Association between polymorphisms in mannose-binding lectin 2 gene with pulmonary tuberculosis susceptibility

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Abstract

Background: Mannose-binding lectin (MBL2) is considered to play a role in the human innate immune response to tuberculosis (TB) infections, and 4 common single nucleotide polymorphisms (SNPs) may be associated with pulmonary tuberculosis (PTB) risk. To examine these potential associations, we performed a comprehensive analysis to assess the relationships between MBL2 polymorphisms and PTB.

Methods: The PubMed, Embase, and SinoMed databases were searched for articles published prior to June 13, 2019. Odds ratios with 95% confidence intervals were calculated to evaluate the strength of the relationships.

Results: There were 37 case-control studies examining the effects of the four SNPs in MBL2 on PTB. A positive association between rs11003125 and PTB risk was observed in the hospital-based subgroup. Moreover, for the combined polymorphism and PTB risk, positive associations were detected not only in the total population but also in those with Asian origins across all source of control subgroups. No associations were found for rs7096206 or rs7095891.

Conclusions: Our current study indicated that several SNPs in MBL2 may be associated with susceptibility to PTB.

Keywords: Mannose-binding lectin, Pulmonary tuberculosis, Polymorphism, Meta-analysis, Susceptibility

Background

Tuberculosis (TB) is a global public health issue that poses serious threats to human health. It has been estimated that 1/3 of the world’s population may be infected with tubercle bacilli, but only 1/10 of individuals infected with Mycobacterium tuberculosis go on to develop TB [1], suggesting that there are inherent individual differences in susceptibility to TB that may be related to nutrition, constitution, specific and nonspecific resistance, and genetic susceptibility [2–6]. In fact, many studies have focused on the genetic variations within genes that increase the risk of TB [7, 8]. Previous case-control association studies have revealed that several human genes might be correlated with TB in certain populations. These genes include interferon-gamma (IFNG), vitamin D receptor (VDR), solute carrier family 11a member 1 (SLC11A1, which is also known as NRAMP1), and mannose-binding lectin (MBL2) [9–12].

The MBL2 gene, which is a member of the complement system, has been hypothesized to play a dual role in the innate immune response to infections by activating the classical lectin pathway and by phagocytosis [13, 14]. MBL and other soluble pattern recognition molecules [collectin-10, collectin-11, and ficolins (ficolin-1, ficolin-2, and ficolin-3)] act as mediators of host defense and participate in the maintenance of tissue homeostasis. They can bind to conserved pathogen-specific structures and altered self-antigens, and they form complexes with pentraxins to
modulate innate immune functions. All these molecules exhibit distinct expressions in different tissue compartments, but all of them are found to varying degrees in the circulatory system. A common feature of these molecules is their ability to interact with a set of serine proteases named MASP (MASP-1, MASP-2, and MASP-3) [15]. Human MBL is encoded by MBL2 on chromosome 10 (10q11.2-q21; OMIM 154545), which comprises four exons. MBL2 is reported to have several genetic polymorphisms that are commonly associated with MBL serum levels. Three point substitutions, located at codons 52, 54, and 57 in exon 1, are supposed to disrupt the assembly of MBL trimers or accelerate the degradation of the protein, thereby causing a decrease in the functional activity of MBL in the serum. These mutations are frequently referred to as variants D, B, and C, respectively, and they are collectively known as O, while A is the wild type. In addition, three other point substitutions have been reported in the nonstructural region: two at positions −550 (H/L variants) and −221 (X/Y variants) in the promoter region and one point mutation at position −4 (P/Q variants) in the 5′-untranslated (UTR) region [16–18].

Many epidemiologic studies, including meta-analyses, suggest that there are relationships between MBL2 gene variations and pulmonary TB (PTB) risk [10, 16, 17, 19–47]. However, ambiguous conclusions have been reported; thus, it is necessary to perform an undated meta-analysis that includes a reanalysis of relevant studies.

Materials and methods

Search strategy and criteria

The PubMed, Embase, and SinoMed databases were searched for articles published prior to June 13, 2019, using the keywords “tuberculosis,” “TB,” “polymorphism,” and “mannose binding lectin 2 or MBL2”. A total of 163 papers were identified, 30 of which were consistent with our criteria. The inclusion criteria for papers were as follows: (i) examined the relationship between PTB susceptibility and MBL variations, (ii) case-control study, and (iii) contained a complete number of genotypes (MM + MW + WW) among cases and controls. The exclusion criteria were as follows: (i) no control group, (ii) incomplete genotype frequency data, (iii) duplicate publication, and (iv) controls did not meet the Hardy-Weinberg equilibrium (HWE) standards.

Data extraction

The essential data are listed as follows: first author name, publication year, original country, race, total samples of case/control, each genotype in cases/controls, source of control and genotype methods. Race was classified as Caucasian, Asian, African, or mixed. The source of control subgroups included population-based (PB) and hospital-based (HB) subgroups. The type of TB included total TB, PTB, and EPTB.

Quality score assessment (NOS)

The NOS was used to assess the quality of each study and to assess the various aspects of the methodology, including the selection of cases, the comparability of groups and the determination of exposure. The total score on the NOS ranges from 0 to 9 stars. Studies with scores greater than 7 are considered high-quality studies [48].

Statistical analysis

We used 95% CIs to measure the correlation between SNPs in MBL2 and PTB risk based on the genotype frequency of the case and control groups. The Z-test was used to determine the statistical significance of the correlations. The heterogeneity between the studies was evaluated using a Q-test based on the χ² method. In the Q-test, a P value greater than 0.05 indicates that there is a lack of heterogeneity between the studies. Because the Q-statistic does not reveal the statistical significance of the heterogeneity, the I² test was applied to better assess the extent of heterogeneity. As a guide, I² values are divided into three categories (<25%, 25–50%, ≥50%), corresponding to low risk, medium risk, and high risk, respectively [49]. If P ≤ 0.05 or I² ≥ 50%, a random effects model was adopted; otherwise, a fixed effects model was used [50, 51]. We accessed the association between SNPs in MBL2 and PTB risk by testing the allelic contrast (X versus Y for rs7096206; L versus H for rs11003125; Q versus P for rs7095891; and O versus A for A/O combined SNP), heterozygote comparison (XY versus YY for rs7096206; LH versus HH for rs11003125; QP versus PP for rs7095891; and OA versus AA for A/O combined SNP), homozygote comparison (XX versus YY for rs7096206; LL versus HH for rs11003125; QQ versus PP for rs7095891; and OO versus AA for A/O combined SNP), recessive genetic model (XX versus XY + YY for rs7096206; LL versus LH + HH for rs11003125; and QQ versus QP + PP for rs7095891; OO versus OA + AA for A/O combined SNP) and dominant genetic model (XX + XY versus YY for rs7096206; LL + LH versus HH for rs11003125; QQ + QP versus PP for rs7095891; and OO + OA versus AA for A/O combined SNP). Sensitivity analysis was applied to assess the stability of the results. The HWE was evaluated by Pearson’s χ² test, and P = 0.05 was considered statistically significant [52]. Publication bias was assessed by both Egger’s and Begg’s tests [53]. All statistical tests were carried out by version 11.0 of the Stata Software (StataCorp LP, College Station, TX, USA).

Genotyping methods

Methods for genotyping the SNPs in MBL2 were derived from the literature in Table 1.
| Ref No | First author | Year | Origin | Ethnicity | Type | Disease | Source of Type | Case Control | Case Control | Method | NOS |
|--------|--------------|------|--------|-----------|------|----------|---------------|--------------|--------------|---------|-----|
| rs7096206 | Liu [10] | 2006 | China | Asian | PB | PTB | | 141 | 212 | 6 | 44 | 91 | 7 | 54 | 151 | 0.43 | PCR-SSP/PCR-SSOP | 7 |
| rs11003125 | Thye [41] | 2011 | Germany | Caucasian | PB | PTB | | 1843 | 2174 | 308 | 7 | 185 | 147 | 5 | 297 | 1871 | 0.577 | DASH-FRET | 7 |
| rs7095891 | Chen [25] | 2015 | China | Asian | PB | PTB | | 226 | 141 | 58 | 101 | 67 | 42 | 10 | 89 | < 0.01 | PCR-SSP | 6 |
|         | Zhang [44] | 2011 | China | Asian | HB | PTB | | 220 | 213 | 29 | 75 | 116 | 51 | 76 | 86 | < 0.01 | PCR-SSP | 6 |
| rs709890 | Liu [10] | 2006 | China | Asian | PB | PTB | | 1953 | 2230 | 308 | 902 | 725 | 319 | 1086 | 825 | 0.205 | DASH-FRET | 7 |
|         | Zhou [46] | 2011 | China | Asian | HB | PTB | | 226 | 231 | 24 | 90 | 112 | 25 | 89 | 117 | 0.201 | PCR-SSP | 6 |
|         | Feng [30] | 2016 | China | Asian | HB | PTB | | 99 | 97 | 7 | 34 | 80 | 8 | 24 | 65 | 0.141 | Taqman | 5 |
|         | Wang [42] | 2009 | China | Asian | PB | PTB | | 449 | 249 | 13 | 114 | 332 | 2 | 64 | 183 | 0.155 | AMLR | 7 |
|         | Zhang [44] | 2011 | China | Asian | HB | PTB | | 220 | 213 | 17 | 31 | 172 | 21 | 36 | 156 | < 0.01 | PCR-SSP | 6 |
|         | Amiri [20] | 2017 | Iran | Asian | PB | PTB | | 100 | 100 | 3 | 21 | 76 | 5 | 26 | 69 | 0.233 | PCR-SSP | 7 |
| First author     | Year | Origin | Ethnicity | Source of Type | Case | Control | Case | Control | Method          | NOS |
|------------------|------|--------|-----------|----------------|------|---------|------|---------|-----------------|-----|
| Garcia-Laorden   | 2006 | Spain  | Caucasian | HB total       | 106  | 344     | 3    | 33      | 70              | 27  | 134  | 183            | 0.721 | PCR-RFLP       | 6   |
| Søborg           | 2003 | Denmark| Caucasian | PB total/White | 59   | 250     | 4    | 18      | 37              | 7   | 86   | 157            | 0.235 | PCR-SSP        | 8   |
| Søborg           | 2003 | Denmark| Caucasian | PB total/Nonwhite | 50   | 250     | 4    | 12      | 34              | 7   | 86   | 157            | 0.235 | PCR-SSP        | 8   |
| Capparelli       | 2009 | Italy  | Caucasian | PTB            | 274  | 288     | 61   | 158     | 55              | 10  | 112  | 166            | 0.087 | Sequencing     | 6   |
| Garcia-Gasalla   | 2014 | Spain  | Caucasian | HB total       | 76   | 106     | 4    | 24      | 48              | 1   | 34   | 71             | 0.156 | PCR-SSP        | 6   |
| Alagarasu        | 2007 | India  | Asian     | HB total       | 275  | 146     | 25   | 87      | 145             | 7   | 53   | 86             | 0.747 | PCR-SSP        | 6   |
| Zhao             | 2014 | China  | Asian     | PTB            | 900  | 870     | 101  | 279     | 520             | 53  | 303  | 514            | 0.352 | PCR-RFLP       | 7   |
| Li [34]          | 2011 | China  | Asian     | PTB            | 231  | 226     | 3    | 57      | 171             | 3   | 37   | 186            | 0.461 | PCR-SSP        | 7   |
| Li [33]          | 2009 | China  | Asian     | PTB            | 141  | 152     | 6    | 56      | 79              | 8   | 38   | 106            | 0.075 | PCR-SSP        | 6   |
| Liu              | 2006 | China  | Asian     | PTB            | 141  | 214     | 2    | 34      | 103             | 4   | 42   | 166            | 0.487 | PCR-SSP/PCR-SSOP | 7   |
| Zhou             | 2012 | China  | Asian     | PTB            | 226  | 231     | 14   | 106     | 106             | 5   | 80   | 146            | 0.114 | PCR-SSP        | 6   |
| Liu              | 2015 | China  | Asian     | PTB            | 112  | 120     | 3    | 29      | 80              | 2   | 22   | 96             | 0.576 | PCR-RFLP       | 7   |
| Fang [29]        | 2011 | China  | Asian     | PTB            | 100  | 100     | 1    | 25      | 74              | 0   | 25   | 75             | 0.153 | PCR-RFLP       | 6   |
| Wu               | 2017 | China  | Asian     | PTB            | 151  | 454     | 2    | 37      | 112             | 8   | 97   | 348            | 0.681 | PCR-RFLP/PCR-SSCP | 6   |
| Singla           | 2011 | India  | Asian     | PTB            | 286  | 397     | 11   | 100     | 175             | 35  | 155  | 207            | 0.441 | PCR-RFLP       | 6   |
| Singla           | 2011 | India  | Asian     | EPTB           | 71   | 397     | 2    | 26      | 43              | 35  | 155  | 207            | 0.441 | PCR-RFLP       | 6   |
| Özbab-Gerçeker   | 2003 | Turkey | Caucasian | PB PTB         | 49   | 100     | 0    | 9       | 40              | 4   | 20   | 76             | 0.09  | PCR             | 7   |
| Wit [28]         | 2011 | South Africa | African | PB total | 499  | 313     | 2    | 134     | 363             | 0   | 102  | 211            | < 0.01 | PCR-RFLP       | 8   |
| Feng [30]        | 2016 | China  | Asian     | PTB            | 381  | 267     | 14   | 177     | 190             | 12  | 176  | 79             | < 0.01 | Taqman         | 5   |
| Wang             | 2009 | China  | Asian     | PTB            | 449  | 249     | 4    | 133     | 312             | 3   | 82   | 164            | 0.038 | AMLR           | 7   |
| Thye [41]        | 2011 | Germany| Caucasian | PB PTB         | 1893 | 1040    | 193  | 815     | 885             | 126  | 426  | 488            | 0.029 | DASH-FRET      | 7   |
| Ceylan           | 2017 | Turkey | Caucasian | HB total      | 69   | 70      | 8    | 13      | 48              | 12  | 11   | 47             | < 0.01 | PCR-RFLP       | 7   |
| Amiri            | 2017 | Iran   | Asian     | PB PTB         | 100  | 100     | 2    | 29      | 69              | 1   | 27   | 72             | 0.374 | PCR-SSP        | 7   |
| Cruz [27]        | 2013 | Brazil | Caucasian | HB PTB         | 119  | 148     | 7    | 41      | 71              | 6   | 34   | 108            | 0.129 | Sequencing     | 6   |
| Cruz [27]        | 2013 | Brazil | Caucasian | EPTB          | 36   | 148     | 1    | 14      | 21              | 6   | 34   | 108            | 0.129 | Sequencing     | 6   |
| Selvaraj [37]    | 1999 | India  | Asian     | PB PTB         | 202  | 109     | 22   | 73      | 107             | 2   | 39   | 68             | 0.175 | PCR-RFLP       | 7   |
| Araújo           | 2013 | Brazil | Caucasian | HB PTB         | 133  | 159     | 2    | 47      | 84              | 2   | 56   | 101            | 0.058 | PCR             | 6   |
| Araújo           | 2013 | Brazil | Caucasian | EPTB          | 34   | 159     | 1    | 15      | 18              | 2   | 56   | 101            | 0.058 | PCR             | 6   |
| Fitness [31]     | 2004 | UK     | Caucasian | PB total      | 322  | 546     | 12   | 105     | 205             | 24  | 160  | 362            | 0.245 | fluorescence PCR/ARMS-PCR | 7   |
| Søborg           | 2007 | Denmark| Caucasian | PB PTB         | 443  | 432     | 22   | 132     | 289             | 30  | 131  | 271            | 0.013 | PCR-RFLP/PCR-SSP | 7   |

HWE Hardy-Weinberg equilibrium; M Mutated allele; W Wide type allele; HB Hospital-based; PB Population-based; TB Tuberculosis; PTB Pulmonary TB; EPTB Extra-pulmonary TB; PCR-FIP Polymerase chain reaction and restrictive fragment length polymorphism; SSP Sequence specific primer; SSOP Sequence-specific oligonucleotide probe; SSCP Single-strand conformation polymorphism; DASH-FRET Dynamic allele-specific hybridization with fluorescence resonance energy transfer; AMLR Allelic-specific multiplex ligase-detection reaction; ARMS Amplification refractory mutation system; NOS Newcastle-Ottawa scale
Results

Study characteristics

A total of 163 articles were retrieved from the PubMed, Embase, and SinoMed databases by using various combinations of the abovementioned keywords. Fifty-three duplicate articles were removed after screening the titles, as shown in Fig. 1. Another 57 articles were removed because they did not contain relevant information. Next, the full texts of 53 articles were evaluated, and 23 additional articles were excluded because they contained duplicate data (4), they were meta-analyses/systematic reviews (10), they examined polymorphisms in other genes (2), or they were not case-control studies (7). Finally, 30 articles examining the association between the 4 SNPs in MBL2 and TB susceptibility were included (12 articles for rs7096206, 11 for rs11003125, 8 for rs7095891 and 30 for the A/O SNP). After filtering out studies that met our exclusion criteria, 9 different case-control studies were included for rs7096206, 6 for rs11003125, 7 for rs7095891, and 15 for the A/O SNP (Table 1). Overall, 37 case-control studies with 12,052 cases of PTB as well as 13,905 controls were included [10, 17, 19–47]. The controls were mainly healthy individuals.

Quantitative synthesis

The associations between the 4 SNPs in MBL2 and PTB risk are shown in Table 2 and Figs. 2, 3, 4, and 5. For rs11003125, although negative associations were found in the total sample and in ethnic subgroups, a positive association was detected in the HB analysis (OR: 1.40,
Table 2 Total and stratified subgroup analysis for 4 SNPs in MBL2 and PTB susceptibility

| Variables | N | Case/Control | M-allele vs. W-allele | MW vs. WW | MM vs. WW | MM + MW vs. WW | MM vs. MW + WW |
|-----------|---|--------------|----------------------|----------|----------|----------------|----------------|
| rs7096206 (XX/XY/YY) | 9 | 3235/3767 | 1.14(0.92–1.40) | 0.001 0.226 690 | 1.17(0.89–1.53) | 0.000 0.264 73.5 | 1.14(0.83–1.57) | 0.470 0.419 0.0 |
| Ethnicity | 7 | 1257/1439 | 1.13(0.86–1.49) | 0.036 0.368 660 | 1.13(0.80–1.61) | 0.002 0.482 71.8 | 1.30(0.84–1.99) | 0.308 0.238 16.0 |
| Caucasian | 2 | 1978/2328 | 1.11(0.75–1.64) | 0.001 0.860 67.1 | 1.24(0.65–2.37) | 0.022 0.504 80.9 | 0.97(0.60–1.58) | 0.922 0.908 0.0 |
| Source of control | 4 | 481/810 | 1.01(0.58–1.76) | 0.001 0.937 82.4 | 0.93(0.48–1.83) | 0.001 0.840 82.5 | 1.77(0.96–3.27) | 0.159 0.069 42.0 |
| PB | 5 | 2754/2957 | 1.04(0.94–1.16) | 0.001 0.114 43.6 | 1.27(0.95–1.70) | 0.012 0.112 69.1 | 0.97(0.67–1.42) | 0.054 0.885 0.0 |
| rs11003125 (LL/LH/HH) | 6 | 2533/2949 | 0.99(0.80–1.22) | 0.001 0.900 662 | 0.93(0.70–1.25) | 0.001 0.049 64.9 | 0.95(0.59–1.49) | 0.001 0.808 56.2 |
| Ethnicity | 4 | 571/627 | 0.87(0.67–1.13) | 0.001 0.293 57.1 | 0.78(0.60–1.01) | 0.001 0.171 40.1 | 0.80(0.49–1.31) | 0.087 0.370 54.4 |
| Caucasian | 2 | 1962/2322 | 1.14(0.98–1.33) | 0.001 0.093 48.8 | 1.12(0.94–1.34) | 0.001 0.330 19.0 | 1.55(0.81–2.96) | 0.018 0.182 43.9 |
| Source of control | 2 | 218/237 | 1.40(1.06–1.85) | 0.001 0.017 0.0 | 1.61(0.94–2.78) | 0.001 0.822 0.0 | 1.91(1.07–3.40) | 0.071 0.029 0.0 |
| Ethnicity | 4 | 2315/2712 | 0.87(0.70–1.08) | 0.001 0.217 62.6 | 0.82(0.59–1.13) | 0.001 0.048 219.6 | 0.70(0.50–0.98) | 0.037 0.039 0.0 |
| Source of control | 6 | 1623/1617 | 1.24(1.10–1.40) | 0.001 0.020 85.4 | 1.37(1.06–1.77) | 0.001 0.713 58.9 | 1.10(0.93–1.31) | 0.086 0.262 0.0 |
| rs7095891 (QQ/QP/PP) | 7 | 3119/3524 | 1.02(0.95–1.11) | 0.001 0.552 34.3 | 0.97(0.87–1.08) | 0.001 0.713 58.9 | 1.10(0.93–1.31) | 0.086 0.262 0.0 |
| Ethnicity | 6 | 1166/1334 | 1.01(0.86–1.18) | 0.001 0.924 44.9 | 0.98(0.81–1.19) | 0.001 0.592 84.3 | 1.14(0.70–1.85) | 0.042 0.589 0.0 |
| Source of control | 3 | 476/773 | 1.19(0.79–1.81) | 0.001 0.046 66.0 | 1.07(0.82–1.41) | 0.001 0.341 0.0 | 1.35(0.77–2.35) | 0.048 0.290 47.7 |
| PB | 4 | 2643/2791 | 1.01(0.93–1.10) | 0.001 0.080 0.0 | 0.95(0.84–1.07) | 0.001 0.817 0.0 | 1.08(0.90–1.30) | 0.078 0.406 0.0 |
| AA/AO/OO | 15 | 3165/3665 | 1.33(1.05–1.70) | 0.001 0.202 85.4 | 1.37(1.06–1.77) | 0.001 0.018 79.8 | 1.82(0.94–3.51) | 0.000 0.073 79.2 |
| Ethnicity | 11 | 2590/2970 | 1.26(1.04–1.52) | 0.001 0.017 61.7 | 1.24(1.01–1.52) | 0.005 0.044 60.3 | 1.51(0.85–2.65) | 0.005 0.157 60.7 |
| Caucasian | 4 | 575/695 | 1.45(0.69–3.06) | 0.001 0.331 92.0 | 1.67(0.76–3.67) | 0.001 0.197 88.4 | 2.26(0.35–14.56) | 0.000 0.393 85.6 |
| Source of control | 9 | 1425/2048 | 1.39(0.93–2.08) | 0.001 0.106 90.8 | 1.52(1.03–2.24) | 0.001 0.037 84.7 | 1.84(0.61–5.56) | 0.000 0.280 87.0 |
| PB | 6 | 1623/1617 | 1.24(1.10–1.40) | 0.001 0.021 199.9 | 1.05(0.90–1.23) | 0.001 0.543 28.6 | 1.94(1.42–2.56) | 0.000 0.030 11.7 |

M Mutated allele; W Wide type allele; HB Hospital-based; PB Population-based; P**; value of Q-test for heterogeneity test; P**; Z-test for the statistical significance of the OR

M: Mutated allele; W: Wide type allele; HB: Hospital-based; PB: Population-based; P*: Value of Q-test for heterogeneity test; P: Z-test for the statistical significance of the OR
**Fig. 2** Forest plot of PTB risk associated with *MBL2* rs11003125 polymorphism (LL vs. HH) in the subgroup about source of control. Square and horizontal lines correspond to specific OR or 95% CI. The area of the squares reflects the weight (inverse proportional variance). Diamonds represent the total OR or 95% CI.

**Fig. 3** Forest plot of PTB risk associated with *MBL2* A/O combined polymorphism (allelic contrast) by the whole samples and ethnicity.
95% CI: 1.06–1.85, \( P \) (heterogeneity): 0.755, \( P \): 0.017, in the allelic contrast; OR: 1.91, 95% CI: 1.07–3.40, \( P \) (heterogeneity): 0.571, \( P \): 0.029, in the homozygous comparison model (Fig. 2); and OR: 1.73, 95% CI: 1.05–2.86, \( P \) (heterogeneity): 0.633, \( P \): 0.033 in the dominant genetic model.

For the A/O combined SNP (AA/AO/OO) polymorphism, the O allele had a positive association with PTB risk in the total sample (heterozygote comparison: OR: 1.37, 95% CI: 1.06–1.7, \( P < 0.001 \) for heterogeneity, \( P \): 0.018; dominant genetic model: OR: 1.41, 95% CI: 1.06–1.86, \( P < 0.001 \) for heterogeneity, \( P \): 0.017; allelic contrast: OR: 1.33, 95% CI: 1.05–1.70, \( P < 0.001 \) for heterogeneity, \( P \): 0.020, Fig. 3). In the subgroup analyses for different ethnicities, a similar significant association was detected for the Asian population (allelic contrast: OR: 1.26, 95% CI: 1.04–1.52, \( P \): 0.001 for heterogeneity, \( P \): 0.017, Fig. 3; heterozygote comparison: OR: 1.24, 95% CI: 1.01–1.52, \( P \): 0.005 for heterogeneity, \( P \): 0.044; dominant genetic model: OR: 1.28, 95% CI: 1.04–1.57, \( P \): 0.003 for heterogeneity, \( P \): 0.021, Fig. 3). Finally, in the subgroup analyses for different sources of control, PTB risk was significantly and positively associated with PB (e.g., allelic contrast: OR: 1.24, 95% CI: 1.10–1.40, \( P \): 0.283 for heterogeneity, \( P \): 0.001, Fig. 4) and HB studies (e.g., heterozygote comparison: OR: 1.52, 95% CI: 1.03–2.24, \( P < 0.001 \) for heterogeneity, \( P \): 0.037, Fig. 5). In addition, no associations were observed for either rs7096206 or rs7095891, which indicated that heterogeneity might exist for these two SNPs (Table 2).

**Publication bias and sensitivity analysis**

Begg’s test and Egger’s test were used to evaluate the publication bias of the included literature. The shape of the funnel plot did not show obvious asymmetry, and Egger’s test did not indicate publication bias (Fig. 6a-h, Table 3). We used sensitivity analysis to determine whether changes in a single study affected the outcome. For rs7096206 and O/A SNPs, two separate studies (Thye et al. for rs7096206, Fig. 7a and Capparelli et al. for O/A SNP, Fig. 7d) may have influenced the total OR according to the sensitivity analysis (data not shown).

**Discussion**

Previous studies on the incidence of TB primarily focused on tubercle bacilli and the effects of environmental risk factors (such as sex, previous group TB, smoking status, drinking status, dominant status, age, group size, rainfall, immigration, number of eligible rovers, public health, economic, conservation importance). In recent decades, the effect of host susceptibility genes on TB has been increasingly recognized along with the
development of genetic susceptibility. However, recent studies on the associations between SNPs in MBL2 and TB have produced different and even contradictory results. Some studies have indicated that mutations in the promoter and exon 1 of MBL2 may lead to the decline of MBL expression in the serum, while lower serum MBL levels can increase infections caused by tubercle bacilli [40, 54], indicating that polymorphisms in MBL2 may exert a protective effect against TB. Other studies have indicated that higher serum levels of MBL can reduce tubercle bacilli infections, which are associated with wild-type MBL2 alleles [5, 27, 55]. These studies suggest that MBL2 variants may increase the risk for TB.

Several meta-analyses have focused on the relationships between MBL2 polymorphisms and susceptibility to TB; however, each meta-analysis has its own conclusion and merits. Cao et al. analyzed 22 studies to assess the effect of MBL2 polymorphisms on TB risk. The rs1800451 polymorphism was associated with decreased TB risk in both the total sample and in some ethnic groups; in addition, A/O, rs7096206 and rs1800450 were likely only related to risk in some ethnic groups [56]. The analysis did not differentiate between the total sample and PTB subgroups. Tong et al. suggested that rs1800450 and rs5030737 polymorphisms were risk factors for susceptibility to TB; nevertheless, rs7095891 and rs1800451 polymorphisms acted as protective factors against TB [57]. Their study did not analyze the differences between the total sample and subgroups of TB. Denholm et al. [16] examined 12 case-control studies of HIV-negative patients and two studies of HIV-positive patients to determine the association of the MBL2 structural gene variants (B, C and D, referred to collectively as O, and A is the wild-type) with TB susceptibility. They did not find a significant association between the MBL2 genotype and PTB infection. By contrast, a meta-analysis of four studies examining MBL levels and susceptibility to TB found a significant association of high MBL levels with susceptibility to TB, although increased serum MBL levels due to the acute-phase reaction could not be ruled out. In addition, Areeshi et al. [58] found a statistically significant association of the C (rs1800451) alleles and genotypes with a reduced risk of TB in the overall population. No significant associations were observed in other variant sites (such as rs1800450, rs5030737, rs7096206, rs11003125, rs7095891 and combined rs1800450 O-alleles). Stratified analysis by ethnicity showed a decreased risk of TB in the African population for rs1800450 (B) and rs1800451 (C) alleles and genotypes. However, no association was observed between other MBL2 polymorphisms and TB risk in Asians. The results indicated a protective role of alleles.
B and C in TB infection. Finally, Shi et al. [59] indicated that individuals carrying the MBL2 codon 54 B allele had an increased risk of TB compared with AA homozygotes, whereas rs7095891 was possibly not associated with TB risk in Chinese.

To our knowledge, the current study is an updated systematic analysis exploring the relationships between MBL2 variants and PTB susceptibility. This analysis involved approximately 12,052 patients with PTB and 13,905 healthy samples. The most important finding of our study was that the rs11003125 L-allele and the A/O combined SNP were risk factors for PTB susceptibility in the HB subgroup, which was similar to findings from a previous meta-analysis. The O allele was also a risk factor for PTB in the Asian and PB subgroups. The aforementioned conclusions were novel concepts that

Fig. 6 Begg’s funnel plot for publication bias test (allelic contrast: a of rs7096206 \( z = -0.19, P = 0.851 \); c of rs11003125 \( z = -0.21, P = 0.835 \); e of rs 7,095,891 \( z = -1.65, P = 0.099 \) and g of A/O combined SNP \( z = -0.74, P = 0.458 \)). Each point represents a separate study for the indicated association. Log \( \log \) OR, natural logarithm of OR. Horizontal line, mean effect size. Egger’s publication bias plot (allelic contrast: b of rs7096206 \( t = 0.56, P = 0.592 \); d of rs11003125 \( t = -0.25, P = 0.812 \); f of rs 7,095,891 \( t = -0.12, P = 0.912 \) and h of A/O combined SNP \( t = -0.02, P = 0.988 \)).
have not been found in previously published meta-analyses.

The above contradictory results from previous meta-analyses further emphasize the controversy about the effect of MBL2 variants on susceptibility to TB. One possible explanation for this effect is that different polymorphisms may have different effects on gene function, resulting in changes in PTB susceptibility. Second, the complex interaction between several genetic and environmental factors may involve the development of PTB. We think these conflicting results among studies and different populations suggests linkage disequilibrium with other nearby genes (e.g., surfactant proteins A1, A2 and D [60] previously associated with TB) rather than a causative association between MBL2 variants and PTB. Third, it is now widely accepted that differences in ethnicities between cases and control measures may be a source of confusion in the compilation of studies. Fourth, research with “negative” results takes longer to publish due to the time-lag bias, and positive research results are published much faster. Fifth, small studies of with “negative” results have never been published, and small studies of similar quality with “positive” results will also be shown in the literature [61–63]. Sixth, rs7096206, rs11003125 and rs7095891 SNPs were not analyzed in the previous three meta-analyses; our study was the first to analyze these SNPs. Furthermore, we focused on PTB but not on total TB or extrapulmonary TB (EPTB), in contrast to previous meta-analyses.

Some limitations in our study should be noted. Initially, we collected all eligible studies; however, the sample size of these studies is not yet large enough, especially in certain ethnic groups. Therefore, not only is the likelihood of I/II type errors high, but there is insufficient statistical capacity to assess the correlations between the 7 SNPs and PTB risk. Second, serum MBL concentration was not assessed in our study, which would have been helpful for detecting and understanding the mechanism of SNPs in the MBL2 gene. Third, other factors such as age, sex, smoking, familial history, disease stage, specific environmental factors and lifestyles should be included. Fourth, only one article [19]

Table 3 Publication bias tests (Begg’s funnel plot and Egger’s test for publication bias test) for 4 SNPs in MBL2.

| Genetic type       | Coefficient | Standard error | t   | P value | 95%CI of intercept | z   | P value |
|--------------------|-------------|----------------|-----|---------|--------------------|-----|---------|
| rs7096206          |             |                |     |         |                    |     |         |
| X-allele vs. Y-allele | 0.719       | 1.282          | 0.56| 0.592   | (−2.312,2.751)     | 0.1 | 0.917   |
| XY vs. YY          | 0.597       | 1.084          | 0.55| 0.599   | (−1.967,3.161)     | −0.1| 1       |
| XX vs. YY          | 0.149       | 0.429          | 0.35| 0.739   | (−0.867,1.615)     | 0.31| 0.754   |
| XX + XY vs. YY     | 0.625       | 1.12           | 0.56| 0.594   | (−0.204,3.274)     | −0.1| 1       |
| XX vs. XY + YY     | 0.147       | 0.434          | 0.34| 0.744   | (−0.878,1.172)     | 0.31| 0.754   |
| rs11003125         |             |                |     |         |                    |     |         |
| L-allele vs. H-allele | −0.597     | 2.35           | −0.25| 0.812  | (−7.122,5.928)     | 0   | 1       |
| LH vs. HH          | −0.477      | 0.808          | −0.59| 0.587  | (−2.721,1.768)     | 0.38| 0.707   |
| LL vs. HH          | 1.899       | 1.558          | 1.22| 0.29   | (−2.426,6.226)     | 0.75| 0.452   |
| LL + LH vs. HH     | −0.495      | 0.899          | −0.55| 0.611  | (−2.993,2.002)     | 0.75| 0.452   |
| LL vs. LH + HH     | −0.15       | 2.385          | −0.06| 0.953  | (−6.772,6.472)     | 0   | 1       |
| rs7095891          |             |                |     |         |                    |     |         |
| Q-allele vs. P-allele | −0.09       | 0.781          | −0.12| 0.912  | (−2.099,1.917)     | 1.5 | 0.133   |
| QP vs. PP          | −0.068      | 0.763          | −0.09| 0.932  | (−2.031,1.893)     | 1.2 | 0.23    |
| QQ vs. PP          | −0.064      | 0.15           | −0.43| 0.687  | (−0.451,0.322)     | 0.3 | 0.764   |
| QQ + QP vs. PP     | −0.077      | 0.775          | −0.1 | 0.924  | (−2.069,1.914)     | 1.2 | 0.23    |
| QQ vs. QP + PP     | −0.065      | 0.149          | −0.44| 0.68   | (−0.448,0.317)     | 0.3 | 0.764   |
| AA/AO/OO           |             |                |     |         |                    |     |         |
| A-allele vs. O-allele | −0.026     | 1.703          | −0.02| 0.988  | (−3.706,3.653)     | 0.69| 0.488   |
| AO vs. OO          | 0.469       | 1.407          | 0.33| 0.744  | (−2.571,3.511)     | 0.4 | 0.692   |
| AA vs. OO          | 0.113       | 0.422          | 0.27| 0.792  | (−0.798,1.025)     | 1.39| 0.166   |
| AA+AO vs. OO       | 0.513       | 1.398          | 0.37| 0.72   | (−2.507,3.533)     | 0.59| 0.533   |
| AA vs. AO + OO     | 0.091       | 0.436          | 0.21| 0.839  | (−0.852,1.033)     | 1.39| 0.166    |
included the subgroups of HIV- and HIV+, anti-TNF drugs, and DM; these groups were not evaluated in other included studies, so we could not analyze the associations within the above groups because of missing information. Fifth, the included studies had a high amount of heterogeneity. In addition, we cannot know whether patients had latent tuberculosis. Finally, all included studies were epidemiological surveys; there were no plausible biological hypotheses or mechanistic studies. We aimed to determine whether there is a relationship between \( MBL2 \) structural gene variants and susceptibility to PTB. Further studies should aim to overcome these limitations.

In summary, our study indicated that the rs11003125 and A/O-combined SNPs in \( MBL2 \) may be related to PTB risk. Larger sample sizes and additional gene-environment interactions should be considered in future studies.

**Fig. 7** Sensitivity analysis between 4 SNPs in \( MBL2 \) and PTB risk (allelic contrast: a for rs7096206; b for rs11003125; c for rs7095891 and d for A/O combined SNP)

**Abbreviations**

- MBL: Mannose-binding lectin; PTB: Pulmonary tuberculosis; ORs: Odds ratios; CIs: Confidence intervals; SNPs: Single nucleotide polymorphisms; HWE: Hardy-Weinberg equilibrium

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WS and LX conceived the study. YL searched the databases and extracted the data. DZ analyzed the data. WZ wrote the draft of the paper. WZ reviewed the manuscript. The author(s) read and approved the final manuscript.

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