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ORIGINAL RESEARCH

Association of MBL2 gene polymorphisms with pulmonary tuberculosis susceptibility: trial sequence meta-analysis as evidence

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Background: Mannose-binding lectin (MBL) or mannose-binding protein (MBP), encoded by MBL2 gene and secreted by the liver, activates complement system through lectin pathway in innate immunity against the host's infection. Conflictingly, a number of MBL2 variants, rs1800450 (A>B), rs1800451 (A>C), rs5030737 (A>D), rs7096206 (Y>X), rs11003125 (H>L), and rs7095891 (P>Q) allele, have been found to be associated with compromised serum levels and pulmonary tuberculosis (PTB) susceptibility. The present meta-analysis study was performed to evaluate the potential association of these MBL2 gene variants with PTB susceptibility.

Materials and methods: A quantitative synthesis was performed on PubMed (Medline), EMBASE, and Google Scholar web database searches. A meta-analysis was performed to calculate the pooled odds ratios and 95% CIs for all the genetic models.

Results: A total of 14 eligible studies were included to analyze their pooled data for associations between alleles, genotypes, and minor allele carriers. The statistical analysis revealed the significant reduced PTB risk with homozygous variant genotype of rs1800451 polymorphism (CC vs AA: P=0.043; OR =0.828, 95% CI =0.689–0.994). Contrary to this, the variant allele of rs5030737 polymorphism showed association with increased PTB risk (D vs A: P=0.026; OR =1.563, 95% CI =1.054–2.317). However, the other genetic models of rs1800450 (A>B), rs7096206 (Y>X), and rs11003125 (H>L) MBL2 gene polymorphisms did not divulge any association with PTB susceptibility.

Conclusion: The current meta-analysis concludes that rs1800451 (A>C) and rs5030737 (A>D) polymorphisms of MBL2 gene play a significant role in PTB susceptibility. Further, well-designed epidemiological studies with larger sample size including consideration of environmental factors are warranted for the future.

Keywords: meta-analysis, mannose-binding lectin, MBL2, pulmonary tuberculosis, PTB, polymorphism

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is one of the most prevalent contagious airborne disease/infection, which is very harmful to the body tissues. In spite of good advancements in the treatment strategies, it is still a major health problem among the public. Lately, many reputed health reports reveal 10.4 million new cases and about 1.4 million deaths caused by TB, globally, in the year 2015. Among the two commonly found TB types, pulmonary tuberculosis (PTB) is one of the most devastating form and remains a leading cause of morbidity and mortality, globally.[1] PTB is a two-stage process including infection of *M. tuberculosis* and progression to the disease. It is a complex disease where both environmental and genetic factors play a role in

infection and spread of the disease. The bacteria *M. tuberculosis* affects approximately one-third of the world's population but only 5%–10% of those infected/affected develop clinical TB during their lifetime.[2] It is suggestive of how host genetic factors largely influence the development of clinical disease following infection with *M. tuberculosis*,[3] which is consistent with animal models of TB as well.[4] Identifying the important susceptibility and resistance genes and their variations in the host will lead to better understanding of PTB pathogenesis and newer approaches for the treatment and prophylaxis. The ability of the host to prevent the proliferation of the dormant *M. tuberculosis* pathogen into a full-fledged disease depends on the competence of the immune system. Thus, understanding the molecular mechanism responsible for protective immunity is a necessary step for the development of improved therapies and PTB control.[5]

The first line of protective immunity to control the initial infection of *M. tuberculosis* is the innate immunity. Variation at genetic level in components of innate immunity, influenced by a variety of factors, leads to PTB susceptibility.[6,7] The human mannose-binding lectin (MBL), or mannose-binding protein (MBP), encoded by the MBL2 gene is mapped on 10q11.2-q21 chromosome. It is a polypeptide of 248 amino acids with 32 kDa size[8] and considered to be an important part of human innate immunity.[9] MBL is a liver-derived collagen-like serum protein. It plays an important role in recognizing the pathogen by its carbohydrate domain present on the surface of a variety of pathogens including *M. tuberculosis*.[10,11] MBL targets the invading microorganisms for phagocytosis and complement-mediated killing. It binds to surface carbohydrates and activate the complement cascade via the lectin pathway.[12] The role of MBL in preventing and controlling infectious diseases has been widely investigated recently.[13]

A lot of variability exists in MBL serum levels in different individuals. Low serum levels of MBL2 or individuals producing low MBL2 genotypes have higher infectious disease risk including PTB.[14,15] Alteration in MBL serum levels in different individuals is attributed to MBL2 gene polymorphisms, which result in the creation of MBL2 genotypes responsible for producing low MBL in ~5% population worldwide.[16] The three commonly known MBL2 gene polymorphisms are present in the structural gene-coding region. They are found at codons: 52 (rs5030737, C>T transition, resulting Arg52Cys substitution, variant allele is known as "D"); 54 (rs1800450, G>A transition, resulting Gly54Asp substitution, variant allele is known as "B"); and 57 (rs1800451, G>A transition, resulting in Gly57Glu substitution, variant

allele is known as "C"). The above said mutations lead to the structural changes in MBL protein, which cause a functional deficiency and a significant reduction in the circulating MBL.[17] These polymorphisms are collectively known as "AO" and reveal the alteration in MBL serum levels. The allele "A" designates the wild-type allele, whereas the allele "O" is indicative of the presence of mutant allele(s) in either of the three polymorphisms.[13] In addition, two other relevant single nucleotide polymorphisms (SNPs) at positions −550 (rs11003125, C>G, "HL" variant, where L is the wild-type allele) and −221 (rs7096206, G>C, "XY" variant, where Y is the wild-type allele) in the promoter region have been identified as protein expression regulators.[18] These polymorphisms may change the transcription rate, which can further lead to change in the concentration of serum MBL. Genotypes containing structural polymorphisms and promoter variants have shown variations in MBL concentrations in different individuals which can be up to 1,000 folds.[13] These polymorphisms affect MBL2 gene which reduces MBL protein level leading to decrease in innate immunity against pathogens. Analysis of the genetic variants of MBL2 gene in PTB appears to be helpful in identifying individuals at higher risk of PTB susceptibility.

A plethora of studies have been conducted in the past to evaluate the effect of MBL2 gene polymorphisms on the progress of infection in PTB.[15,19–31] The results of these studies are contradictory. The reason for their contradiction is probably their small sample size which lacks adequate power to detect the effects of MBL2 gene polymorphisms on PTB. This weakness can be overcome by the use of meta-analysis, a statistical tool that explores the risk factors associated with different genetic diseases. A meta-analysis employs a quantitative method to combine the data drawn from individual studies with small sample sizes to provide a reliable conclusion. We, therefore, performed the current meta-analysis to identify the effect of the abovementioned MBL2 polymorphisms on overall PTB risk.

Materials and methods
Study search and online databases

A systematic search was performed on various scholarly databases like PubMed, Medline, EMBASE, and Google Scholar. The combination of the keywords used for the search was "MBL OR MBL2 OR MBP OR mannose-binding protein OR mannose-binding lectin" gene (polymorphism OR mutation OR variant) AND tuberculosis OR PTB Susceptibility/Risk (last updated on December 2017). The titles and abstracts of the hits obtained by the above search criteria were evaluated.

The most relevant publications were obtained after applying the eligibility criteria for thorough examination. In addition to the online database search, the reference lists of the selected research articles were also screened to find any missed relevant article during the initial search.

Criteria for inclusion and exclusion of the studies

To facilitate the proper interpretation of this study, heterogeneity was minimized. The following criteria were applied to select and include the published studies in this meta-analysis: 1) the study must have a case–control design investigating MBL2 gene polymorphism and PTB risk, 2) the patients included in the study should be confirmed PTB cases and controls should be TB free, 3) the study should have genotypic frequency available for both cases and controls, 4) the study should be published in English language only, and 5) the study should have used statistically acceptable data collection and analysis strategy. In addition to these criteria, in cases where the same case series was included in multiple articles, the most recent study with highest number of cases was included in this study. The main reasons followed for exclusion of the studies from this meta-analysis were as follow: 1) duplicate studies or overlapping publications, 2) the study designs based only on PTB cases, 3) the articles with no genotype frequency reported, and 4) the data of reviews and abstracts.

The information related to the identification and selection of the pertinent studies, by following the inclusion/exclusion criteria mentioned above, for the present meta-analysis has been given as PRISMA 2009 flow diagram (Figure 1).

Strategy for literature search

Two researchers (RKM and SK) individually examined all the titles and abstracts of the retrieved published articles using the designated online web database search in a sequential order. The full texts of all the articles, possibly qualified, were also retrieved. To evaluate the appropriateness of the study for the inclusion in this pooled analysis, one researcher (RKM) systematically examined all the full-text retrieved publications. Afterward, the second researcher (SK) performed the same procedure of text evaluation independently by selecting randomly 10% of the full-text articles. During the selection process, full agreement was found between the two researchers regarding study exclusion and selection criteria. After the selection of the final set of the eligible studies, another researcher (SAD) extrapolated the pertinent data from all the included studies. This step of data extrapolation was cross-checked by another researcher (MAK), independently, by collecting the information from all the selected articles. Discrepancies and discords occurred during the study selection were resolved amicably with thorough discussion in the presence of an adjudicator (SH).
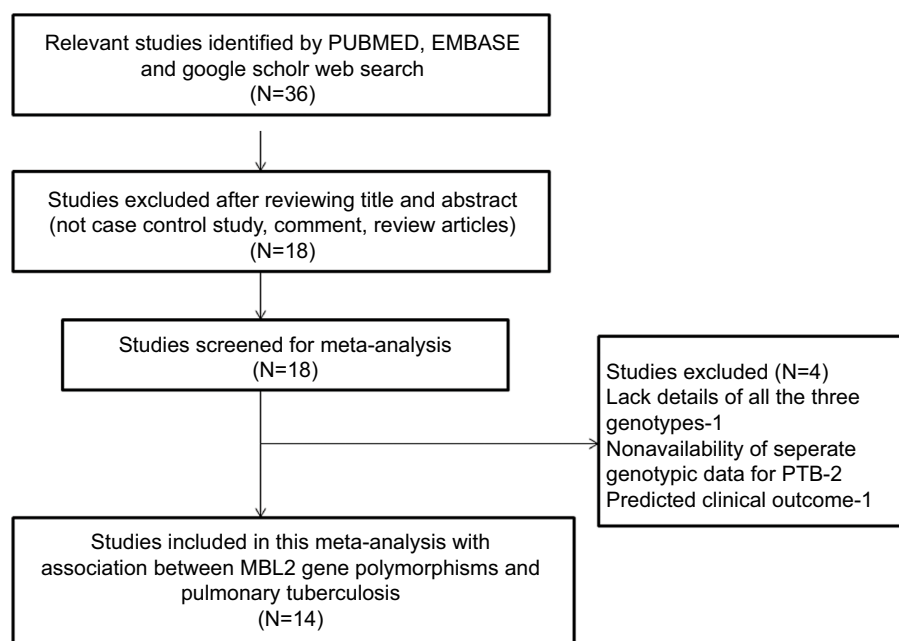

Figure 1 PRISMA 2009 flow diagram depicting identification and selection process (inclusion/exclusion) of the relevant published articles dealing with MBL2 gene polymorphisms and pulmonary tuberculosis risk for the present meta-analysis.

Screening of the studies

The electronic searches performed on PubMed (Medline), EMBASE, and Google Scholar web databases resulted in short-listing of 36 research articles in the preliminary stage. All the articles were examined thoroughly for their relevance by checking their titles, abstracts, and full texts for this meta-analysis. The research articles predicting survival in MBL2 polymorphic PTB patients or considering MBL2 variants as indicators for therapeutic response were excluded from this study. Also excluded were studies reporting expression of MBL2 at mRNA or protein level, and the review articles. Only studies with a case–control or cohort design with genotypic frequencies available for all the three genotypes were included in this meta-analysis. Beside the selected database search, the reference articles cited in the potential retrieved studies were also checked carefully for other potentially relevant articles, but no germane study was found. After many rounds of careful screening (using the sequential approach) by applying the pre-set inclusion and exclusion criteria as shown in PRISMA 2009 flow diagram (Figure 1), 14 eligible original studies were considered worth to be included for this meta-analysis. These studies dealt with MBL2 rs1800450 (A>B), rs1800451 (A>C), rs5030737 (A>D), rs7096206 (Y>X), rs11003125 (H>L), and rs7095891 (P>Q) gene polymorphisms and PTB risk (Table 1).

Newcastle–Ottawa Scale (NOS) criteria for quality evaluation

For NOS evaluation, two independent investigators (RKM and SAD) separately performed the methodological quality assessment of the retrieved studies. The established NOS criteria for quality score analysis was used for the methodological quality assessment of the included studies.[32] The NOS criteria focuses on three main aspects: 1) subject selection: 0–4 points/star; 2) comparability of subject: 0–2 points/star; 3) and clinical outcome: 0–3 points/star. The studies scoring five or more stars were considered of medium to high quality.[32,33] In case of difference in the number of stars assigned to a particular study by the two investigators, the issue was fully debated and resolved by a thorough discussion with a third investigator, SH.

Extraction and evaluation of the data quality

Two investigators (RKM and SK) independently summarized the methodological quality assessment and data extracted from all the eligible and retrieved articles by following the standard procedure. To confirm the accuracy of the summarized data, a data-collection form was used while strictly following the criteria stated above. The major summarized characteristics from the retrieved studies were as follows: the

Table 1 Main characteristics of all the studies included in this meta-analysis

First author and year	Country	Ethnicity	Control	Cases	Methods	SNP	Association
Wu et al 2015[19]	China	Asian	453	151	PCR-RFLP	P>Q, Y>X, H>L, A>B	No
da Cruz et al 2013[20]	Brazil	Mixed	148	119	Sequencing	H>L, Y>X, A>O, A>D, A>B, A>C	A>O, A>C risk
Araújo et al 2013[21]	Brazil	Mixed	159	133	PCR	A>B, A>C, A>D, A>O	No
Singla et al 2012[22]	India	Asian	392	286	PCR-RFLP	A>B	Yes
Thye et al 2011[31]	Ghana	African	2,236	1,953	Pyrosequencing	H>L, Y>X, P>Q, A>C	A>C
Capparelli et al 2009[15]	Italy	Caucasian	288	277	PCR	A>O	Protective
Cosar et al 2008[23]	Turkey	Caucasian	99	27	PCR-RFLP	A>B	Protective
Alagarasu et al 2007[24]	India	Asian	146	225	PCR-SSP	A>B, A>D, A>C, A>O, Y>X	Y>X, A>O
Søborg et al 2007[25]	Tanzania	African	426	424	PCR-SSP	A>B, A>D, A>C, A>O	No
Liu et al 2006[26]	China	Asian	293	152	PCR-SSP	H>L, P>Q, Y>X, A>B	No
Selvaraj et al 2006[27]	India	Asian	58	48	PCR-SSOP	A>O	No
Ozbaş-Gerçeker et al 2003[28]	Turkey	Caucasian	100	49	PCR	A>B	No
Selvaraj et al 1999[29]	India	Asian	109	202	PCR	A>B, A>C, A>D, A>O	A>C
Bellamy et al 1998[30]	Gambia	African	422	397	PCR	A>B, A>C	Protective A>C

Notes: MBL2 gene variants designated as rs1800450 (A>B), rs1800451 (A>C), rs5030737 (A>D), rs7096206 (Y>X), rs11003125 (H>L), rs7095891 (P>Q), combined rs1800450, rs1800451, rs5030737 (A>O).
Abbreviations: PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSOP, polymerase chain reaction-sequence-specific oligonucleotide probes; PCR-SSP, polymerase chain reaction-sequence-specific amplification; SNP, single nucleotide polymorphism.

first author, the year of publication, the country of origin, the ethnicity of cases and controls and their number, the type of study, and the genotypic frequencies. The disagreements/discrepancies, on any data item of the selected studies, between RKM and SK were resolved by open scientific discussion with the third arbitrator (SH) in order to reach a final consensus.

Statistical analyses

The pooled ORs and their corresponding 95% CIs were estimated in order to assess the association between MBL2 gene polymorphism and PTB risk. The chi-square-based Q-test was used to examine heterogeneity assumption.[34] A P-value <0.05 was the threshold for heterogeneity significance. In case of no heterogeneity, the data from single comparison was combined using a fixed-effects model;[35] otherwise, a random-effects model was used for pooling the data.[36] Additionally, for inter-study variability quantification, I^2 statistics was used. Higher values suggested an increasing degree of heterogeneity.[37] The chi-squared test was used to calculate the Hardy–Weinberg equilibrium (HWE) among the controls. The funnel plot asymmetry was calculated using Egger's regression test (linear regression approach) on the natural logarithm scale of the OR. The significance of the intercept was measured by t-test, wherein the P-value <0.05 was the representation of statistically significant publication bias. A uniform resource locator http://www.meta-analysis.com/pages/comparisons.html was used for comparative evaluation of the "meta-analysis" programs. The Comprehensive Meta-Analysis V2 software program (Biostat, Englewood, NJ, USA) was used to analyze all the statistical parameters in this meta-analysis.

Trial sequential analysis

According to the Cochrane handbook, the best meta-analysis includes all the eligible trials in the analysis. Though it may not be sufficient evidence, there are chances that sometimes meta-analysis may lead to bias (systematic errors) or chance (random errors). In order to reduce these errors, Trial sequential analysis (TSA) tool from Copenhagen Trial Unit, Center for Clinical Intervention Research, Denmark, was used. TSA helps in calculating the required information size, adjusts threshold for statistical significance, and estimates the power of current conclusion.[32,38–40] When the TSA monitoring boundary crosses with the Z-curve before the required information size is reached, it confirms the robust evidence indicating the need for no further trials. When the case is reverse, further trials are necessarily required to be

done in order to cross the monitoring boundaries. The Trial Sequential Analysis software (version 0.9, http://www.ctu.dk/tsa/) was used for this analysis. We performed two-sided hypothesis testing for the analysis and fixed type I error rate (α) at 5%. The results were combined by a DerSimonian–Laird random effects model. Sequential efficacy and harm monitoring boundaries that control type I error were constructed using Lan–DeMets version of the O'Brien–Fleming α-spending function, and the futility monitoring boundaries (for type II error) were constructed with an O'Brien–Fleming β-spending function.

Results

Quality assessment and characteristics of the selected studies

The major characteristics like genotypic distribution, minor allele frequency (MAF) in the controls/cases, and PTB susceptibility for all the 14 studies included in the present meta-analysis have been presented in Tables 2 and 3. All the 14 studies were evaluated for their quality according to the scoring system of NOS, and the majority of the studies (approximately 80%) were found to score five stars or more. The quality NOS scoring revealed moderate to good quality of all the studies included in this pooled analysis (Table 4).

Publication bias diagnosis, heterogeneity evaluation, and quantitative synthesis

The presence or absence of the publication bias in the included studies was checked by funnel plot asymmetry and Egger's regression statistics (P-value <0.05 considered as significant publication bias level). The shape of the funnel plots obtained and the outcomes of Egger's test showed absence/presence of publication bias in all the five comparative genetic models of MBL2 gene polymorphisms. Likewise, the presence/absence of heterogeneity in the included MBL2 gene polymorphism studies for all the five genetic models of this meta-analysis was evaluated by using Q-test and I^2 statistics. For each MBL2 polymorphism, random-effects model was applied to synthesize the data in the presence of heterogeneity, whereas fixed-effects model was adopted in the absence of heterogeneity. The outcomes of publication bias and heterogeneity evaluation and quantitative synthesis for each MBL2 polymorphism have been given in the following sections.

MBL2 rs1800450 polymorphism

A total of eleven case–control studies provided the sufficient data (including 2,258 controls and 1,789 PTB cases)

Table 2 Genotypic distribution of MBL2 gene polymorphism included in meta-analysis: first

First author and year	Controls									HWE
	Genotype rs1800450			Minor allele		Genotype rs1800450			Minor allele	
	AA	**AB**	**BB**	**MAF**		**AA**	**AB**	**BB**	**MAF**	***P*-value**
Wu et al 2015[19]	348	97	8	0.124		112	37	2	0.135	0.459
da Cruz et al 2013[20]	124	21	3	0.091		95	22	2	0.109	0.079
Araújo et al 2013[21]	101	48	0	0.161		84	35	0	0.147	0.019
Singla et al 2012[22]	207	155	30	0.274		175	100	11	0.213	0.895
Cosar et al 2008[23]	71	27	1	0.146		23	4	0	0.074	0.366
Alagarasu et al 2007[24]	86	33	4	0.166		120	42	12	0.189	0.704
Søborg et al 2007[25]	271	13	1	0.026		289	9	0	0.015	0.063
Liu et al 2006[26]	166	42	4	0.117		103	34	4	0.148	0.487
Ozbaş-Gerçeker et al 2003[28]	76	20	4	0.14		40	9	0	0.091	0.090
Selvaraj et al 1999[29]	84	24	1	0.119		137	51	14	0.195	0.615
Bellamy et al 1998[30]	183	5	0	0.013		198	7	0	0.017	0.853
	Genotype rs1800451					Genotype rs1800451				
	AA	**AC**	**CC**			**AA**	**AC**	**CC**		
da Cruz et al 2013[20]	140	8	0	0.027		133	22	0	0.070	0.735
Araújo et al 2013[21]	101	2	0	0.009		84	4	0	0.022	0.920
Thye et al 2011[31]	1,002	977	257	0.333		885	815	194	0.317	0.421
Alagarasu et al 2007[24]	86	12	1	0.070		120	11	1	0.049	0.439
Søborg et al 2007[25]	271	112	20	0.188		289	115	20	0.182	0.065
Selvaraj et al 1999[29]	103	5	1	0.032		176	25	1	0.066	0.006
Bellamy et al 1998[30]	183	192	42	0.330		198	159	29	0.281	0.417
	Genotype rs5030737					Genotype rs5030737				
	AA	**AD**	**DD**			**AA**	**AD**	**DD**		
da Cruz et al 2013[20]	138	9	1	0.037		108	10	1	0.050	0.067
Araújo et al 2013[21]	101	6	0	0.028		84	8	0	0.043	0.765
Alagarasu et al 2007[24]	86	8	0	0.042		120	26	2	0.101	0.666
Søborg et al 2007[25]	271	6	0	0.010		289	8	0	0.013	0.855
Selvaraj et al 1999[29]	99	10	0	0.045		186	9	7	0.056	0.615

Abbreviations: HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency.

Table 3 Genotypic distribution of MBL2 gene polymorphisms included in this meta-analysis: second

First author and year	Controls					Cases				HWE
	Combined rs1800450, 1800451, 5030737			Minor allele		Combined rs1800450, 1800451, 5030737			Minor allele	
	AA	**AO**	**OO**	**MAF**		**AA**	**AO**	**OO**	**MAF**	***P*-value**
da Cruz et al 2013[20]	108	34	6	0.155		71	41	7	0.231	0.128
Araújo et al 2013[21]	101	56	2	0.188		84	47	2	0.191	0.057
Capparelli et al 2009[15]	166	112	10	0.229		55	158	61	0.510	0.087
Alagarasu et al 2007[24]	86	53	7	0.229		120	82	24	0.287	0.747
Søborg et al 2007[25]	271	131	30	0.221		289	132	22	0.198	0.013
Selvaraj et al 2006[27]	37	18	3	0.206		24	19	5	0.302	0.678
Selvaraj et al 1999[29]	68	39	2	0.197		107	73	22	0.289	0.175
	Genotype rs7096206					Genotype rs7096206				
	YY	**YX**	**XX**			**YY**	**YX**	**XX**		
Wu et al 2015[19]	318	120	15	0.165		97	47	7	0.201	0.379
da Cruz et al 2013[20]	110	32	6	0.148		75	40	4	0.201	0.076
Thye et al 2011[31]	1,663	486	31	0.125		1,437	396	26	0.120	0.502
Alagarasu et al 2007[24]	72	61	13	0.297		136	79	10	0.22	0.987
Liu et al 2006[26]	151	54	7	0.160		91	44	6	0.198	0.430
	Genotype rs11003125					Genotype rs11003125				
	HH	**HL**	**LL**			**HH**	**HL**	**LL**		
Wu et al 2015[19]	46	64	41	0.483		101	248	104	0.503	0.062
da Cruz et al 2013[20]	19	61	68	0.665		8	45	66	0.743	0.366
Thye et al 2011[31]	9	287	1,878	0.929		7	266	1,570	0.924	0.576
Liu et al 2006[26]	49	105	58	0.521		44	66	31	0.453	0.911

Abbreviations: HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency.

to calculate the ORs. Publication bias did not exist and heterogeneity was found in one genetic model (Table 5; Figure SI1). The pooled ORs revealed that MBL2 A>B gene polymorphism demonstrated no association with PTB risk in allelic contrast (B vs A: P=0.999; OR =1.000, 95% CI =0.799–1.251), homozygous (BB vs AA: P=0.495; OR =0.848, 95% CI =0.527–1.363), heterozygous (BA vs AA: P=0.717; OR =0.969, 95% CI =0.820–1.146), dominant (BB+ BA vs AA: P=0.704; OR =0.969, 95% CI =0.824–1.140), and recessive (BB vs BA+ AA: P=0.581; OR =0.876, 95% CI =0.547–1.402) genetic models, respectively (Figure 2).

In the stratification analysis based on the ethnicity, five studies were included for the analysis in the Asian population. No publication bias existed and heterogeneity was found in four genetic models (Table 6; Figure SI2). No significant relationship was observed with PTB in allelic contrast (B vs A: P=0.461; OR =1.131, 95% CI =0.815–1.571), homozygous (BB vs AA: P=0.582; OR =1.313, 95% CI =0.498–3.465), heterozygous (BA vs AA: P=0.947; OR =0.993, 95% CI =0.815–1.211), dominant (BB+ BA vs AA: P=0.605; OR

=1.083, 95% CI =0.800–1.467), and recessive (BB vs BA+ AA: P=0.576; OR =1.298, 95% CI =0.521–3.231), respectively (Figure 3).

MBL2 rs1800451 polymorphism

A total of seven case–control studies were included for this analysis accumulating 3,515 controls and 3,281 PTB cases. No publication bias was observed, whereas heterogeneity was found in three genetic models (Table 7; Figure SI3). The pooled ORs revealed that homozygous (CC vs AA: P=0.043; OR =0.828, 95% CI =0.689–0.994) genetic model was associated with reduced risk to PTB. However, other genetic models, allelic contrast (C vs A: P=0.921; OR =0.990, 95% CI =0.804–1.217), heterozygous (CA vs AA: P=0.724; OR =1.050, 95% CI =0.800–1.378), dominant (CC+ CA vs AA: P=0.856; OR =1.025, 95% CI =0.788–1.332), and recessive (CC vs CA + AA: P=0.093; OR =0.861, 95% CI =0.722–1.026), did not show any association with PTB (Figure 4).

The stratification analysis based on the ethnicity included three studies for the analysis of the African population. Publication bias and heterogeneity were absent (Table 8; Figure SI4). A reduced risk was observed with allelic (C vs A: P=0.025; OR =0.912, 95% CI =0.842–0.989) and homozygous (CC vs AA: P=0.047; OR =0.830, 95% CI =0.690–0.997) genetic models. On the other hand, heterozygous (CA vs AA: P=0.132; OR =0.918, 95% CI =0.822–1.026), dominant (CC+ CA vs AA: P=0.052; OR =0.901, 95% CI =0.812–1.001), and recessive (CC vs CA + AA: P=0.100; OR =0.863, 95% CI =0.723–1.029) genetic models did not show any risk with PTB (Figure 5).

MBL2 rs5030737 polymorphism

A total of five case–control studies were included, which comprises a sum of 735 controls and 876 confirmed PTB cases. There was no publication bias and heterogeneity (Table 9; Figure SI5). The pooled ORs revealed that variant allele was found to be associated with the increased risk (D vs A:

Table 4 Quality assessment conducted according to the NOS for all the included studies

First author and year	Quality indicators		
	Selection	**Comparability**	**Exposure**
Wu et al 2015[19]	***	*	**
da Cruz et al 2013[20]	***	*	**
Araújo et al 2013[21]	***	*	**
Singla et al 2012[22]	***	*	***
Thye et al 2011[31]	****	*	***
Capparelli et al 2009[15]	***	*	**
Cosar et al 2008[23]	**	*	**
Alagarasu et al 2007[24]	***	*	*
Søborg et al 2007[25]	***	*	*
Liu et al 2006[26]	***	*	***
Selvaraj et al 2006[27]	***	*	*
Ozbaş-Gerçeker et al 2003[28]	*	*	**
Selvaraj et al 1999[29]	***	*	**
Bellamy et al 1998[30]	**	*	**

Abbreviation: NOS, Newcastle–Ottawa Scale.

Table 5 Statistics to test the publication bias and heterogeneity (rs1800450 Overall)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	**95% CI**	**P-value**	**Q-value**	**P**$_{\text{heterogeneity}}$	**I² (%)**	
B vs A	0.21	−2.33 to 2.74	0.86	20.21	0.03	50.52	Random
BB vs AA	0.70	−1.52 to 2.91	0.48	12.76	0.12	37.29	Fixed
BA vs AA	0.05	−1.90 to 1.99	0.96	9.34	0.50	0.00	Fixed
BB + BA vs AA	0.08	−2.28 to 2.45	0.94	14.27	0.16	29.90	Fixed
BB vs BA + AA	0.60	−1.50 to 2.71	0.52	11.61	0.17	31.11	Fixed

Study name	Statistics for each study					OR and 95% CI	Relative weight
B vs A	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.102	0.751	1.618	0.498	0.619		12.79
da Cruz et al 2013	1.222	0.693	2.156	0.692	0.489		8.85
Araujo et al 2013	0.898	0.559	1.442	−0.446	0.656		10.70
Singla et al 2012	0.717	0.556	0.925	−2.559	0.010		16.18
Cossar et al 2008	0.466	0.156	1.389	−1.370	0.171		3.50
Alagarasu et al 2007	1.170	0.762	1.798	0.718	0.473		11.69
Søborg et al 2007	0.567	0.246	1.307	−1.331	0.183		5.34
Liu et al 2006	1.309	0.842	2.035	1.196	0.232		11.42
Ozbaş-Gerçeker et al 2003	0.621	0.281	1.373	−1.176	0.240		5.75
Selvaraj et al 1999	1.795	1.113	2.894	2.400	0.016		10.61
Bellamy et al 1998	1.289	0.406	4.096	0.430	0.667		3.18
Combined	1.000	0.799	1.251	−0.001	0.999		

0.01 0.1 1 10 100

Study name	Statistics for each study					OR and 95% CI	Relative weight
BB vs AA	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	0.777	0.163	3.712	−0.317	0.752		9.22
da Cruz et al 2013	0.870	0.143	5.312	−0.151	0.880		6.89
Singla et al 2012	0.434	0.211	0.891	−2.275	0.023		43.56
Cossar et al 2008	1.014	0.040	25.750	0.009	0.993		2.16
Alagarasu et al 2007	2.150	0.671	6.893	1.288	0.198		16.62
Søborg et al 2007	0.313	0.013	7.707	−0.711	0.477		2.20
Liu et al 2006	1.612	0.394	6.585	0.665	0.506		11.38
Ozbaş-Gerçeker et al 2003	0.210	0.011	3.996	−1.039	0.299		2.60
Selvaraj et al 1999	8.584	1.109	66.470	2.059	0.040		5.38
Combined	0.848	0.527	1.363	−0.682	0.495		

0.01 0.1 1 10 100

Study name	Statistics for each study					OR and 95% CI	Relative weight
BA vs AA	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.185	0.768	1.830	0.766	0.443		14.89
da Cruz et al 2013	1.367	0.710	2.632	0.936	0.349		6.55
Araujo et al 2013	0.877	0.520	1.479	−0.493	0.622		10.27
Singla et al 2012	0.763	0.553	1.053	−1.645	0.100		27.10
Cossar et al 2008	0.457	0.145	1.445	−1.333	0.183		2.12
Alagarasu et al 2007	0.912	0.535	1.555	−0.338	0.735		9.88
Søborg et al 2007	0.649	0.273	1.543	−0.978	0.328		3.75
Liu et al 2006	1.305	0.780	2.183	1.013	0.311		10.61
Ozbaş-Gerçeker et al 2003	0.855	0.356	2.051	−0.351	0.726		3.67
Selvaraj et al 1999	1.303	0.747	2.272	0.933	0.351		9.09
Bellamy et al 1998	1.294	0.404	4.149	0.433	0.665		2.07
Combined	0.969	0.820	1.146	−0.362	0.717		

0.01 0.1 1 10 100

Study name	Statistics for each study					OR and 95% CI	Relative weight
BB+BA vs AA	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.154	0.755	1.765	0.661	0.508		14.60
da Cruz et al 2013	1.305	0.698	2.440	0.834	0.404		6.73
Araujo et al 2013	0.877	0.520	1.479	−0.493	0.622		9.63
Singla et al 2012	0.710	0.521	0.967	−2.170	0.030		27.48
Cossar et al 2008	0.441	0.140	1.390	−1.397	0.162		2.00
Alagarasu et al 2007	1.046	0.633	1.727	−0.176	0.861		10.47
Søborg et al 2007	0.603	0.257	1.416	−1.162	0.245		3.62
Liu et al 2006	1.331	0.812	2.184	1.133	0.257		10.75
Ozbaş-Gerçeker et al 2003	0.713	0.303	1.678	−0.776	0.438		3.59
Selvaraj et al 1999	1.594	0.933	2.723	1.708	0.088		9.19
Bellamy et al 1998	1.294	0.404	4.149	0.433	0.665		1.94
Combined	0.969	0.824	1.140	−0.381	0.704		

0.01 0.1 1 10 100

Study name	Statistics for each study					OR and 95% CI	Relative weight
BB vs BA+AA	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	0.747	0.157	3.555	−0.367	0.714		9.09
da Cruz et al 2013	0.826	0.136	5.027	−0.207	0.836		6.79
Singla et al 2012	0.483	0.238	0.980	−2.015	0.044		44.13
Cossar et al 2008	1.194	0.047	30.134	0.108	0.180		2.13
Alagarasu et al 2007	2.204	0.694	7.002	1.340	0.180		16.57
Søborg et al 2007	0.318	0.013	7.831	−0.701	0.483		2.16
Liu et al 2006	1.518	0.373	6.173	0.583	0.560		11.26
Ozbaş-Gerçeker et al 2003	0.217	0.011	4.105	−1.019	0.308		2.56
Selvaraj et al 1999	8.043	1.043	62.008	2.000	0.045		5.31
Combined	0.876	0.547	1.402	−0.552	0.581		

0.01 0.1 1 10 100

◁ Decreases | Increases ▷

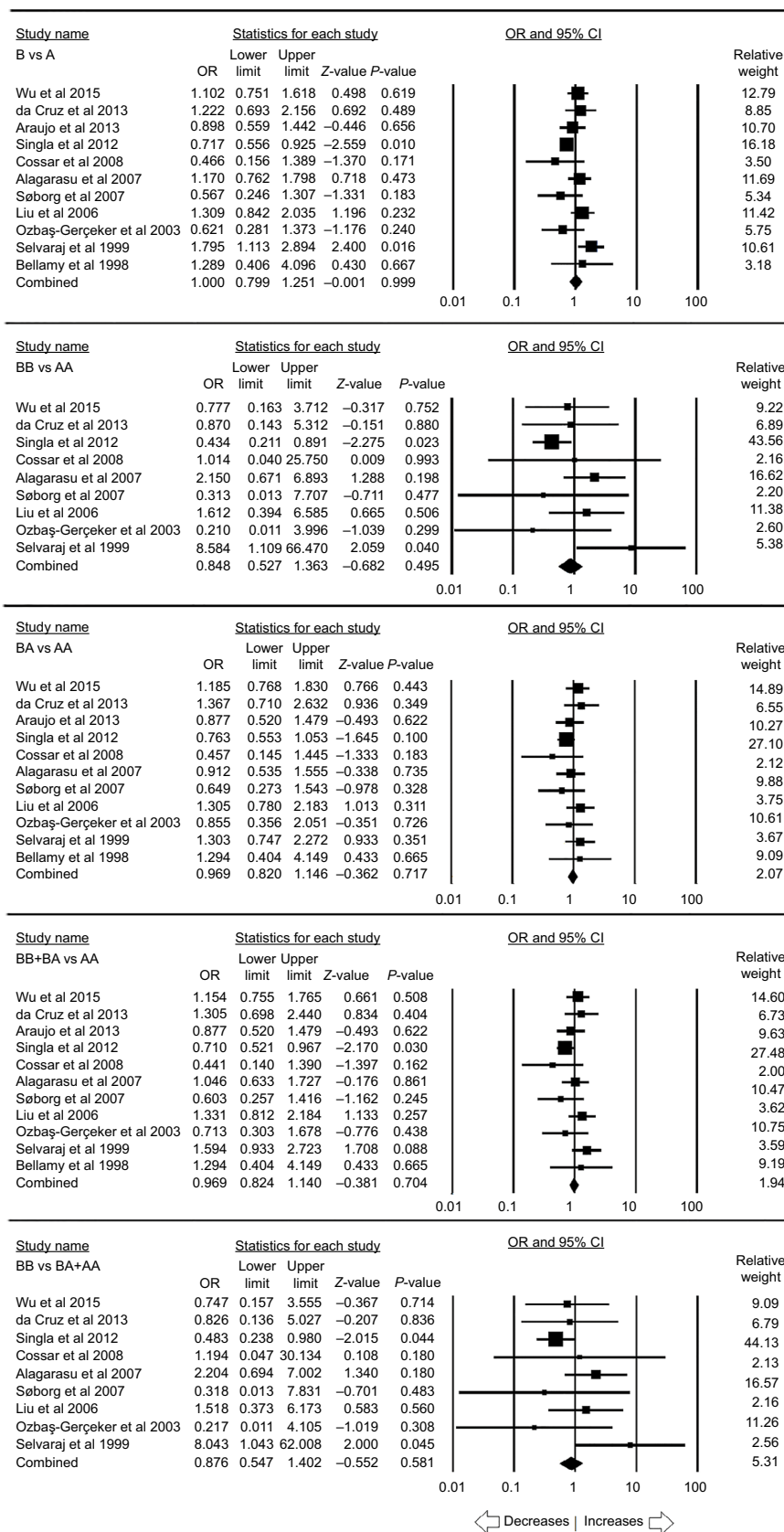**Figure 2** Forest plot of ORs with 95% CI of PTB risk associated with the MBL2 rs1800450 (A>B) gene polymorphism for the overall population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
Abbreviation: PTB, pulmonary tuberculosis.

Table 6 Statistics to test the publication bias and heterogeneity (rs1800450 Asian)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% CI	P-value	Q-value	P$_{heterogeneity}$	I^2 (%)	
B vs A	6.83	4.07 to 9.58	0.00	14.49	0.01	72.40	Random
BB vs AA	3.58	−0.66 to 7.84	0.07	11.46	0.02	65.08	Random
BA vs AA	3.82	−1.56 to 9.21	0.11	5.30	0.26	24.53	Fixed
BB + BA vs AA	6.06	1.82 to 10.30	0.02	9.37	0.05	57.33	Random
BB vs BA + AA	3.24	−1.01 to 7.49	0.09	10.26	0.04	61.02	Random

Table 7 Statistics to test the publication bias and heterogeneity (rs1800451 overall)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% CI	P-value	Q-value	P$_{heterogeneity}$	I^2 (%)	
C vs A	1.07	−0.93 to 3.07	0.22	14.49	0.02	58.58	Random
CC vs AA	−0.29	−1.57 to 0.99	0.52	1.29	0.86	0.001	Fixed
CA vs AA	1.19	−1.00 to 3.38	0.22	15.61	0.02	61.57	Random
CC + CA vs AA	1.18	−1.02 to 3.39	0.23	15.91	0.01	62.28	Random
CC vs CA + AA	−0.26	−1.16 to 0.64	0.42	0.71	0.95	0.001	Fixed

Table 8 Statistics to test the publication bias and heterogeneity (rs1800451 African)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% CI	P-value	Q-value	P$_{heterogeneity}$	I^2 (%)	
C vs A	−0.89	−23.14 to 21.35	0.70	2.09	0.35	4.29	Fixed
CC vs AA	−0.53	−16.60 to 15.54	0.75	1.22	0.54	0.00	Fixed
CA vs AA	−1.08	−21.67 to 19.50	0.62	1.78	0.41	0.00	Fixed
CC + CA vs AA	−1.10	−24.87 to 22.66	0.66	2.22	0.33	10.05	Fixed
CC vs CA + AA	−0.31	−11.52 to 10.69	0.78	0.59	0.74	0.00	Fixed

P=0.026; OR =1.563, 95% CI =1.054–2.317) of PTB in comparison to wild allele A. Other genetic models, homozygous (DD vs AA: P=0.168; OR =3.244, 95% CI =0.610–17.263), heterozygous (DA vs AA: P=0.258; OR =1.281, 95% CI =0.834–1.969), dominant (DD+ DA vs AA: P=0.088; OR =1.432, 95% CI =0.947–2.164), and recessive (DD vs DA + AA: P=0.177; OR =3.164, 95% CI =0.595–16.829), were not associated with any risk to PTB (Figure 6).

MBL2 combined rs1800450, rs1800451, rs5030737 polymorphism

A total of seven case–control studies provided enough data to calculate ORs, including 1,340 controls and 1,445 PTB cases. Publication bias was not found, but heterogeneity was present in all the genetic models (Table 10; Figure SI6). The pooled ORs revealed that combined gene polymorphism was not associated with PTB in allelic contrast (O vs A: P=0.063; OR =1.524, 95% CI =0.978–2.375), homozygous (OO vs AA: P=0.070; OR =2.797, 95% CI =0.920–8.508), heterozygous (OA vs AA: P=0.095; OR =1.481, 95% CI =0.934–2.347),

dominant (OO+ OA vs AA: P=0.075; OR =1.619, 95% CI =0.953–2.749), and recessive (OO vs OA+AA: P=0.061; OR =2.297, 95% CI =0.962–5.485) genetic models (Figure 7).

The stratification analysis based on the ethnicity included three studies from the Asian population. There was no publication bias and heterogeneity (Table 11; Figure SI7). Increased risk was observed with allelic (O vs A: P=0.001; OR =1.502, 95% CI =1.183–1.907), homozygous (OO vs AA: P=0.001; OR =3.092, 95% CI =1.567–6.104) and recessive (OO vs OA+ AA: P=0.002; OR =2.855, 95% CI =1.464–5.569) genetic models. Other genetic models, heterozygous (OA vs AA: P=0.241; OR =1.201, 95% CI =0.884–1.631) and dominant (OO+ OA vs AA: P=0.023; OR =1.404, 95% CI =1.048–1.880), did not reveal any risk with PTB (Figure 8).

MBL2 rs7096206 polymorphism

A total of five case–control studies were included which provided 3,139 controls and 1,201 PTB cases. There was no publication bias, but heterogeneity was found in three genetic models (Table 12; Figure SI8). The pooled ORs

Study name						OR and 95% CI		Relative weight
B vs A	OR	Lower limit	Upper limit	Z-value	P-value			
Wu et al 2015	1.102	0.751	1.618	0.498	0.619			20.39
Singla et al 2012	0.717	0.556	0.925	−2.559	0.010			24.16
Alagarasu et al 2007	1.170	0.762	1.798	0.718	0.473			19.05
Liu et al 2006	1.309	0.842	2.035	1.196	0.232			18.71
Selvaraj et al 1999	1.795	1.113	2.894	2.400	0.016			17.68
Combined	1.131	0.815	1.571	0.737	0.461			

0.1   0.2   0.5   1   2   5   10

Study name						OR and 95% CI		Relative weight
BB vs AA	OR	Lower limit	Upper limit	Z-value	P-value			
Wu et al 2015	0.777	0.163	3.172	−0.317	0.752			17.63
Singla et al 2012	0.434	0.211	0.891	−2.275	0.023			27.60
Alagarasu et al 2007	2.150	0.671	6.893	1.288	0.198			22.15
Liu et al 2006	1.612	0.394	6.585	0.665	0.506			19.32
Selvaraj et al 1999	8.584	1.109	66.470	2.059	0.040			13.29
Combined	1.131	0.498	3.465	0.550	0.582			

0.01   0.1   1   10   100

Study name						OR and 95% CI		Relative weight
BA vs AA	OR	Lower limit	Upper limit	Z-value	P-value			
Wu et al 2015	1.185	0.768	1.830	0.766	0.443			20.80
Singla et al 2012	0.763	0.553	1.053	−1.645	0.100			37.87
Alagarasu et al 2007	0.912	0.535	1.555	−0.338	0.735			13.80
Liu et al 2006	1.305	0.780	2.183	1.013	0.311			14.83
Selvaraj et al 1999	1.303	0.747	2.272	0.933	0.351			12.70
Combined	0.993	0.815	1.211	−0.066	0.947			

0.01   0.1   1   10   100

Study name						OR and 95% CI		Relative weight
BB+BA vs AA	OR	Lower limit	Upper limit	Z-value	P-value			
Wu et al 2015	1.154	0.755	1.765	0.661	0.508			20.94
Singla et al 2012	0.710	0.521	0.967	−2.170	0.030			25.94
Alagarasu et al 2007	1.046	0.633	1.727	0.176	0.861			18.01
Liu et al 2006	1.331	0.812	2.184	1.133	0.257			18.25
Selvaraj et al 1999	1.594	0.933	2.723	1.708	0.088			16.86
Combined	1.083	0.800	1.467	0.517	0.605			

0.1   0.2   0.5   1   2   5   10

Study name						OR and 95% CI		Relative weight
BB vs BA+AA	OR	Lower limit	Upper limit	Z-value	P-value			
Wu et al 2015	0.747	0.157	3.555	−0.367	0.714			17.23
Singla et al 2012	0.483	0.238	0.980	−2.015	0.044			28.72
Alagarasu et al 2007	2.204	0.694	7.002	1.340	0.180			22.30
Liu et al 2006	1.518	0.373	6.173	0.583	0.560			19.08
Selvaraj et al 1999	8.043	1.043	62.008	2.000	0.045			12.67
Combined	1.298	0.521	3.231	0.560	0.576			

0.01   0.1   1   10   100

⇐ Decreases | Increases ⇒

Figure 3 Forest plot of ORs with 95% CI of PTB risk associated with the MBL2 rs1800450 (A>B) gene polymorphism for the Asian population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
Abbreviation: PTB, pulmonary tuberculosis.

Figure 4 Forest plot of ORs with 95% CI of PTB risk associated with the rs1800451 (A>C) gene polymorphism for the overall population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
Abbreviation: PTB, pulmonary tuberculosis.

Study name					OR and 95% CI			
C vs A		Statistics for each study						
	OR	Lower limit	Upper limit	Z-value	P-value			Relative weight
Thye et al 2011	0.930	0.848	1.021	−1.529	0.126			75.35
Søborg et al 2007	0.962	0.751	1.233	−0.303	0.762			10.47
Bellamy et al 1998	0.790	0.639	0.978	−2.162	0.031			14.17
Combined	0.912	0.842	0.989	−2.239	0.025			

0.5   1   2

Study name					OR and 95% CI			
CC vs AA		Statistics for each study						
	OR	Lower limit	Upper limit	Z-value	P-value			Relative weight
Thye et al 2011	0.855	0.695	1.051	−1.486	0.137			78.95
Søborg et al 2007	0.938	0.494	1.781	−0.196	.0.844			8.23
Bellamy et al 1998	0.638	0.382	1.067	−1.712	0.087			12.82
Combined	0.830	0.690	0.997	−1.990	0.047			

0.1   0.2   0.5   1   2   5   10

Study name					OR and 95% CI			
CA vs AA		Statistics for each study						
	OR	Lower limit	Upper limit	Z-value	P-value			Relative weight
Thye et al 2011	0.944	0.830	1.075	−0.863	0.388			72.69
Søborg et al 2007	0.963	0.707	1.311	−0.241	0.810			12.85
Bellamy et al 1998	0.765	0.572	1.024	−1.802	0.072			14.46
Combined	0.918	0.822	1.026	−1.508	0.132			

0.5   1   2

Study name					OR and 95% CI			
CC+CA vs AA		Statistics for each study						
	OR	Lower limit	Upper limit	Z-value	P-value			Relative weight
Thye et al 2011	0.926	0.819	1.047	−1.231	0.218			72.84
Søborg et al 2007	0.959	0.716	1.284	−0.281	0.779			12.93
Bellamy et al 1998	0.743	0.562	0.980	−2.099	0.036			14.23
Combined	0.901	0.812	1.001	−1.943	0.052			

0.5   1   2

Study name					OR and 95% CI			
CC vs CA+AA		Statistics for each study						
	OR	Lower limit	Upper limit	Z-value	P-value			Relative weight
Thye et al 2011	0.879	0.721	1.070	−1.284	0.799			79.65
Søborg et al 2007	0.948	0.502	1.790	−0.165	0.869			7.68
Bellamy et al 1998	0.725	0.442	1.190	−1.272	0.203			12.67
Combined	0.863	0.723	1.029	−1.644	0.100			

0.1   0.2   0.5   1   2   5   10
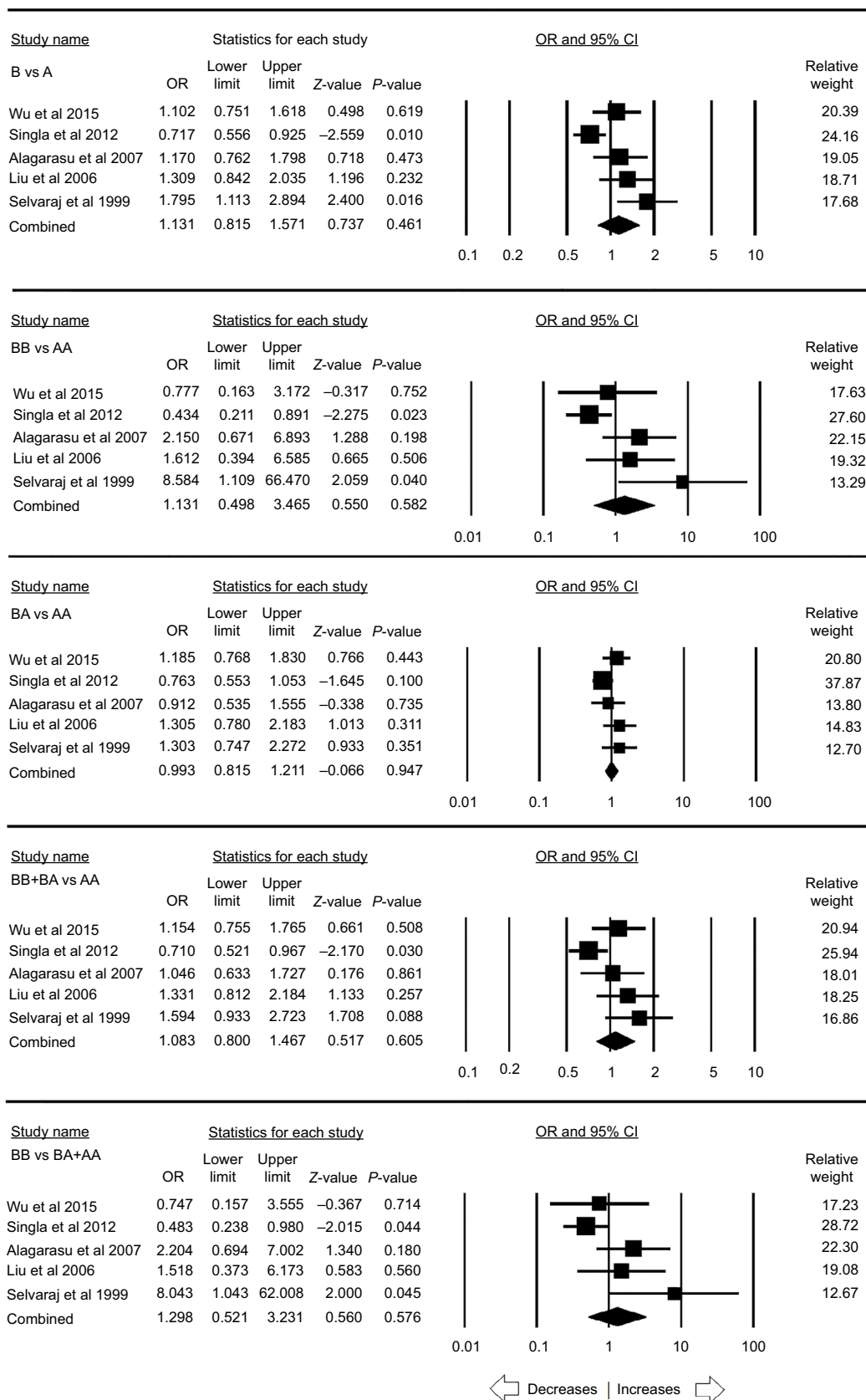
⟨ Decreases | Increases ⟩

Figure 5 Forest plot of ORs with 95% CI of PTB risk associated with the rs1800451 (A>C) gene polymorphism for the African population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
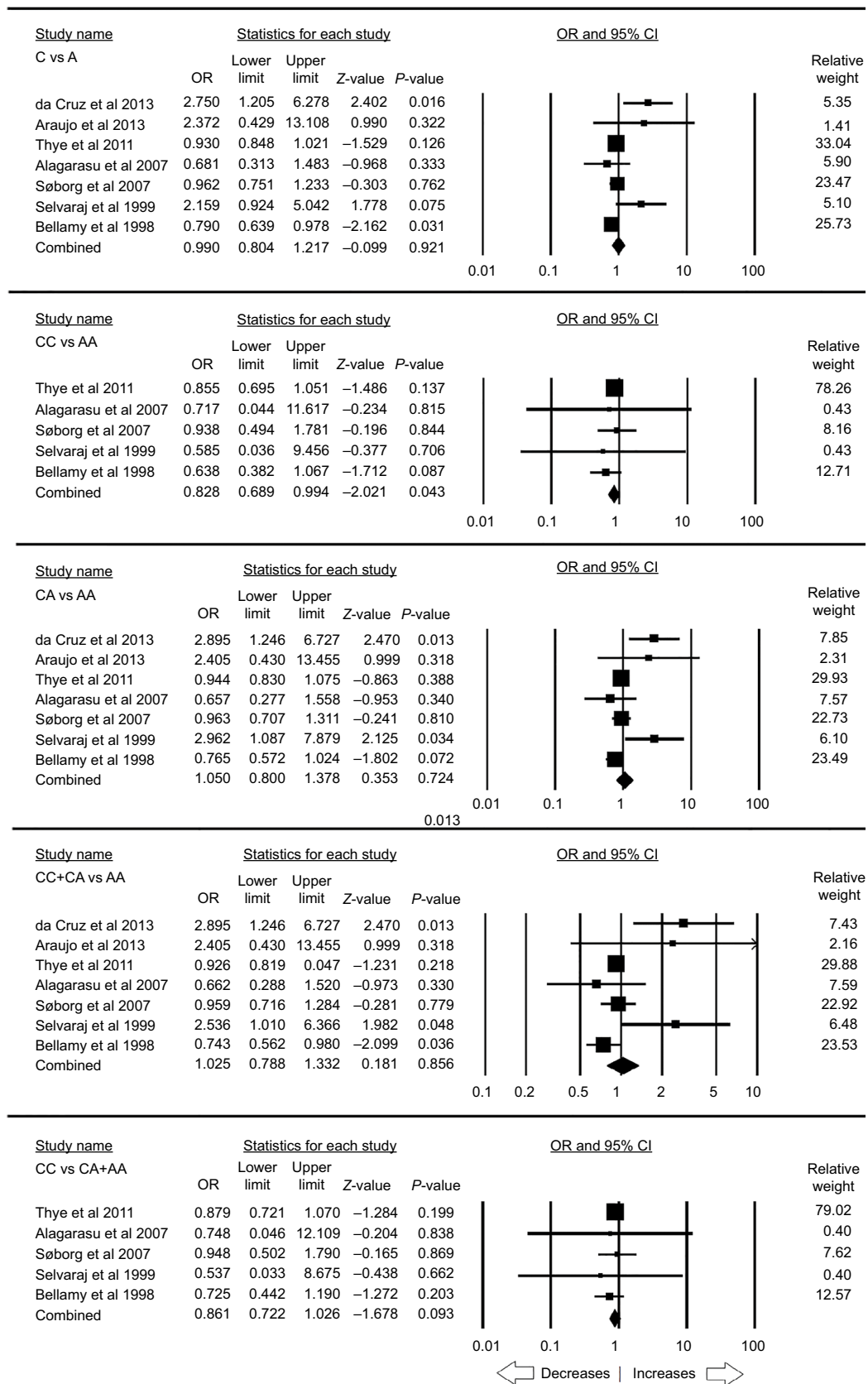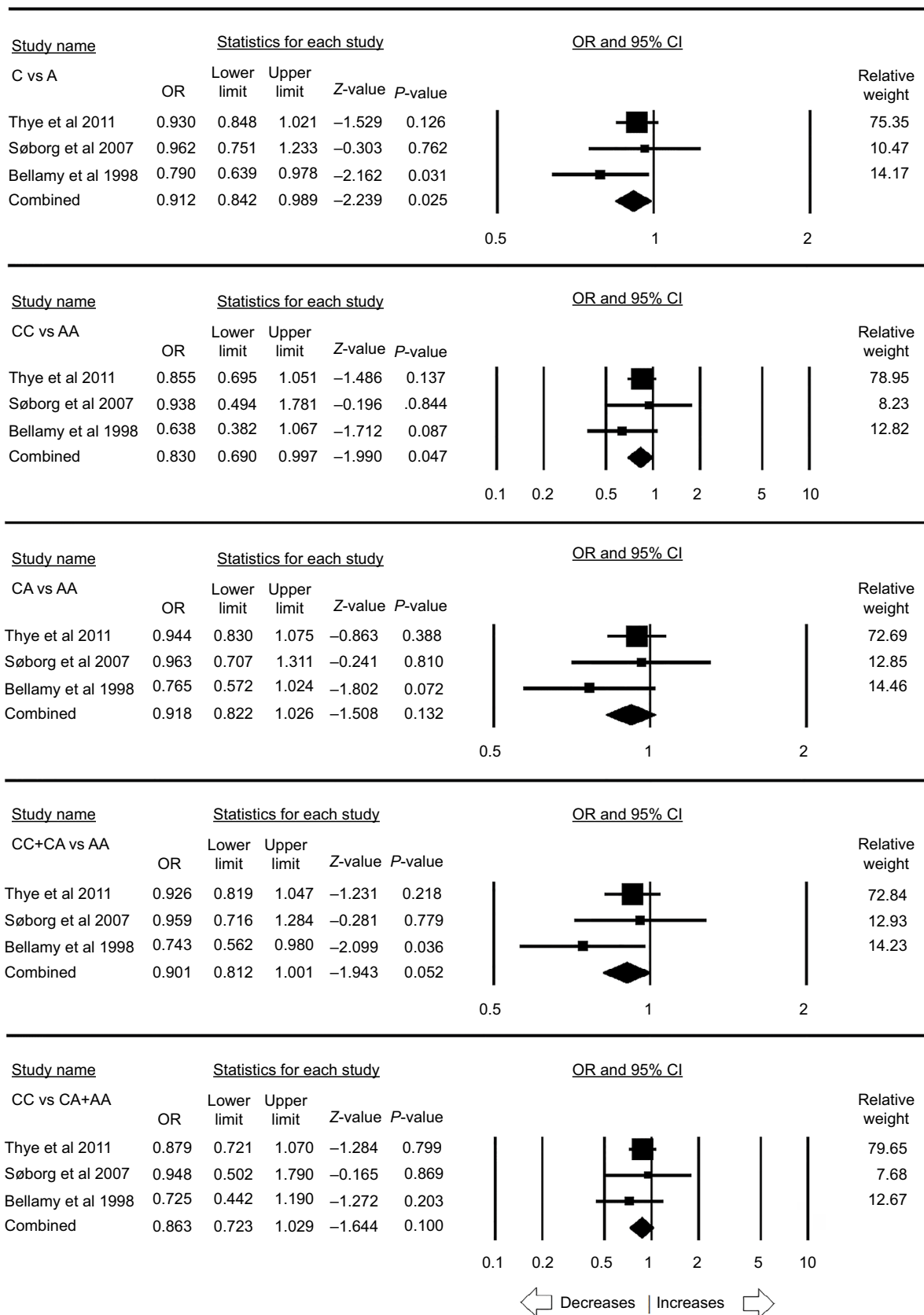**Abbreviation:** PTB, pulmonary tuberculosis.

Table 9 Statistics to test the publication bias and heterogeneity (rs5030737 overall)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% CI	*P*-value	Q-value	$P_{\text{heterogeneity}}$	I^2 (%)	
D vs A	−0.81	−8.87to 7.25	0.77	1.98	0.74	0.00	Fixed
DD vs AA	5.91	−153.15 to 165.67	0.72	0.81	0.67	0.00	Fixed
DA vs AA	−2.07	−22.86 to 18.71	0.77	6.43	0.17	37.77	Fixed
DD + DA vs AA	−0.0002	−12.68 to 12.68	0.99	3.36	0.50	0.00	Fixed
DD vs DA + AA	5.22	−165.83 to 176.28	0.76	0.87	0.65	0.00	Fixed

Table 10 Statistics to test the publication bias and heterogeneity (combined overall)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% CI	*P*-value	Q-value	$P_{\text{heterogeneity}}$	I^2 (%)	
O vs A	0.14	−11.91 to 12.18	0.98	67.58	0.00	91.12	Random
OO vs AA	1.29	−6.66 to 9.24	0.69	50.46	0.00	88.11	Random
OA vs AA	1.46	−8.71 to 11.63	0.73	42.54	0.00	85.89	Random
OO + OA vs AA	2.34	−9.59 to 14.27	0.64	61.81	0.00	90.29	Random
OO vs OA + AA	1.16	−5.02 to 7.36	0.65	31.66	0.00	81.05	Random

Table 11 Statistics to test the publication bias and heterogeneity (combined Asian)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% CI	*P*-value	Q-value	$P_{\text{heterogeneity}}$	I^2 (%)	
O vs A	1.38	−18.90 to 21.54	0.56	0.69	0.71	0.00	Fixed
OO vs AA	1.69	−25.74 to 29.13	0.58	1.48	0.48	0.00	Fixed
OA vs AA	1.95	0.11 to 3.78	0.05	0.65	0.72	0.00	Fixed
OO + OA vs AA	1.72	−8.37 to 11.82	0.27	0.60	0.74	0.00	Fixed
OO vs OA + AA	1.46	−28.82 to 31.73	0.65	0.56	0.46	0.00	Fixed

revealed that Y>X polymorphism was not associated with PTB in allelic contrast (X vs Y: *P*=0.657; OR =1.056, 95% CI =0.830–1.344), homozygous (XX vs YY: *P*=0.707; OR =0.932, 95% CI =0.647–1.344), heterozygous (XY vs YY: *P*=0.476; OR =1.107, 95% CI =0.838–1.462), dominant (XX+ YX vs YY: *P*=0.548; OR =1.091, 95% CI =0.821–1.449), and recessive (XX vs XY+YY: *P*=0.685; OR =0.928, 95% CI =0.646–1.333) genetic models (Figure 9).

The ethnicity-based stratification analysis included three studies from the Asian population. Publication bias was not found, whereas heterogeneity was detected in two genetic models (Table 13; Figure SI9). Likewise, no risk was observed with allelic (X vs Y: *P*=0.905; OR =1.027, 95% CI =0.661–1.598), homozygous (XX vs YY: *P*=0.662; OR =0.884, 95% CI =0.509–1.536), heterozygous (XY vs YY: *P*=0.659; OR =1.059, 95% CI =0.822–1.363), dominant (XX+ YX vs YY: *P*=0.866; OR =1.042, 95% CI =0.642–1.691), and recessive (XX vs XY+YY: *P*=0.676; OR =0.890, 95% CI =0.517–1.534) genetic models (Figure 10).

MBL2 rs11003125 polymorphism

Four case–control studies were included to calculate the pooled ORs, including 2,685 controls and 2,556 PTB cases, wherein no publication bias was found but three genetic models showed heterogeneity (Table 14; Figure SI10). The pooled ORs did not demonstrate any risk with PTB in allelic contrast (L vs H: *P*=0.995; OR =0.999, 95% CI =0.805–1.241), homozygous (LL vs HH: *P*=0.878; OR =1.026, 95% CI =0.736–1.431), heterozygous (LH vs HH: *P*=0.430; OR =1.240, 95% CI =0.727–2.113), dominant (LL+ LH vs HH: *P*=0.537; OR =1.182, 95% CI =0.695–2.012), and recessive (LL vs LH+ HH: *P*=0.256; OR =0.918, 95% CI =0.791–1.064) genetic models (Figure 11).

The results of meta-analysis of MBL2 gene polymorphisms, ie, rs1800450 A>B, rs1800451 A>C, rs5030737 A>D, combined rs1800450, rs1800451, rs5030737 A>O, rs7096206 Y>X, and rs11003125 H>L and their association with PTB susceptibility have been summarized in Table 15.
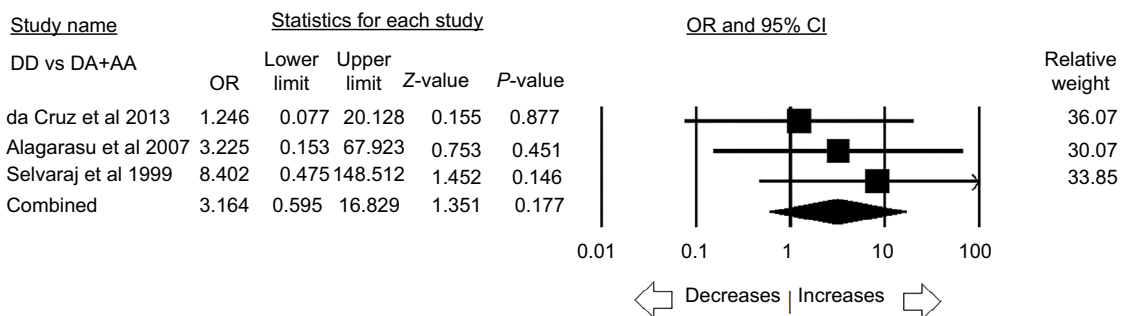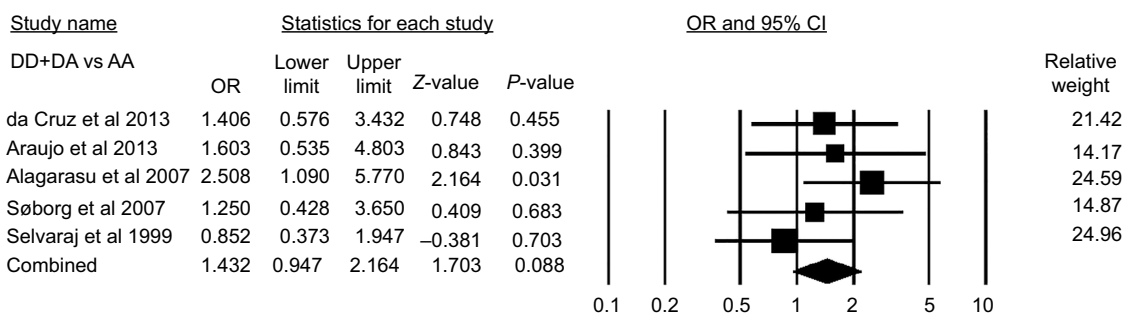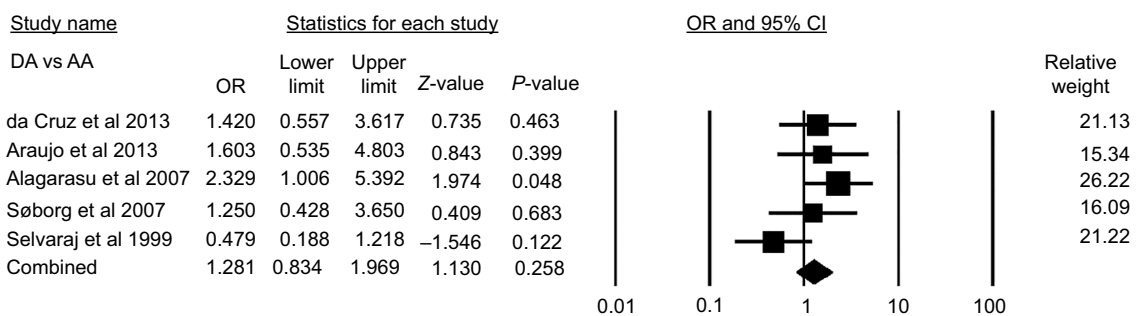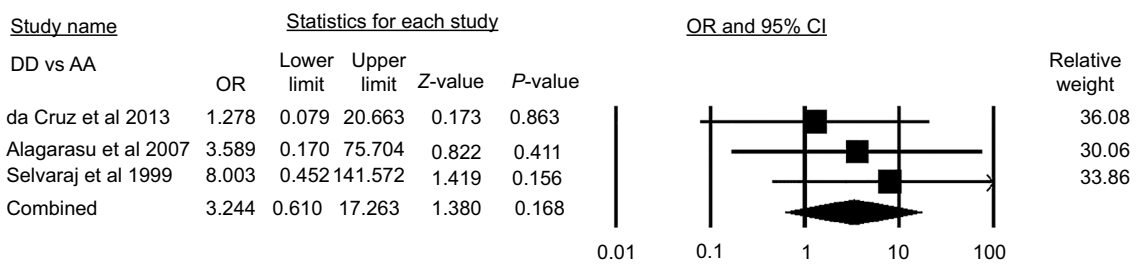
Study name | Statistics for each study | OR and 95% CI

D vs A

Study name	OR	Lower limit	Upper limit	Z-value	P-value	Relative weight
da Cruz et al 2013	1.376	0.596	3.176	0.747	0.455	22.15
Araujo et al 2013	1.576	0.537	4.628	0.827	0.408	13.36
Alagarasu et al 2007	2.538	1.137	5.662	2.274	0.023	24.07
Søborg et al 2007	1.247	0.430	3.617	0.406	0.685	13.67
Selvaraj et al 1999	1.256	0.586	2.689	0.586	0.558	26.74
Combined	1.563	1.054	2.317	2.223	0.026	

0.01   0.1   1   10   100

Study name | Statistics for each study | OR and 95% CI

DD vs AA

Study name	OR	Lower limit	Upper limit	Z-value	P-value	Relative weight
da Cruz et al 2013	1.278	0.079	20.663	0.173	0.863	36.08
Alagarasu et al 2007	3.589	0.170	75.704	0.822	0.411	30.06
Selvaraj et al 1999	8.003	0.452	141.572	1.419	0.156	33.86
Combined	3.244	0.610	17.263	1.380	0.168	

0.01   0.1   1   10   100

Study name | Statistics for each study | OR and 95% CI

DA vs AA

Study name	OR	Lower limit	Upper limit	Z-value	P-value	Relative weight
da Cruz et al 2013	1.420	0.557	3.617	0.735	0.463	21.13
Araujo et al 2013	1.603	0.535	4.803	0.843	0.399	15.34
Alagarasu et al 2007	2.329	1.006	5.392	1.974	0.048	26.22
Søborg et al 2007	1.250	0.428	3.650	0.409	0.683	16.09
Selvaraj et al 1999	0.479	0.188	1.218	−1.546	0.122	21.22
Combined	1.281	0.834	1.969	1.130	0.258	

0.01   0.1   1   10   100

Study name | Statistics for each study | OR and 95% CI

DD+DA vs AA

Study name	OR	Lower limit	Upper limit	Z-value	P-value	Relative weight
da Cruz et al 2013	1.406	0.576	3.432	0.748	0.455	21.42
Araujo et al 2013	1.603	0.535	4.803	0.843	0.399	14.17
Alagarasu et al 2007	2.508	1.090	5.770	2.164	0.031	24.59
Søborg et al 2007	1.250	0.428	3.650	0.409	0.683	14.87
Selvaraj et al 1999	0.852	0.373	1.947	−0.381	0.703	24.96
Combined	1.432	0.947	2.164	1.703	0.088	

0.1   0.2   0.5   1   2   5   10

Study name | Statistics for each study | OR and 95% CI

DD vs DA+AA

Study name	OR	Lower limit	Upper limit	Z-value	P-value	Relative weight
da Cruz et al 2013	1.246	0.077	20.128	0.155	0.877	36.07
Alagarasu et al 2007	3.225	0.153	67.923	0.753	0.451	30.07
Selvaraj et al 1999	8.402	0.475	148.512	1.452	0.146	33.85
Combined	3.164	0.595	16.829	1.351	0.177	

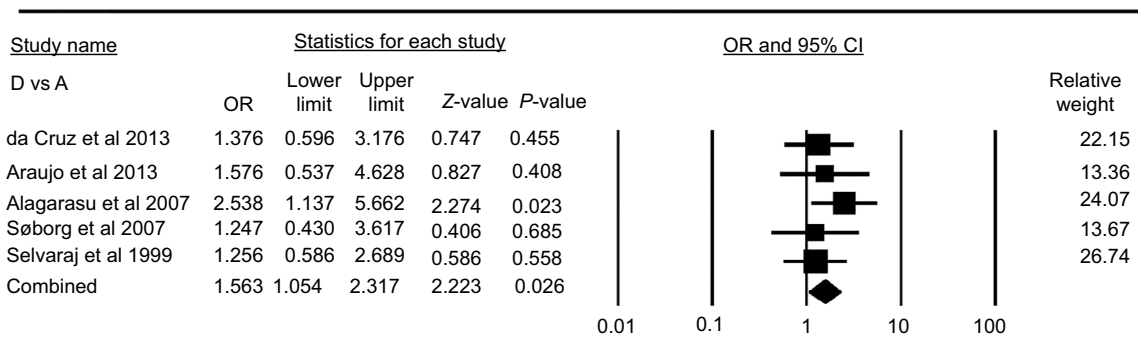0.01   0.1   1   10   100

Decreases | Increases

Figure 6 Forest plot of ORs with 95% CI of PTB risk associated with the rs5030737 (A>D) gene polymorphism for the overall population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
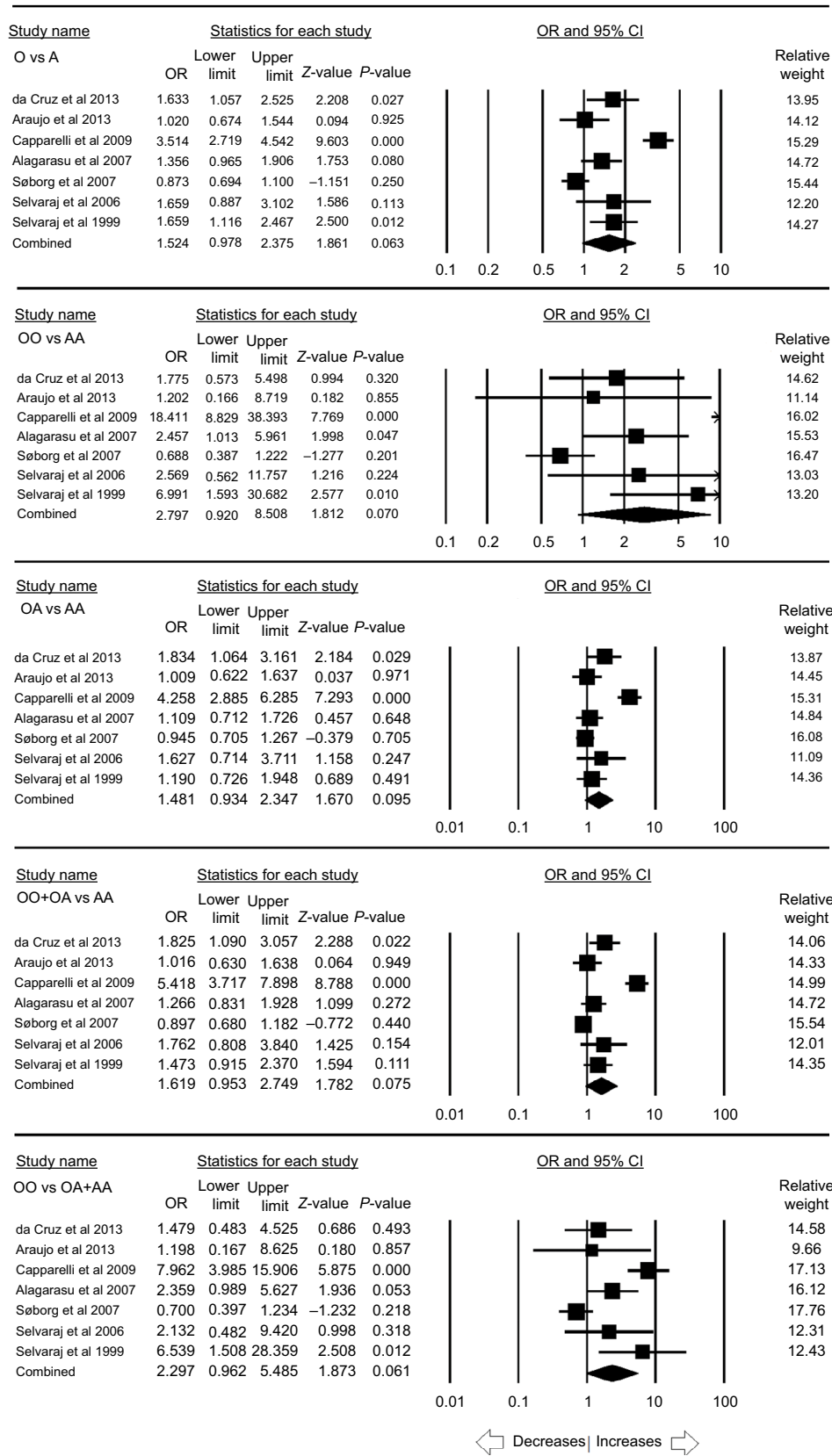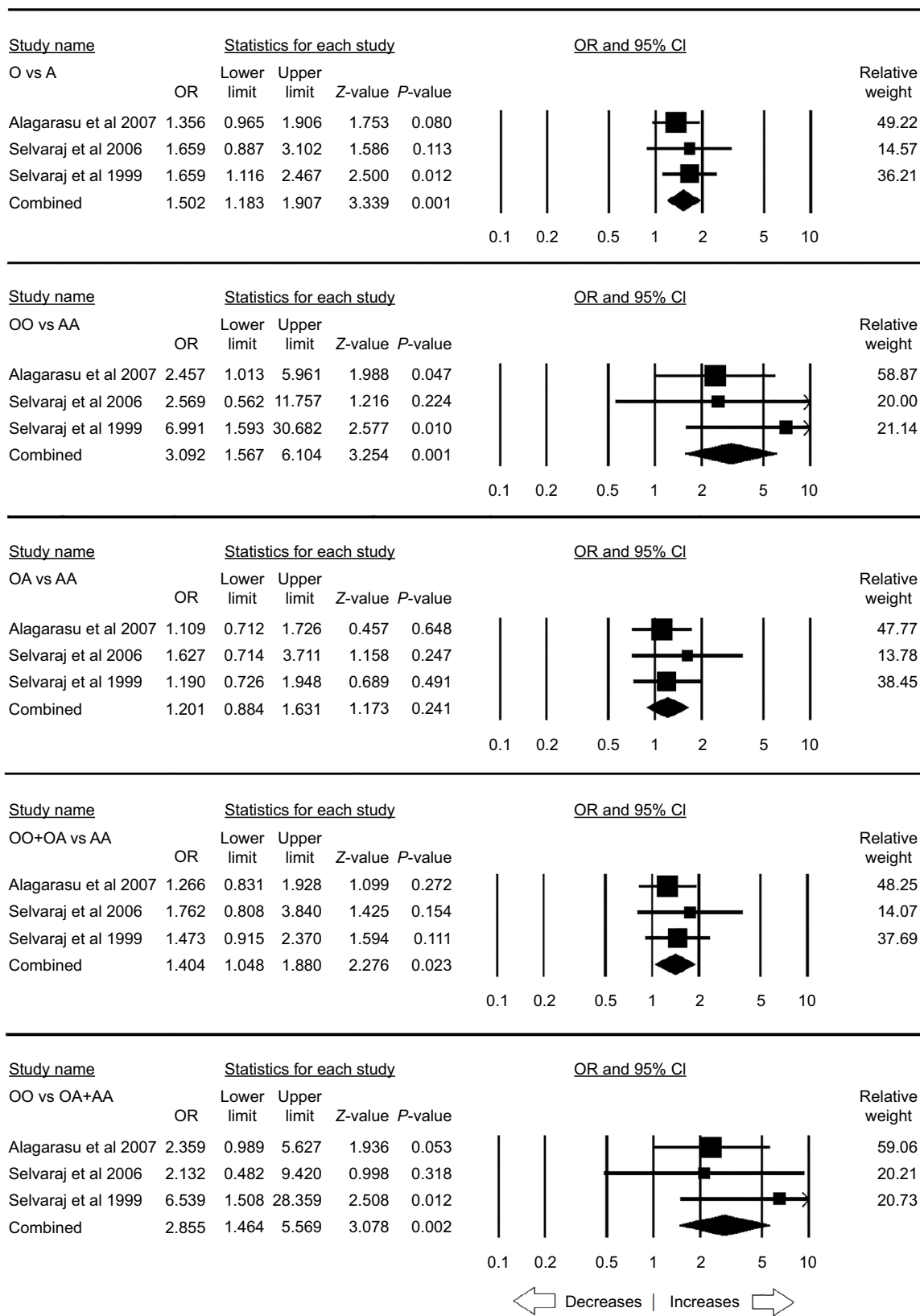**Abbreviation:** PTB, pulmonary tuberculosis.

Study name	Statistics for each study					OR and 95% CI	Relative weight
O vs A	OR	Lower limit	Upper limit	Z-value	P-value		
da Cruz et al 2013	1.633	1.057	2.525	2.208	0.027		13.95
Araujo et al 2013	1.020	0.674	1.544	0.094	0.925		14.12
Capparelli et al 2009	3.514	2.719	4.542	9.603	0.000		15.29
Alagarasu et al 2007	1.356	0.965	1.906	1.753	0.080		14.72
Søborg et al 2007	0.873	0.694	1.100	−1.151	0.250		15.44
Selvaraj et al 2006	1.659	0.887	3.102	1.586	0.113		12.20
Selvaraj et al 1999	1.659	1.116	2.467	2.500	0.012		14.27
Combined	1.524	0.978	2.375	1.861	0.063		

0.1 0.2 0.5 1 2 5 10

Study name	Statistics for each study					OR and 95% CI	Relative weight
OO vs AA	OR	Lower limit	Upper limit	Z-value	P-value		
da Cruz et al 2013	1.775	0.573	5.498	0.994	0.320		14.62
Araujo et al 2013	1.202	0.166	8.719	0.182	0.855		11.14
Capparelli et al 2009	18.411	8.829	38.393	7.769	0.000		16.02
Alagarasu et al 2007	2.457	1.013	5.961	1.998	0.047		15.53
Søborg et al 2007	0.688	0.387	1.222	−1.277	0.201		16.47
Selvaraj et al 2006	2.569	0.562	11.757	1.216	0.224		13.03
Selvaraj et al 1999	6.991	1.593	30.682	2.577	0.010		13.20
Combined	2.797	0.920	8.508	1.812	0.070		

0.1 0.2 0.5 1 2 5 10

Study name	Statistics for each study					OR and 95% CI	Relative weight
OA vs AA	OR	Lower limit	Upper limit	Z-value	P-value		
da Cruz et al 2013	1.834	1.064	3.161	2.184	0.029		13.87
Araujo et al 2013	1.009	0.622	1.637	0.037	0.971		14.45
Capparelli et al 2009	4.258	2.885	6.285	7.293	0.000		15.31
Alagarasu et al 2007	1.109	0.712	1.726	0.457	0.648		14.84
Søborg et al 2007	0.945	0.705	1.267	−0.379	0.705		16.08
Selvaraj et al 2006	1.627	0.714	3.711	1.158	0.247		11.09
Selvaraj et al 1999	1.190	0.726	1.948	0.689	0.491		14.36
Combined	1.481	0.934	2.347	1.670	0.095		

0.01 0.1 1 10 100

Study name	Statistics for each study					OR and 95% CI	Relative weight
OO+OA vs AA	OR	Lower limit	Upper limit	Z-value	P-value		
da Cruz et al 2013	1.825	1.090	3.057	2.288	0.022		14.06
Araujo et al 2013	1.016	0.630	1.638	0.064	0.949		14.33
Capparelli et al 2009	5.418	3.717	7.898	8.788	0.000		14.99
Alagarasu et al 2007	1.266	0.831	1.928	1.099	0.272		14.72
Søborg et al 2007	0.897	0.680	1.182	−0.772	0.440		15.54
Selvaraj et al 2006	1.762	0.808	3.840	1.425	0.154		12.01
Selvaraj et al 1999	1.473	0.915	2.370	1.594	0.111		14.35
Combined	1.619	0.953	2.749	1.782	0.075		

0.01 0.1 1 10 100

Study name	Statistics for each study					OR and 95% CI	Relative weight
OO vs OA+AA	OR	Lower limit	Upper limit	Z-value	P-value		
da Cruz et al 2013	1.479	0.483	4.525	0.686	0.493		14.58
Araujo et al 2013	1.198	0.167	8.625	0.180	0.857		9.66
Capparelli et al 2009	7.962	3.985	15.906	5.875	0.000		17.13
Alagarasu et al 2007	2.359	0.989	5.627	1.936	0.053		16.12
Søborg et al 2007	0.700	0.397	1.234	−1.232	0.218		17.76
Selvaraj et al 2006	2.132	0.482	9.420	0.998	0.318		12.31
Selvaraj et al 1999	6.539	1.508	28.359	2.508	0.012		12.43
Combined	2.297	0.962	5.485	1.873	0.061		

0.01 0.1 1 10 100

◁ Decreases | Increases ▷

Figure 7 Forest plot of ORs with 95% CI of PTB risk associated with MBL2 combined rs1800450, rs1800451, rs5030737 (A>O) gene polymorphism for the overall population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
Abbreviation: PTB, pulmonary tuberculosis.

Study name		Statistics for each study				OR and 95% CI	Relative weight
O vs A	OR	Lower limit	Upper limit	Z-value	P-value		
Alagarasu et al 2007	1.356	0.965	1.906	1.753	0.080		49.22
Selvaraj et al 2006	1.659	0.887	3.102	1.586	0.113		14.57
Selvaraj et al 1999	1.659	1.116	2.467	2.500	0.012		36.21
Combined	1.502	1.183	1.907	3.339	0.001		

0.1 0.2 0.5 1 2 5 10

Study name		Statistics for each study				OR and 95% CI	Relative weight
OO vs AA	OR	Lower limit	Upper limit	Z-value	P-value		
Alagarasu et al 2007	2.457	1.013	5.961	1.988	0.047		58.87
Selvaraj et al 2006	2.569	0.562	11.757	1.216	0.224		20.00
Selvaraj et al 1999	6.991	1.593	30.682	2.577	0.010		21.14
Combined	3.092	1.567	6.104	3.254	0.001		

0.1 0.2 0.5 1 2 5 10

Study name		Statistics for each study				OR and 95% CI	Relative weight
OA vs AA	OR	Lower limit	Upper limit	Z-value	P-value		
Alagarasu et al 2007	1.109	0.712	1.726	0.457	0.648		47.77
Selvaraj et al 2006	1.627	0.714	3.711	1.158	0.247		13.78
Selvaraj et al 1999	1.190	0.726	1.948	0.689	0.491		38.45
Combined	1.201	0.884	1.631	1.173	0.241		

0.1 0.2 0.5 1 2 5 10

Study name		Statistics for each study				OR and 95% CI	Relative weight
OO+OA vs AA	OR	Lower limit	Upper limit	Z-value	P-value		
Alagarasu et al 2007	1.266	0.831	1.928	1.099	0.272		48.25
Selvaraj et al 2006	1.762	0.808	3.840	1.425	0.154		14.07
Selvaraj et al 1999	1.473	0.915	2.370	1.594	0.111		37.69
Combined	1.404	1.048	1.880	2.276	0.023		

0.1 0.2 0.5 1 2 5 10

Study name		Statistics for each study				OR and 95% CI	Relative weight
OO vs OA+AA	OR	Lower limit	Upper limit	Z-value	P-value		
Alagarasu et al 2007	2.359	0.989	5.627	1.936	0.053		59.06
Selvaraj et al 2006	2.132	0.482	9.420	0.998	0.318		20.21
Selvaraj et al 1999	6.539	1.508	28.359	2.508	0.012		20.73
Combined	2.855	1.464	5.569	3.078	0.002		

0.1 0.2 0.5 1 2 5 10

⬅ Decreases | Increases ➡

Figure 8 Forest plot of ORs with 95% CI of PTB risk associated with MBL2 combined rs1800450, rs1800451, rs5030737 (A>O) gene polymorphism for the Asian population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
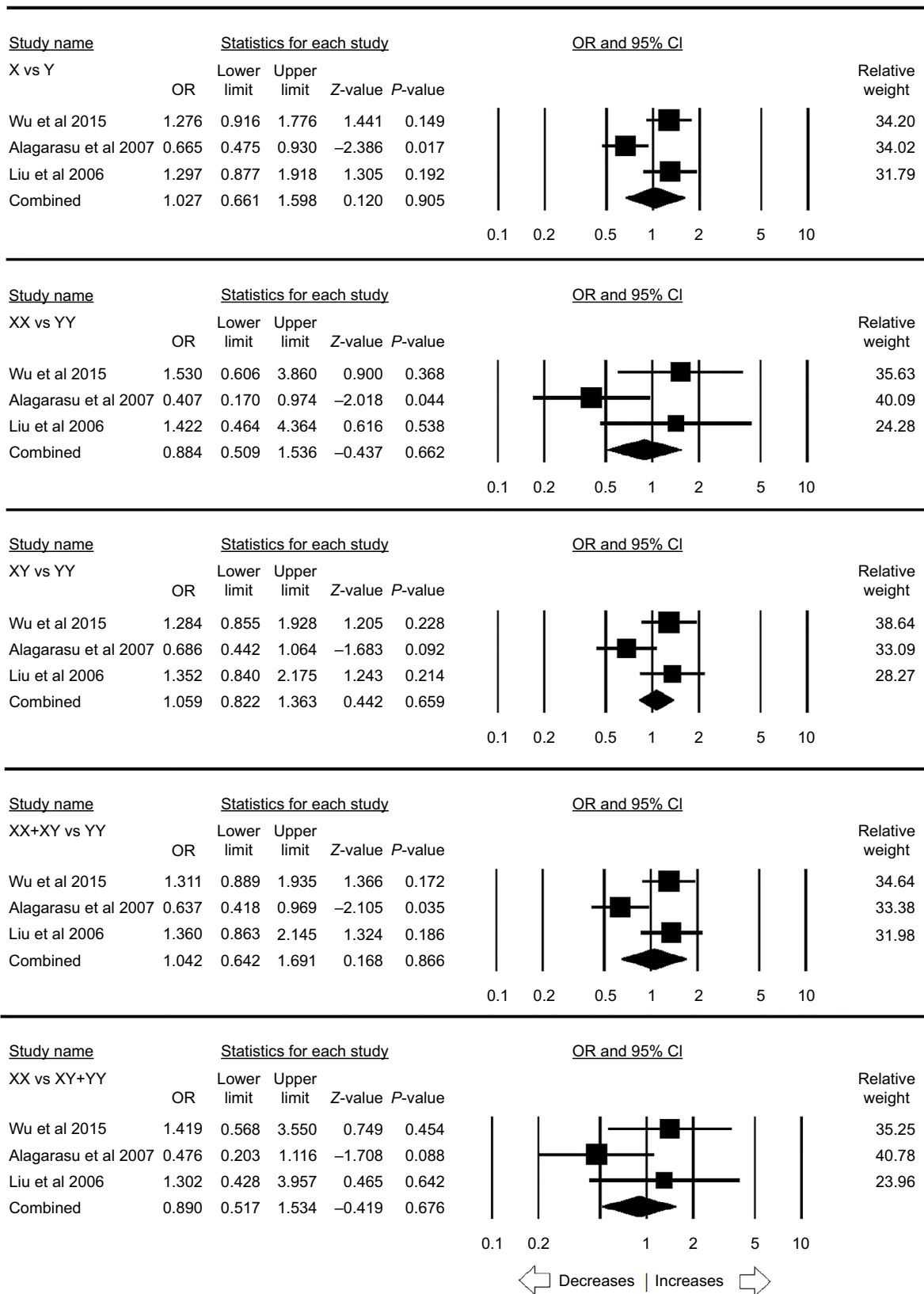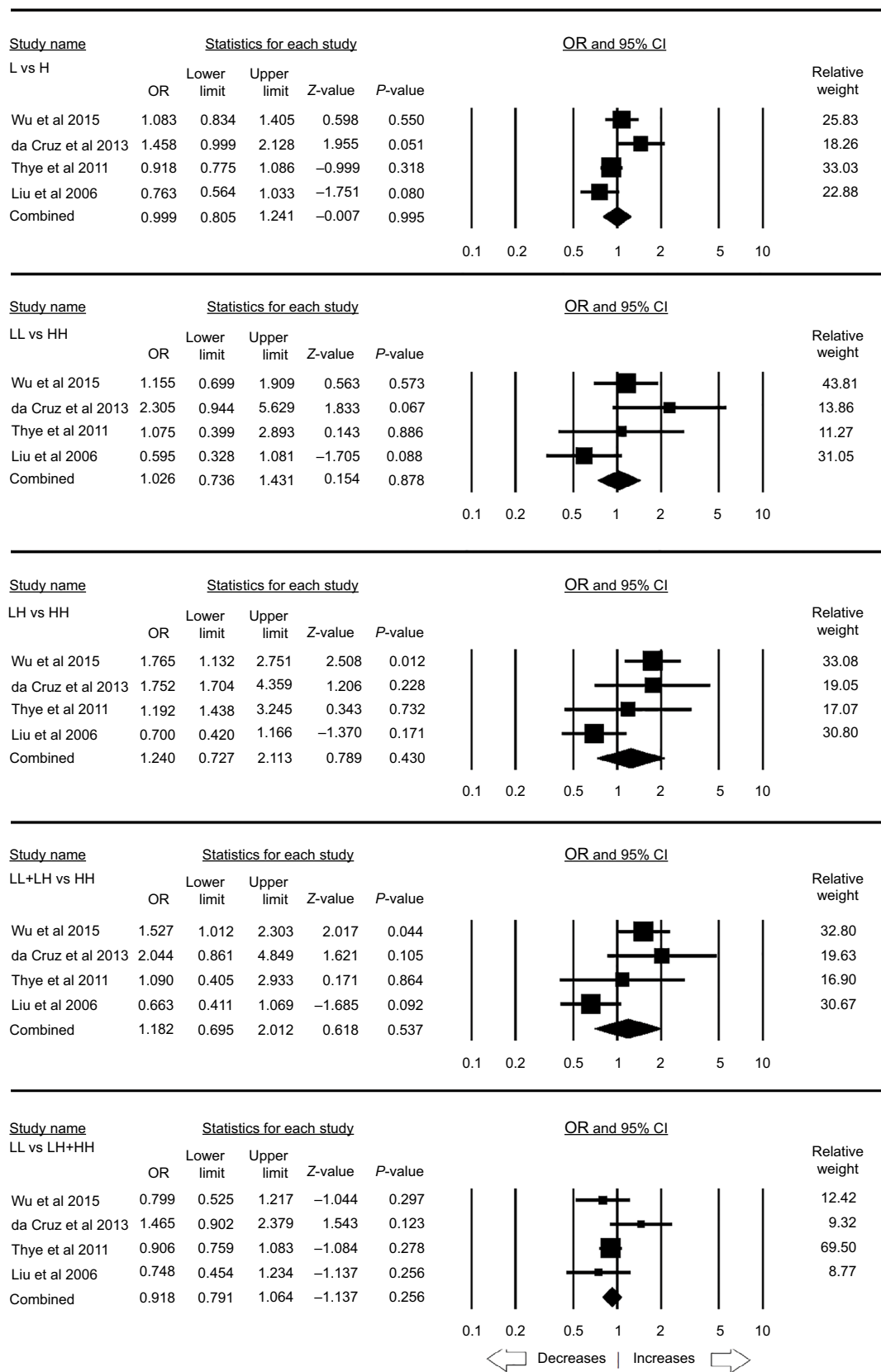**Abbreviation:** PTB, pulmonary tuberculosis.

Table 12 Statistics to test the publication bias and heterogeneity (rs7096206 overall)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% CI	*P*-value	Q-value	$P_{heterogeneity}$	I^2 (%)	
X vs Y	1.37	–4.30 to 7.03	0.50	12.54	0.01	68.11	Random
XX vs YY	0.28	–5.45 to 6.02	0.88	5.13	0.27	22.10	Fixed
XY vs YY	1.56	–2.99 to 6.11	0.35	11.08	0.03	63.13	Random
XX + XY vs YY	1.44	–3.74 to 6.62	0.44	12.55	0.01	68.13	Random
XX vs XY + YY	0.01	–4.88 to 4.91	0.99	3.62	0.46	0.00	Fixed

Table 13 Statistics to test the publication bias and heterogeneity (rs7096206 Asian)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% CI	*P*-value	Q-value	$P_{heterogeneity}$	I^2 (%)	
X vs Y	9.80	–272.33 to 291.93	0.73	9.46	0.009	78.85	Random
XX vs YY	7.87	–117.43 to 133.17	0.57	5.07	0.08	60.57	Fixed
XY vs YY	0.09	–273.75 to 273.95	0.99	5.63	0.06	64.50	Fixed
XX + XY vs YY	–0.39	–321.95 to –321.15	0.99	7.93	0.02	74.78	Random
XX vs XY + YY	6.45	–90.85 to 103.75	0.55	3.52	0.17	43.15	Fixed

Table 14 Statistics to test the publication bias and heterogeneity (rs11003125 overall)

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for the meta-analysis
	Intercept	95% CI	*P*-value	Q-value	$P_{heterogeneity}$	I^2 (%)	
L vs H	2.21	–10.49 to 14.91	0.53	7.98	0.05	62.39	Random
LL vs HH	1.88	–11.54 to 15.31	0.61	6.58	0.09	54.42	Fixed
LH vs HH	0.14	–12.97 to 13.24	0.97	7.81	0.05	61.58	Random
LL + LH vs HH	0.67	–12.35 to 13.69	0.85	8.64	0.03	65.26	Random
LL vs LH + HH	0.39	–6.83 to 7.59	0.84	4.65	0.20	35.43	Fixed

Sensitivity analysis

To examine the influence of each individual study on the overall risk of PTB, sensitivity analysis was accomplished. Leave-one-out sensitivity analysis (excluding single case–control study at a time) was performed and the pooled ORs recomputed for each genetic variant of MBL2. The same was tested during the subgroup analysis by the ethnicity. The ORs estimated for each polymorphism of MBL2 gene after excluding a single study did not show any major difference from the primary values (rs1800450 [A>B] [Overall: Figure SI11, Asian: Figure SI12]; rs1800451 [A>C] [Overall: Figure SI13, African: Figure SI14]; rs5030737 [A>D] [Overall: Figure SI15]; combined rs1800450, rs1800451, rs5030737 [A>O] [Overall: Figure SI16, Asian: Figure SI17]; rs7096206 [Y>X] [Overall: Figure SI18, Asian: Figure SI19], rs11003125 [H>L] [Overall: Figure SI20]) of these genetic variants. This analysis guaranteed the stability of the overall results of this meta-analysis.

Trial sequential analysis

TSA was used to investigate the relevance of MBL2 rs1800450 A>B, rs1800451 A>C, rs5030737 A>D, combined rs1800450, rs1800451, rs5030737 A>O, rs7096206 Y>X, and rs11003125 H>L gene polymorphisms with PTB susceptibility. The dominant model was used to study all these polymorphisms. As shown in Figure 12, the required information size for MBL2 rs1800450, rs1800451, and rs5030737 polymorphisms was 5,876, 24,257 and 3,611 patients, respectively. However, the accrued information size remained 4,047, 6,796, and 1,611. Similarly, for the promoter variants rs7096206, rs11003125, and combined structural polymorphism (A>O) of MBL2, the accrued information size was 4,340, 5,241 and 2,785, but the required information size was 19,554, 12,897, and 40,517, respectively (Figure 13). As depicted in Figures 12 and 13, the cumulative *Z*-curve of all the studied polymorphisms did not cross the trial monitoring boundary before reaching the required information size,
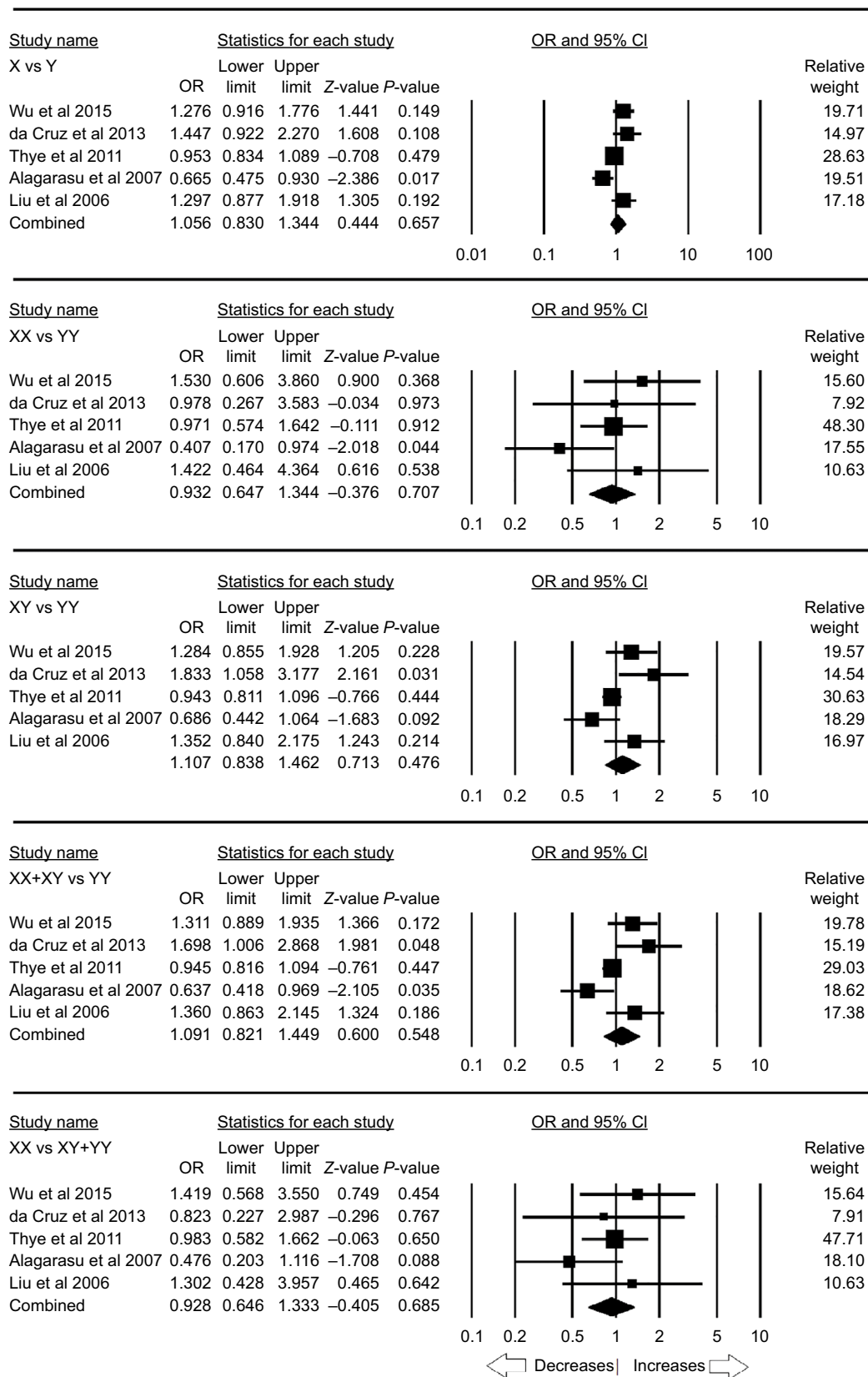
Figure 9 Forest plot of ORs with 95% CI of PTB risk associated with MBL2 rs7096206 (Y>X) gene polymorphism for the overall population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
Abbreviation: PTB, pulmonary tuberculosis.

Study name						OR and 95% CI	Relative
X vs Y		Statistics for each study					weight
	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.276	0.916	1.776	1.441	0.149		34.20
Alagarasu et al 2007	0.665	0.475	0.930	−2.386	0.017		34.02
Liu et al 2006	1.297	0.877	1.918	1.305	0.192		31.79
Combined	1.027	0.661	1.598	0.120	0.905		

0.1 0.2 0.5 1 2 5 10

Study name						OR and 95% CI	Relative
XX vs YY		Statistics for each study					weight
	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.530	0.606	3.860	0.900	0.368		35.63
Alagarasu et al 2007	0.407	0.170	0.974	−2.018	0.044		40.09
Liu et al 2006	1.422	0.464	4.364	0.616	0.538		24.28
Combined	0.884	0.509	1.536	−0.437	0.662		

0.1 0.2 0.5 1 2 5 10

Study name						OR and 95% CI	Relative
XY vs YY		Statistics for each study					weight
	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.284	0.855	1.928	1.205	0.228		38.64
Alagarasu et al 2007	0.686	0.442	1.064	−1.683	0.092		33.09
Liu et al 2006	1.352	0.840	2.175	1.243	0.214		28.27
Combined	1.059	0.822	1.363	0.442	0.659		

0.1 0.2 0.5 1 2 5 10

Study name						OR and 95% CI	Relative
XX+XY vs YY		Statistics for each study					weight
	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.311	0.889	1.935	1.366	0.172		34.64
Alagarasu et al 2007	0.637	0.418	0.969	−2.105	0.035		33.38
Liu et al 2006	1.360	0.863	2.145	1.324	0.186		31.98
Combined	1.042	0.642	1.691	0.168	0.866		

0.1 0.2 0.5 1 2 5 10

Study name						OR and 95% CI	Relative
XX vs XY+YY		Statistics for each study					weight
	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.419	0.568	3.550	0.749	0.454		35.25
Alagarasu et al 2007	0.476	0.203	1.116	−1.708	0.088		40.78
Liu et al 2006	1.302	0.428	3.957	0.465	0.642		23.96
Combined	0.890	0.517	1.534	−0.419	0.676		

0.1 0.2 0.5 1 2 5 10

Decreases | Increases

Figure 10 Forest plot of ORs with 95% CI of PTB risk associated with MBL2 rs7096206 (Y>X) gene polymorphism for the Asian population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
Abbreviation: PTB, pulmonary tuberculosis.

Study name		Statistics for each study				OR and 95% CI	Relative weight
L vs H	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.083	0.834	1.405	0.598	0.550		25.83
da Cruz et al 2013	1.458	0.999	2.128	1.955	0.051		18.26
Thye et al 2011	0.918	0.775	1.086	−0.999	0.318		33.03
Liu et al 2006	0.763	0.564	1.033	−1.751	0.080		22.88
Combined	0.999	0.805	1.241	−0.007	0.995		

0.1 0.2 0.5 1 2 5 10

Study name		Statistics for each study				OR and 95% CI	Relative weight
LL vs HH	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.155	0.699	1.909	0.563	0.573		43.81
da Cruz et al 2013	2.305	0.944	5.629	1.833	0.067		13.86
Thye et al 2011	1.075	0.399	2.893	0.143	0.886		11.27
Liu et al 2006	0.595	0.328	1.081	−1.705	0.088		31.05
Combined	1.026	0.736	1.431	0.154	0.878		

0.1 0.2 0.5 1 2 5 10

Study name		Statistics for each study				OR and 95% CI	Relative weight
LH vs HH	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.765	1.132	2.751	2.508	0.012		33.08
da Cruz et al 2013	1.752	1.704	4.359	1.206	0.228		19.05
Thye et al 2011	1.192	1.438	3.245	0.343	0.732		17.07
Liu et al 2006	0.700	0.420	1.166	−1.370	0.171		30.80
Combined	1.240	0.727	2.113	0.789	0.430		

0.1 0.2 0.5 1 2 5 10

Study name		Statistics for each study				OR and 95% CI	Relative weight
LL+LH vs HH	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	1.527	1.012	2.303	2.017	0.044		32.80
da Cruz et al 2013	2.044	0.861	4.849	1.621	0.105		19.63
Thye et al 2011	1.090	0.405	2.933	0.171	0.864		16.90
Liu et al 2006	0.663	0.411	1.069	−1.685	0.092		30.67
Combined	1.182	0.695	2.012	0.618	0.537		

0.1 0.2 0.5 1 2 5 10

Study name		Statistics for each study				OR and 95% CI	Relative weight
LL vs LH+HH	OR	Lower limit	Upper limit	Z-value	P-value		
Wu et al 2015	0.799	0.525	1.217	−1.044	0.297		12.42
da Cruz et al 2013	1.465	0.902	2.379	1.543	0.123		9.32
Thye et al 2011	0.906	0.759	1.083	−1.084	0.278		69.50
Liu et al 2006	0.748	0.454	1.234	−1.137	0.256		8.77
Combined	0.918	0.791	1.064	−1.137	0.256		

0.1 0.2 0.5 1 2 5 10

◁ Decreases | Increases ▷

Figure 11 Forest plot of ORs with 95% CI of PTB risk associated with MBL2 rs11003125 (H>L) gene polymorphism for the overall population.
Notes: Black squares represent the value of OR and the size of the square indicates the inverse proportion relative to its variance. Horizontal lines represent the 95% CI of OR.
Abbreviation: PTB, pulmonary tuberculosis.

Table 15 Summary of the results of association of MBL2 gene polymorphisms and PTB risk (overall and ethnicity-wise analysis)

MBL2 gene polymorphisms	Association	Ethnicity
rs1800450 A>B	Overall	Asian
B vs A	No risk	No risk
BB vs AA	No risk	No risk
BA vs AA	No risk	No risk
BB + BA vs AA	No risk	No risk
BB vs BA + AA	No risk	No risk
rs1800451 A>C	Overall	African
C vs A	No risk	Reduced risk
CC vs AA	Reduced risk	Reduced risk
CA vs AA	No risk	No risk
CC + CA vs AA	No risk	No risk
CC vs CA + AA	No risk	No risk
rs5030737 A>D	Overall	Not studied
D vs A	Increased risk	Not studied (due to inadequate studies)
DD vs AA	No risk	
DA vs AA	No risk	
DD + DA vs AA	No risk	
DD vs DA + AA	No risk	
Combined rs1800450, 1800451, rs5030737 O>A	Overall	Asian
O vs A	No risk	Increased risk
OO vs AA	No risk	Increased risk
OA vs AA	No risk	No risk
OO + OA vs AA	No risk	No risk
OO vs OA + AA	No risk	Increased risk
rs7096206 Y>X	Overall	Asian
X vs Y	No risk	No risk
XX vs YY	No risk	No risk
XY vs YY	No risk	No risk
XX + YX vs YY	No risk	No risk
XX vs XY + YY	No risk	No risk
rs11003125 H>L	Overall	Not studied
L vs H	No risk	
LL vs HH	No risk	Not studied (due to inadequate studies)
LH vs HH	No risk	
LL + LH vs HH	No risk	
LL vs LH + HH	No risk	

Abbreviation: PTB, pulmonary tuberculosis.

indicating the cumulative evidence was not sufficient and further trials are needed (Figures 12 and 13).

Discussion

The passing years have proved the worth of SNPs as the most common and effective type of genetic variations studied in correlation with susceptibility to various diseases and have the potential to be considered as the markers for many complex diseases.[41] The differences in susceptibility to infections are determined by the host genetic factors and the first line of the host defense is innate immunity. Therefore, genetic variations in components of innate immunity may influence susceptibility to infections.[6]

The humoral immunity against PTB is mediated by the innate immune components with the help of interference by many complement proteins. The diverse pattern-recognizing receptors or soluble pathogen-recognizing molecules (PRMs) enable innate immune system to recognize molecular motifs on pathogenic surfaces.[6] One of the C-type soluble PRMs is MBL, which is secreted as a part of the acute-phase response by the liver. The MBL plays an important role in recognizing, initiating, regulating, and amplifying the innate immune defense.[42]

The MBL triggers the lectin complement pathway after it recognizes the target microorganisms. The multiple opsonin C3b fragments are developed by this activation of
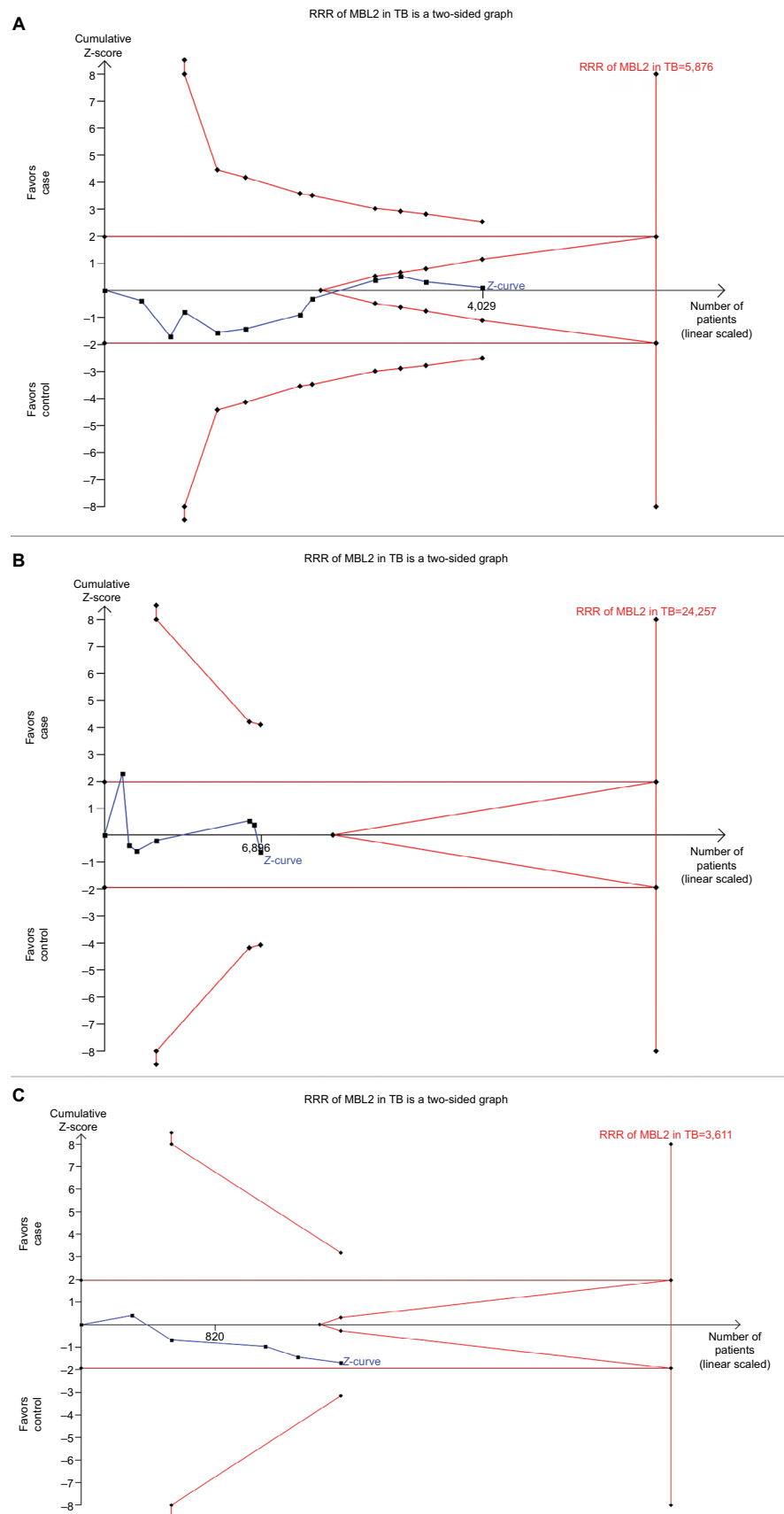
Figure 12 Trial sequence analysis of all the included studies dealing with MBL2 gene polymorphisms, based on dominant genetic model, and PTB risk: (**A**) rs1800450 (A>B), (**B**) rs1800451 (A>C), and (**C**) rs5030737 (A>D).
Abbreviations: PTB, pulmonary tuberculosis; RRR, relative risk reduction.

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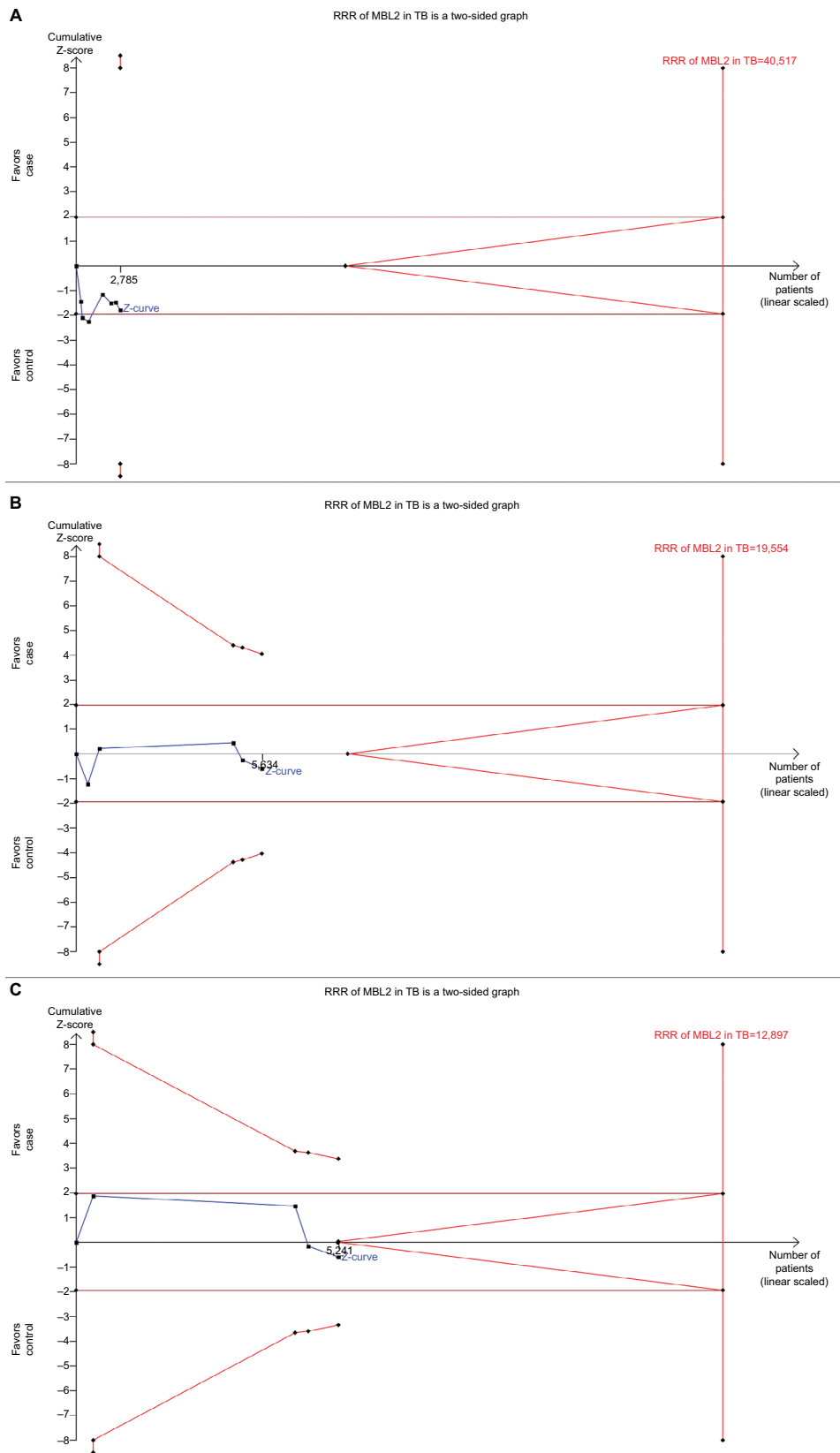
Figure 13 Trial sequence analysis of all the included studies dealing with MBL2 gene polymorphisms, based on dominant genetic model, and PTB risk: (**A**) combined rs1800450, rs1800451, rs5030737 (A>O), (**B**) rs7096206 (Y>X), and (**C**) rs11003125 (H>L).
Abbreviation: PTB, pulmonary tuberculosis.

complement cascade, which eventually causes phagocytosis of the pathogen primarily by receptors of CR1 (CD35). The MBL is also believed to promote opsonophagocytosis of organisms directly and the clearance of apoptotic cells through various putative receptors.[43]

Since MBL plays an important role in microorganism recognition during different stages of immunity, it possibly plays a significant role in the interaction of *M. tuberculosis* with the host. The MBL/MBP, a product of MBL2 gene, binds to the mannose groups present on several types of bacteria. MBP forms complexes with *Mycobacteria* and during diffusion in the blood enables their enhanced macrophage uptake. Thus, MBP binds and opsonizes *Mycobacteria* in order to boost their phagocytosis.[44] Earlier studies suggest that it is the phosphatidylinositol mannoside present on *M. tuberculosis* that binds with human MBP.[45] Lipoarabinomannan present in *M. tuberculosis* cell wall acts as a binding protein, thereby enabling their uptake by the host macrophages. The variations in MBL protein serum levels have been reported to be influenced by SNPs located within the MBL2 gene promoter region and exon 1 by several studies.[19–31] Inherited deficiency of MBL may impair the innate immune function, which may further lead to increased risk for the development of various infectious diseases including PTB.[18]

Previously, several case–control studies have reported the association of MBL2 gene polymorphisms and PTB susceptibility with inconsistency and lack of clarity. This may be because of their small sample sizes and ethnic variations leading to inadequate statistical power. Therefore, the current study was conducted to solve this conflict to provide a strong statistical basis and evidence for association of MBL2 gene polymorphisms and PTB susceptibility. The cumulative large sample size generates pooled ORs with sufficient statistical power and reduced random errors advantage.[46]

This is the first dedicated meta-analytic study to evaluate the association between MBL2 gene polymorphisms and overall PTB susceptibility. This analysis included 14 studies considering all the eligible criteria. Most of the included studies have clearly described sample sizes, genotypes, case and healthy control descriptions. We found a significant reduced PTB risk associated with variant allele and homozygous genotype of rs1800451 (A>C) polymorphism. This suggests that individuals carrying homozygous genotype for MBL2 polymorphism may have a reduced risk for PTB in general. The homozygous variant may have a protective effect and helps the host in resisting infection and thereby PTB susceptibility. The enhanced resistance to mycobacterial infection might lead to high frequency of MBP variant

alleles in diverse populations.[47] Conversely, variant allele of rs5030737 (A>D) showed increased risk to PTB. This indicates the dual role played by MBL2 polymorphism as a modifying gene in PTB development. Our data reiterate the support to the findings reporting involvement of the effects of combined host gene polymorphisms in the progression of *M. tuberculosis* infection. However, further large sample studies involving diverse populations are required for the confirmation.

Other MBL2 genetic polymorphisms, rs1800450 (A>B); combined polymorphisms rs1800450, rs1800451, rs5030737 (A>O); rs7096206 (Y>X); rs11003125 (H>L) did not show association with any increased or decreased risk of PTB in this analysis. Further investigations based on subgroup ethnicity found that rs1800451 (A>C) was associated with decreased PTB risk in the African population. Also, the combined polymorphisms (A>O) showed an increased PTB risk in the Asian population. However, the conclusions for the subgroup ethnicity analysis were suffered by the small sample size limitation which further warrants the studies to be conducted on a larger scale.

PTB is a multifactorial disease, which suggests that its susceptibility depends not only on the host genetic factors but also on the characteristics of infecting *Mycobacteria* and its interactions with other environmental factors.[48] The host and *M. tuberculosis* have evolved simultaneously over time, and the individual strains have adapted to their respective populations.[49] Hence, MBL2 gene polymorphisms alone could not be attributed for PTB predisposition.

As this study showed significant heterogeneity, we tried to minimize the likelihood of heterogeneity problem by performing the data analysis using random-effects model to obtain wider 95% CI. In addition, when studies were stratified by ethnicity, low heterogeneity was found in both, Asian and African population. Hence, we considered that the racial differences and ethnic origin of the study population, inadequate selection criteria of the subjects, and small sample size of each included study might be responsible for the foremost source of heterogeneity. Though, there are some limitations warranting to be addressed: firstly, the studies published in the English language and available from the selected electronic databases were included for this analysis, which makes it probable that some studies published in other languages or indexed in other electronic databases may have been missed; secondly, our results are based on unadjusted ORs; thirdly, our study is deficient in testing of gene–environment interactions because of insufficiency of the data available in the primary selected studies.

In opposition to the above stated limitations, the current study was complemented with several advantages as well including the testing of the publication bias and sensitivity analysis. No obvious publication bias was observed, and the results were robust as no single study yielded an obvious effect on the pooled ORs and the corresponding CIs during sensitivity analysis.

Conclusion

A meta-analysis is a powerful technique that provides a consensus using available data from different individual studies. The results of this study demonstrated that MBL2 rs1800451 (A>C) and rs5030737 (A>D) gene polymorphisms play a significant role in the risk of PTB disease. PTB has a significant public health impact. Hence, studies with a definite concept and character for MBL2 gene and infection or replication of *M. tuberculosis* are needed. The findings of this pooled study will help in augmenting the understanding associated with the role of MBL2 rs1800451 (A>C) and rs5030737 (A>D) gene polymorphisms and also aid in identifying the individuals prone to PTB infection. This eventually could be advantageous in achieving optimal therapeutic interventions to individual PTB patients. This study will also prove helpful for complete genotype profiling of MBL2 gene for PTB susceptibility and thereby would greatly assist in global control and outcome of this infectious disease. Moreover, this study also instigates the execution of studies with large sample sizes to decipher the potential molecular mechanism underlying PTB infection, ultimately aiding in development of molecular approaches for the detection of susceptible genotypes.

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Author contributions

Conceived and designed the study and experiments: RKM, MAK, AH, SAD, AJ, MW, AKP, ML, NA, SK, BNM, and SH. Performed the experiments: RKM, MAK, AH, SAD, AJ, AKP, SK, and SH. Analyzed the data: RKM, SAD, AKP, SK, and SH. Contributed reagents/materials/analysis tools: MAK, AH, MW, ML, NA, and BNM. Wrote the paper: RKM, SAD, AJ, SK, and SH. All authors reviewed the manuscript. All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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