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Associations between Tumor Necrosis Factor-Alpha Polymorphisms and the Risk of Tuberculosis: A Meta-Analysis

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Abstract

Background: Tuberculosis (TB) is a global infectious disease that seriously threatens human health, but the association between tumor necrosis factor-alpha (TNF-α, TNF) gene and TB remains controversial.

Methods: Relevant studies published in English or Chinese up to April 12, 2019, were searched from PubMed, Embase, Metstr, Web of Science, Medline, and CNKI databases. The associations were estimated by Odds Ratios (ORs) and 95% Confidence Intervals (CIs). The heterogeneity was evaluated by a Chi^2 based Q test and an I^2 test Cochran Q test. Begg's and Egger's tests were used to assess the publication bias.

Results: Forty studies involving 5790 patients with TB and 6529 healthy controls were selected. Our results showed that the TNF Single Nucleotide Polymorphisms (SNPs) rs361525, rs1800629, and rs1799724 rather than rs1800630 were significantly associated with TB risk in the overall cohort. Furthermore, in the subgroup analyses by ethnicity, we found that:1) SNPrs361525 was associated with a decreased TB risk under the dominant genetic model (OR=0.41, 95% CI [0.28,0.59], *P*<0.00001), but an increased TB risk under recessive genetic model (OR=2.45, 95% CI [1.70, 3.51], *P*<0.00001) in Asian population. 2) SNPrs1800629 was significantly associated with a decreased TB risk under the homozygote genetic model (OR=0.14, 95% CI [0.06, 0.32], *P*<0.00001; OR=0.59, 95% CI [0.38, 0.90], *P*=0.02) and the dominant genetic model (OR=0.15, 95% CI [0.07, 0.36], *P*<0.0001; OR=0.64, 95% CI [0.42, 0.99], P=0.04) in African or Asian population. 3) SNPrs1799724 was associated with an increased TB risk under the homozygote genetic model (OR=2.21, 95% CI [1.02, 4.79], *P*=0.04) and the dominant genetic model (OR=2.05, 95% CI [1.33, 3.16], *P*=0.001), and a decreased TB risk under the recessive genetic model (OR=0.49, 95% CI [0.32, 0.75], *P*=0.001) in Asian population.

Conclusions: This meta-analysis suggested that TNFSNPsrs361525, rs1800629, and rs1799724 rather than rs1800630 might be associated with susceptibility to TB, especially in the Asian population.

Keywords: Tumor necrosis factor-alpha; Tuberculosis; Single nucleotide polymorphisms; Meta-analysis; Susceptibility

Abbreviations

CI: Confidence Intervals; CNKI: China National Knowledge Infrastructure; EPTB: Extrapulmonary TB; HIV: Human Immunodeficiency Virus; MHC: Major Histocompatibility Complex; OATB: Osteoarticular TB; Ors: Odds Ratios; PTB: Pulmonary TB; SNPs: Single Nucleotide Polymorphisms; STB: Spinal TB; TB: Tuberculosis; TNF-α: Tumor Necrosis Factor-alpha; WHO: World Health Organization

Introduction

Tuberculosis (TB) is a significant human infectious disease that has been considered severe and lethal, responsible for 1.3 million deaths in 2017 globally [1]. As the World Health Organization (WHO) reports, 1/3 of the people in the world have been infected by *Mycobacterium tuberculosis*, whereas only 10% of these infected individuals ever progress to disease [2], which means that the risk of developing TB in humans is strongly dependent on host-pathogen interactions, the environment,

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Table 1: Quality criteria for the included studies.

Quality parameter	Score[a]			
	3	2	1	0
No. of case patients	>200	>100 and ≤200	>50 and ≤100	≤50
No. of hospitals or centers	≥4	3	2	1
SNP detection method[b]	DNA sequencing	AS-PCR, ARMS-PCR, RT-PCR, M-PCR	PCR-RFLP, PCR-SSP	NA
Matching of case and control subjects[c]	A+G+N	A+S, A+N, or S+N	A, S, or N	None
HIV	Negative	-	-	NA

a: The scores based on following studies, 1) Wei L, Zeng Y, Wang J, et al. Predicting sustained viral response to hepatitis C using a rapid and simple IL28B rs8099917 genotyping assay. Antiviral Res. 2012; 94: 54-56. 2)Liu S, Zhang H, Gu C, et al. Associations Between Hepatitis B Virus Mutations and the Risk of Hepatocellular Carcinoma: A Meta-Analysis. J Natl Cancer Inst. 2009; 101: 1066-1082.
b: AS-PCR: Allele-Specific Polymerase Chain Reaction; ARMS-PCR: Amplification Refractory Mutation System-Polymerase Chain Reaction; RT-PCR: Real-Time Polymerase Chain Reaction; PCR-RFLP: Polymerase Chain Reaction with Restriction Fragment Length Polymorphism; PCR-SSP: Polymerase Chain Reaction with Sequence-Specific Primers; M-PCR: Multiplex Polymerase Chain Reaction.
c: A=Age; G=Gender; N=Nationality.

and the genetic background [3]. Recently, some studies have proven that TB risk is associated with polymorphisms in candidate genes related to the immune system and inflammatory response [4-6].

Tumor Necrosis Factor-alpha (TNF-α) is an important cytokine in the pathogenesis of several inflammatory diseases [7], and the gene encoding it is located on chromosome 6 within the Major Histocompatibility Complex (MHC) class III region. The associations between TNF polymorphisms and the risk of contracting several inflammatory diseases have been widely reported [8-14]. A growing number of studies indicated that TNF-α plays an important role in forming microbiocidal granulomas and inhibiting *M. tuberculosis* proliferation [15-17]. Thousands of Single Nucleotide Polymorphisms (SNPs) in TB patients have been identified based on increasing numbers of individual gene sequences and whole genomes [18]. Accordingly, a phylogenetic tree was constructed using those SNPs, and an evolutionary hypothesis for lineages of *M. tuberculosis* was proposed [19]. Previous studies have showed that certain SNPs of TNF gene were associated with the risk of TB or pulmonary TB in different populations, such as rs361525 (-238G>A) [20-32], rs673 (-244G>A) [28], rs1800629 (-308G>A) [20,22-40], rs1800750 (-376G>A) [31], rs1799724 (-857C>T) [20,22,25,26,28,29,41], rs1800630 (-863C>A) [20,22,24,25,28,29,41], rs1799964 (-1031T>C) [22], TNF -224G>A [20], and TNF +488G>A [32]. However, the conclusions of these studies were inconsistent or even contrary. To avoid the errors caused by a single study, we performed a meta-analysis based on case-control designed studies to evaluate the associations between 4 SNPs (rs361525, rs1800629, rs1799724, and rs1800630) and susceptibility to TB.

Methods

Ethics committee and institutional review board

Ethical approval was not necessary since this was a meta-analysis of published articles.

Search strategy

PubMed, Embase, Metstr, Web of Science, Medline, and China National Knowledge Infrastructure (CNKI), http://www.cnki.net/) were used to search publications on the associations between TNF polymorphisms and TB susceptibility until April 12, 2019. All papers were identified with a literature search using the terms "tuberculosis" or "TB" and "TNF-α" or "tumor necrosis factor-alpha" and "polymorphisms" or "polymorphism." The searched publications were limited to English or Chinese language journals.

Inclusion and exclusion criteria

Publications were considered candidates if they meet the following criteria: 1) It was case-control designed study; 2) The study should evaluate the associations between TNF polymorphisms and TB susceptibility; 3) Data of genotype frequencies in TB patients and healthy controls were available; 4) The study should be openly published in peer-reviewed journals. Publications were excluded if: 1) The study belonged to a review or meta-analysis; 2) The study focused on TB treatment, other diseases, other gene mutations, or animals; 3) The full text was unavailable; 4) The study was performed in patients with potential confounding diseases; 5) The study was based on family members or sibling pairs rather than on the unrelated subjects.

Data extraction and assessment of study quality

Data from the included articles were independently extracted by two authors (WP Gong and LY Duan) and reviewed by the third author (XQ Wu) according to our data extraction form. Disagreements were resolved by discussion. The following data were extracted from each included study: publication year, first author, country or area, ethnicity, sample size (cases and controls), number of hospitals or centers, TB type, Human Immunodeficiency Virus (HIV) status, mutation site, genotype information, mutation detection method, age, gender, and nationality.

Two authors (WP Gong and LY Duan) independently conducted assessments of the study quality by using a 15-point scoring system (Table 1). Disagreements were resolved by consensus. The scoring system consisted of elements such as the number of case-patients, number of hospitals or centers, SNP detection method, matching of case and control subjects (age, gender, and nationality), and HIV status, which might be necessary for enhancing the quality of included studies. The overall score was divided into three categories according to the distribution of relative quality scores of all the included studies: 1) High-quality studies: overall score≥9; 2) Medium-quality studies: 6≤ overall score <9; 3) Low-quality studies: overall score <6.

Statistical analysis

Reviewer Manager 5 software (Cochrane Community, London, UK) was used to determine the associations between TNF polymorphisms and TB susceptibility by Z test, and the results were presented as Odds Ratios (ORs) with their corresponding 95% Confidence Intervals (95% CI). The heterogeneity of included publications was evaluated by a Chi^2 based Q test and an I^2 test; two different effect models were used according to the I^2 value of heterogeneity assessment. If there was no significant heterogeneity

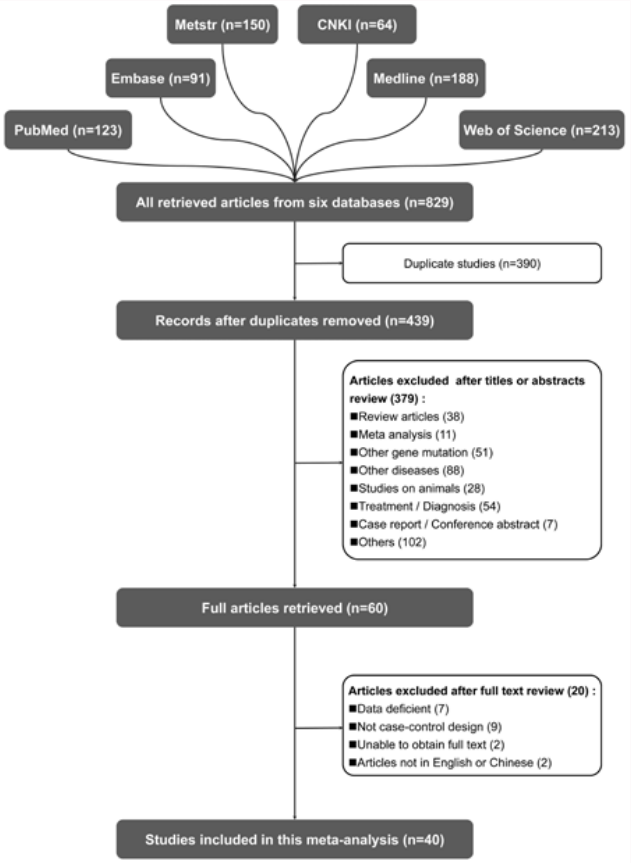

Figure 1: Flow chart of the search strategy and study selection process.

among the included studies (Pheterogeneity>0.01 and I2<50%), the Fixed-effect model was used [42]; otherwise, the Random-effect model was used [43]. Five comparison genetic models (allele model, homozygote model, heterozygote model, dominant model, and recessive model) were used to evaluate the association between the chosen polymorphisms of the TNF gene and TB risk. Sensitivity analysis was conducted to evaluate the influence of the individual study on the pooled results by removing one study each time. The potential publication bias was evaluated by using the Begg test and Egger regression test in Stata 15 software (Stata Corp LLC, Texas, USA). $P<0.05$ indicates a significant difference.

Results

Characteristics of included studies

We used unified search terms to search the literature in 6 databases (see Table S1, Supplemental Content, which illustrates the search terms in six databases). The results showed that 829 articles were retrieved from these databases (Figure 1). A total of 439 articles were selected in the primary elections after excluding duplicated literature. Then, 379 articles were excluded by reading the titles and abstracts, and 20 articles that did not meet the inclusion criteria were excluded by reading the full text. Finally, a total of 40 articles that met the inclusion criteria were included in this meta-analysis [20,22-41,44-62].

The characteristics of these included studies are listed in Table 2. There were 6529 cases of healthy controls, and 5790 cases of TB in our meta-analysis, including 4395 cases of Pulmonary TB (PTB), 481 cases of Spinal TB (STB), 208 cases of Extra Pulmonary TB (EPTB), 231 cases of Osteoarticular TB (OATB), and 475 cases where TB types were not available. Among these included studies, 3 studies were performed in an African population [36,38,56], 29 in Asian population [20,22-29,32,33,35,39,41,44-52,54,58-62], and 8 in a Caucasian population [30,31,34,37,40,53,55,57]. Furthermore, the HIV status was available in 15 studies (37.5%), and quality scores of 26 studies (60%) were higher than 5, which suggested that the methodological quality was high. In addition, a total of 9 TNF SNPs were involved in these studies, including rs673, rs361525, rs1799724, rs1799964, TNF +488G>A, rs1800629, rs1800630, rs1800750, and TNF -224G>A, and the distribution of these SNPs among 40 studies was listed in Table 3. Finally, 4 SNPs (rs361525, rs1800629, rs1799724, and rs1800630) were analyzed in our meta-analysis based on their high distribution frequencies (see Table S2, Supplemental Content, which illustrates the genotype distributions in cases and controls).

Meta-analysis of the association between 4 SNPs and TB susceptibility by overall cohort and ethnicity subgroup

This meta-analysis showed no association between SNP rs1800630 and TB sensitivity under any genetic models in the overall cohort and ethnicity subgroups (Table 4). However, our meta-analysis revealed associations between the remaining SNPs (rs361525, rs1800629, and rs1799724) and TB risk (Table 4).

SNP rs361525 polymorphism

Twenty-four case-control studies on the relationship between rs361525 polymorphism and TB risk were identified, including 3,431 cases, and 3,934 controls. In the overall cohort analysis, significant heterogeneity was observed in the allele genetic model, the homozygotegenetic model, and the heterozygote genetic model, but not in the dominant genetic model and recessive genetic model. Thus the Random-effect model and Fixed-effect model were used, respectively (Table 4). Our results showed that rs361525 polymorphism was significantly associated with decreased TB risk under the dominant genetic model but with increased TB risk under the recessive genetic model in the overall population (Table 4). To determine the source of heterogeneity, the stratified analysis by ethnicity was performed. It was found that the rs361525 polymorphism has a significant association with TB risk in the Asian population rather than the African or Caucasian population. Meta-analysis showed that rs361525 polymorphism was significantly associated with decreased TB risk under the dominant genetic model (Figure 2A), but with increased TB risk under the recessive genetic model (Figure 2B) in the Asian population.

SNP rs1800629 polymorphism

Thirty-eight case-control studies on the relationship between rs1800629 polymorphism and TB risk were identified, including 4,945 cases, and 5,683 controls. In the overall cohort analysis, significant heterogeneity was observed in the allele genetic model and the heterozygote genetic model, but not in the homozygotegenetic model, the dominant genetic model, and the recessive genetic model (Table 4). Therefore, the Random-effect model was used in the former, and the Fixed-effect model was used in the latter. Overall, rs1800629 polymorphism was significantly associated with decreased TB risk under the homozygote genetic model, the dominant genetic model, and the recessive genetic model (Table 4). In the stratified analysis by ethnicity, the rs1800629 polymorphism has a significant association with TB risk in African and Asian populations rather than the Caucasian population. Our results showed that rs1800629 polymorphism was significantly associated with a decreased TB risk

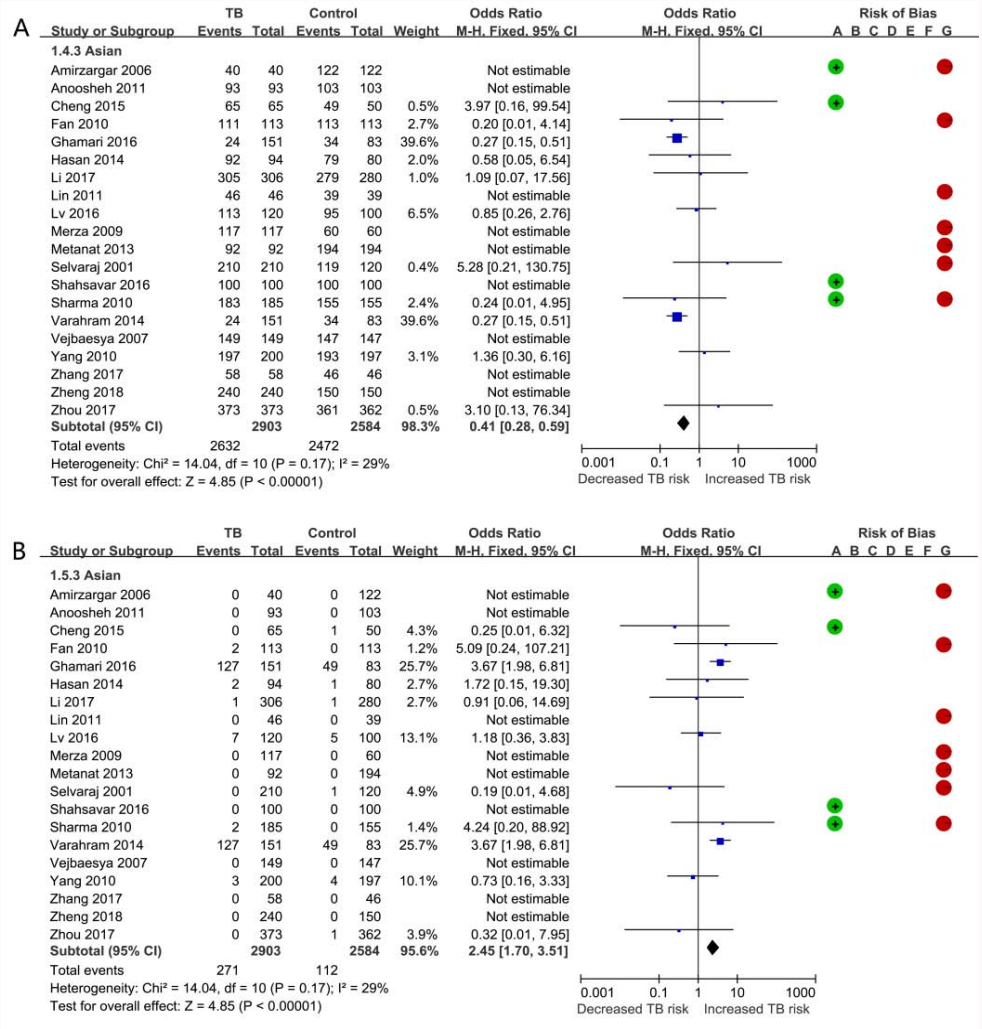

Figure 2: Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of individual studies for associations between the rs361525 polymorphism and TB in the Asian population under the dominant genetic model (A), and the recessive genetic model (B). Blue squares represent study-specific estimates, the horizontal lines represent 95% CIs, and the black diamonds represent summary estimates with corresponding 95% CIs. The size of the squares and diamonds means the weight assigned to each study. Risk of bias legend, (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Incomplete outcome data (attrition bias); (F) Selective reporting (reporting bias); (G) Other bias.

under the homozygote genetic model and the dominant genetic model in the African or Asian population (Figure 3).

SNP rs1799724 polymorphism

Ten case-control studies on the relationship between rs1799724 polymorphism and TB risk were identified, including 2,446 cases, and 1,866 controls. In the overall cohort analysis, there was no significant heterogeneity in the homozygotegenetic model, dominant genetic model, and recessive genetic model, and the Fixed-effect model was used in three genetic models (Table 4). In contrast, significant heterogeneity was observed in the allele genetic model and heterozygote genetic model. Thus the Random-effect model was used. In total population, the data indicated that the rs1799724 polymorphism was significantly associated with increased TB risk under the homozygote genetic model, and the dominant genetic model, but with decreased TB risk under the recessive genetic model (Table 4). In the stratified analysis by ethnicity, the rs1799724 polymorphism has a significant association with TB risk in the Asian population rather than the African or Caucasian population. An ethnicity-specific meta-analysis revealed that rs1799724 polymorphism was significantly associated with increased TB risk under the homozygotegenetic model (Figure 4A) and the dominant genetic model (Figure 4B), but it was opposite under the recessive genetic model (Figure 4C) in the Asian population.

Meta-analysis of the association between 4 SNPs and TB susceptibility by confounders

To further assess the role of these 4 SNPs in susceptibility to TB, we performed subgroup analyses based on potential confounders such as the number of hospitals or centers, TB types, and HIV status. We found significant associations between 4 SNPs and TB susceptibility in the number of hospitals or centers, TB types, and HIV status subgroups (Table 5).

Number of hospitals or centers: For the rs361525 polymorphism, decreased TB risk was observed in the single-center source population under the allele model, the homozygote genetic model, the heterozygote model, and the dominant genetic model, and an increased TB risk under the recessive genetic model. Interestingly,

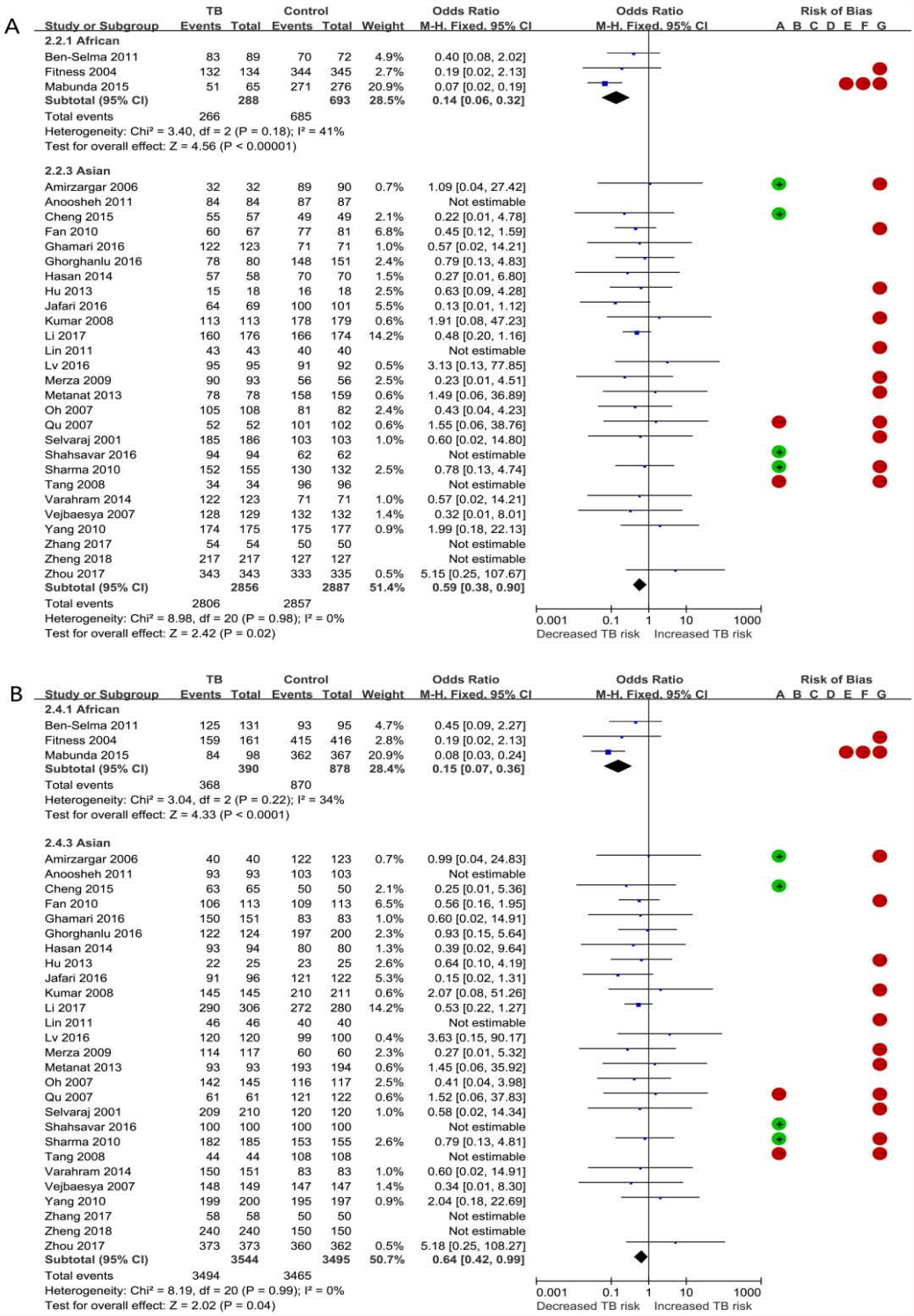

Figure 3: Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of individual studies for associations between the rs1800629 polymorphism and TB under the homozygote genetic model (A) and the dominant genetic model (B) in African or Asian population.

for the rs1800629 polymorphism, similar results were observed in the multi-center source population under five genetic models. Unlike rs361525 and rs1800629, rs1799724 polymorphism had a significantly increased TB susceptibility under the homozygote genetic model, and the dominant genetic model in both single-center source population and multi-center source population, respectively. On the contrary, rs1799724 polymorphism had a significantly decreased TB susceptibility under the recessive genetic model in the population of both sources.

TB types

For the rs361525 polymorphism, decreased TB risk was observed in PTB rather than other TB types (including EPTB, STB, OATB, and NA listed in Table 2 under the homozygote genetic model, and the

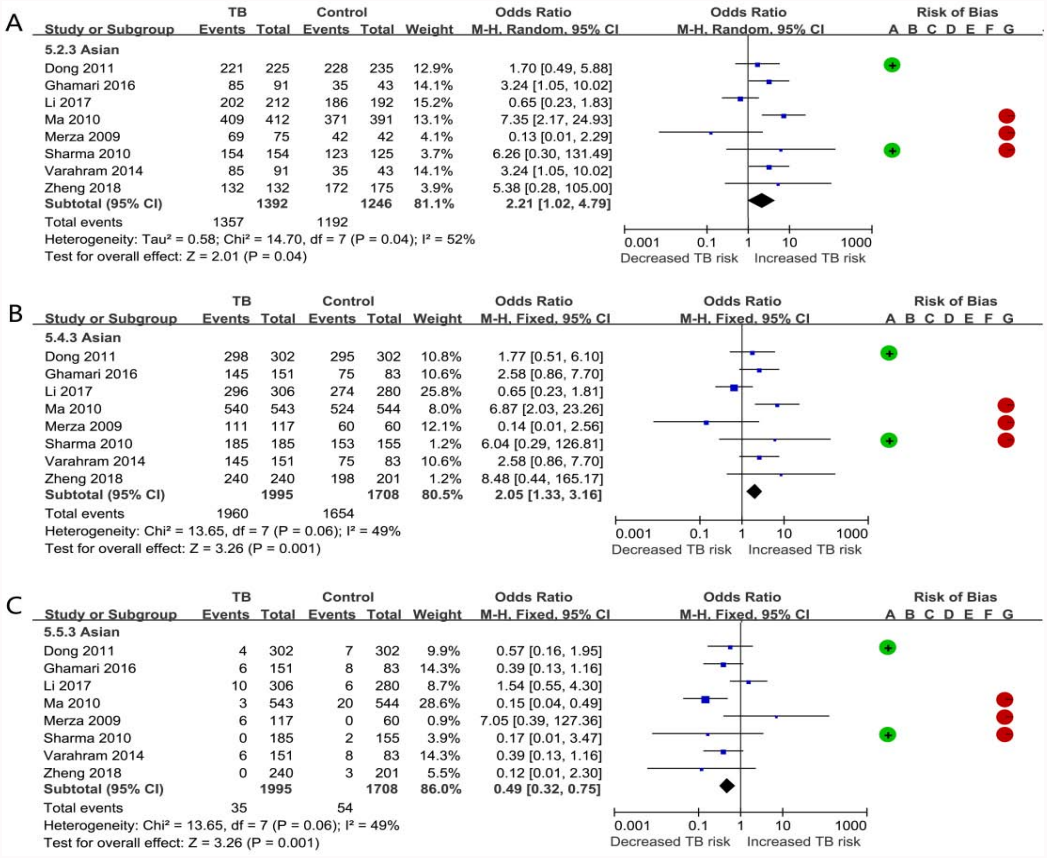

Figure 4: Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies for associations between the rs1799724 polymorphism and TB under the allele genetic model (A), the homozygote genetic model (B), the dominant genetic model(C), and the recessive genetic model (D) in Asian population.

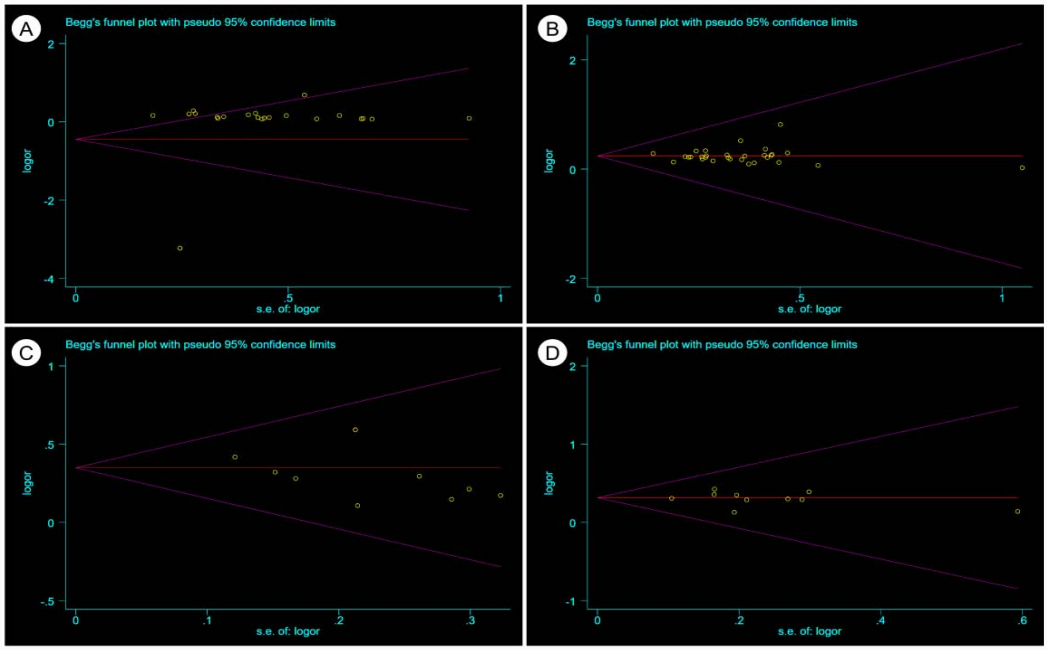

Figure 5: Begg's funnel plot analysis for the evaluation of potential publication bias in 40 included articles under the allele genetic model. (A) rs361525, (B) rs1800629, (C) rs1799724 and (D) rs1800630.

dominant genetic model, but an increased TB risk under the recessive genetic model. For the rs1800629 polymorphism, the similar results were observed in PTB rather than other TB types under the homozygote genetic model, the dominant genetic model, and the recessive genetic model. Differently, rs1799724 polymorphism had a significantly increased TB susceptibility under the homozygote

Table 2: Characteristics of studies included in the meta-analysis.

No	Studies		Country or area	Ethnicity	Sample size Cases/ controls	HWE[a]	Source of population[b]	Type of TB[c]	HIV status	Mutation site	Mutation detection method[d]	Cases		Matching factors e			Quality score[f]
	Year	First author										Mean age (year)	Gender (Male/ Female)	Age	Gender	nationality	
1	2018	Zheng, M.F.	China	ES Asian	240/150	>0.05	1	STB	Negative	-224, rs361525, rs1800629, rs1799724, and rs1800630	DNA sequencing	NA	NA	+	+	+	12
2	2017	Li, Q.F.	China	ES Asian	306/280	0.67	2	PTB	NA	rs361525, rs1800629, rs1799724, rs1800630, and rs1799964	PCR-RFLP	47.69±13.37	173/133	+	+	+	8
3	2017	Ceylan, E.	Turkey	Caucasian	69/70	NA	1	NA	NA	rs1800629	PCR-RFLP	37.8 ± 12.7	47/22	+	+	+	5
4	2017	Zhou. Y.	China	ES Asian	373/362	>0.05	4	NA	NA	rs361525, rs1800629	M-PCR	45.11±14.53	199/174	-	-	+	9
5	2017	Zhang, Y. K.	China	ES Asian	58/50	NA	1	STB	Negative	rs361525, rs1800629	PCR-SSP	37.21±13.15	40/18	+	+	+	9
6	2016	Shahsavar, F.	Iran	SW Asian	100/100	NA	1	PTB	NA	rs361525, and rs1800629	PCR-RFLP	39.65 ± 3.87	40/60	+	+	+	5
7	2016	Lv, Y.J.	China	ES Asian	120/100	>0.05	1	OATB	Negative	rs1800629, rs361525, and rs1800630	PCR-RFLP	40.1 ± 8.5	72/48	+	+	+	9
8	2016	Jafari, M.	Iran	SW Asian	96/122	>0.05	3	PTB	NA	rs1800629	ARMS-PCR	51 ± 31	56/40	-	-	+	6
9	2016	Ghorghanlu, S.	Iran	SW Asian	124/200	0.91	3	NA	Negative	rs1800629	AS-PCR	NA	71/53	-	-	+	10
10	2016	Ghamari, E.	Iran	SW Asian	151/83	NA	1	PTB	NA	rs361525, rs1800629, rs1799724, andrs1800630	PCR-RFLP	49.2±21.2	78/73	+	+	+	6
11	2015	Mabunda, N.	Mozambique	African	102/456	0.52	3	PTB	Negative	rs1800629	RT-PCR	33.8 ± 13	57/45	-	-	+	10
12	2015	Cheng, Z.G.	China	ES Asian	65/50	>0.05	1	OATB	Negative	rs361525, rs1800629	AS-PCR	39.24±13.56	38/27	+	+	+	10
13	2015	Caliskan, T.	Turkey	Caucasian	92/42	0.44	3	PTB	NA	rs1800629	DNA sequencing	29.75 ± 13.87	70/22	+	+	+	9
14	2014	Hasan, K. K.	Iraq	SW Asian	94/80	0.39	1	PTB	NA	rs361525, rs1800629	PCR-SSP	43.5±1.7	70/24	+	+	+	5
15	2014	Varahram, M.	Iran	SW Asian	151/83	0.48	1	PTB	NA	rs361525, rs1800629, and rs1799724	PCR-RFLP	48.7±22.1	78/73	+	+	+	6
16	2013	Hu, Y.L.	China	ES Asian	25/25	NA	1	NA	NA	rs1800629	PCR-RFLP	NA	NA	-	-	+	2
17	2013	Metanat, M.	Iran	SW Asian	100/194	0.52	1	PTB/ EPTB	NA	rs361525, and rs1800629	PCR-SSP	NA	49/51	+	+	+	5
18	2011	Ben-Selma, W.	Tunisia	African	131/95	0.95	1	PTB/ EPTB	Negative	rs1800629	PCR-RFLP	44 and 39 g	68/63	+	+	+	9
19	2011	Lin, C. Y.	China	ES Asian	46/40	1	1	OATB	NA	rs361525, rs1800629	AS-PCR	39.2±13.6	29/17	+	+	+	5
20	2011	Dong, J.	China	ES Asian	302/302	NA	1	PTB	Negative	rs1799724	ARMS-PCR	34.7±16.2	219/83	+	+	+	11
21	2011	Anoosheh, S.	Iran	SW Asian	93/103	0.39	2	PTB	NA	rs361525, -244, rs1800629, rs1799724 and rs1800630	PCR-RFLP	50.04	NA	-	+	+	5
22	2010	Sharma, S.	India	ES Asian	185/155	1	2	PTB	Negative	rs361525, rs1800629, rs1799724, rs1800630, and rs1799964	NA	32.16 ± 13.8	78/107	-	-	+	7
23	2010	Fan, H. M.	China	ES Asian	113/113	0.77	1	PTB	NA	rs361525, rs1800629	PCR-RFLP	71.1	113/0	+	+	+	6
24	2010	Ma, M.J.	China	ES Asian	543/544	0.04	2	PTB	NA	rs1799724, and rs1800630	ARMS-PCR	34.75 ± 16.67	151/392	+	+	+	9
25	2010	Yang, H.	China	ES Asian	200/197	>0.05	2	PTB	NA	rs361525, rs1800629	PCR-SSP	33.1 ± 10.7	112/88	-	-	+	5
26	2009	Merza, M.	Iran	SW Asian	117/60	0.79	1	PTB	NA	rs361525, -244, rs1800629, rs1799724, rs1800630	PCR-RFLP	NA	NA	+	+	+	6
27	2009	Trajkov, D.	Macedonia	Caucasian	75/301	0.1089	2	PTB	NA	rs361525, and rs1800629	PCR-SSP	20-59	NA	-	-	+	4
28	2008	Tang, M. Q.	China	ES Asian	44/108	0.54	1	PTB	NA	rs1800629	PCR-RFLP	NA	NA	-	-	+	2
29	2008	Kumar, V.	India	ES Asian	145/211	0.12	3	NA	NA	rs1800629	ARMS-PCR	33.9	91/54	+	+	+	9
30	2008	Ates, O.	Turkey	Caucasian	128/80	1	1	NA	NA	rs361525, rs1800629, and rs1800750	ARMS-PCR	47.84 ± 12.6	80/48	+	+	+	7
31	2007	Qu, Y.	China	ES Asian	61/122	0.11	1	PTB	Negative	rs1800629	PCR-RFLP	69.3±5.9	61/0	+	+	+	8
32	2007	Vejbaesya, S.	Thailand	ES Asian	149/147	0.51	1	PTB	Negative	+488, rs361525, and rs1800629	PCR-SSP	17-70	87/62	+	+	+	9
33	2007	Oh, J. H.	Korea	ES Asian	145/117	0.18	2	PTB	Negative	rs1800629	ARMS-PCR	49.8 and 47 g	100/45	+	+	+	12
34	2006	Oral, H. B.	Turkey	Caucasian	81/50	>0.05	1	NA	NA	rs1800629	PCR-SSP	NA	NA	+	+	+	5
35	2006	Amirzargar, A. A.	Iran	SW Asian	41/123	0.27	1	PTB	NA	rs361525, rs1800629	PCR-SSP	NA	NA	-	-	+	2
36	2005	Correa, P. A.	Colombia	Caucasian	135/430	0.82	1	PTB	Negative	rs361525, rs1800629	PCR-RFLP	40±16	17/118	-	+	+	8
37	2004	Fitness, J.	Malawi	African	181/533	0.1536	1	NA	Negative	rs361525, rs1800629, rs1800630	ARMS-PCR	>15	NA	+	+	+	10
38	2003	Scola, L.	Sicilia	Caucasian	45/114	0.81	1	PTB	NA	rs1800629	ARMS-PCR	NA	NA	+	+	+	5
39	2002	Delgado, J. C.	Cambodia	Caucasian	358/106	NA	1	PTB	Negative	rs1800629, rs1799724, rs1800630, rs1799964	PCR-RFLP	42.2±14.1	134/224	-	-	+	8
40	2001	Selvaraj, P.	India	ES Asian	210/120	0.4	2	PTB	NA	rs361525, rs1800629	NA	37.7±1.1	164/46	-	-	+	5

a: HWE=Hardy-Weinberg Equilibrium, the data listed here indicate the HWE value of controls.
b: Source of population was obtained from each full article, the number in each form represent the number of hospitals or centers registered by TB patients. NA means this information was not given in the article.
c: EPTB=Extrapulmonary TB; OATB=Osteoarticular tuberculosis; PTB=Pulmonary TB; STB=Spinal TB; TB=tuberculosis.
d: ARMS-PCR=Amplification Refractory Mutation System-Polymerase Chain Reaction; AS-PCR=Allele-Specific PCR; DNA=Deoxyribonucleic Acid; M-PCR=Multiplex Polymerase Chain Reaction; PCR-RFLP=Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; PCR-SSP=Polymerase Chain Reaction-Sequence Specific Primers; RT-PCR=Real Time-Polymerase Chain Reaction.
e: There are three matching factors in this meta-analysis, age, gender, and nationality. If age, gender and nationality were matched in case group and control group, it was labeled +, otherwise it was labeled as -.
f: Studies that received an overall score of 9 or higher were classified as high-quality studies, those with an overall score of 6-8 were classified as medium-quality studies, and those with an overall score of 5 or lower were considered low-quality studies for the purpose of this analysis. These cut points were chosen according to the distribution of relative quality scores of all included studies.
g: The TB patients were divided into different groups, such as PTB and EPTB. Each number indicates the mean age of each group of TB patients, respectively.

Table 3: Distribution of gene polymorphism of studies included in the meta-analysis.

First author	Year	SNP*								
		TNF-224	rs361525	rs673	rs1800629	rs1800750	TNF+488	rs1799724	rs1800630	rs1799964
Amirzargar, A. A.	2006	○	●	○	●	○	○	○	○	○
Anoosheh, S.	2011	○	●	●	●	○	○	●	●	○
Ates, O.	2008	○	●	○	●	●	○	○	○	○
Ben-Selma, W.	2011	○	○	○	●	○	○	○	○	○
Caliskan, T.	2015	○	○	○	●	○	○	○	○	○
Ceylan, E.	2017	○	○	○	●	○	○	○	○	○
Cheng, Z.G.	2015	○	●	○	●	○	○	○	○	○
Correa, P. A.	2005	○	●	○	●	○	○	○	○	○
Delgado, J. C.	2002	○	○	○	●	○	○	●	●	●
Dong, J.	2011	○	○	○	○	○	○	●	○	○
Fan, H. M.	2010	○	●	○	●	○	○	○	○	○
Fitness, J.	2004	○	●	○	●	○	○	○	●	○
Ghamari, E.	2016	○	●	○	●	○	○	●	●	○
Ghorghanlu, S.	2016	○	○	○	●	○	○	○	○	○
Hasan, K. K.	2014	○	●	○	●	○	○	○	○	○
Hu, Y.L.	2013	○	○	○	●	○	○	○	○	○
Jafari, M.	2016	○	○	○	●	○	○	○	○	○
Kumar, V.	2008	○	○	○	●	○	○	○	○	○
Li, Q.F.	2017	○	●	○	●	○	○	●	●	●
Lin, C. Y.	2011	○	●	○	●	○	○	○	○	○
Lv, Y.J.	2016	○	●	○	●	○	○	○	●	○
Ma, M.J.	2010	○	○	○	○	○	○	●	●	○
Mabunda, N.	2015	○	○	○	●	○	○	○	○	○
Merza, M.	2009	○	●	●	●	○	○	●	●	○
Metanat, M.	2013	○	●	○	●	○	○	○	○	○
Oh, J. H.	2007	○	○	○	●	○	○	○	○	○
Oral, H. B.	2006	○	○	○	●	○	○	○	○	○
Qu, Y.	2007	○	○	○	●	○	○	○	○	○
Scola, L.	2003	○	○	○	●	○	○	○	○	○
Selvaraj, P.	2001	○	●	○	●	○	○	○	○	○
Shahsavar, F.	2016	○	●	○	●	○	○	○	○	○
Sharma, S.	2010	○	●	○	●	○	○	●	●	○
Tang, M. Q.	2008	○	○	○	●	○	○	○	○	○
Trajkov, D.	2009	○	●	○	●	○	○	○	○	○
Varahram, M.	2014	○	●	○	●	○	○	●	○	○
Vejbaesya, S.	2007	○	●	○	●	○	●	○	○	○
Yang, H.	2010	○	●	○	●	○	○	○	○	○
Zhang, Y.K.	2017	○	●	○	●	○	○	○	○	○
Zhou. Y.	2017	○	●	○	●	○	○	○	○	○
Zheng, M.F.	2018	●	●	○	●	○	○	●	●	○

*: ● = Presence of SNP, ○ = absence of SNP

Table 4: Meta-analysis of the genetic polymorphisms of the TNF-α gene and susceptibility to TB by ethnicity and overall cohort.

SNP[a]	Comparison	Studies	Participants	Test of association[b]		Test of heterogeneity			Models[d]
				OR (95%CI)	*P*value	Chi^2	I^2	$P_{heterogeneity}$ [c]	
rs361525 (TNF-238)									
African	G *vs* A	1	1428	1.25 [0.74, 2.11]	0.4	NA	NA	NA	R
	GG *vs* AA	1	626	Not estimable	NA	NA	NA	NA	R
	GG *vs* GA	1	714	1.27 [0.74, 2.17]	0.39	NA	NA	NA	R
	GG+GA *vs* AA	1	714	Not estimable	NA	NA	NA	NA	R
	AA *vs* GA+GG	1	714	Not estimable	NA	NA	NA	NA	R
Caucasian	G *vs* A	3	2298	0.67 [0.32, 1.41]	0.29	4.59	56%	0.1	R
	GG *vs* AA	3	955	0.97 [0.11, 8.75]	0.98	0.08	0%	0.78	F
	GG *vs* GA	3	1146	0.58 [0.26, 1.30]	0.19	4.94	60%	0.24	R
	GG+GA *vs* AA	3	1149	1.11 [0.12, 10.01]	0.93	0.02	0%	0.9	F
	AA *vs* GA+GG	3	1149	0.90 [0.10, 8.17]	0.93	0.02	0%	0.9	F
Asian	G *vs* A	20	10974	0.71 [0.47, 1.06]	0.09	92.91	80%	<0.00001	R
	GG *vs* AA	20	5012	0.49 [0.19, 1.23]	0.13	28.15	64%	0.002	R
	GG *vs* GA	20	5104	0.68 [0.45, 1.02]	0.06	60.81	69%	<0.00001	R
	GG+GA *vs* AA	20	5487	0.41 [0.28, 0.59]	<0.00001	14.04	29%	0.17	F
	AA *vs* GA+GG	20	5487	2.45 [1.70, 3.51]	<0.00001	14.04	29%	0.17	F
Total	G *vs* A	24	14700	0.73 [0.52, 1.02]	0.06	105.67	78%	<0.00001	R
	GG *vs* AA	24	6593	0.51 [0.22, 1.20]	0.12	29.57	59%	0.003	R
	GG *vs* GA	24	6964	0.70 [0.49, 0.99]	0.05	77.72	70%	<0.00001	R
	GG+GA *vs* AA	24	7350	0.42 [0.29, 0.60]	<0.00001	14.88	19%	0.25	F
	AA *vs* GA+GG	24	7350	2.38 [1.67, 3.39]	<0.00001	14.88	19%	0.25	F
rs1800629 (TNF-308)									
African	G *vs* A	3	2536	0.58 [0.32, 1.04]	0.07000	10.78	81%	0.005	R
	GG *vs* AA	3	981	0.14 [0.06, 0.32]	<0.00001	3.4	41%	0.18	F
	GG *vs* GA	3	1238	0.70 [0.47, 1.06]	0.09	3.61	45%	0.16	R
	GG+GA *vs* AA	3	1268	0.15 [0.07, 0.36]	<0.0001	3.04	34%	0.22	F
	AA *vs* GA+GG	3	1268	0.05 [0.02, 0.08]	0.26	25.91	92%	<0.00001	R
Caucasian	G *vs* A	8	4352	1.19 [0.95, 1.49]	0.33000	11.43	39%	0.12	R
	GG *vs* AA	8	1841	1.17 [0.66, 2.08]	0.58000	5.58	0%	0.47	F
	GG *vs* GA	8	2114	1.24 [0.94, 1.63]	0.12	13.99	50%	0.05	F
	GG+GA *vs* AA	8	2176	1.15 [0.65, 2.04]	0.62	5.59	0%	0.47	F
	AA *vs* GA+GG	8	2176	0.00 [-0.02, 0.01]	0.69	7.32	4%	0.4	F
Asian	G *vs* A	27	14078	0.81 [0.65, 1.00]	0.05	74.54	65%	<0.00001	R
	GG *vs* AA	27	5743	0.59 [0.38, 0.90]	0.02	8.98	0%	0.98	F
	GG *vs* GA	27	6959	0.80 [0.63, 1.02]	0.07	76.56	66%	<0.00001	R
	GG+GA *vs* AA	27	7039	0.64 [0.42, 0.99]	0.04	8.19	0%	0.99	F
	AA *vs* GA+GG	27	7039	0.01 [0.00, 0.01]	0.05	21.69	0%	0.71	F
Total	G *vs* A	38	20966	0.84[0.70, 1.01]	0.06	116.87	68%	<0.00001	R
	GG *vs* AA	38	8565	0.58[0.42, 0.79]	0.0005	35.28	15%	0.23	F
	GG *vs* GA	38	10311	0.85[0.70, 1.04]	0.11	102.45	64%	<0.00001	R
	GG+GA *vs* AA	38	10483	0.61 [0.45, 0.83]	0.002	32.02	6%	0.037	F
	AA *vs* GA+GG	38	10483	0.01 [0.00, 0.01]	0.002	53.69	31%	0.04	F
rs1799724 (TNF-857)									
African	C *vs* T	1	392	0.41 [0.23, 0.72]	0.002	NA	NA	NA	R
	CC *vs* TT	1	136	3.08 [0.15, 65.52]	0.47	NA	NA	NA	F
	CC *vs* CT	1	194	0.26 [0.14, 0.51]	<0.00001	NA	NA	NA	R
	CC+CT *vs* TT	1	196	4.61 [0.22, 97.19]	0.33	NA	NA	NA	F
	TT *vs* CT+CC	1	196	0.22 [0.01, 4.58]	0.33	NA	NA	NA	F
Caucasian	C *vs* T	1	926	0.91 [0.48, 1.71]	0.76	NA	NA	NA	R

	CC *vs* TT	1	442	1.10 [0.39, 3.11]	0.85	NA	NA	NA	F
	CC *vs* CT	1	443	0.55 [0.16, 1.91]	0.35	NA	NA	NA	R
	CC+CT *vs* TT	1	463	1.13 [0.40, 3.18]	0.82	NA	NA	NA	F
	TT *vs* CT+CC	1	463	0.89 [0.31, 2.50]	0.82	NA	NA	NA	F
Asian	C *vs* T	8	7406	0.99 [0.68, 1.44]	0.95	57.08	88%	<0.00001	R
	CC *vs* TT	8	2638	2.21 [1.02, 4.79]	0.04	14.70	52%	0.04	R
	CC *vs* CT	8	3614	0.91 [0.58, 1.42]	0.67	57.83	88%	<0.00001	R
	CC+CT *vs* TT	8	3703	2.05 [1.33,3.16]	0.001	13.65	49%	0.06	F
	TT *vs* CT+CC	8	3703	0.49 [0.32, 0.75]	0.001	13.65	49%	0.06	F
Total	C *vs* T	10	8724	0.91 [0.64, 1.28]	0.58	67.99	87%	<0.00001	R
	CC *vs* TT	10	3216	1.96 [1.32, 2.91]	0.0008	16.16	44%	0.06	F
	CC *vs* CT	10	4251	0.78 [0.50, 1.21]	0.27	72.68	88%	<0.00001	R
	CC+CT *vs* TT	10	4362	1.92 [1.30, 2.84]	0.001	15.03	40%	0.09	F
	TT *vs* CT+CC	10	4362	0.52 [0.35, 0.77]	0.001	15.03	40%	0.09	F
rs1800630 (TNF-863)									
African	C *vs* A	1	1164	1.29 [0.88, 1.90]	0.19	NA	NA	NA	R
	CC *vs* AA	1	440	1.00 [0.25, 3.93]	1	NA	NA	NA	R
	CC *vs* CA	1	572	1.42 [0.91, 2.20]	0.12	NA	NA	NA	R
	CC+CA *vs* AA	1	582	0.92 [0.24, 3.61]	0.91	NA	NA	NA	R
	AA *vs* CA+CC	1	582	1.08 [0.28, 4.25]	0.91	NA	NA	NA	R
Caucasian	C *vs* A	1	924	1.18 [0.86, 1.64]	0.31	NA	NA	NA	R
	CC *vs* AA	1	266	1.54 [0.78, 3.06]	0.22	NA	NA	NA	R
	CC *vs* CA	1	412	1.04 [0.65, 1.66]	0.87	NA	NA	NA	R
	CC+CA *vs* AA	1	462	1.51 [0.79, 2.89]	0.21	NA	NA	NA	R
	AA *vs* CA+CC	1	462	0.66 [0.35, 1.26]	0.21	NA	NA	NA	R
Asian	C *vs* A	8	6460	0.87 [0.67, 1.13]	0.31	20.58	66%	0.004	R
	CC *vs* AA	8	2315	0.62 [0.28, 1.35]	0.23	14.27	51%	0.05	R
	CC *vs* CA	8	3118	0.93 [0.68, 1.27]	0.65	20.41	66%	0.005	R
	CC+CA *vs* AA	8	3230	0.64 [0.29, 1.41]	0.27	14.80	53%	0.04	R
	AA *vs* CA+CC	8	3230	1.56 [0.71, 3.46]	0.27	14.80	53%	0.04	R
Total	C *vs* A	10	8548	0.95 [0.76, 1.19]	0.64	27.54	67%	0.001	R
	CC *vs* AA	10	3021	0.77 [0.41, 1.45]	0.42	19.53	54%	0.02	R
	CC *vs* CA	10	4102	0.99 [0.76, 1.27]	0.91	23.91	62%	0.004	R
	CC+CA *vs* AA	10	4274	0.79 [0.42, 1.46]	0.44	19.71	54%	0.02	R
	AA *vs* CA+CC	10	4274	1.27 [0.69, 2.37]	0.44	19.71	54%	0.02	R

a: SNP=Single Nucleotide Polymorphism.
b: The statistical method used in Test of association is Mantel-Haenszel method. OR=Odds Ratio, CI=Confidence Interval.
c: Pheterogeneity=*P* value of heterogeneity.
d: R=Random-effect model, F=Fixed-effect model. The effect model used in test of heterogeneity was determined by the I^2 and Pheterogeneity value of total.

genetic model and the dominant genetic model, but a decreased TB susceptibility considerably under the recessive genetic model in PTB type. Furthermore, a reduced TB risk was observed in other TB types under the allele genetic model and the heterozygote genetic model. For the rs1800630 polymorphism, only a significantly increased TB risk was found in the other TB types under the heterozygote genetic model.

HIV status

For the rs361525 polymorphism, decreased TB risk was observed in the HIV negative population under the allele model and the heterozygote model. In addition, we also found a decreased TB risk under the dominant genetic model, and an increased TB risk under the recessive genetic model in HIV NA population. For the rs1800629 polymorphism, a decreased TB risk was found in the HIV negative population under the homozygote genetic model and the dominant genetic model, but an increased TB risk under the recessive genetic model. For rs1799724 polymorphism, opposite results were observed in the HIV NA population under the homozygote genetic model, the dominant genetic model, and the recessive genetic model.

Sensitivity analysis and potential publication bias

To determine the robustness of the pooled results, we conducted a sensitivity analysis by sequentially removing each study. In our present meta-analysis, there was statistically significant heterogeneity in all 4 SNPs. First, for rs361525 polymorphism, significant heterogeneity was observed under the allele genetic model, the homozygote genetic model, and the heterozygote model, and sensitivity analysis showed that there were four studies [25,26,30,54] respectively influencing the result of the I^2 values and Pheterogeneity. Second, for rs1800629 polymorphism, significant heterogeneity was observed under the allele genetic model and the heterozygote genetic model, the I^2 values

Table 5: Results of subgroup analysis by number of hospitals or centers, TB types, and HIV status.

Sub group	Studies	Case/ control	Allele model				Homozygote model				Heterozygote model				Dominant model				Recessive model			
			OR (95% CI)[a]	*P*	I^2	$P_{heterogeneity}$[b]	OR (95% CI)	*P*	I^2	$P_{heterogeneity}$	OR (95% CI)	*P*	I^2	$P_{heterogeneity}$	OR (95% CI)	*P*	I^2	$P_{heterogeneity}$	OR (95% CI)	*P*	I^2	$P_{heterogeneity}$
rs361525 (TNF-238)																						
Number of hospitals or centers[c]																						
1	17	1989/2416	0.64 [0.42, 0.98]	0.04	0.8	< 0.00001	0.27 [0.10, 0.70]	0.007	0.59	0.02	0.59 [0.36, 0.97]	0.04	0.77	< 0.00001	0.34 [0.23, 0.50]	< 0.00001	0.04	0.4	2.92 [1.98, 4.32]	< 0.00001	0.04	0.4
≥2	7	1442/1518	0.89 [0.61, 1.29]	0.54	0.28	0.22	1.22 [0.42, 3.55]	0.71	0	0.73	0.85 [0.60, 1.22]	0.38	0.09	0.36	1.16 [0.43, 3.12]	0.77	0	0.74	0.86 [0.32, 2.33]	0.77	0	0.74
TB types																						
PTB	16	2220/2569	0.73 [0.48, 1.12]	0.15	0.82	< 0.00001	0.37 [0.15, 0.93]	0.03	0.56	0.02	0.70 [0.44, 1.12]	0.14	0.76	< 0.00001	0.36 [0.24, 0.52]	< 0.00001	0.02	0.42	2.80 [1.91, 4.10]	< 0.00001	0.02	0.42
Others[d]	9	1311/1559	0.70 [0.44, 1.10]	0.12	0.37	0.12	0.91 [0.30, 2.76]	0.86	0	0.39	0.61 [0.34, 1.08]	0.09	0.5	0.04	1.05 [0.36, 3.09]	0.92	0	0.38	0.95 [0.32, 2.78]	0.92	0	0.38
HIV status																						
HIV Negative	8	1133/1615	0.63 [0.45, 0.89]	0.009	0.48	0.06	0.76 [0.28, 2.06]	0.59	0	0.7	0.57 [0.35, 0.91]	0.02	0.64	0.007	0.85 [0.33, 2.17]	0.73	0	0.67	1.18 [0.46, 3.01]	0.73	0	0.67
HIV NA	16	2298/2319	0.82 [0.50, 1.36]	0.44	0.84	< 0.00001	0.46 [0.16, 1.29]	0.14	0.65	0.004	0.79 [0.49, 1.27]	0.33	0.71	< 0.00001	0.37 [0.25, 0.55]	< 0.00001	0.24	0.23	2.69 [1.83, 3.95]	< 0.00001	0.24	0.23
rs1800629 (TNF-308)																						
Number of hospitals or centers																						
1	25	2803/3106	0.84 [0.64, 1.10]	0.21	0.7	< 0.00001	0.82 [0.53, 1.25]	0.35	0	0.85	0.81 [0.59, 1.10]	0.17	0.7	< 0.00001	0.86 [0.56, 1.33]	0.51	0	0.92	1.16 [0.75, 1.78]	0.51	0	0.92
≥2	11	1957/2432	0.77 [0.60, 0.98]	0.04	0.66	0.001	0.40 [0.25, 0.63]	< 0.0001	0.46	0.05	0.80 [0.65, 0.99]	0.04	0.36	0.11	0.43 [0.27, 0.67]	0.0003	0.41	0.08	2.35 [1.48, 3.72]	0.0003	0.41	0.08
TB types																						
PTB	23	3105/3617	0.81 [0.63, 1.03]	0.08	75%	< 0.00001	0.48 [0.34, 0.69]	< 0.0001	12%	0.3	0.84 [0.65, 1.09]	0.19	70%	< 0.00001	0.51 [0.36, 0.74]	0.0003	0%	0.47	1.94 [1.36, 2.78]	0.0003	0%	0.47
Others	15	1886/2210	0.86 [0.66, 1.13]	0.29	52%	0.01	1.05 [0.55, 2.03]	0.88	4%	0.4	0.80 [0.60, 1.06]	0.12	47%	0.02	1.12 [0.58, 2.16]	0.73	0%	0.45	0.89 [0.46, 1.71]	0.73	0%	0.45
HIV status																						
HIV Negative	14	2050/2622	0.80 [0.59, 1.08]	0.15	72%	< 0.00001	0.50 [0.32, 0.78]	0.002	49%	0.03	0.81 [0.59, 1.11]	0.18	59%	0.006	0.52 [0.33, 0.81]	0.004	43%	0.05	1.93 [1.24, 3.02]	0.004	43%	0.05
HIV NA	24	2895/3061	0.87 [0.69, 1.10]	0.24	67%	< 0.00001	0.67 [0.43, 1.03]	0.07	0%	0.79	0.87 [0.66, 1.13]	0.29	68%	< 0.00001	0.72 [0.47, 1.11]	0.14	0%	0.85	1.39 [0.90, 2.15]	0.14	0%	0.85
rs1799724 (TNF-857)																						
Number of hospitals or centers																						
1	6	1319/784	0.86 [0.50, 1.48]	0.59	89%%	< 0.00001	1.72 [1.04, 2.84]	0.04	0.27	0.24	0.74 [0.36, 1.52]	0.42	0.89	< 0.00001	1.68 [1.02, 2.76]	0.04	0.12	0.34	0.60 [0.36, 0.98]	0.04	0.12	0.34
≥2	4	1127/1082	0.98 [0.61, 1.56]	0.92	85%%	0.0002	2.38 [1.25, 4.52]	0.008	0.69	0.02	0.85 [0.49, 1.46]	0.56	0.85	0.0002	2.35 [1.24, 4.45]	0.009	0.69	0.02	0.43 [0.22, 0.81]	0.009	0.69	0.02
TB types																						
PTB	9	2206/1716	1.05 [0.80, 1.37]	0.75	0.75	< 0.0001	1.91 [1.28, 2.84]	0.001	0.49	0.05	0.95 [0.70, 1.30]	0.77	0.71	0.0005	1.84 [1.24, 2.73]	0.003	0.43	0.08	0.54 [0.37, 0.81]	0.003	0.43	0.08
Others	1	240/150	0.30 [0.20, 0.45]	< 0.00001	NA[e]	NA	5.38 [0.28, 105.00]	0.27	NA	NA	0.18 [0.11, 0.30]	< 0.00001	NA	NA	8.48 [0.44, 165.17]	0.16	NA	NA	0.12 [0.01, 2.30]	0.16	NA	NA
HIV status																						
HIV Negative	4	1085/713	0.76 [0.39, 1.48]	0.42	0.88	< 0.00001	1.71 [0.84, 3.44]	0.14	0	0.58	0.57 [0.23, 1.43]	0.23	0.91	< 0.00001	1.83 [0.91, 3.68]	0.09	0	0.48	0.55 [0.27, 1.09]	0.09	0	0.48
HIV NA	6	1361/1153	1.03 [0.70, 1.51]	0.88	0.83	< 0.0001	2.09 [1.30, 3.37]	0.002	0.64	0.02	0.96 [0.63, 1.48]	0.87	0.8	0.0001	1.96 [1.22, 3.14]	0.005	0.6	0.03	0.51 [0.32, 0.82]	0.005	0.6	0.03
rs1800630 (TNF-863)																						
Number of hospitals or centers																						
1	6	1167/1032	1.15 [0.95, 1.38]	0.15	0%%	0.83	1.39 [0.76, 2.53]	0.28	0.05	0.39	1.18 [0.94, 1.47]	0.16	0	0.63	1.34 [0.71, 2.55]	0.37	0.11	0.35	0.74 [0.39, 1.41]	0.37	0.11	0.35
≥2	4	1127/1082	0.75 [0.51, 1.12]	0.16	81%%	0.001	0.46 [0.19, 1.12]	0.09	0.61	0.05	0.81 [0.50, 1.31]	0.4	0.81	0.001	0.49 [0.20, 1.18]	0.11	0.63	0.04	2.06 [0.84, 5.03]	0.11	0.63	0.04
TB types																						
PTB	7	1753/1331	0.88 [0.67, 1.17]	0.38	0.74	0.0009	0.80 [0.38, 1.70]	0.57	0.65	0.009	0.87 [0.64, 1.18]	0.38	0.65	0.008	0.83 [0.40, 1.73]	0.63	0.65	0.009	1.20 [0.58, 2.50]	0.63	0.65	0.009

Others	3	541/783	1.15 [0.87, 1.51]	0.32	0	0.45	0.65 [0.16, 2.66]	0.55	0.23	0.27	1.38 [1.01, 1.89]	0.05	0	0.82	0.61 [0.15, 2.50]	0.49	0.23	0.27	1.65 [0.40, 6.78]	0.49	0.23	0.27
HIV status																					
HIV Negative	5	1084/1044	1.11 [0.93, 1.33]	0.23	0	0.71	1.21 [0.77, 1.92]	0.41	0	0.44	1.16 [0.92, 1.45]	0.2	0	0.55	1.23 [0.79, 1.91]	0.36	0	0.41	0.81 [0.52, 1.26]	0.36	0	0.41
HIV NA	5	1210/1070	0.81 [0.55, 1.18]	0.27	0.76	0.002	0.55 [0.18, 1.67]	0.29	0.52	0.08	0.84 [0.54, 1.31]	0.45	0.76	0.002	0.58 [0.20, 1.70]	0.32	0.51	0.09	1.73 [0.59, 5.10]	0.32	0.51	0.09

a: The statistical method used in Test of association is Mantel-Haenszel method. OR=Odds Ratio, CI=Confidence Interval.
b: $P_{heterogeneity}$=*P* value of heterogeneity.
c: Number of hospitals or centers were obtained from each full article, the number in each form represent the number of hospitals or centers registered by TB patients.
d: Others, the other TB types including EPTB, STB, OATB, and NA.
e: NA=Not Applicable.

Table 6: Begg's and Egger's tests for the evaluation of potential publication bias under allele genetic model.

SNP	Groups	Number of studies	Begg's regression analysis	Egger's regression analysis		
			P-value	Intercept [95% confidence interval]	*P*-value	t-value
rs361525	Pooled	24	0.000	2.852263 [-1.438772, 7.143298]	0.181	1.38
	African	1	NA	NA	NA	NA
	Caucasian	3	0.296	-0.1117765 [-1.270911, 1.047358]	0.436	-1.23
	Asian	20	0.013	6.270712 [1.051285, 11.49014]	0.021	2.53
rs1800629	Pooled	38	0.943	0.0303175 [-0.03660599, 0.4266949]	0.877	0.16
	African	3	0.296	1.509799 [-6.030845, 9.050444]	0.238	2.54
	Caucasian	8	0.902	-0.1145969 [-1.79884, 1.569646]	0.873	-0.17
	Asian	27	0.575	-0.1341091 [-0.5513733, 0.2831551]	0.513	-0.66
rs1799724	Pooled	10	0.128	-0.8502204 [-2.69953, 0.9990891]	0.320	-1.06
	African	1	NA	NA	NA	NA
	Caucasian	1	NA	NA	NA	NA
	Asian	8	0.621	-0.4462863 [-3.165534, 2.272961]	0.702	-0.40
rs1800630	Pooled	10	0.592	-0.1729943 [-1.028426, 0.6824379]	0.653	-0.47
	African	1	NA	NA	NA	NA
	Caucasian	1	NA	NA	NA	NA
	Asian	8	0.711	-0.1642557 [-1.005393, 0.6768819]	0.650	-0.48

NA=Not Applicable

were less than 50%, and Pheterogeneity was higher than 0.01 after removing two studies [23,36]. Third, for rs1799724 polymorphism, there was significant heterogeneity under the allele genetic model and the heterozygote genetic model, and the heterogeneity disappeared after excluding three studies [20,41,49]. Finally, for rs1800630 polymorphism, the I^2 values and Pheterogeneity in the allele genetic model and the heterozygote genetic model were changed by removing three studies [22,28,29].

Moreover, to evaluate the publication bias of the included studies in our meta-analysis, Begg's test, Egger's test, and funnel plots were performed under the allele genetic model of each SNP by pooled (Figure 5 and Table 6) and ethnicity subgroups (Figure S1-S4, Table 6). The results showed that the funnel plots of rs1799724, rs1800629 and rs1800630 did not reveal apparent asymmetry under the allele model by pooled (Figure 5) or subgroups, and the results of Egger's test and Begg's test also showed no publication bias (Table 6). However, the funnel plot of rs361525 revealed evident asymmetry under the allele genetic model in the pooled population (Figure 5A), and the publication bias is derived from the Asian population (Figure S1B). The same results were showed by Begg's test (Table 6, *P*=0.013) and Egger's test (Table 6, *P*=0.021). The potential sources of the bias in rs361525 might be contributed by following factors: (1) The quality of two included studies [25,26] is questionable because they both came from the same research institute and their genotype distribution was significantly inconsistent with other studies. Furthermore, we found that publication bias disappeared when we removed them; (2) Ten included studies have high risk of bias (showed as solid circles in Figure 2-4) in sample size [40,47,50,54,60], the ratio of case and control [27,30,40,49,50,54,56,57], TB combined with other diseases [33,50-52,55], SNP genotyping method was not given [29,58], and others mistakes [36,37,41], which might induce the publication biases; (3) Studies with null results should have the same scientific value as studies with significant results, but statistically significant results are three times more likely to be published than papers with invalid results [63].

Discussion

TB has existed for thousands of years and is a major global health problem. Prevention of new *M. tuberculosis* infection and its progression to TB are critical to reducing the burden of disease and death caused by TB. For the past few years, accumulating evidence has indicated that the genetic background of the host influences the outcome of some infectious diseases [64,65], including TB. Genome-Wide Association Studies (GWAS) and meta-analyses have been used to analyze the genetic basis of TB, and some susceptibility genes and SNPs have been identified [21,66-70].

The TNF gene, a locus on the human chromosome 6 and mouse chromosome 17, is well known as encoding cytokine TNF-α for

granuloma formation in a TB infection. Previous studies have proven that deficiency of TNF in a mouse model could result in failing to form organized granulomas and accelerating the death of *M. tuberculosis*-infected mice [71], which indicated that TNF played a key role in formation and maintenance of granuloma as well as inhibiting *M. tuberculosis* dissemination in an animal model. Subsequently, similar evidence was observed in human beings [72]. With the development of genetics and molecular biology, the accumulated data showed that several polymorphisms of TNF gene were associated with TB in different populations, including TNF +488G>A) [32], TNF -224G>A [20], rs361525 [20,22-32], rs673 [28], rs1800629 [20,22-32,34-40], rs1800750 [31], rs1799724 [20,22,25,26,28,29,41], rs1800630 [20,22,24,25,28,29,41], and rs1799964 [22]. However, the results of these studies were always inconsistent. Several factors may explain the discrepancy between the results of different studies: 1) Differences in ethnic genetic background led to differences in the results of these studies; 2) Other confounders, such as the number of cases and controls, patient selection criteria, SNP detection method, and HIV status, may have affected the consistency and reliability of the results; 3) Environmental factors might play an important role in TB infection and disease development.

To avoid these disadvantages of individual study, we performed this meta-analysis to evaluate the associations between TNF polymorphism and TB susceptibility. In the overall analysis, no significant association was observed between the rs1800630 polymorphism and TB risk under any genetic models. However, significant associations were found between rs361525, rs1800629, as well as rs1799724 polymorphisms and TB risk. Furthermore, in the stratified analysis by ethnicity, our meta-analysis demonstrated that these three SNPs were associated with TB risk in the Asian population and African population, especially in the Asian population. Our meta-analysis was consistent with three previous meta-analyses [21,69,70], but was contrary to 3 other previous meta-analyses conducted by Pacheco et al., [73], Zhang et al., [74], and Wang et al., [75]. These meta-analyses did not find any association between TNFSNPs rs361525 and rs1800629 and TB susceptibility. The possible reasons for this inconsistency may be the following aspects: inclusion of small sample size in the previous meta-analyses, non-uniformly defined cases, and different ethnic sub-groups among various studies.

Comparing with previous meta-analyses, this meta-analysis has several advantages: 1) The candidate studies were retrieved from 6 databases, and the number of finally included studies was more than any those in the previous meta-analysis, which enhanced the reliability and integrity of our research; 2) More than ten newly published articles were included in this meta-analysis, which provided a more accurate overview for the relationship between TNF SNPs and TB risk; 3) We were the first to detect the association between SNPs rs361525, rs1800629, rs1799724, and rs1800630 and TB risk under five genetic models; 4) crucial several confounding factors including TB types, number of hospitals or centers, and HIV status were included in this meta-analysis. However, there were several limitations in this meta-analysis: 1) The number of included studies in the African population was only three, which might reduce the accuracy and reliability of this meta-analysis; 2) Only articles written in English and Chinese were included in our meta-analysis; other language articles and unpublished data were omitted, which might cause publication bias and data inaccuracy; 3) Cohort studies were not included in the meta-analysis, cohort studies will allow the evaluation of a causal relationship between the SNPs and TB risk; 4) The relationship between TNFSNPs and other confounders such as age, gender, BMI (Body Mass Index), and environmental factors were not discussed in this study.

Conclusion

In summary, this meta-analysis suggested that TNFSNPs rs361525, rs1800629, and rs1799724rather than rs1800630were significantly associated with TB susceptibility, especially in Asians. Additionally, the essential confounding factors, such as TB types, number of hospitals or centers, and HIV status, might play an important role in TB susceptibility. These findings provide new insights into the association of SNPs in the inflammation and immune-related TNF with susceptibility to TB. It is necessary to confirm our results by performing further studies with a large sample size, different ethnic groups, and potential confounder factors in the future.

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