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, $p = 0.041$) 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 (C/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 various 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]. Several 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 susceptibility. To our knowledge, this is the most comprehensive meta-analysis to investigate the associations of the *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, genotype 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 χ^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 Begg'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.

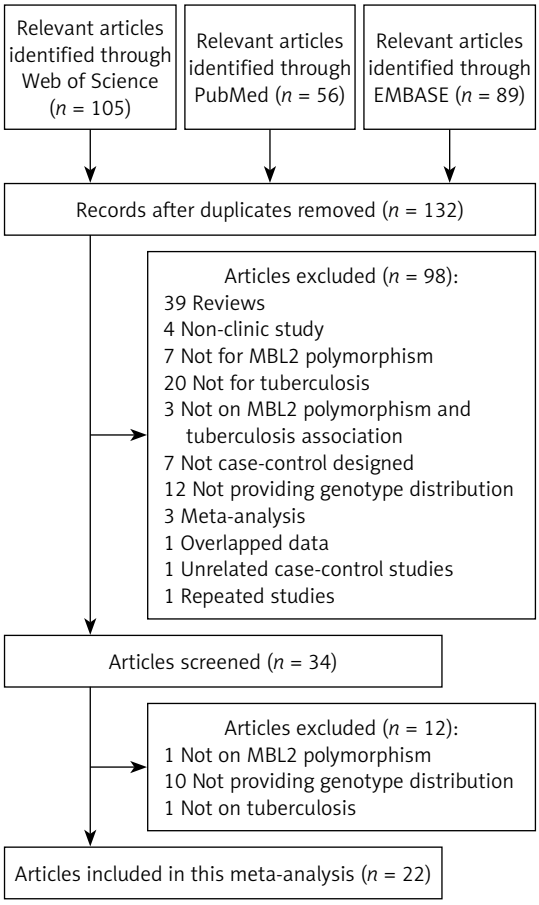

Figure 1. Flowchart for study selection

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, $p = 0.100$, $p^a = 0.061$; GG vs. GC + CC: OR = 0.80, 95% CI: 0.64–1.01, $p = 0.058$, $p^a = 0.010$) (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, $p = 0.003$, $p^a = 0.634$; GG vs. GC + CC: OR = 0.69, 95% CI: 0.56–0.85, $p < 0.001$, $p^a = 0.381$) (Table III, Figure 2). 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, $p = 0.022$, $p^a = 0.152$) remained statistically significant in polymerase chain reaction sequence-specific primer (PCR-SSP) studies (Table III).

MBL2 rs11003125 polymorphism

Four case-control studies (2370 cases and 2760 controls) on the relationship between the

Table I. Main characteristics of included studies summarized for the meta-analysis

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
					Part of the body	Cases	Controls	Cases	Controls					
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	Garcıa-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	Cases: positive: 33%; Control: positive: 2.5%	rs7096206 rs1800450 rs5030737 rs1800451 rs11003125 rs7095891
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	Pyro-sequencing, 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

Table I. Cont.

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
					Part of the body	Cases	Controls	Cases	Controls					
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	Cappar-elli	Italy	Italian	PB	Pulmonary tuberculosis	277	288	47 ±17	40 ±17	Chest radiography and sputum smears	PCR-se-quencing	Household contacted	Negative	rs11003125 rs7096206 rs7095891
2008	Cosar	Turkish	Turkish	PB	Pulmonary tuberculosis (27) and extra-pulmo-nary tuberculosis (17)	44	99	7.02 ±4.5	7.38 ±4.07	Culture, clinical and radiological findings	PCR-RFLP	Healthy persons	Negative	rs1800450
2007	Alaga-rasu	India	Indian (Dravid-ian)	PB	Pulmonary tuberculosis (226) and extra-pulmonary tuberculosis (31)	257	297	35.37 ±10.8	32.87 ±8.76	Clinical, radiograph-ic, bacteriological findings, AFB smear	PCR-se-quencing	Healthy persons	Cases: positive (109); negative (148) Control: positive (151); negative (146)	rs5030737 rs1800450 rs1800451
2007	Soborg	Tanza-nia	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, radiograph-ic, AFB smear and culture	PCR-SSOP	Healthy persons	Negative	rs5030737 rs1800450 rs1800451

Table I. Cont.

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
					Part of the body	Cases	Controls	Cases	Controls					
2006	Garcia-Laorden	Spain	Spanish	PB	Pulmonary tuberculosis	233	344	\	\	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	\	\	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	\	\	Culture positive or microscopy	PCR-SSP	Healthy persons	Negative	rs5030737 rs1800450 rs1800451
2003	Ozbas-Gercecker	Turkey	Turkish	PB	Pulmonary tuberculosis	118	100	(27–47); (6 m–3 y)	(25–45)	Not available	PCR-RFLP	Healthy persons	Negative	rs1800450
2000	Selvaraj	India	Indian	PB	Pulmonary tuberculosis	67	44	37.1 ±1.7	38.5 ±1.5	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^a	
rs7096206 X/Y:				Recessive
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:				Recessive
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:				Codominant
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:				Recessive
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:				Dominant
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:				Codominant
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:				Recessive
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^a – P-value of Q-test for heterogeneity test.

rs11003125 polymorphisms 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, $p^a < 0.001$; CG vs. CC + GG: OR = 1.00, 95% CI: 0.87–1.16, p = 0.946, p^a = 0.290) (Table III).

MBL2 rs7095891 polymorphism

Three case-control studies (2325 cases and 2668 controls) on the relationship between the 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

Table III. Meta-analysis results

	N	Case/control	Allele comparison	*P*	*P*[a]	Genetic model comparison		*P*	*P*[a]
			OR (95% CI)				OR (95% CI)		
rs7096206									
Total	6595	3154/3441	1.15 (0.97–1.36)	0.100	0.061	Dominant	1.09 (0.78–1.52)	0.610	0.957
						Recessive	0.80 (0.64–1.01)	0.058	0.010
Ethnicity:									
Asian	1696	849/847	**1.31 (1.10–1.57)***	**0.003**[Δ]	0.634	Recessive	**0.69 (0.56–0.85)***	**0.000**[Δ]	0.381
American	303	155/148	1.35 (0.88–2.07)*	0.173	/	Recessive	0.65 (0.39–1.06)*	0.084	/
African	4596	2150/2446	0.95 (0.85–1.08)*	0.451	0.955	Recessive	1.05 (0.92–1.20)*	0.476	0.788
Genotype methods:									
PCR-SSP	2253	1140/1113	1.21 (1.04–1.40)*	0.016	0.241	Recessive	**0.76 (0.59–0.96)***	**0.022**[Δ]	0.152
Sequencing	4342	2014/2328	1.06 (0.78–1.46)	0.699	0.131	Recessive	0.88 (0.55–1.40)	0.585	0.061
A/O									
Total	4193	1980/2213	1.35 (0.96–1.88)	0.083	0.000	Dominant	**0.49 (0.26–0.93)**	**0.028**[Δ]	0.000
						Recessive	0.74 (0.49–1.10)	0.132	0.000
Ethnicity:									
European	1321	583/738	1.49 (0.49–4.52)	0.480	0.000	Recessive	0.60 (0.15–2.41)	0.474	0.000
American	629	322/307	1.32 (1.00–1.75)*	0.054	0.182	Recessive	**0.71 (0.51–0.99)***	**0.041**[Δ]	0.129
Asian	1065	569/496	**1.34 (1.10–1.64)***	**0.004**[Δ]	0.211	Recessive	0.79 (0.62–1.02)*	0.066	0.285
African	1178	506/672	0.83 (0.67–1.02)*	0.076	/	Recessive	1.30 (0.99–1.71)*	0.062	/
Genotype methods:									
PCR-SSP	541	185/356	1.15 (0.84–1.57)*	0.392	0.056	Recessive	1.00 (0.69–1.46)*	0.988	0.496
Sequencing	303	155/148	**1.62 (1.07–2.44)***	**0.022**[Δ]	/	Recessive	**0.54 (0.33–0.88)***	**0.013**[Δ]	/
PCR-RFLP	997	462/535	1.05 (0.64–1.71)	0.845	0.021	Recessive	0.97 (0.58–1.62)	0.893	0.046
PCR-SSOP	1236	647/589	1.26 (0.73–2.18)	0.401	0.003	Recessive	0.43 (0.08–2.19)	0.568	0.019
PCR-Sequencing	1116	531/585	1.97 (0.64–6.13)	0.240	0.000	Recessive	0.85 (0.49–1.10)	0.307	0.000

Table III. Cont.

	N	Case/control	Allele comparison	*P*	*P*[a]	Genetic model comparison		*P*	*P*[a]
			OR (95% CI)				OR (95% CI)		
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	/	Codominant	0.98 (0.62–1.54)*	0.920	/
Asian	810	372/438	0.83 (0.68–1.02)*	0.078	0.440	Codominant	0.81 (0.61–1.07)*	0.139	0.533
African	4017	1843/2174	1.09 (0.92–1.30)*	0.296	/	Codominant	1.10 (0.92–1.32)*	0.280	/
Genotype methods:									
Sequencing	303	155/148	0.73 (0.51–1.03)*	0.074	/	Codominant	0.98 (0.62–1.54)*	0.920	/
Pyro-sequencing	4017	1843/2174	1.09 (0.92–1.30)*	0.296	/	Codominant	1.10 (0.92–1.32)*	0.280	/
PCR-SSP	810	372/438	0.83 (0.68–1.02)*	0.078	0.440	Codominant	0.81 (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	Recessive	0.78 (0.40–1.53)*	0.467	0.950
African	1443	759/684	0.84 (0.45–1.54)*	0.564	0.359	Recessive	1.20 (0.65–2.23)*	0.560	0.353
Asian	684	386/298	1.45 (0.91–2.32)*	0.114	0.631	Recessive	0.81 (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

Table III. Cont.

	N	Case/control	Allele comparison	*P*	*P*[a]	Genetic model comparison		*P*	*P*[a]
			OR (95% CI)				OR (95% CI)		
Ethnicity:									
American	303	155/148	1.27 (0.75–2.15)	0.379	/	Dominant	1.58 (0.26–9.61)*	0.618	/
Asian	2329	1143/1186	1.14 (0.79–1.63)	0.482	0.001	Dominant	0.84 (0.36–1.94)	0.688	0.037
African	1963	1021/942	0.79 (0.57–1.10)*	0.160	0.522	Dominant	0.90 (0.14–5.75)*	0.914	0.314
European	361	162/199	**0.42 (0.25–0.72)***	**0.001**[Δ]	0.338	Dominant	3.34 (0.55–20.33)*	0.190	0.520
Genotype methods:									
Sequencing	303	155/148	1.27 (0.75–2.15)*	0.379	/	Dominant	1.58 (0.26–9.61)*	0.618	/
PCR-RFLP	2100	1099/1001	**0.68 (0.57–0.83)***	**< 0.001**[Δ]	0.224	Dominant	**2.08 (1.15–3.78)***	**0.015**[Δ]	0.554
PCR-SSP	1691	760/931	1.18 (0.92–1.51)*	0.186	0.155	Dominant	0.77 (0.33–1.77)*	0.533	0.700
PCR-sequencing	459	212/247	0.88 (0.62–1.25)*	0.475	/	Dominant	0.70 (0.30–1.66)*	0.422	/
PCR-SSOP	393	407/297	**1.72 (1.10–2.66)***	**0.016**[Δ]	0.604	Dominant	**0.12 (0.02–0.96)***	**0.045**[Δ]	/
rs1800451									
Total	8415	3950/4465	**0.93 (0.86–1.00)***	**0.050**[Δ]	0.152	Codominant	0.97 (0.88–1.07)*	0.563	0.113
Ethnicity:									
American	512	261/251	**2.59 (1.23–5.43)***	**0.012**[Δ]	0.727	Codominant	**2.70 (1.27–5.74)***	**0.010**[Δ]	0.698
African	7540	3518/4022	**0.92 (0.86–0.99)***	**0.035**[Δ]	0.460	Codominant	0.96 (0.88–1.06)*	0.472	0.509
Asian	363	171/192	0.70 (0.37–1.34)*	0.288	/	Codominant	0.73 (0.36–1.48)*	0.377	/
Genotype methods:									
Sequencing	303	155/148	**2.75 (1.21–6.28)***	**0.016**[Δ]	/	Codominant	**2.90 (1.25–6.73)***	**0.013**[Δ]	/
PCR-RFLP	1746	847/899	1.02 (0.82–1.26)*	0.877	0.492	Codominant	1.07 (0.84–1.36)*	0.604	0.362
Pyro-sequencing	4129	1893/2236	0.93 (0.85–1.02)*	0.118	/	Codominant	0.97 (0.86–1.10)*	0.679	/
PCR-sequencing	363	171/192	0.71 (0.37–1.34)*	0.288	/	Codominant	0.73 (0.36–1.48)*	0.377	/
PCR-SSP	1071	498/573	0.95 (0.74–1.21)*	0.661	0.590	Codominant	0.91 (0.68–1.23)*	0.552	0.178
PCR-SSOP	803	386/417	**0.79 (0.64–0.98)***	**0.031**[Δ]	/	Codominant	0.82 (0.62–1.08)*	0.166	/

Table III. Cont.

	N	Case/control	Allele comparison OR (95% CI)	*P*	P^a	Genetic model comparison	OR (95% CI)	*P*	P^a
rs7095891									
Total	4993	2325/2668	1.02 (0.93–1.11)*	0.707	0.585	Dominant	0.90 (0.76–1.06)*	0.212	0.814
						Recessive	1.02 (0.91–1.15)*	0.723	0.731
Ethnicity:									
African	4183	1953/2230	1.03 (0.94–1.12)*	0.531	/	Recessive	1.01 (0.89–1.14)*	0.932	/
Asian	810	372/438	0.86 (0.62–1.20)*	0.377	0.830	Recessive	1.16 (0.81–1.67)*	0.408	0.799
Genotype methods:									
Pyro-sequencing	4183	1953/2230	1.03 (0.94–1.12)*	0.531	/	Recessive	1.01 (0.89–1.14)*	0.932	/
PCR-SSP	810	372/438	0.86 (0.62–1.20)*	0.377	0.830	Recessive	1.16 (0.81–1.67)*	0.408	0.799

*N – number of comparisons, OR – odds ratio, P-value for OR; P^a – P-value of Q-test for heterogeneity test; bold type: OR with statistical significance; $^ap < 0.05$, considered statistically significant; *Fixed-effect model was used when p-value for heterogeneity test > 0.1.*

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, $p = 0.707$, $p^a = 0.585$; CC vs. CT + TT: OR = 1.02, 95% CI: 0.91–1.15, $p = 0.723$, $p^a = 0.731$) (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, $p = 0.225$, $p^a = 0.787$; AA vs. AD + DD: OR = 0.90, 95% CI: 0.66–1.22, $p = 0.489$, $p^a = 0.770$) (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, $p = 0.610$, $p^a = 0.001$; AA + AB vs. BB: OR = 0.83, 95% CI: 0.62–1.10, $p = 0.742$, $p^a = 0.156$) (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, $p = 0.001$, $p^a = 0.338$) (Table III, Figure 3). When stratified by genotyping method, the allele comparison (B/A: OR = 0.68, 95% CI: 0.57–0.83, $p < 0.001$, $p^a = 0.224$) and dominant genetic model (AA + AB vs. BB: OR = 2.08, 95% CI: 1.15–3.78, $p = 0.015$, $p^a = 0.554$) remained statistically significant

Table IV. Distribution of gene polymorphisms of studies included in the meta-analysis

SNP	Year	First author	Cases					Controls					HWE	
													χ^2	*P*-value
rs7096206			**YY**	**YX**	**XX**	**Y**	**X**	**YY**	**YX**	**XX**	**Y**	**X**		
	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	García-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			**LL**	**HL**	**HH**	**L**	**H**	**LL**	**HL**	**HH**	**L**	**H**		
	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			**AA**	**AD**	**DD**	**A**	**D**	**AA**	**AD**	**DD**	**A**	**D**		
	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	
													χ^2	*P*-value
rs1800450			**AA**	**AB**	**BB**	**A**	**B**	**AA**	**AB**	**BB**	**A**	**B**		
	2013	da Cruz	122	31	2	275	35	124	21	3	269	27	3.0756	0.0795
	2013	Araujo	102	50	0	254	50	101	48	0	250	48	5.4927	**0.0191**
	2011	Singla	218	126	13	562	152	207	155	30	569	215	0.0174	0.8951
	2011	de Wit	363	63	2	789	67	211	50	0	472	50	2.9288	0.0870
	2011	Li Y	171	57	3	399	63	186	37	3	409	43	0.5442	0.4607
	2008	Cosar	40	4	0	84	4	71	27	1	169	29	0.8162	0.3663
	2008	Alagarasu	156	44	12	356	68	169	68	10	406	88	0.8828	0.3474
	2007	Soborg	289	9	0	587	9	271	13	1	555	15	3.4429	0.0635
	2006	Liu W	103	34	4	240	42	166	42	4	374	50	0.4824	0.4873
	2003	Soborg	71	16	3	158	22	157	48	3	362	54	0.0960	0.7567
	2003	Ozbas-Gercek-er	101	16	1	218	18	76	20	4	172	28	2.8708	0.0902
	1999	Selvaraj	137	51	14	325	79	84	24	1	192	26	0.2519	0.6157
	1998	Bellamy	198	7	0	403	7	183	5	0	371	5	0.0341	0.8534
rs1800451			**AA**	**AC**	**CC**	**A**	**C**	**AA**	**AC**	**CC**	**A**	**C**		
	2013	da Cruz	133	22	0	288	22	140	8	0	288	8	0.1142	0.7354
	2013	Araujo	102	4	0	208	4	101	2	0	204	2	0.0099	0.9207
	2011	Thye	885	815	193	2585	1201	1002	977	257	2981	1491	0.6457	0.4217
	2011	de Wit	363	56	0	782	56	211	39	0	461	39	1.7892	0.1810
	2008	Alagarasu	156	14	1	326	16	169	21	2	359	25	1.9782	0.1596
	2007	Soborg	289	115	20	693	155	271	112	20	654	152	3.4039	0.0650
	2004	Fitness	205	105	12	515	129	362	160	24	884	208	1.3527	0.2448
	2003	Soborg	71	2	1	144	4	157	13	0	327	13	0.2687	0.6042
	1999	Selvaraj	176	25	1	377	27	103	5	1	211	7	7.4832	**0.0062**
	1998	Bellamy	198	159	29	555	217	183	192	42	558	276	0.6585	0.4171
rs7095891			**PP**	**PQ**	**QQ**	**P**	**Q**	**PP**	**PQ**	**QQ**	**P**	**Q**		
	2011	Thye	725	920	308	2370	1536	825	1086	319	2736	1724	1.6089	0.2046
	2011	Li Y	189	39	3	417	45	181	41	4	403	49	0.8556	0.3550
	2006	Liu W	118	22	1	258	24	171	39	2	381	43	0.0185	0.8918

HWE – Hardy-Weinberg equilibrium.

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, $p = 0.016$, $p^a = 0.604$) 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 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

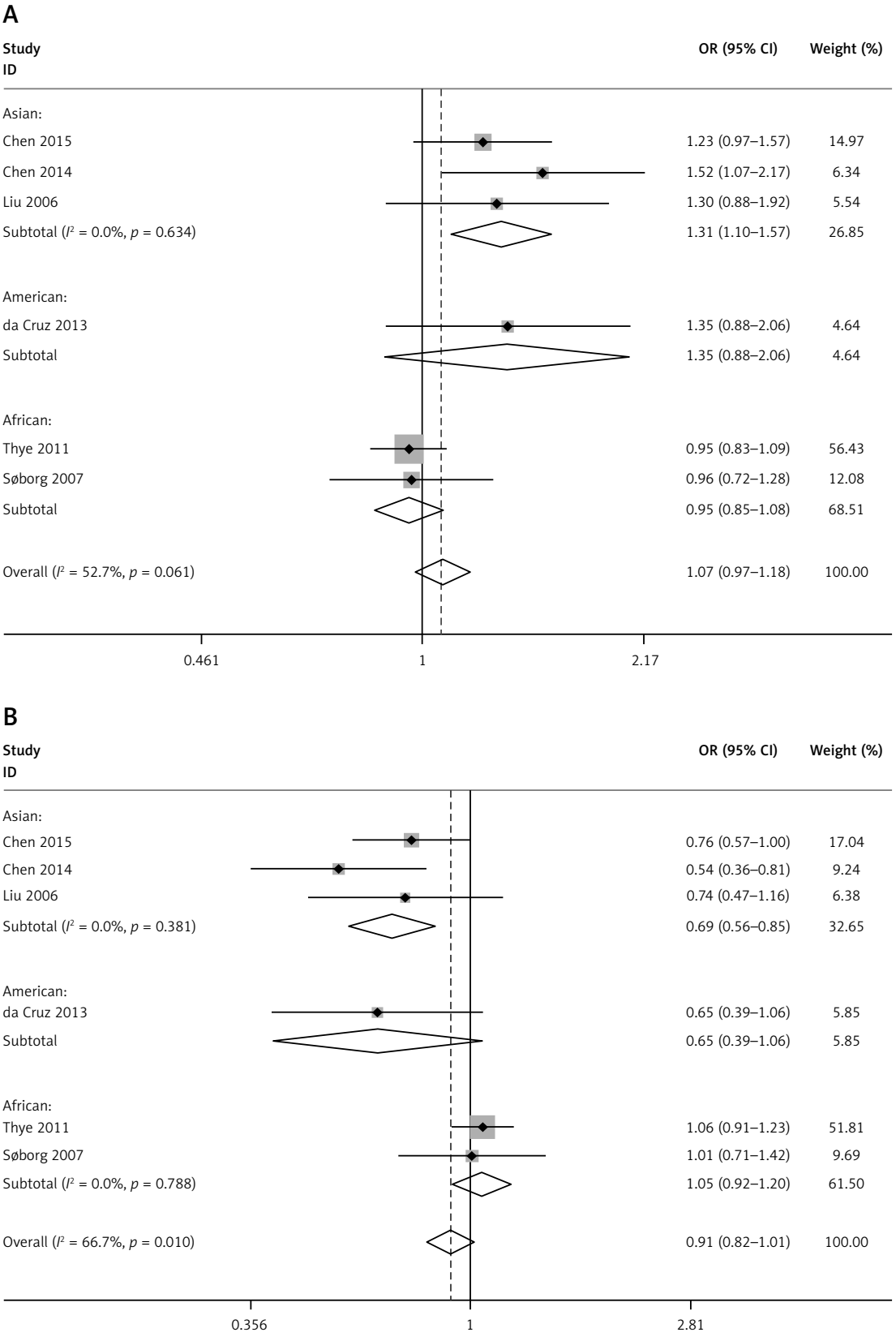

Figure 2. Forest plot of tuberculosis risk associated with MBL2 rs7096206 polymorphism (**A** – allele comparison: C allele vs. G allele. **B** – recessive comparison: GG vs. GC + CC)

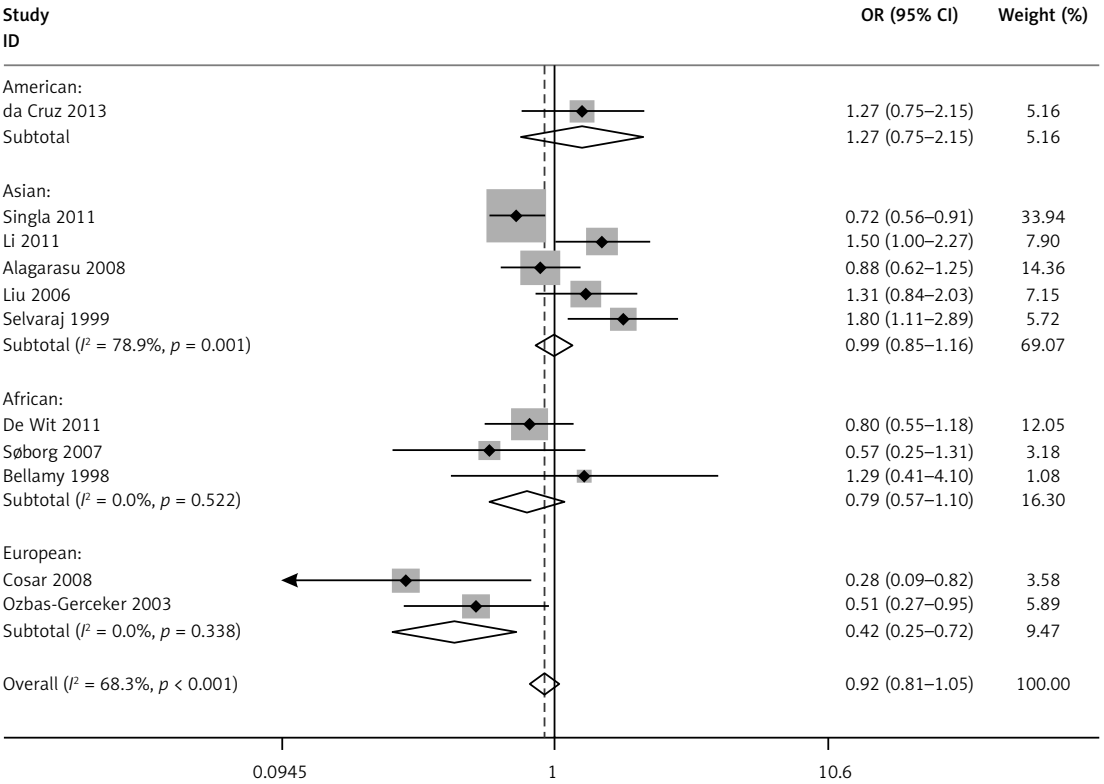

Figure 3. Forest plot of tuberculosis risk associated with MBL2 rs1800450 polymorphism (allele comparison: B allele vs. A allele)

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^a = 0.727; AC vs. AA + CC: OR = 2.70, 95% CI: 1.27–5.74, p = 0.010, p^a = 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^a = 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^a = 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^a = 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^a = 0.129), suggesting genetic diversity among ethnicities (Table III, Figure 5). For the subgroup analysis by genotyping method, the allele 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)

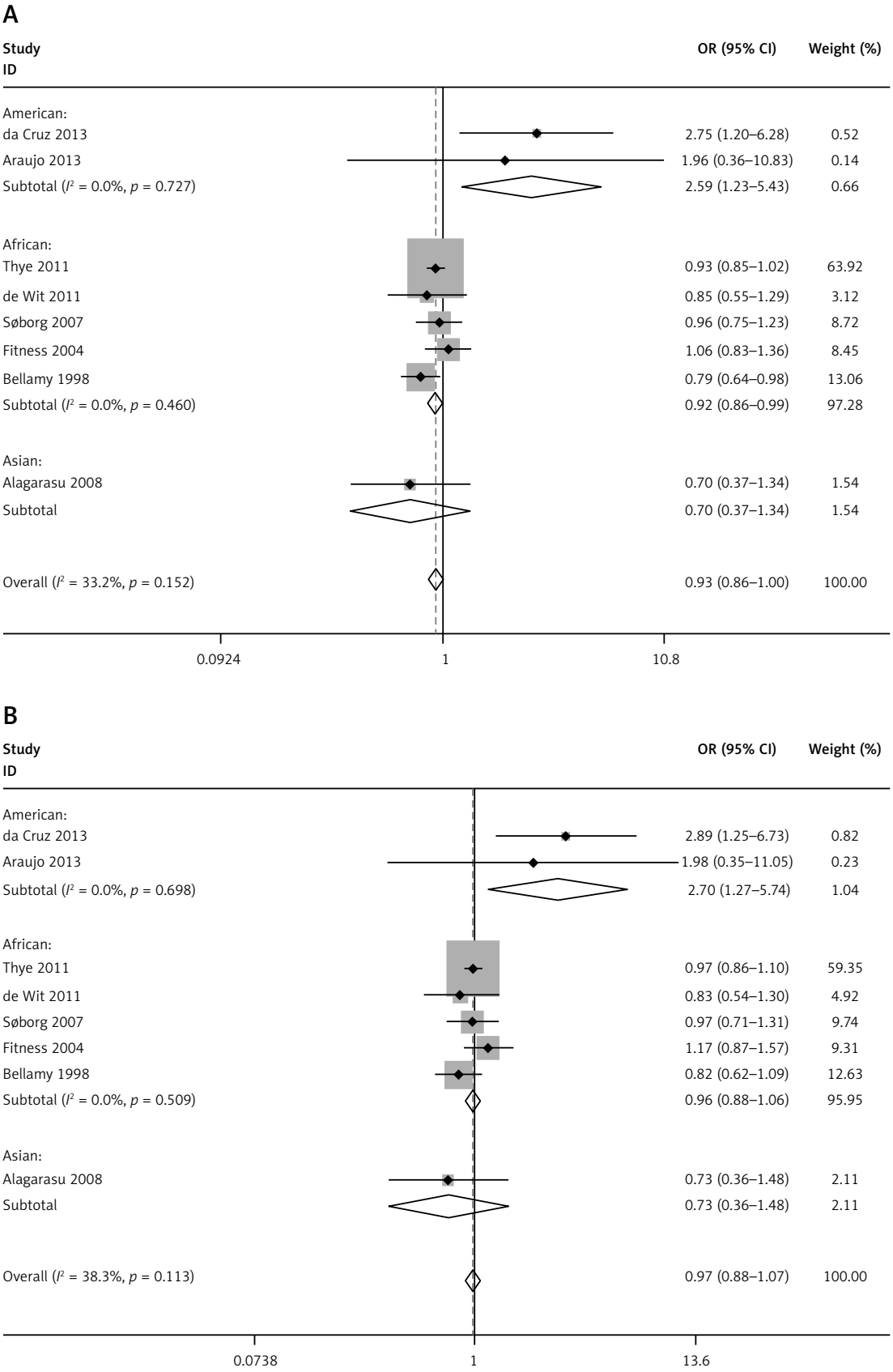

Figure 4. Forest plot of tuberculosis risk associated with MBL2 rs1800451 polymorphism (**A** – allele comparison: C allele vs. A allele. **B** – codominant comparison: AC vs. AA + CC)

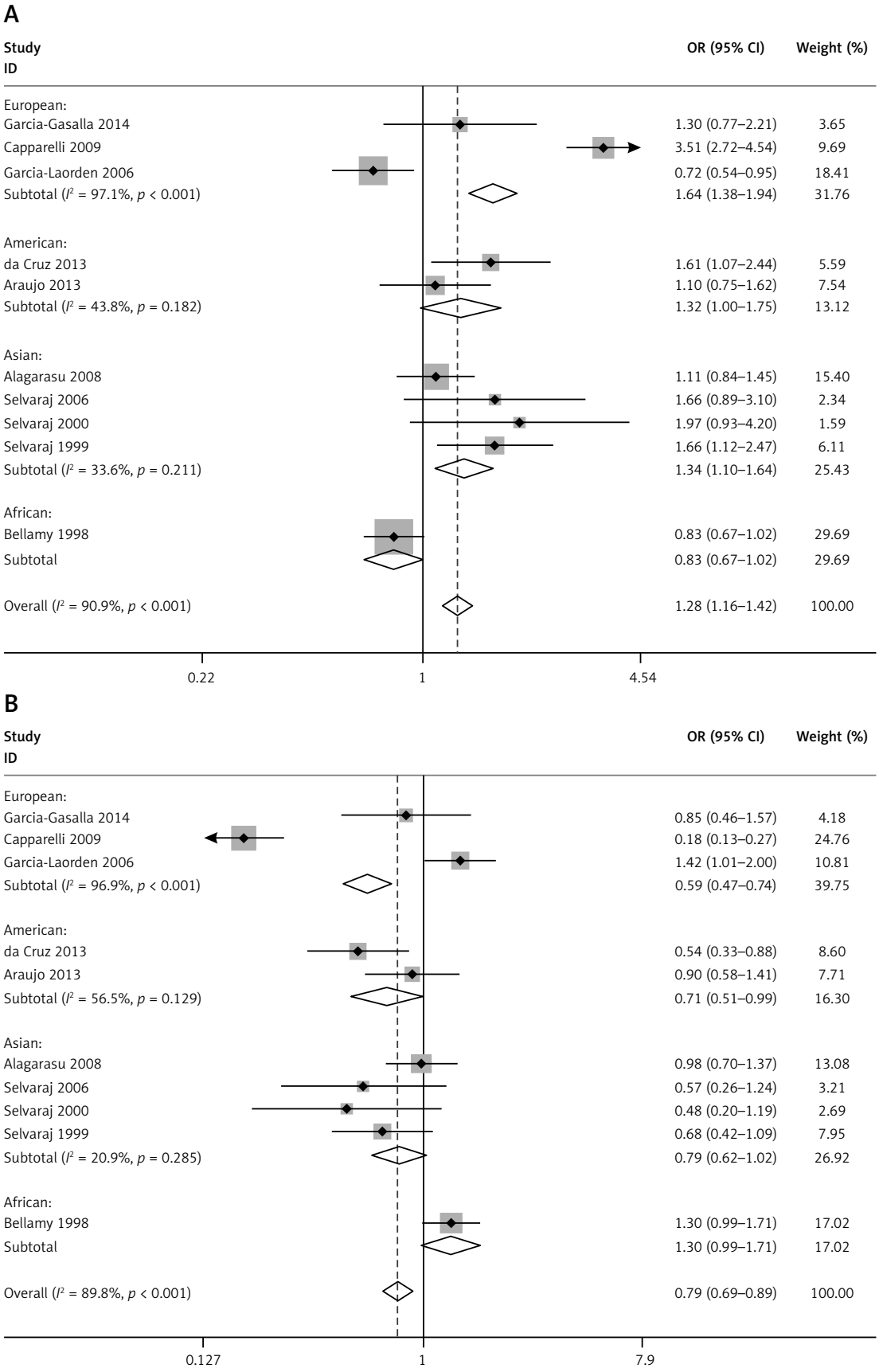

Figure 5. Forest plot of tuberculosis risk associated with MBL2 exon 1 polymorphisms. **A** – Comparison of the MBL2 exon 1 polymorphisms allele comparison (O allele vs. A allele) with tuberculosis risk. **B** – Comparison of the MBL2 exon 1 polymorphisms recessive comparison (AA vs. AO + OO) with tuberculosis risk

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 rs709589). 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

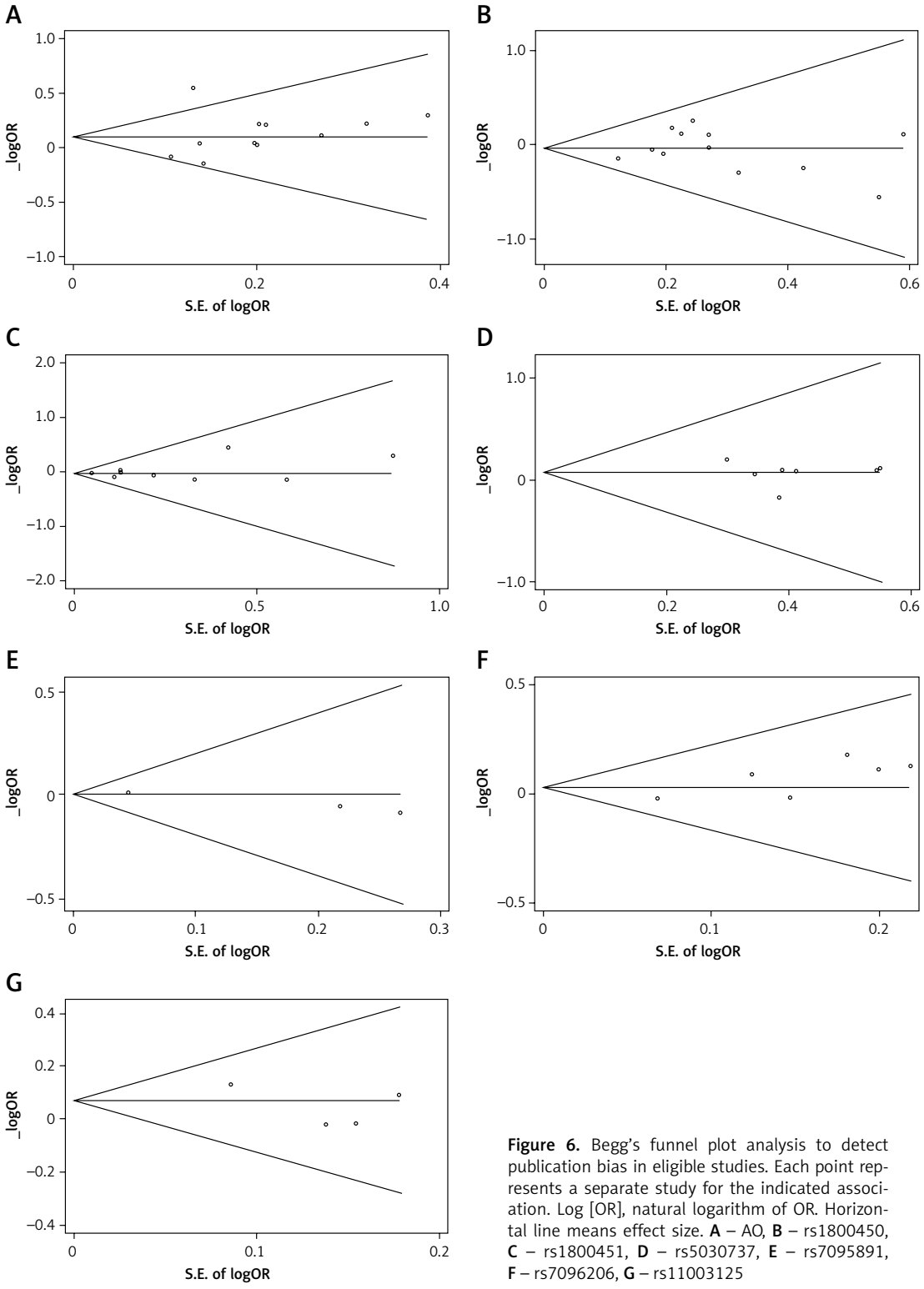

Figure 6. Begg's funnel plot analysis to detect publication bias in eligible studies. Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line means effect size. **A** – AO, **B** – rs1800450, **C** – rs1800451, **D** – rs5030737, **E** – rs7095891, **F** – rs7096206, **G** – rs11003125

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 confounding 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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