (47) | Not available | rs5030737, rs1800450, rs1800451 |
| 1998 | Bellamy | Gambia | Gambian | PB | Pulmonary tuberculosis | 397/422 | \ | \ | TB/leprosy clinics | PCR-SSOP | Healthy persons | Negative | rs1800450, rs1800451 |

PB – population-based, HB – hospital-based, AFB – acid-fast bacilli, HIV – human immunodeficiency virus, MDR – multi-drug resistance for isoniazid and rifampicin, PPD – purified protein derivative, SNPs – single nucleotide polymorphisms, TB – tuberculosis, PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism.
Table II. Multiple comparisons of genotype effects

| Genotype | Pooled OR examination |
|----------|------------------------|
|          | OR (95%CI) | P-value | P* |
| rs7096206 X/Y: |          |          |    |
| YY vs. XX (OR1) | 0.964 (0.689–1.347) | 0.829 | 0.970 |
| XY vs. XX (OR2) | 1.290 (1.004–1.657) | 0.047 | 0.005 |
| YY vs. XY (OR3) | 0.828 (0.587–1.168) | 0.282 | 0.739 |
| A/O T/C: |          |          |    |
| CC vs. TT (OR1) | 1.973 (0.935–4.163) | 0.075 | 0.000 |
| CT vs. TT (OR2) | 1.179 (0.852–1.633) | 0.321 | 0.000 |
| CC vs. CT (OR3) | 1.547 (0.954–2.507) | 0.077 | 0.001 |
| rs11003125 H/L: |          |          |    |
| LL vs. HH (OR1) | 0.716 (0.501–1.024) | 0.062 | 0.501 |
| LH vs. HH (OR2) | 0.890 (0.692–1.144) | 0.798 | 0.052 |
| LL vs. LH (OR3) | 0.911 (0.645–1.286) | 0.454 | 0.432 |
| rs5030737 A/D: |          |          |    |
| DD vs. AA (OR1) | 2.985 (0.712–12.510) | 0.135 | 0.718 |
| AD vs. AA (OR2) | 1.021 (0.746–1.395) | 0.898 | 0.499 |
| DD vs. AD (OR3) | 3.054 (0.696–13.395) | 0.139 | 0.510 |
| rs1800450 A/B: |          |          |    |
| BB vs. AA (OR1) | 0.989 (0.544–1.797) | 0.971 | 0.117 |
| AB vs. AA (OR2) | 0.911 (0.717–1.157) | 0.443 | 0.014 |
| BB vs. AB (OR3) | 1.074 (0.621–1.856) | 0.798 | 0.232 |
| rs1800451 A/C: |          |          |    |
| CC vs. AA (OR1) | 0.833 (0.697–0.995) | 0.044 | 0.709 |
| AC vs. AA (OR2) | 0.955 (0.802–1.138) | 0.607 | 0.085 |
| CC vs. AC (OR3) | 0.894 (0.747–1.070) | 0.222 | 0.699 |
| rs7095891 P/Q: |          |          |    |
| QQ vs. PP (OR1) | 1.089 (0.906–1.309) | 0.362 | 0.815 |
| PQ vs. PP (OR2) | 0.953 (0.841–1.080) | 0.449 | 0.845 |
| QQ vs. PQ (OR3) | 1.133 (0.948–1.353) | 0.169 | 0.882 |

OR = odds ratio, CI = confidence interval. P-value for OR, P* = P-value of Q-test for heterogeneity test.

MBL2 rs11003125 polymorphism

Four case-control studies (2370 cases and 2760 controls) on the relationship between the rs11003125 polymorphism and the risk of TB were included in the meta-analysis. For rs11003125, the estimated OR1 (GG vs. CC), OR2 (CG vs. CC) and OR3 (GG vs. CG) were 0.716 (95% CI: 0.501–1.024), 0.890 (95% CI: 0.693–1.144) and 0.911 (95% CI: 0.645–1.286) (Table II). Thus, we mainly pooled ORs for allele comparison and the codominant genetic model in the subgroup analysis by ethnicity. The pooled examination revealed no significant association between rs11003125 polymorphism and the risk of tuberculosis (G/C: OR = 0.89, 95% CI: 0.58–1.35, p = 0.572, p* < 0.001; CG vs. CC + GG: OR = 1.00, 95% CI: 0.87–1.16, p = 0.946, p* = 0.290) (Table III).

MBL2 rs7095891 polymorphism

Three case-control studies (2325 cases and 2668 controls) on the relationship between the
## Table III. Meta-analysis results

| rs7096206 | N | Case/control | Allele comparison | OR (95% CI) | P | p* | Genetic model comparison | OR (95% CI) | P | p* |
|-----------|---|--------------|------------------|-------------|---|----|--------------------------|-------------|---|----|
|           |   | Total        |                  |             |   |    | Dominant                  |             |   |    |
|           |   | 6595         | 3154/3441        | 1.15 (0.97–1.36) | 0.100 | 0.061 | 1.09 (0.78–1.52) | 0.610 | 0.957 |
|           |   | Ethnicity:   |                  |             |   |    |                             |             |   |    |
|           |   | Asian        |                  | 1.31 (1.10–1.57)* | 0.003 | 0.634 | 0.69 (0.56–0.85)* | 0.000 | 0.381 |
|           |   | American     |                  | 1.35 (0.88–2.07)* | 0.173 | /   | 0.65 (0.39–1.06)* | 0.084 | /   |
|           |   | African      |                  | 0.95 (0.85–1.08)* | 0.451 | 0.955 | 1.05 (0.92–1.20)* | 0.476 | 0.788 |
|           |   | Genotype methods: |            |             |   |    |                             |             |   |    |
|           |   | PCR-SSP      |                  | 1.21 (1.04–1.40)* | 0.016 | 0.241 | 0.76 (0.59–0.96)* | 0.022 | 0.152 |
|           |   | Sequencing   |                  | 1.06 (0.78–1.46) | 0.699 | 0.131 | 0.88 (0.55–1.40) | 0.585 | 0.061 |
|           |   | A/O          |                  | 1.35 (0.96–1.88) | 0.083 | 0.000 | 0.49 (0.26–0.93) | 0.028 | 0.000 |
|           |   | Ethnicity:   |                  |             |   |    |                             |             |   |    |
|           |   | European     |                  | 1.49 (0.49–4.52) | 0.480 | 0.000 | 0.60 (0.15–2.41) | 0.474 | 0.000 |
|           |   | American     |                  | 1.32 (1.00–1.75)* | 0.054 | 0.182 | 0.71 (0.51–0.99)* | 0.041 | 0.129 |
|           |   | Asian        |                  | 1.34 (1.10–1.64)* | 0.004 | 0.211 | 0.79 (0.62–1.02)* | 0.066 | 0.285 |
|           |   | African      |                  | 0.83 (0.67–1.02)* | 0.076 | /   | 1.30 (0.99–1.71)* | 0.062 | /   |
|           |   | Genotype methods: |            |             |   |    |                             |             |   |    |
|           |   | PCR-SSP      |                  | 1.15 (0.84–1.57)* | 0.392 | 0.056 | 1.00 (0.69–1.46)* | 0.988 | 0.496 |
|           |   | Sequencing   |                  | 1.62 (1.07–2.44)* | 0.022 | /   | 0.54 (0.33–0.88)* | 0.013 | /   |
|           |   | PCR-RFLP     |                  | 1.05 (0.64–1.71) | 0.845 | 0.021 | 0.97 (0.58–1.62) | 0.893 | 0.046 |
|           |   | PCR-SSOP     |                  | 1.26 (0.73–2.18) | 0.401 | 0.003 | 0.43 (0.08–2.19) | 0.568 | 0.019 |
|           |   | PCR-Sequencing |            | 1.97 (0.64–6.13) | 0.240 | 0.000 | 0.85 (0.49–1.10) | 0.307 | 0.000 |
| Allele comparison | N | Case/control | OR (95% CI) | P | P* |
|-------------------|---|--------------|-------------|---|----|
| **rs11003125**    |   |              |             |   |    |
| Total             | 5130 | 2370/2760 | 0.89 (0.73–1.09) | 0.254 | 0.068 |
| Codominant        | 1.00 (0.87–1.16)* | 0.946 | 0.290 |
| **Ethnicity:**    |   |              |             |   |    |
| American          | 303 | 155/148 | 0.73 (0.51–1.03)* | 0.074 | / |
| TR (0.62–1.54)* | 0.920 | / |
| Asian             | 810 | 372/438 | 0.83 (0.68–1.02)* | 0.078 | 0.440 |
| TR (0.61–1.07)* | 0.139 | 0.533 |
| African           | 4017 | 1843/2174 | 1.09 (0.92–1.30)* | 0.296 | / |
| TR (0.92–1.32)* | 0.280 | / |
| **Genotype methods:** |   |              |             |   |    |
| Sequencing        | 303 | 155/148 | 0.73 (0.51–1.03)* | 0.074 | / |
| TR (0.62–1.54)* | 0.920 | / |
| Pyro-sequencing   | 4017 | 1843/2174 | 1.09 (0.92–1.30)* | 0.296 | / |
| TR (0.92–1.32)* | 0.280 | / |
| PCR-SSP           | 810 | 372/438 | 0.83 (0.68–1.02)* | 0.078 | 0.440 |
| TR (0.61–1.07)* | 0.139 | 0.533 |
| **rs5030737**     |   |              |             |   |    |
| Total             | 2647 | 1410/1237 | 1.20 (0.90–1.60)* | 0.225 | 0.787 |
| Dominant          | 0.27 (0.07–1.04)* | 0.058 | 0.705 |
| Recessive         | 0.90 (0.66–1.22)* | 0.489 | 0.770 |
| **Ethnicity:**    |   |              |             |   |    |
| American          | 520 | 265/255 | 1.25 (0.66–2.39) | 0.491 | 0.924 |
| TR (0.40–1.53)* | 0.467 | 0.950 |
| African           | 1443 | 759/684 | 0.84 (0.45–1.54) | 0.564 | 0.359 |
| TR (0.65–2.23) | 0.560 | 0.353 |
| Asian             | 684 | 386/298 | 1.45 (0.91–2.32) | 0.114 | 0.631 |
| TR (0.49–1.32) | 0.394 | 0.272 |
| **Genotype methods:** |   |              |             |   |    |
| Sequencing        | 303 | 155/148 | 1.23 (0.55–2.74)* | 0.621 | / |
| Recessive         | 0.79 (0.34–1.87)* | 0.593 | / |
| PCR-RFLP          | 819 | 488/331 | 0.85 (0.46–1.57) | 0.595 | 0.326 |
| Recessive         | 1.19 (0.64–2.21) | 0.590 | 0.319 |
| PCR-sequencing    | 373 | 184/189 | 1.59 (0.89–2.85) | 0.121 | / |
| Recessive         | 0.66 (0.36–1.22) | 0.183 | / |
| PCR-SSP           | 841 | 381/460 | 1.17 (0.66–2.07) | 0.587 | 0.891 |
| Recessive         | 0.87 (0.48–1.58) | 0.647 | 0.852 |
| PCR-SSOP          | 311 | 202/109 | 1.26 (0.59–2.69) | 0.558 | / |
| Recessive         | 1.17 (0.51–2.68) | 0.703 | / |
| **rs1800450**     |   |              |             |   |    |
| Total             | 4956 | 2481/2475 | 0.94 (0.74–1.19) | 0.610 | 0.001 |
| Dominant          | 1.07 (0.73–1.55) | 0.742 | 0.156 |
| Recessive         | 1.09 (0.85–1.40) | 0.508 | 0.003 |
| Case/control Allele comparison |
|-------------------------------|
|                 | OR (95% CI) | OR (95% CI) |
|                 |             |             |
|                 | P           | P           |
|                 |             |             |
| **Table III.**  |             |             |
| **Cont.**       |             |             |
| **N**           |             |             |
| **Case/control**|             |             |
| **Allele comparison** |         |             |
| **Genetic model comparison** |         |             |
| **P**           |             |             |
| **P**           |             |             |
| **Ethnicity:**  |             |             |
| **American**    |             |             |
| **155/148**     | 1.27 (0.75–2.15) | 0.379         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Dominant**    |             |             |
| **0.618**       |             |             |
| **Asian**       |             |             |
| **232/9**       | 1.14 (0.79–1.63) | 0.462         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Dominant**    |             |             |
| **0.160**       |             |             |
| **African**     |             |             |
| **196/3**       | 1.29 (1.07–1.31) | 0.100         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Dominant**    |             |             |
| **0.001**       |             |             |
| **European**    |             |             |
| **361/199**     | 0.92 (0.62–1.40) | 0.075         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Dominant**    |             |             |
| **0.338**       |             |             |
| **Total**       |             |             |
| **8415/4465**   | 0.93 (0.86–1.00) | 0.501         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Codominant**  |             |             |
| **0.152**       |             |             |

| **Ethnicity:**  |             |             |
| **American**    |             |             |
| **512/18**      | 2.59 (1.23–5.46) | 0.032         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Codominant**  |             |             |
| **0.073**       |             |             |
| **African**     |             |             |
| **7540/2762**   | 2.75 (1.21–6.28) | 0.046         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Codominant**  |             |             |
| **0.338**       |             |             |

| **Genotype methods:** |             |             |
| **Sequencing**        |             |             |
| **8415/4465**         | 2.75 (1.21–6.28) | 0.046         |
| **OR**                |             |             |
| **(95% CI)**          |             |             |
| **Codominant**        |             |             |
| **0.338**             |             |             |

| **Ethnicity:**  |             |             |
| **American**    |             |             |
| **155/148**     | 1.27 (0.75–2.15) | 0.379         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Dominant**    |             |             |
| **0.618**       |             |             |
| **Asian**       |             |             |
| **232/9**       | 1.14 (0.79–1.63) | 0.462         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Dominant**    |             |             |
| **0.160**       |             |             |
| **African**     |             |             |
| **196/3**       | 1.29 (1.07–1.31) | 0.100         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Dominant**    |             |             |
| **0.001**       |             |             |
| **European**    |             |             |
| **361/199**     | 0.92 (0.62–1.40) | 0.075         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Dominant**    |             |             |
| **0.338**       |             |             |
| **Total**       |             |             |
| **8415/4465**   | 0.93 (0.86–1.00) | 0.501         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Codominant**  |             |             |
| **0.152**       |             |             |

| **Ethnicity:**  |             |             |
| **American**    |             |             |
| **512/18**      | 2.59 (1.23–5.46) | 0.032         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Codominant**  |             |             |
| **0.073**       |             |             |
| **African**     |             |             |
| **7540/2762**   | 2.75 (1.21–6.28) | 0.046         |
| **OR**          |             |             |
| **(95% CI)**    |             |             |
| **Codominant**  |             |             |
| **0.338**       |             |             |

| **Genotype methods:** |             |             |
| **Sequencing**        |             |             |
| **8415/4465**         | 2.75 (1.21–6.28) | 0.046         |
| **OR**                |             |             |
| **(95% CI)**          |             |             |
| **Codominant**        |             |             |
| **0.338**             |             |             |
Genetic polymorphisms of MBL2 and tuberculosis susceptibility: a meta-analysis of 22 case-control studies

Table III. Cont.

| rs7095891 | N | Case/control Allele comparison | OR (95% CI) | P | Genetic model comparison | OR (95% CI) | P |
|-----------|---|--------------------------------|-------------|---|--------------------------|-------------|---|
| Genetic model comparison | P               | Case/control Allele comparison | OR (95% CI) | P |
| Dominant | 0.90 (0.76–1.06)* | 1.02 (0.94–1.11)* | 0.922 |
| Recessive | 1.01 (0.88–1.14)* | 1.01 (0.88–1.14)* | 0.922 |
| rs7095891 polymorphism and the risk of TB were included in the meta-analysis. For rs7095891, the estimated OR1 (TT vs. CC), OR2 (CT vs. CC) and OR3 (TT vs. CT) were 1.089 (95% CI: 0.906–1.309), 0.953 (95% CI: 0.841–1.080) and 1.133 (95% CI: 0.948–1.353) (Table II). Thus, we mainly pooled ORs for allele comparison and the recessive genetic model in the subgroup analysis by ethnicity. The pooled examination revealed no significant association between rs7095891 polymorphism and the risk of tuberculosis (T/C: OR = 1.02, 95% CI: 0.93–1.11, p = 0.707, p<sub>a</sub> = 0.585; CC vs. CT + TT: OR = 1.02, 95% CI: 0.91–1.15, p = 0.723, p<sub>a</sub> = 0.731) (Table III).

MBL2 rs5030737 polymorphism

Seven case-control studies (1410 cases and 1237 controls) on the relationship between the rs5030737 polymorphism and the risk of TB were included in the meta-analysis. For rs5030737, the estimated OR1 (DD versus AA), OR2 (AD vs. AA) and OR3 (DD vs. AD) were 2.985 (95% CI: 0.712–12.51), 1.021 (95% CI: 0.746–1.395) and 3.054 (95% CI: 0.696–13.40) (Table II). Thus, we mainly pooled ORs for allele comparison and the recessive genetic model in the subgroup analysis by ethnicity. The pooled examination revealed no significant association between rs5030737 polymorphism and the risk of tuberculosis (D/A: OR = 1.20, 95% CI: 0.90–1.60, p = 0.225, p<sub>a</sub> = 0.787; AA vs. AD + DD: OR = 0.90, 95% CI: 0.66–1.22, p = 0.489, p<sub>a</sub> = 0.770) (Table III).

MBL2 rs1800450 polymorphism

Thirteen case-control studies contained sufficient data for analysis of the relationship between the rs1800450 polymorphism and the risk of TB. The distribution of genotypes from the study of Mauro et al. was not consistent with HWE (Table IV), so only twelve studies (2481 cases and 2493 controls) were included in the meta-analysis [20]. For rs1800450, the estimated OR1 (BB vs. AA), OR2 (AB vs. AA) and OR3 (BB vs. AB) were 0.989 (95% CI: 0.544–1.797), 0.911 (95% CI: 0.717–1.157) and 1.074 (95% CI: 0.621–1.856) (Table II). Thus, we mainly pooled ORs for allele comparison and the dominant genetic model in the subgroup analysis by ethnicity. The pooled examination revealed no significant association between rs1800450 polymorphism and the risk of tuberculosis (B/A: OR = 0.94, 95% CI: 0.74–1.19, p = 0.610, p<sup>2</sup> = 0.001; AA + AB vs. BB: OR = 0.83, 95% CI: 0.62–1.10, p = 0.742, p<sup>2</sup> = 0.156) (Table III). When stratified by ethnicity, a significantly decreased risk was found among Europeans in allele contrast (B/A: OR = 0.42, 95% CI: 0.25–0.72, p = 0.001, p<sup>2</sup> = 0.338 (Table III, Figure 3). When stratified by genotyping method, the allele comparison (B/A: OR = 0.68, 95% CI: 0.57–0.83,
| SNP    | Year | First author | Cases   | Controls | HWE | P-value |
|--------|------|--------------|---------|----------|-----|---------|
|        |      |              | YY      | YX       | XX  | Y       | X       | YY      | YX       | XX  | Y       | X       | χ²   | P-value |
| rs7096206 | 2015 | Chen         | 325     | 166      | 12   | 816     | 190     | 296     | 113      | 10  | 705     | 133     | 0.0411 | 0.8393 |
|         | 2014 | Chen         | 123     | 77       | 5    | 323     | 87      | 159     | 49       | 8   | 367     | 65      | 2.7405 | 0.0978 |
|         | 2013 | da Cruz      | 101     | 49       | 5    | 251     | 59      | 110     | 32       | 6   | 252     | 44      | 3.1437 | 0.0762 |
|         | 2011 | Thye         | 1437    | 396      | 26   | 3270    | 448     | 1663    | 486      | 31  | 3812    | 548     | 0.4491 | 0.5028 |
|         | 2007 | Soborg       | 182     | 96       | 13   | 460     | 122     | 166     | 85       | 15  | 417     | 115     | 0.8652 | 0.3523 |
|         | 2006 | Liu W        | 91      | 44       | 6    | 226     | 56      | 151     | 54       | 7   | 356     | 68      | 0.6227 | 0.4300 |
|        |      | A/O          | AA      | AO       | OO   | A       | O       | AA      | AO       | OO   | A       | O       |       |         |
|         | 2014 | Garcia-Gasalla | 48     | 24       | 4    | 120     | 32      | 71      | 34       | 1   | 176     | 36      | 2.0077 | 0.1565 |
|         | 2013 | da Cruz      | 92      | 55       | 8    | 239     | 71      | 108     | 34       | 6   | 250     | 46      | 2.3077 | 0.1287 |
|         | 2013 | Araujo       | 102     | 62       | 3    | 266     | 68      | 101     | 56       | 2   | 258     | 60      | 3.5960 | 0.0579 |
|         | 2009 | Capparelli   | 55      | 158      | 61   | 268     | 280     | 166     | 112      | 10  | 444     | 132     | 2.9226 | 0.0873 |
|         | 2008 | Alagarasu    | 145     | 87       | 25   | 377     | 137     | 169     | 109      | 19  | 447     | 147     | 0.0638 | 0.8006 |
|         | 2007 | Soborg       | 289     | 132      | 22   | 710     | 176     | 271     | 131      | 30  | 673     | 191     | 6.1675 | 0.0130 |
|         | 2006 | Selvaraj     | 24      | 19       | 5    | 67      | 29      | 37      | 18       | 3   | 92      | 24      | 0.1713 | 0.6789 |
|         | 2006 | Garcia-Laorden | 144   | 79       | 10   | 367     | 99      | 183     | 134      | 27  | 500     | 188     | 0.1273 | 0.7213 |
|         | 2003 | Soborg       | 71      | 30       | 8    | 172     | 46      | 157     | 86       | 7   | 400     | 100     | 1.4063 | 0.2357 |
|         | 2000 | Selvaraj     | 32      | 24       | 6    | 88      | 36      | 22      | 9        | 1   | 53      | 11      | 0.0046 | 0.9458 |
|         | 1999 | Selvaraj     | 107     | 73       | 22   | 287     | 117     | 68      | 39       | 2   | 175     | 43      | 1.8374 | 0.1753 |
|         | 1998 | Bellamy      | 198     | 166      | 33   | 562     | 232     | 183     | 197      | 42  | 563     | 281     | 1.0967 | 0.2950 |
| rs11003125 | 2013 | da Cruz      | 82      | 63       | 10   | 227     | 83      | 68      | 61       | 19  | 197     | 99      | 0.8147 | 0.3667 |
|         | 2011 | Thye         | 1570    | 265      | 8    | 3405    | 281     | 1878    | 287      | 9   | 4043    | 305     | 0.3115 | 0.5768 |
|         | 2011 | Li Y         | 105     | 92       | 34    | 302     | 160     | 89      | 106      | 31  | 284     | 168     | 0.0040 | 0.9498 |
|         | 2006 | Liu W        | 44      | 66       | 31    | 154     | 128     | 49      | 105      | 58  | 203     | 221     | 0.0124 | 0.9114 |
| rs5030737 | 2013 | da Cruz      | 142     | 12       | 1    | 296     | 14      | 138     | 9        | 1   | 285     | 11      | 3.3406 | 0.0676 |
|         | 2013 | Araujo       | 102     | 8        | 0     | 212     | 8       | 101     | 6        | 0   | 208     | 6       | 0.0890 | 0.7654 |
|         | 2011 | de Wit        | 363     | 15       | 0     | 741     | 15      | 211     | 13       | 0   | 435     | 13      | 0.2000 | 0.6547 |
|         | 2008 | Alagarasu    | 156     | 26       | 2     | 338     | 30      | 169     | 20       | 0   | 358     | 20      | 0.5899 | 0.4425 |
|         | 2007 | Soborg       | 289     | 8        | 0     | 586     | 8       | 271     | 6        | 0   | 548     | 6       | 0.0332 | 0.8554 |
|         | 2003 | Soborg       | 71      | 12       | 1     | 154     | 14      | 157     | 25       | 1   | 339     | 27      | 0.0001 | 0.9965 |
|         | 1999 | Selvaraj     | 186     | 9        | 7     | 381     | 23      | 99      | 10       | 0   | 208     | 10      | 0.2519 | 0.6157 |
**Table IV. Cont.**

| SNP      | Year | First author | Cases | Controls | HWE | $\chi^2$ | $P$-value |
|----------|------|--------------|-------|----------|-----|---------|-----------|
| rs1800450 |      |              |       |          |     |         |           |
|          | 2013 | da Cruz      | 122   | 31       | 2    | 275     | 35        |
|          |      |              | 124   | 21       | 3    | 269     | 27        |
|          | 2013 | Araujo       | 102   | 50       | 0    | 254     | 50        |
|          |      |              | 50    | 101      | 48   | 0       | 250       |
|          | 2011 | Singla       | 218   | 126      | 13   | 562     | 152       |
|          |      |              | 207   | 155      | 30   | 569     | 215       |
|          | 2011 | de Wit        | 363   | 63       | 2    | 789     | 67        |
|          |      |              | 211   | 50       | 0    | 472     | 50        |
|          | 2011 | Li Y          | 171   | 57       | 3    | 399     | 63        |
|          |      |              | 186   | 37       | 3    | 409     | 43        |
|          | 2008 | Cosar         | 40    | 4        | 0    | 84      | 4         |
|          |      |              | 71    | 27       | 1    | 169     | 29        |
|          | 2008 | Alagarasu     | 156   | 44       | 12   | 356     | 68        |
|          |      |              | 169   | 68       | 10   | 406     | 88        |
|          | 2007 | Soborg        | 289   | 9        | 0    | 587     | 9         |
|          |      |              | 271   | 13       | 1    | 555     | 15        |
|          | 2006 | Liu W         | 103   | 34       | 4    | 240     | 42        |
|          |      |              | 166   | 42       | 4    | 374     | 50        |
|          | 2003 | Soborg        | 71    | 16       | 3    | 158     | 22        |
|          |      |              | 157   | 48       | 3    | 362     | 54        |
|          | 2003 | Ozbas-Gerceker | 101  | 16       | 1    | 218     | 18        |
|          |      |              | 76    | 20       | 4    | 172     | 28        |
|          | 1999 | Selvaraj      | 137   | 51       | 14   | 325     | 79        |
|          |      |              | 84    | 24       | 1    | 192     | 26        |
|          | 1998 | Bellamy       | 198   | 7        | 0    | 403     | 7         |
|          |      |              | 183   | 5        | 0    | 371     | 5         |
| rs1800451 |      |              |       |          |     |         |           |
|          | 2013 | da Cruz       | 133   | 22       | 0    | 288     | 22        |
|          |      |              | 140   | 8        | 0    | 288     | 8         |
|          | 2013 | Araujo        | 102   | 4        | 0    | 208     | 4         |
|          |      |              | 101   | 2        | 0    | 204     | 2         |
|          | 2011 | Thye          | 885   | 815      | 193  | 2585    | 1201      |
|          |      |              | 1002  | 977      | 257  | 2981    | 1491      |
|          | 2011 | de Wit        | 363   | 56       | 0    | 782     | 56        |
|          |      |              | 211   | 39       | 0    | 461     | 39        |
|          | 2008 | Alagarasu     | 156   | 14       | 1    | 326     | 16        |
|          |      |              | 169   | 21       | 2    | 359     | 25        |
|          | 2007 | Soborg        | 289   | 115      | 20   | 693     | 155       |
|          |      |              | 271   | 112      | 20   | 654     | 152       |
|          | 2004 | Fitness       | 205   | 105      | 12   | 515     | 129       |
|          |      |              | 362   | 160      | 24   | 884     | 208       |
|          | 2003 | Soborg        | 71    | 2        | 1    | 144     | 4         |
|          |      |              | 157   | 13       | 0    | 327     | 13        |
|          | 1999 | Selvaraj      | 176   | 25       | 1    | 377     | 27        |
|          |      |              | 103   | 5        | 1    | 211     | 7         |
|          | 1998 | Bellamy       | 198   | 159      | 29   | 555     | 217       |
|          |      |              | 183   | 192      | 42   | 558     | 276       |
| rs7095891 |      |              |       |          |     |         |           |
|          | 2011 | Thye          | 725   | 920      | 308  | 2370    | 1536      |
|          |      |              | 825   | 1086     | 319  | 2736    | 1724      |
|          | 2011 | Li Y          | 189   | 39       | 3    | 417     | 45        |
|          |      |              | 181   | 41       | 4    | 403     | 49        |
|          | 2006 | Liu W         | 118   | 22       | 1    | 258     | 24        |
|          |      |              | 171   | 39       | 2    | 381     | 43        |

HWE – Hardy-Weinberg equilibrium.

$p < 0.001$, $p^2 = 0.224$ and dominant genetic model (AA + AB vs. BB: OR = 2.08, 95% CI: 1.15–3.78, $p = 0.015$, $p^2 = 0.554$) remained statistically significant in PCR-RFLP studies. We also found a significant association of TB in polymerase chain reaction sequence-specific oligonucleotide probe (PCR-SSOP) studies for two comparison models: the allele model (B/A: OR = 1.72, 95% CI: 1.10–2.66, $p = 0.016$, $p^2 = 0.604$) and the dominant model (AA + AB vs. BB: OR = 0.12, 95% CI: 0.02–0.96, $p = 0.045$) (Table III).

**MBL2 rs1800451 polymorphism**

Excluding the study of Selvaraj et al., which was not consistent with HWE (Table IV) [36], nine
A

| Study ID  | OR (95% CI) Weight (%) |
|-----------|------------------------|
| Asian:    |                        |
| Chen 2015 | 1.23 (0.97–1.57) 14.97 |
| Chen 2014 | 1.52 (1.07–2.17) 6.34  |
| Liu 2006  | 1.30 (0.88–1.92) 5.54  |
| Subtotal  | 1.31 (1.10–1.57) 26.85 |
| American: |                        |
| da Cruz 2013 | 1.35 (0.88–2.06) 4.64  |
| Subtotal  | 1.35 (0.88–2.06) 4.64  |
| African:  |                        |
| Thye 2011 | 0.95 (0.83–1.09) 56.43 |
| Søborg 2007 | 0.96 (0.72–1.28) 12.08 |
| Subtotal  | 0.95 (0.85–1.08) 68.51 |
| Overall   | 1.07 (0.97–1.18) 100.00 |

B

| Study ID  | OR (95% CI) Weight (%) |
|-----------|------------------------|
| Asian:    |                        |
| Chen 2015 | 0.76 (0.57–1.00) 17.04 |
| Chen 2014 | 0.54 (0.36–0.81) 9.24  |
| Liu 2006  | 0.74 (0.47–1.16) 6.38  |
| Subtotal  | 0.69 (0.56–0.85) 32.65 |
| American: |                        |
| da Cruz 2013 | 0.65 (0.39–1.06) 5.85  |
| Subtotal  | 0.65 (0.39–1.06) 5.85  |
| African:  |                        |
| Thye 2011 | 1.06 (0.91–1.23) 51.81 |
| Søborg 2007 | 1.01 (0.71–1.42) 9.69  |
| Subtotal  | 1.05 (0.92–1.20) 61.50 |
| Overall   | 0.91 (0.82–1.01) 100.00 |

Figure 2. Forest plot of tuberculosis risk associated with MBL2 rs7096206 polymorphism (A – allele comparison: C allele vs. G allele, B – recessive comparison: GG vs. GC + CC)
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case-control studies (3950 cases and 4465 controls) on the relationship between the rs1800451 polymorphism and the risk of TB were included in the meta-analysis. For rs1800451, the estimated OR1 (CC vs. AA), OR2 (AC vs. AA) and OR3 (CC vs. AC) were 0.833 (95% CI: 0.697–0.995), 0.955 (95% CI: 0.802–1.138) and 0.894 (95% CI: 0.747–1.070) (Table II). Thus, we mainly pooled ORs for allele comparison and the codominant genetic model in the subgroup analysis by ethnicity. The pooled examination revealed a significant association between rs1800451 polymorphism and the risk of tuberculosis (C/A: OR = 0.93, 95% CI: 0.86–1.00, \( p = 0.050 \), \( p_a = 0.152 \)) (Table III).

When performing a meta-analysis by ethnicity, increased risk of TB was found among Americans (C/A: OR = 2.59, 95% CI: 1.23–5.43, \( p = 0.012 \), \( p^* = 0.727 \); AC vs. AA + CC: OR = 2.70, 95% CI: 1.27–5.74, \( p = 0.010 \), \( p^* = 0.698 \)), and a protective effect was observed among Africans (C/A: OR = 0.92, 95% CI: 0.86–0.99, \( p = 0.035 \), \( p^* = 0.460 \)) (Table III, Figure 4). For the subgroup analysis by genotyping method, the allele comparison (C/A: OR = 2.75, 95% CI: 1.21–6.28, \( p = 0.016 \)) and recessive genetic model (AC vs. AA + CC: OR = 2.90, 95% CI: 1.25–6.73, \( p = 0.013 \)) remained statistically significant in sequencing studies. We also found a decreased risk of TB in PCR-SSOP studies in the allele model (C/A: OR = 0.79, 95% CI: 0.64–0.98, \( p = 0.031 \)) (Table III).

MBL2 exon 1 polymorphisms

Excluding the study of Søborg et al., which was not consistent with HWE (Table IV) [28], eleven case-control studies (1980 cases and 2213 controls) on the relationship between the MBL2 exon 1 polymorphisms (wild-type (AA) versus any MBL2 variant allele (OA/OO) genotype) and the risk of TB were included in the meta-analysis. The estimated OR1 (OO vs. AA), OR2 (AO vs. AA) and OR3 (OO vs. AO) were 1.973 (95% CI: 0.935–4.163), 1.179 (95% CI: 0.852–1.633) and 1.547 (95% CI: 0.954–2.507) (Table II). Thus, we mainly pooled OR for allele comparison and the recessive genetic model in the subgroup analysis by ethnicity. Overall, a significant association between exon 1 gene polymorphisms and the risk of TB was observed (AA + AO vs. OO: OR = 0.49, 95% CI: 0.26–0.93, \( p = 0.028 \), \( p^* = 0.000 \)) (Table III). The results of subgroup analysis based on ethnicity indicated that MBL2 O allele carriers (AO and/or OO) in Asian populations were associated with increased risk of TB (O/A: OR = 1.34, 95% CI: 1.10–1.64, \( p = 0.004 \), \( p^* = 0.211 \)), and a significant protective effect was detected between MBL2 exon 1 polymorphisms and TB risk in Americans under recessive models (AA vs. AO + OO: OR = 0.71, 95% CI: 0.51–0.99, \( p = 0.041 \), \( p^* = 0.129 \), suggesting genetic diversity among ethnicities (Table III, Figure 5). For the subgroup analysis by genotyping method, the allele

| Study ID | OR (95% CI) | Weight (%) |
|---------|-------------|------------|
| American: | | |
| da Cruz 2013 | 1.27 (0.75–2.15) | 5.16 |
| Subtotal | 1.27 (0.75–2.15) | 5.16 |
| Asian: | | |
| Singla 2011 | 0.72 (0.56–0.91) | 33.94 |
| Li 2011 | 1.50 (1.00–2.27) | 7.90 |
| Alagarasu 2008 | 0.88 (0.62–1.25) | 14.36 |
| Liu 2006 | 1.31 (0.84–2.03) | 7.15 |
| Selvaraj 1999 | 1.80 (1.11–2.89) | 5.72 |
| Subtotal (\( I^2 = 78.9\% \), \( p = 0.001 \)) | 0.99 (0.85–1.16) | 69.07 |
| African: | | |
| De Wit 2011 | 0.80 (0.55–1.18) | 12.05 |
| Søborg 2007 | 0.57 (0.25–1.31) | 3.18 |
| Bellamy 1998 | 1.29 (0.41–4.10) | 1.08 |
| Subtotal (\( I^2 = 0.0\% \), \( p = 0.522 \)) | 0.79 (0.57–1.10) | 16.30 |
| European: | | |
| Cosar 2008 | 0.28 (0.09–0.82) | 3.58 |
| Ozbas-Gerceker 2003 | 0.51 (0.27–0.95) | 5.89 |
| Subtotal (\( I^2 = 0.0\% \), \( p = 0.338 \)) | 0.42 (0.25–0.72) | 9.47 |
| Overall (\( I^2 = 68.3\% \), \( p < 0.001 \)) | 0.92 (0.81–1.05) | 100.00 |

Figure 3. Forest plot of tuberculosis risk associated with MBL2 rs1800450 polymorphism (allele comparison: B allele vs. A allele)
Figure 4. Forest plot of tuberculosis risk associated with MBL2 rs1800451 polymorphism (A – allele comparison: C allele vs. A allele. B – codominant comparison: AC vs. AA + CC)
Figure 5. Forest plot of tuberculosis risk associated with MBL2 exon 1 polymorphisms. A – Comparison of the MBL2 exon 1 polymorphisms allele comparison (O allele vs. A allele) with tuberculosis risk. B – Comparison of the MBL2 exon 1 polymorphisms recessive comparison (AA vs. AO + OO) with tuberculosis risk.
Comparison (O/A: OR = 1.62, 95% CI: 1.07–2.44, \( p = 0.022 \)) and recessive genetic model (AA vs. AO + OO: OR = 0.54, 95% CI: 0.33–0.88, \( p = 0.013 \)) remained statistically significant in sequencing studies (Table III).

**Sensitivity analysis**

Sensitivity analysis was performed to evaluate the root of heterogeneity by sequentially excluding individual studies. Statistically similar results were obtained for the allele model of rs5030737, rs1800450, rs1800451, MBL2 A/O, rs11003125, rs7096206 and rs7095891 by excluding studies one after another. This indicates that this meta-analysis is stable and reliable in nature.

**Publication bias**

The publication bias of included studies was assessed by Begg's funnel plot and Egger's test. The funnel plots did not reveal any evidence of obvious asymmetry under the allele model (A/O, \( p = 0.161 \); rs1800450, \( p = 0.732 \); rs1800451, \( p = 0.754 \); rs5030737, \( p = 0.764 \); rs7095891, \( p = 0.296 \); rs11003125, \( p = 0.462 \); rs7096206, \( p = 0.452 \)), and Egger's test also did not show any statistically significant evidence of publication bias under the allele model (A/O, \( p = 0.547 \); rs1800450, \( p = 0.946 \); rs1800451, \( p = 0.538 \); rs5030737, \( p = 0.682 \); rs7095891, \( p = 0.051 \); rs11003125, \( p = 0.109 \); rs7096206, \( p = 0.049 \)), which indicated low risk of publication bias in this meta-analysis (Figure 6).

**Discussion**

The outcome of TB is modulated by the environment as well as *Mycobacterium tuberculosis* and hosts. Many investigations have confirmed that the genes for host susceptibility to disease appear to play the critical roles in the development of TB. MBL2 is an innate immune protein and plays a critical role in tuberculosis infection, which is elevated in active tuberculosis infection as part of an acute-phase reaction [8]. Several polymorphisms of the MBL2 gene have been identified, six of which are known for their functional effect (rs1800450, rs5030737, rs1800451, rs11003125, rs7096206 and rs7095891). A number of studies have been performed to investigate the impact of MBL2 gene polymorphism on susceptibility to TB in different regions and among different races. However, the clinical studies have yielded inconsistent results. To investigate these controversial issues further, we performed a comprehensive meta-analysis on the correlation between the MBL2 polymorphisms and tuberculosis risk.

Based on a meta-analysis of 12 studies, Denholm et al. found no statistically significant association between MBL2 genotype and pulmonary TB infection [38]. Our meta-analysis, which involved 22 studies including 7056 cases and 7764 controls, showed that the MBL2 rs7096206 and A/O polymorphisms were risk factors of TB in Asian, but not in European or African populations. Because the included participants of this meta-analysis mainly came from China and India, the results may be applicable only to East Asians. Therefore, people from East Asia who carry the MBL2 rs7096206 and A/O gene polymorphisms may have a 31% and 34% increased TB risk, respectively.

Interestingly, the total results showed that MBL2 rs1800451 polymorphism was a protective factor, which means that persons who carry the MBL2 rs1800451 gene polymorphism may have a 7% decreased TB risk compared with the control group. In contrast, the subgroup analysis indicated that the MBL2 rs1800451 polymorphism might increase TB risk in Americans, but not in Asians or Africans. The contradiction between the overall result and subgroup result may reflect the small number of included participants belonging to the American group. Hence, more well-designed studies are required, focusing on more ethnicities to confirm the results in the future. Unfortunately, the present results suggest no significant association between the MBL2 rs5030737, rs11003125 and rs7095891 gene polymorphisms and TB risk.

Some limitations of this meta-analysis should be considered. First, some detailed information, such as age, HIV status, and types of TB (pulmonary TB and extra-pulmonary TB), was not all available, which limited our further assessment by performing stratified analysis based on those confounding factors. Secondly, some SNPs such as rs7095891 contained only 3 studies in this systematic analysis. The limited number of studies and small sample sizes restricted the power of the study. Thirdly, the significant between-study heterogeneity detected in some comparisons, different patient populations and different sources of controls may contribute to the heterogeneity. Fourthly, three studies deviated from HWE [20, 28, 36], making the sample a poor representation. We therefore conducted the meta-analyses after exclusion of these studies. However, this exclusion did not materially affect the results. Fifthly, our study could not assess gene-gene and gene-environment interactions due to the limited information of included studies. Finally, the small sample sizes in some subgroup analyses may have limited statistical power to estimate the possible risk for MBL2 polymorphisms. Only two articles on Americans were included, so we must be careful when we refer to the result. Thus, more studies are needed to confirm the association between MBL2 and tuberculosis risk, especially in different ethnic populations.
In conclusion, our meta-analysis suggested that MBL2 rs7096206 and A/O gene polymorphisms may be risk factors contributing to TB susceptibility, especially in East Asia. However, the MBL2 rs1800451 gene polymorphism may be a protective factor for TB risk. The findings of our study could be pooled in a future meta-analysis of multiple studies, providing more power to detect an association. It is critical that larger scale and well-designed epidemiological studies based on different ethnicities be performed to re-evaluate the association. Moreover, additional future studies should include more detailed information concerning the potential confound-
ing factors and multiple SNPs to extend our investigations.

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Conflict of interest

The authors declare no conflict of interest.

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