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Lack of Association Between the *IL1B* (−511 and +3954), *IL1RN* VNTR Polymorphisms and Tuberculosis Risk: A Meta-analysis

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Abstract
Background Several recent studies have provided evidence that polymorphisms in the interleukin-1 (*IL1*) gene are implicated in tuberculosis (TB). However, results of different studies are inconsistent. The aim of this study was to perform a meta-analysis investigating the association of the *IL1B* (−511 and +3954) and *IL1RN* VNTR polymorphisms with TB risk.
Methods A systematic review of the English literature was conducted by searching Pubmed, Scopus, and ISI Web of Knowledge databases for relevant studies. Pooled odds ratios (OR) with 95 % confidence intervals (CI) were calculated using fixed effects models. Between-study heterogeneity and publication bias were also evaluated.
Results Nine case–control studies including 3327 participants were reviewed and analyzed. Our results did not indicate any association of the *IL1B* (−511 and +3954) and *IL1RN* VNTR polymorphisms with TB risk in the overall populations. The pooled OR of the *IL1B* −511 polymorphism was 1.09 (95 % CI 0.87–1.36) for the dominant model, 1.11 (0.89–1.38) for the recessive model, 1.15 (0.87–1.50) for the homozygote model, and 1.07 (0.94–1.23) for the allelic comparison model. ORs for the *IL1B* +3954 and *IL1RN* VNTR polymorphisms were similar. In subgroup analysis stratified by ethnicity, the results revealed no association between these polymorphisms and TB risk in black people, Asians, and Caucasians, respectively. We did not identify significant between-study heterogeneity across all studies, and there was no evidence of publication bias.
Conclusions Our results indicate there is a lack of association between the *IL1B* (−511 and +3954), *IL1RN* VNTR polymorphisms and TB risk.

Keywords Interleukin-1 · Meta-analysis · Polymorphism · Tuberculosis

Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (Mtb) remains a major source of morbidity and mortality worldwide [1]. According to the World Health Organization (WHO), approximately 2 million individuals die of TB and 9 million become infected each year. Although TB is a highly infective disease, only 10 % of infected persons ever develop clinical disease [2]. The susceptibility to active TB can be influenced by complex interactions between environmental and host genetic factors. Several lines of evidence from genome-wide linkage studies and association-based candidate gene studies have defined a number of susceptibility genes for the development of active TB, including genes encoding major histocompatibility complex (MHC), human homologue of the murine natural resistance-associated macrophage protein 1 (NRAMP1), vitamin D receptor (VDR), cluster of differentiation (CD14), and tumor necrosis factor-alpha (TNF-α) [3, 4]. A better understanding of the genetic regulation of susceptibility to TB may help unravel pathogenesis of the disease and improve treatment.

The IL-1 family of cytokines consists of IL-1A, IL-1B, and IL-1 receptor antagonist (IL-1RA). IL-1A and IL-1B are proinflammatory cytokines involved in initiating and

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propagating immune and inflammatory reactions. IL1RA binds to the IL1 receptor and acts as a competitive inhibitor of the other two. The genes encoding for these cytokines are located close to one another on chromosome 2q13-14 and have several common polymorphic variations. *IL1B* has two base-exchange polymorphisms, at position −511 in the promoter region (rs16944) and at position +3954 in exon 5 (rs1143634) [5]. The *IL1RN* gene has a variable number tandem repeat (VNTR) polymorphism in intron 2 which is characterized by 86 base pair (bp) tandem repeats (rs2234663) [6]. Several studies have evaluated the relationship of these polymorphisms with TB risk in black people, Asians, and Caucasians [7–15]. However, the results obtained are controversial. We sought to summarize the current evidence on the association between the *IL1B* (−511 and +3954) and *IL1RN* VNTR polymorphisms and TB by systematically reviewing the literature and performing a meta-analysis.

Materials and Methods

Selection of Studies

We conducted an extensive search of Pubmed, Scopus, and ISI Web of Knowledge databases (from inception to May 2015) using the following key words: "interleukin-1," "IL-1," "rs16944," "rs1143634," "rs2234663," "tuberculosis," "polymorphism," and "gene." Only papers published in the English language were considered for inclusion. A secondary search consisted of manual scrutiny of the reference lists of original studies and review articles identified by the electronic searches to find other eligible studies. Two authors independently sorted all studies from the searches using titles and abstracts; discrepancies were resolved by mutual consent. Human studies, regardless of sample size, were included if they met the following criteria: (1) case–control studies; (3) sufficient data for examining an odds ratio (OR) with 95 % confidence interval (95 % CI). The exclusion criteria were (1) family-based studies; (2) animal studies; (3) insufficient data; (4) duplicated data; and (5) studies published in languages other than English.

Data Extraction

For each study, the following data were extracted independently by two authors using standard forms: first author, year of publication, country of origin, ethnicity, disease type, HIV status of subjects, case and control sample size, genotyping method, and genotype distribution for each variant investigated in cases and controls. The ethnicity of each study population was defined as the ethnic group of 90 % or more of the study subjects.

Statistical Analysis

The association between each variant and the risk of TB was examined based on the dominant, recessive, homozygote, and allelic comparison models. The significance of the summary OR was determined by the Z test, with $P < 0.05$ considered statistically significant. The heterogeneity between studies was tested using the Q-statistic, and the heterogeneity was considered significant at $P < 0.10$. In the absence of significant heterogeneity, summary OR and 95 % CI were estimated under the fixed effects model (Mantel–Haenszel) [16]; otherwise, the random effects model (DerSimonian–Laird) was employed [17]. A fixed effects model considers only within-study heterogeneity, whereas a random effects model allows for both between-study and within-study heterogeneity. To determine if genetic differences of the included populations in the various studies played a role in obtaining discordant results between studies, subgroup analyses were performed based on ethnicity. A sensitivity analysis which examines the effect of excluding specific studies was also considered. Publication bias was evaluated through the Begg's test. For publication bias, $P < 0.05$ was considered statistically significant. As fewer than ten studies qualified for each polymorphism, funnel plots were not performed to assess publication bias. The distribution of genotypes in control subjects of each individual population was tested for departure of Hardy–Weinberg equilibrium (HWE) by means of the χ^2 test. For the *IL1RN* VNTR polymorphism, L signifies any long allele embracing allele 1, 3, 4, or 5. All statistical analyses were performed using Stata version 11.0.

Results

Study Characteristics

Figure 1 presents a flow chart of the retrieved and excluded studies with specification of reasons. We reviewed 117 titles and abstracts and obtained 12 full-text papers. We identified nine case–control studies that met the inclusion criteria, with a total of 1772 cases and 1555 controls [7–15]. The characteristics of the individual studies included in the meta-analysis are provided in Table 1. Three studies were performed in black people [7, 8, 10], three studies were undertaken in Asians [9, 12, 14], and three studies were conducted in Caucasians [11, 13, 15]. Eight studies evaluated only pulmonary TB [7, 9–15], whereas one study

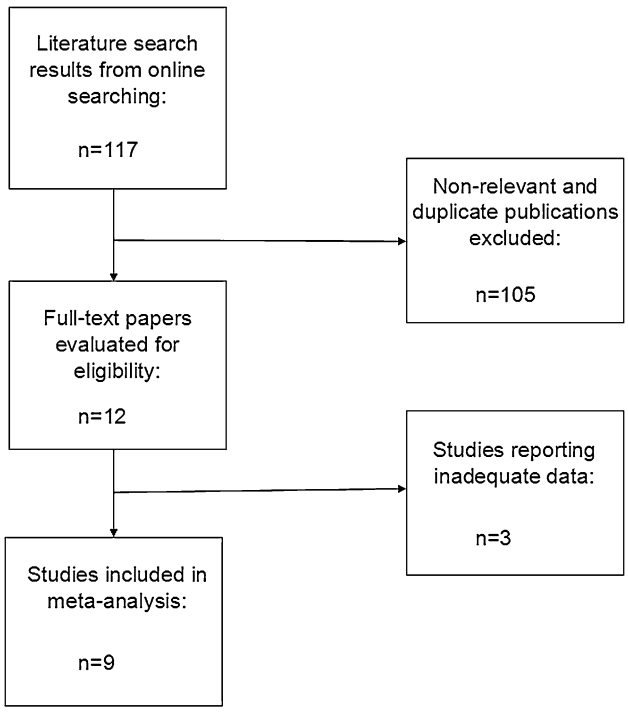

Fig. 1 Study selection process

investigated both pulmonary TB and extrapulmonary TB [8]. Although the study by Delgado et al. examined the *IL1RN* VNTR polymorphism [9], we did not include it in the meta-analysis for evaluating the *IL1RN* VNTR polymorphism because no eligible data were provided. Besides, we did not include the study by Awomoyi et al. for assessing the *IL1B* −511 and *IL1RN* VNTR polymorphisms because of duplicated data [10].

No Association Between the *IL1B* −511 Polymorphism and TB Risk

The *IL1B* −511 polymorphism was analyzed in five studies with 990 cases and 821 controls [7–9, 11, 12]. In terms of ethnicity, two studies were performed in black people [7, 8], two studies were conducted in Asians [9, 12], and one study was undertaken in Caucasians [11]. No association between this polymorphism and TB risk was found in the overall populations in dominant (OR = 1.09, 95 % CI 0.87–1.36, $P = 0.460$), recessive (OR = 1.11, 95 % CI 0.89–1.38, $P = 0.370$), homozygote (OR = 1.15, 95 % CI 0.87–1.50, $P = 0.328$), and allelic comparison (OR = 1.07, 95 % CI 0.94–1.23, $P = 0.310$) models (Table 2; Fig. 2). After the exclusion of the study by Sun et al., whose genotypic distribution in controls deviated from HWE [12], the results did not significantly alter from the corresponding pooled ORs (data not shown). In subgroup analysis stratified by ethnicity, the meta-analyses indicated no significant association of this polymorphism with TB in any of the genetic models in black people, Asians, and Caucasians, respectively (Table 2; Fig. 2). The combined OR was 1.02 (95 % CI 0.76–1.38), 1.31 (95 % CI 0.89–1.91), and 0.77 (95 % CI 0.35–1.70) for the dominant model in black people, Asians, and Caucasians, respectively (Table 2; Fig. 2). ORs for other genetic models were similar (Table 2). There was no significant heterogeneity across all studies (Table 2).

No Association of the *IL1B* +3954 Polymorphism with TB

The *IL1B* +3954 polymorphism was assessed in six studies with 969 cases and 821 controls [8–11, 13, 14]. Among them, two studies were undertaken in black people [8, 10], two studies were conducted in Asians [9, 14], and two studies were performed in Caucasians [11, 13]. The pooled effect estimates among all studies did not suggest any association between the *IL1B +3954* polymorphism and TB risk in the overall populations in dominant (OR = 1.04, 95 % CI 0.79–1.38, $P = 0.772$), recessive (OR = 1.07, 95 % CI 0.79–1.44, $P = 0.679$), homozygote (OR = 1.03, 95 % CI 0.61–1.72, $P = 0.920$), and allelic comparison (OR = 1.04, 95 % CI 0.87–1.26, $P = 0.652$) models (Table 2; Fig. 3). After excluding the study by Wilkinson et al., whose genotypic distribution in controls deviated from HWE [8], the results did not significantly alter from the corresponding pooled ORs (data not shown). In subgroup analysis based on ethnicity, no association between this polymorphism and TB was found in black people, Asians, and Caucasians, respectively (Table 2; Fig. 3). There was no evidence of significant heterogeneity across all studies (Table 2).

No Association Between the *IL1RN* VNTR Polymorphism and TB Risk

This polymorphism was evaluated in three studies with 758 cases and 781 controls [7, 8, 15]. Among them, two studies were performed in black people [7, 8], whereas one study was undertaken in Caucasians [15]. The meta-analysis of available data showed no evidence for a significant association between the *IL1RN* VNTR polymorphism and TB risk in the overall populations in dominant (OR = 0.86, 95 % CI 0.64–1.15, $P = 0.315$), recessive (OR = 1.08, 95 % CI 0.60–1.95, $P = 0.802$), homozygote (OR = 1.06, 95 % CI 0.58–1.92, $P = 0.857$), and allelic comparison (OR = 0.91, 95 % CI 0.71–1.17, $P = 0.446$) models (Table 2; Fig. 4). After the exclusion of the study by Hashemi et al. [15], whose genotypic distribution in controls deviated from HWE, the results did not significantly alter from the corresponding pooled ORs (data not shown).

Table 1 Characteristics of included studies

First author	Country	Year	Ethnicity	Disease type	Cases	Controls	HIV status of subjects	Polymorphisms	Genotyping method
Bellamy	UK and Gambia	1998	Black people	PTB	408	417	Negative	*IL1B* −511 and *IL1RN* VNTR	Hybridization with digoxigenin-labeled sequence-specific oligonucleotides; PCR-based assay
Wilkinson	USA and UK	1999	Black people	PTB and ETB	89	114	Negative	*IL1B* −511, *IL1B* +3954 and *IL1RN* VNTR	PCR-based assay
Delgado	USA and Cambodia	2002	Asian	PTB	358	106	Negative	*IL1B* −511, *IL1B* +3954 and *IL1RN* VNTR	PCR-SSP
Awomoyi	Gambia, USA and UK	2005	Black people	PTB	335	298	Negative	*IL1B* −511, *IL1B* +3954 and *IL1RN* VNTR	PCR–RFLP
Amirzargar	Iran	2006	Caucasian	PTB	41	123	NR	*IL1B* −511 and *IL1B* +3954	PCR-SSP
Sun	China and Australia	2007	Asian	PTB	98	65	NR	*IL1B* −511	An oligochip-based method
Naslednikova	Russia	2009	Caucasian	PTB	78	82	NR	*IL1B* +3954	PCR–RFLP
Meenakshi	India	2013	Asian	PTB	100	100	NR	*IL1B* +3954	PCR–RFLP
Hashemi	Iran and Canada	2015	Caucasian	PTB	265	250	NR	*IL1RN* VNTR	PCR-based assay

ETB extrapulmonary tuberculosis, *HIV* human immunodeficiency virus, *NR* not reported, *PCR* polymerase chain reaction, *PCR–RFLP* polymerase chain reaction–restriction fragment length polymorphism, *PCR-SSP* polymerase chain reaction with sequence-specific primers, *PTB* pulmonary tuberculosis, *UK* United Kingdom

Table 2 Meta-analysis of the association of the *IL1B* and *IL1RN* polymorphisms with TB

Polymorphism	*n*	Cases/controls	Dominant		Recessive		Homozygote		Allele contrast	
			OR (95 % CI)	P_{het}	OR (95 % CI)	P_{het}	OR (95 % CI)	P_{het}	OR (95 % CI)	P_{het}
IL1B −511										
Total	5	990/821	1.09 (0.87–1.36)	0.435	1.11 (0.89–1.38)	0.676	1.15 (0.87–1.50)	0.609	1.07 (0.94–1.23)	0.664
Black people	2	494/529	1.02 (0.76–1.38)	0.160	1.01 (0.77–1.32)	0.951	1.01 (0.71–1.44)	0.304	1.01 (0.85–1.20)	0.402
Asian	2	456/171	1.31 (0.89–1.91)	0.828	1.25 (0.82–1.92)	0.485	1.42 (0.87–2.31)	0.533	1.23 (0.95–1.57)	0.615
Caucasian	1	40/121	0.77 (0.35–1.70)	NA	1.71 (0.74–3.93)	NA	1.25 (0.47–3.35)	NA	1.09 (0.66–1.80)	NA
IL1B +3954										
Total	6	969/821	1.04 (0.79–1.38)	0.501	1.07 (0.79–1.44)	0.889	1.03 (0.61–1.72)	0.703	1.04 (0.87–1.26)	0.530
Black people	2	392/412	0.96 (0.57–1.62)	0.178	1.08 (0.77–1.51)	0.252	1.06 (0.48–2.31)	0.128	1.04 (0.79–1.35)	0.142
Asian	2	458/206	0.90 (0.58–1.42)	0.283	1.02 (0.44–2.38)	0.556	0.92 (0.38–2.21)	0.470	0.94 (0.66–1.35)	0.278
Caucasian	2	119/203	1.30 (0.81–2.10)	0.910	1.02 (0.35–2.99)	0.950	1.16 (0.37–3.46)	0.999	1.19 (0.81–1.74)	0.999
IL1RN VNTR										
Total	3	758/781	0.86 (0.64–1.15)	0.366	1.08 (0.60–1.95)	0.511	1.06 (0.58–1.92)	0.536	0.91 (0.71–1.17)	0.543
Black people	2	493/531	0.74 (0.48–1.14)	0.292	1.41 (0.58–3.38)	0.356	1.34 (0.55–3.29)	0.350	0.85 (0.58–1.23)	0.322
Caucasian	1	265/250	0.98 (0.66–1.47)	NA	0.87 (0.39–1.93)	NA	0.87 (0.39–1.95)	NA	0.96 (0.68–1.36)	NA

CI confidence interval, *IL1* interleukin-1, *NA* not applicable, *OR* odds ratio, P_{het} *P* value for heterogeneity, *TB* tuberculosis

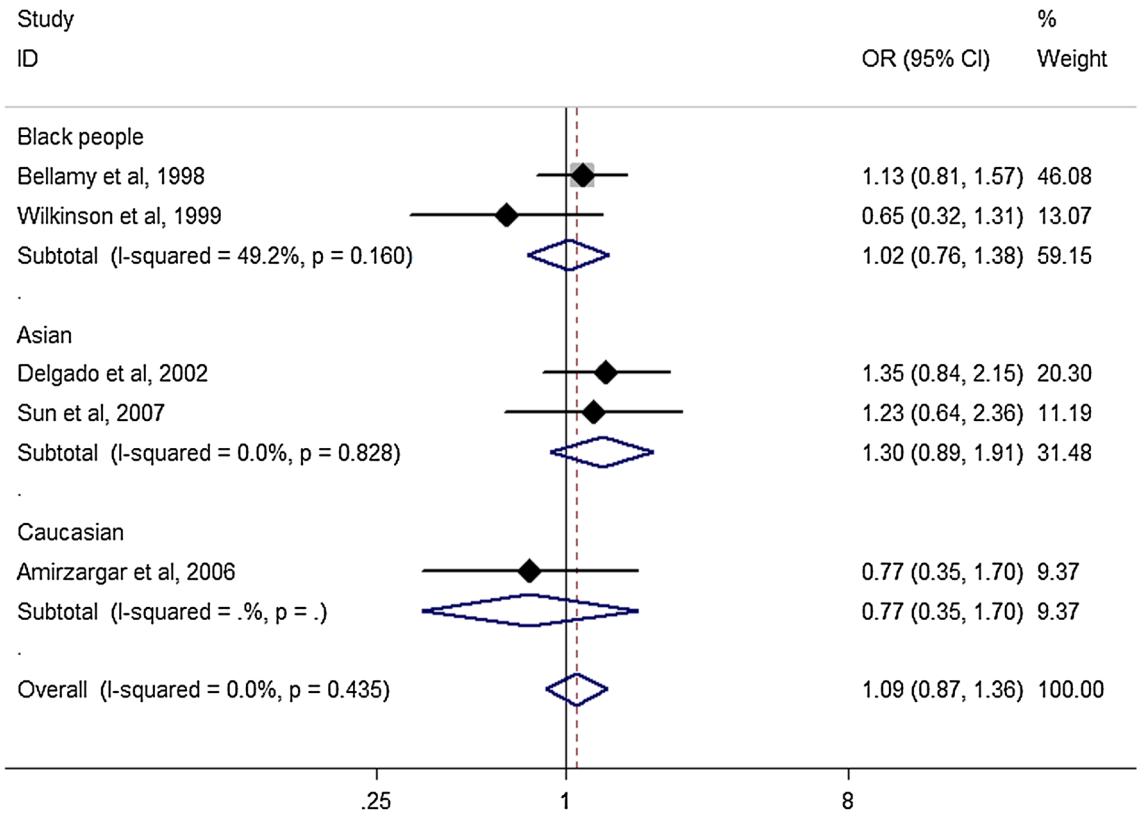

Fig. 2 Forest plot for included studies examining the association between the *IL1B* −511 polymorphism and tuberculosis risk under dominant model

Subgroup analysis by ethnicity also did not find any significant association between this polymorphism and TB in black people and Caucasians, respectively (Table 2; Fig. 4). No significant heterogeneity was found among all studies (Table 2).

Sensitivity Analysis and Publication Bias

The meta-analysis was performed multiple times each with a different and single study removed to detect whether the observed effect was unduly influenced by any one study. The corresponding pooled ORs for dominant, recessive, homozygote, and allelic comparison models were not significantly altered. Begg's test was used to evaluate publication bias. There was no evidence of publication bias (Table 3).

Discussion

IL-1B is a potent proinflammatory cytokine and important mediator of immune responses mainly produced by monocytes and macrophages [18]. IL-1B activates immune cells such as CD4 and CD8 T cells, upregulates expression of adhesion molecules, and induces expression of a number of other proinflammatory cytokines and other inflammation-associated proteins [19]. It was reported that alveolar macrophages from patients with active TB produced high levels of IL-1B [20]. In addition, lung epithelial lining fluid (ELF) levels of IL-1B were found to be significantly correlated with pulmonary TB status [21]. Moreover, local production of large amounts of IL-1B was correlated with significant tissue necrosis in lung lesions of pulmonary TB patients with a large cavity (≥4 cm) [22]. IL-1RA binds to IL-1 receptors and prevents the interaction of IL-1B with its receptors. The IL1-RA/IL-1B ratio is critical in determining the severity of inflammatory responses. Both serum and ELF IL-1RA levels were found to be elevated in active pulmonary TB patients [21, 23]. In addition, the ratio of concentrations of IL-1RA to IL-1B in the cerebrospinal fluid was higher in TB compared with pyogenic meningitis [24]. Given the important role of IL-1B and IL-1RA in host immune defense against Mtb and in local inflammation, *IL1B* and *IL1RN* were considered as candidate genes for TB.

The *IL1B* −511 and *IL1B* +3954 polymorphisms can influence IL-1B production, whereas allele-2 (two repeats) of the *IL1RN* VNTR polymorphism is associated with

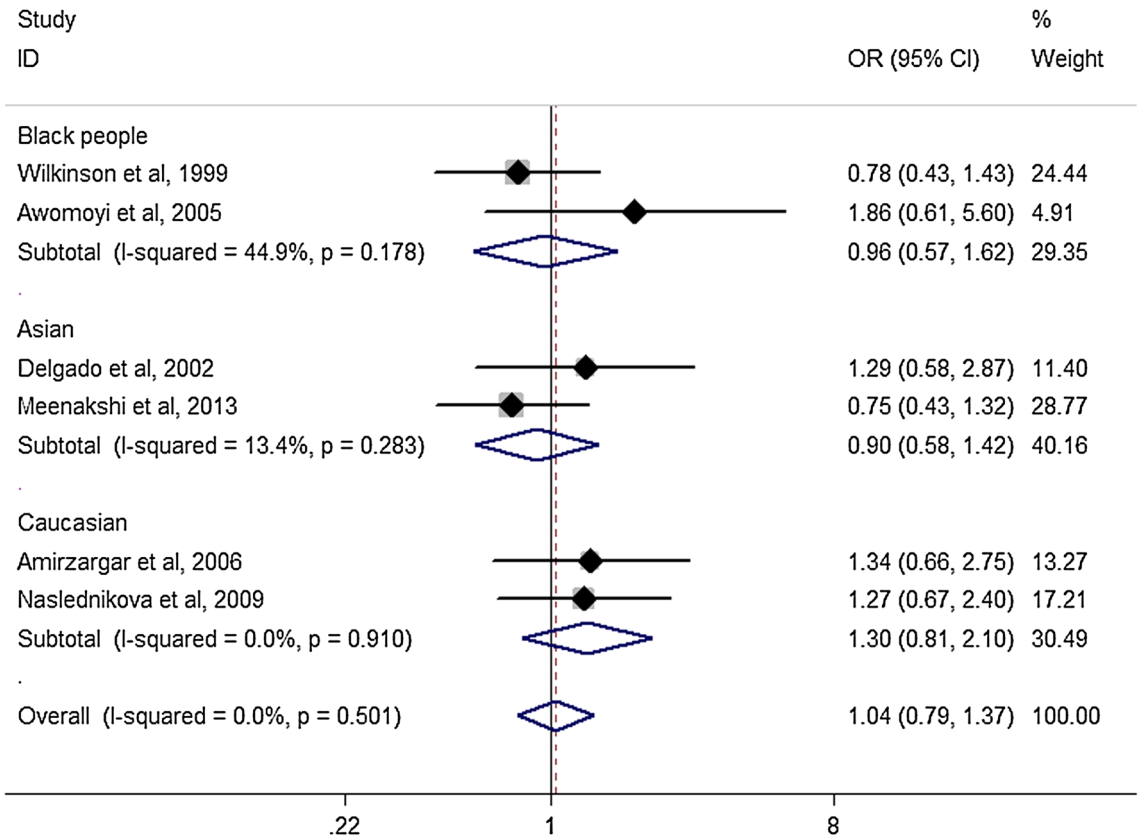

Fig. 3 Forest plot for included studies examining the association between the *IL1B* +3954 polymorphism and tuberculosis risk under dominant model

increased IL-1RA levels and decreased IL-1A production in human monocyte cultures [25]. This meta-analysis evaluated the relationship of the *IL1B* −511, *IL1B* +3954, and *IL1RN* VNTR polymorphisms with TB using eligible data from published case–control studies. No association between these polymorphisms and TB risk was found in the overall populations in dominant, recessive, homozygote, and allelic comparison models. In subgroup analysis stratified by ethnicity, we still did not find any association of these polymorphisms with TB in black people, Asians, and Caucasians, respectively.

Several factors provide consistency for our results. First, although we combined data of published studies from different geographic origin, we did not identify significant between-study heterogeneity across all studies ($P > 0.10$). Second, for all variants, sensitivity analyses by excluding each of the involved study in turn did not change the pattern of results. Third, there was no evidence of publication bias. Therefore, consistent results were obtained in this meta-analysis. Since the sample size of this meta-analysis was relatively small, future studies using large number of subjects are warranted to confirm our findings.

The genes for *IL1B* and *IL1RN* are clustered together on chromosome 2q13-14, and there is strong linkage dislibrium (LD) within this region. When the causal variant is not identified, haplotype-based analysis might be more powerful for association studies in which there is LD in the region of interest. The study by Wilkinson et al. found that the *IL1RN* VNTR $A2^{-}$/*IL1B* +3954 $A1^{+}$ haplotype was more common in patients with tuberculous pleurisy in comparison with healthy Mtb-sensitized control subjects, although genotype frequency of either polymorphism did not differ between groups [8]. However, other studies included in this meta-analysis did not perform haplotype association analysis for the *IL1* gene polymorphisms except the study by Wilkinson et al. [8]. Therefore, we were unable to evaluate haplotype association in this meta-analysis due to limitation of data. Future association studies should take into account haplotypic analysis when evaluating the *IL1B* and *IL1RN* polymorphisms, which will provide additional information for the role of these polymorphisms in TB.

Some limitations of this meta-analysis need to be considered. First, only published studies were included in our analysis. Other potentially eligible, but unpublished studies with either positive or negative effects may have been missed. In spite of this possibility, we did not identify publication bias. Second, because HIV infection was a risk

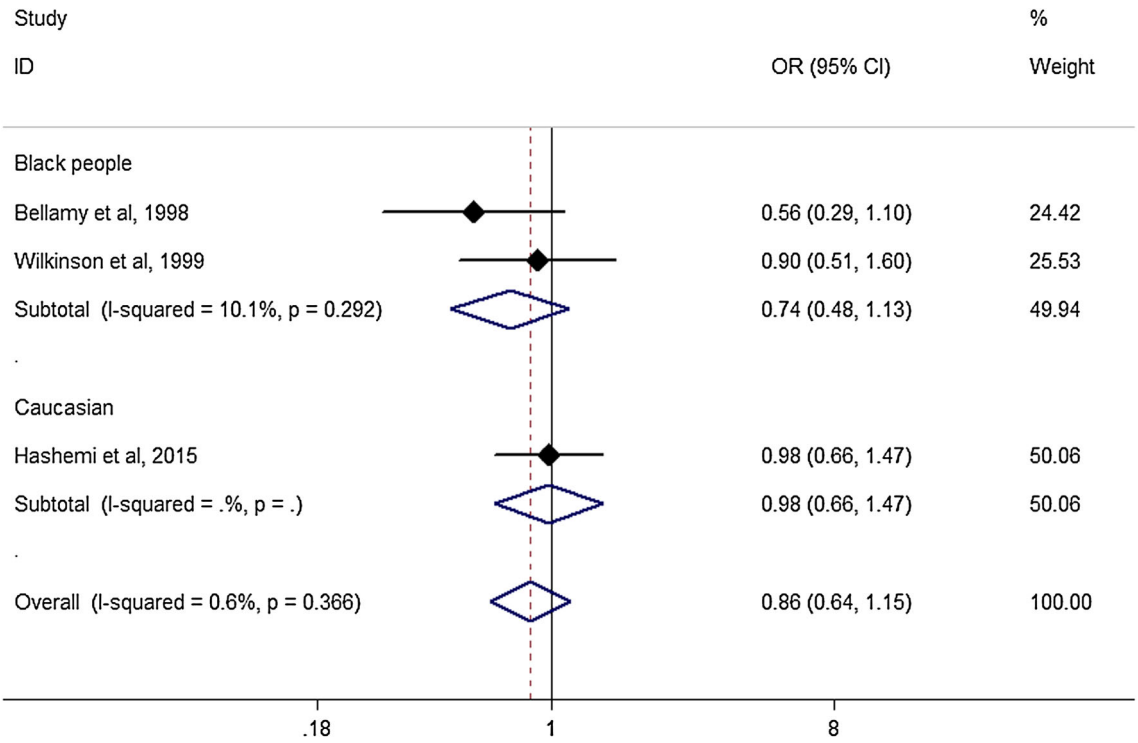

Fig. 4 Forest plot for included studies examining the association between the *IL1RN* VNTR polymorphism and tuberculosis risk under dominant model

Table 3 Results of Begg's test for evaluating publication bias

Polymorphism	*P* for dominant	*P* for recessive	*P* for homozygote	*P* for allele contrast
IL1B −511	0.462	0.221	0.806	1.000
IL1B +3954	0.060	1.000	0.707	1.000
IL1RN VNTR	0.296	0.296	0.296	0.296

factor for TB [26], it is better to report HIV status of subjects when assessing the association of *IL1B* and *IL1RN* polymorphisms with TB. However, among the included studies, only four studies reported negative HIV infection in participants [7–10], and the other five studies did not provide any information on it [11–15]. Therefore, we were unable to adjust this confounding factor in the pooled analysis. Third, due to limited availability of published results, we did not investigate other polymorphisms in the *IL1* gene family, such as the *IL1A*-889 and *IL1B* -31 polymorphisms. We expect that a more comprehensive estimation of the association of the *IL1* cluster gene region with TB could be obtained when more studies become available.

In conclusion, the results of our meta-analysis demonstrate that the *IL1B* −511, *IL1B* +3954, and *IL1RN* VNTR polymorphisms are not associated with TB risk.

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Compliance with Ethical Standards

Conflicts of interest None.

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