Meta-Analysis of Observational Studies in Epidemiology

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3'UTR polymorphisms in *NRAMP1* are associated with the susceptibility to pulmonary tuberculosis: A MOOSE-compliant meta-analysis

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Abstract

Many studies have investigated the association between the 3'UTR polymorphism in natural resistance-associated macrophage protein 1 (*NRAMP1*) and the risk of pulmonary tuberculosis (PTB), Revealing inconclusive results. This study aimed to investigate the correlation between the *NRAMP1* 3'UTR polymorphism and the risk of PTB.

This meta-analysis included 29 case–control studies to better and comprehensively assess this correlation. Pooled odds ratios (ORs) and 95% confidence interval (95% CIs) were calculated to assess the strength of the association.

These 29 case–control studies included 4672 cases and 6177 controls. The *NRAMP1* 3'UTR polymorphism displayed a significant positive correlation with the risk of PTB in 3 models (for del/del vs ins/ins: OR = 1.22, 95% CI = 1.01–1.47; for Ins/del vs ins/ins: OR = 1.19, 95% CI 1.08–1.30; for Ins/del + del/del vs ins/ins: OR = 1.25, 95% CI = 1.08–1.45). A stratified analysis by ethnicity revealed that the *NRAMP1* 3'UTR polymorphism was associated with an increased risk of PTB in the Asian population, but not in Caucasian, African, and South American populations.

The present results indicate that the *NRAMP1* 3'UTR polymorphism may be considered a risk factor for PTB in the Asian population.

Abbreviations: 95% CI = 95% confidence interval, GWAS = genome-wide association studies, HIV = human immunodeficiency virus, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa scale, NRAMP1 = natural resistance associated macrophage protein 1, OR = odds ratios, PTB = pulmonary tuberculosis, SLC11A1 = solute carrier family 11A member 1, TB = tuberculosis.

Keywords: meta-analysis, NRAMP1, polymorphism, pulmonary tuberculosis

1. Introduction

Tuberculosis (TB), a chronic infectious disease caused by *Mycobacterium tuberculosis*, is a major cause of worldwide mortality and morbidity. In 2016, 10.4 million new cases were reported, and 1.7 million individuals died of TB. Most of the individuals with TB reportedly reside in India China, Philippines, Pakistan, Nigeria, and South Africa.[1] The precise mechanisms underlying TB pathogenesis remain unknown. Weakened immunity, human immunodeficiency virus (HIV) infections, alcohol abuse, advanced age, chronic corticosteroid therapy, diabetes, socio-economic status, and malnutrition are the prominent risk factors of TB.[2] Not all individuals exposed to the similar risk factors develop tuberculosis, thus suggesting the involvement of genetic factors, including single-nucleotide polymorphisms, in TB pathogenesis.

When *M tuberculosis* infects the body, the immune system produces a barrage of defensive protein molecules, recruiting phagocytic cells, which eliminate the pathogen. Natural resistance-associated macrophage protein 1 (*NRAMP1)* is also referred to as the solute carrier family 11 proton-coupled divalent metal ion transporter membrane1 (*SLC11A1*), which plays an important role in the immune response to mycobacterial infections. *NRAMP1* encodes a divalent transition metal (Fe and Mn) transporter that localizes on the lysosomal membrane.[3] Iron is an essential mycobacterial nutrient that also influences the generation of reactive oxygen and nitrogen intermediates. Therefore, NRAMP1 is involved in resistance to intracellular pathogens, including Leishmania, Salmonella, and Mycobacteria. *NRAMP1* is associated with various infectious diseases and inflammatory diseases. It primarily contains 4 polymorphisms, rs17235416 (3'UTR), rs17235409 (D543N), rs3731865 (INT4), and rs34448891 (5=(GT)n). Among these polymorphisms, 3'UTR polymorphisms have been widely investigated for their association with TB. A functionally significant TGTG del allele in *NRAMP1* leads to reduced production of NRAMP1 when compared to the TGTG+ allele and may be correlated with the risk of TB.

Numerous studies have investigated the association between the *NRAMP1* 3'UTR polymorphism and the risk of pulmonary tuberculosis (PTB) in different regions,[4–29] revealing inconclusive results. A case–control study by Medapati et al[29] reported that the *NRAMP1* 3'UTR polymorphism is significantly associated with the susceptibility to TB among Indian

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YL and EZ equally contribute to this work.

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individuals. However, Jafari[28] reported no significant association between these 2 aspects. Hence, the present meta-analysis aimed to better and comprehensively assess the correlation between the *NRAMP1* 3'UTR polymorphism and the risk of PTB.

2. Materials and methods

2.1. Search strategy

We performed a comprehensive search in PubMed, Elsevier, and the Cochrane Library (update till January 1, 2019), using the following keywords

("tuberculosis" or "TB" or "mycobacteria"), ("polymorphism" or "mutation" or "variant"), and ("Natural resistance associated macrophage protein 1" or "NRAMP1" or "Solute carrier family 11A member 1 or SLC11A1" or "rs17235416"). Articles in all languages were included. Furthermore, additional related articles were identified through screening of the references of relevant articles. In case of a duplicate publication, the largest study was selected. The present study was conducted in accordance with the PRISMA guidelines for systematic reviews and meta-analyses.[30] Ethical approval was not necessary since this study is a meta-analysis.

2.2. Inclusion and exclusion criteria

Following were the inclusion criteria of this meta-analysis:

(1) case–control or cohort studies on the *NRAMP1* 3'UTR polymorphism and the risk of PTB;
(2) sufficient data estimating odds ratios (ORs) with 95% confidence intervals (95% CIs).

The major exclusion criteria were as follows:

(1) meta-analyses, letters, reviews, or editorial comments;
(2) studies were not irrelevant to TGTG ins/del;
(3) not PTB;
(4) studies with insufficient data;
(5) other than case–control study;
(6) genotype distributions were not in accordance with Hardy–Weinberg equilibrium (HWE) in the control group.

2.3. Data extraction and quality assessment

For all studies, EZ and LZ extracted the data independently and reached a consensus. Any disagreement was resolved through discussion among the 3 authors. The following information was collected from all eligible studies: the first author, year of publication, country of origin, ethnicity, source of controls, number of case and control subjects, HIV status, genotype frequencies in case and control groups, and HWE. We evaluated the quality of all of the studies included according to Newcastle–Ottawa scale (NOS).[31] The NOS contains 3 categories which are selection(0–4 points), comparability(0–2 points), and exposure (0–3 points). The total scores ranged from 0 to 9.

2.4. Statistical analysis

The association between the *NRAMP1* 3'UTR polymorphism and the risk of PTB was evaluated using crude ORs with 95% CIs. To assess heterogeneity, the Cochrane Q test and the I-squared (I^2) metric were used. If the I^2 metric was $<50\%$, indicating a lack of heterogeneity among studies, A fixed-effects model (the Mantel–Haenszel method) was used. Otherwise, the random-effects model (the DerSimonian and Laird method) was applied.[32] In addition, subgroup analyses based on ethnicity (Asian, Caucasian, African, and South American) were carried out. Funnel plot analysis and Egger test were conducted to identify a publication bias of the meta-analysis.[33] All statistical analyses were performed using STATA 11.0 software (STATA Corp., College Station, TX) and *P* values were 2-tailed.

3. Results

3.1. Characteristics of eligible studies

In accordance with the flowchart shown in Figure 1, 211 studies were retrieved through our initial literature search. After excluding duplicate articles, reviews, letters, comments, and irrelevant studies, 50 studies remained for further evaluation. After reading full-text articles, 24 studies were excluded. Finally, 26 eligible studies including 29 case–control studies, including 4672 cases and 6177 controls were included (Fig. 1). The major characteristics of identified studies were summarized in Table 1. These studies included 18 studies on Asians, 4 studies on Caucasians, 5 studies on Africans, and 2 studies on South American populations.

3.2. Quantitative synthesis

Table 2 summarizes the results of this meta-analysis. Overall, the *NRAMP1* 3'UTR polymorphism was significantly associated with the risk of PTB in 3 models (for del/del vs ins/ins: OR = 1.22, 95% CI = 1.01–1.47; for Ins/del vs ins/ins: OR = 1.19, 95% CI 1.08–1.30; for Ins/del + del/del vs ins/ins: OR = 1.25, 95% CI = 1.08–1.45); however, the recessive model did not reveal this significant association (for del/del vs ins/ins + Ins/del: OR = 1.18, 95% CI 0.98–1.42). In a stratified analysis by ethnicity, the present meta-analysis revealed that the *NRAMP1* 3'UTR polymorphism was associated with an increased risk of PTB in the Asian population (for del/del vs ins/ins: OR = 2.08, 95% CI = 1.45–2.98; for Ins/del vs ins/ins: OR = 1.49, 95% CI 1.29–1.73, Figure 2; for Ins/del + del/del vs ins/ins: OR = 1.57, 95% CI = 1.36–1.18; for del/del vs ins/ins + Ins/del: OR = 1.89, 95% CI 1.33–2.69), but not in the Caucasian, African, and South American populations. In a stratified analysis by HIV status, the *NRAMP1* 3'UTR polymorphism was significantly associated with the risk of PTB in HIV- individuals in 2 models (for Ins/del vs ins/ins: OR = 1.26, 95% CI = 1.06–1.49; for Ins/del + del/del vs ins/ins: OR = 1.28, 95% CI = 1.07–1.54), but not in the HIV+ individuals.

3.3. Publication bias

Funnel plot analysis and Egger's test were conducted to assess publication bias. Egger test did not reveal any evidence of publication bias in the Ins/del versus ins/ins models ($t = 0.14$, $P = .888$) and in the dominant model ($t = 0.81$, $P = .423$); however, publication bias was detected in the del/del vs. ins/

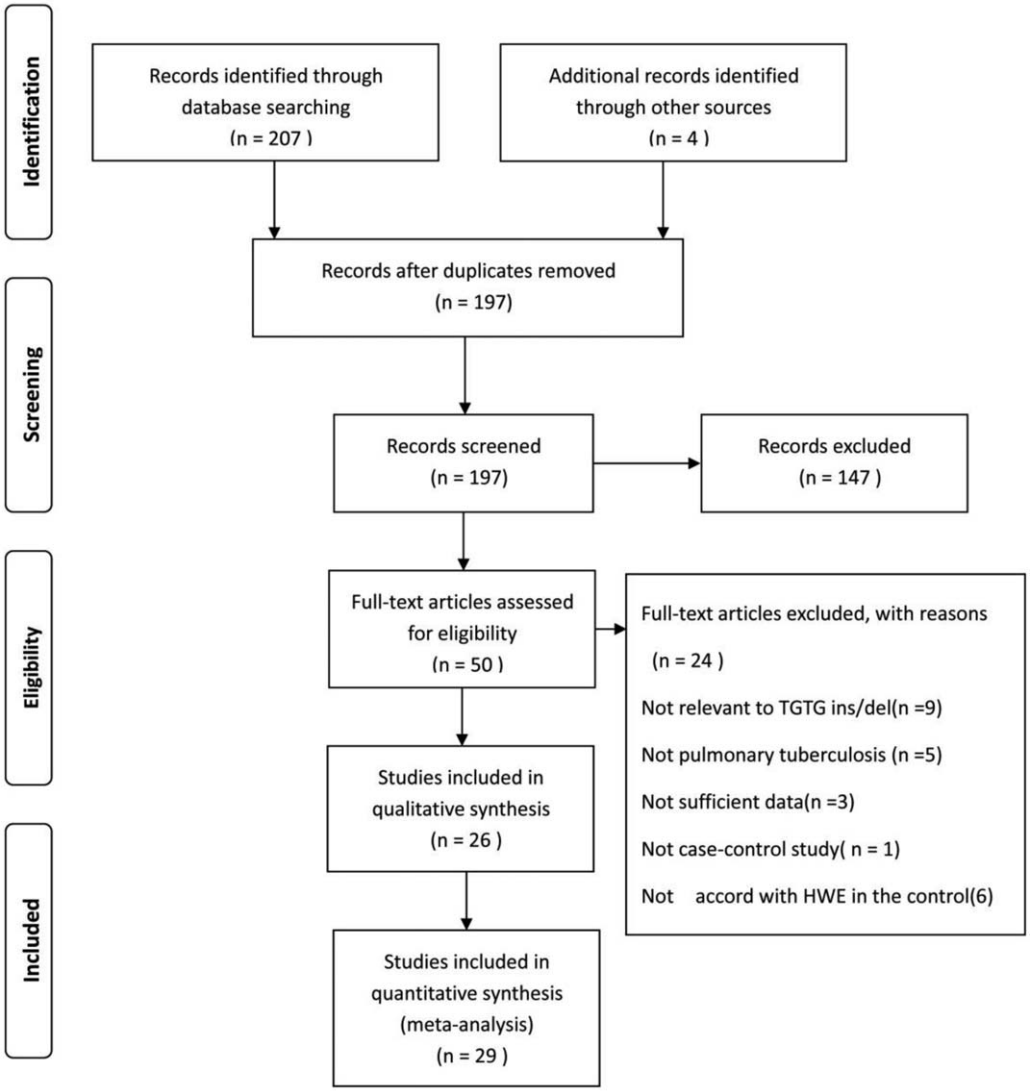

Figure 1. Flow chart of included studies in the current meta-analysis.

ins models ($t=2.65$, $P=.014$, Fig. 3) and in the recessive model ($t=2.43$, $P=.023$).

4. Discussion

The innate immune response activates early events during a *M tuberculosis* infection. *NRAMP1* plays an important role in the immune response to a mycobacterial infection. Therefore, this meta-analysis aimed to better and comprehensively assess the correlation between the *NRAMP1* 3'UTR polymorphism and the risk of PTB. The present study reports a significant correlation between the *NRAMP1* 3'UTR polymorphism and the risk of PTB in overall and Asian populations.

Many epidemiological studies have investigated the association between the *NRAMP1* 3'UTR polymorphism and the risk of PTB. In 2006, a meta-analysis by Li et al[34] reported that 3'UTR polymorphisms are significantly associated with the risk of PTB. Subsequently, a meta-analysis by Meilang et al[35] on PTB and extra-PTB reported that 3'UTR polymorphisms increased the risk of TB in comparison with their corresponding common alleles. Furthermore, stratified analyses by ethnicity, which assessed the forms of TB, confirmed the results of Li et al. This meta-analysis includes 29 recent case–control studies including 4672 cases and 6177 controls to better and comprehensively assess the correlation between the *NRAMP1* 3'UTR polymorphism and the risk of PTB. The present results are similar to those of 2 previous meta-analyses. The 3'UTR del/del and ins/del genotypes were significantly associated with a higher risk than the 3'UTR ins/ins genotype.

In 2000, the association between the *NRAMP1* 3'UTR polymorphism and the risk of PTB was first investigated by Ryu et al.[5] They revealed a significant relationship of the ins/del genotype variant with the risk of PTB among Koreans, but not in the del/del genotype. A case–control study by Medapati et al[29] reported that the *NRAMP1* 3'UTR polymorphism is significantly associated with the susceptibility to TB in the Indian population. However, Taype et al[9] reported did not report an association in

Table 1

Main characteristics of studies included in this meta-analysis.

First author	Yr	Country	Ethnicity	Source of controls	No. of pat/con	HIV status of cases	NRAMP1						*P* for HWE	Results of NOS
							case			control				
							ins/ins	ins/del	del/del	ins/ins	ins/del	del/del		
Ryu[4]	2000	Korea	Asian	healthy individuals	192/192	NR	146	43	3	164	27	1	.922	6
Liaw1[5]	2002	China	Asian	healthy individuals	49/48	negative	34	12	3	33	12	3	.214	6
Liaw2[5]	2002	China	Asian	healthy individuals	29/31	positive	17	12	0	22	8	1	.797	6
Abe[6]	2003	Japan	Asian	healthy individuals	95/90	negative	76	18	1	76	14	0	.424	7
Liu[7]	2003	China	Asian	healthy individuals	120/240	negative	74	44	2	178	56	6	.530	8
Fitness1[8]	2004	Malawi	African	healthy individuals	435/709	positive	126	74	17	353	287	69	.342	8
Fitness2[8]	2004	Malawi	African	healthy individuals	218/709	negative	112	91	15	353	287	69	.342	8
Taype[9]	2006	Peru	South American	healthy individuals	507/513	negative	345	144	18	378	120	15	.154	9
Hsu[10]	2006	China	Asian	healthy individuals	85/79	NR	44	38	3	46	28	5	.791	8
Vejbaesya[11]	2007	Thailand	Asian	healthy individuals	149/147	negative	102	42	5	106	34	7	.063	6
Sborg1[12]	2007	Tanzania	African	healthy individuals	442/431	mixed	241	166	35	248	150	33	.128	7
Sborg2[12]	2007	Tanzania	African	healthy individuals	251/431	negative	139	90	22	204	119	25	.191	7
Sahiratmadja[13]	2007	Netherlands	Caucasian	healthy individuals	214/363	negative	141	66	7	226	116	21	.241	9
Asai[14]	2008	Japan	Asian	healthy individuals	57/51	negative	25	26	6	31	15	5	.143	7
Farnia[15]	2008	Iran	Asian	staff of the hospital	71/39	negative	68	2	1	37	2	0	.869	6
Chen[16]	2009	China	Asian	healthy individuals	140/139	negative	84	50	6	101	36	2	.546	6
Merza[17]	2009	Sweden	Caucasian	staff of the hospital	117/60	NR	110	7	0	57	3	0	.843	8
Hatta[18]	2010	Indonesia	Asian	healthy individuals	58/198	NR	33	20	5	115	77	6	.103	6
de Wit[19]	2011	South Africa	African	healthy individuals	492/312	negative	393	85	14	261	48	3	.635	7
Solgun[20]	2011	Turkey	Caucasian	healthy individuals	49/50	NR	46	3	0	45	5	0	.710	6
Nugraha[21]	2011	Indonesia	Asian	staff of the hospital	78/43	NR	35	14	29	28	13	2	.758	6
Ben-Selma[22]	2012	Tunisian	Caucasian	healthy individuals	168/127	negative	80	67	21	60	52	15	.474	7
Sapkota[23]	2012	Japan	Asian	healthy individuals	111/211	negative	101	9	1	176	34	1	.637	6
Tiksnadi[24]	2013	Indonesia	Asian	healthy individuals	123/123	NR	75	43	5	85	31	7	.082	6
Wu F[25]	2013	Chinese	Asian	healthy individuals	213/211	negative	138	63	12	167	41	3	.790	9
Fernandez-Mestre[26]	2015	Venezuela	South American	staff of the hospital	89/50	negative	57	29	3	29	21	0	.060	6
Wu LL[27]	2015	Chinese	Asian	healthy individuals	151/453	negative	97	50	4	361	87	5	.925	8
Jafari [28]	2016	Iran	Asian	healthy individuals	96/122	NR	91	5	0	113	9	0	.672	7
Medapati[29]	2017	India	Asian	healthy individuals	91/88	negative	72	13	6	83	5	0	.784	6

HWE = *P* value for Hardy–Weinberge quilibrium in controls, NOS = Newcastle–Ottawa scale, NR = not reported.

the Peruvian population. These contradictory results may be explained on the basis of the present results, suggesting that the risk of PTB conferred by the variant allele may be modified by race. The present meta-analysis reported that the *NRAMP1* 3'UTR polymorphism was associated with an increased risk of PTB in the Asian population, but not in Caucasian, African, and South American populations.

Despite the strengths of the present study, some limitations should be acknowledged. First, upon subgroup analysis by ethnicity, the *NRAMP1* 3'UTR polymorphism was not associated with the risk of PTB in Caucasian, African, and South American populations. However, the sample size was relatively small in Caucasian, South American, and African populations, thus potentially decreasing the statistical power of the results to

Table 2

Summary ORs and 95% CI of Association between 3'UTR polymorphism and pulmonary tuberculosis risk.

Subgroup	n	del/del vs ins/ins		Ins/del vs ins/ins		Ins/del + del/del vs ins/ins		del/del vs ins/ins + Ins/del	
		OR95% CI	I^2	OR95% CI	I^2	OR95% CI	I^2	OR95% CI	I^2
Total	29	1.22 (1.01–1.47)	35.5%	1.19 (1.08–1.30)	45.1%	1.25 (1.08–1.45)	54.3%	1.18 (0.98–1.42)	32.3%
Ethnicity									
Asian	18	2.08 (1.45–2.98)	22.9%	1.49 (1.29–1.73)	31.3%	1.57 (1.36–1.81)	35.9%	1.89 (1.33–2.69)	30.0%
Caucasian	4	0.78 (0.45–1.36)	24.5%	0.93 (0.70–1.23)	0%	0.90 (0.69–1.18)	0%	0.81 (0.47–1.38)	25.1%
African	5	0.97 (0.74–1.27)	42.9%	1.01 (0.87–1.17)	28.8%	1.01 (0.88–1.16)	49.4%	0.97 (0.75–1.27)	30.8%
South American	2	1.42 (0.72–2.78)	0%	1.05 (0.58–1.89)	60.5%	1.23 (0.95–1.58)	46.2%	1.34 (0.69–2.62)	0%
HIV status of cases									
Positive	2	0.68 (0.39–1.19)	0%	1.03 (0.41–2.59)	65.2%	0.95 (0.42–2.13)	58.2%	0.77 (0.44–1.33)	0%
Negative	19	1.25 (0.98–1.59)	23.1%	1.26 (1.06–1.49)	49.9%	1.28 (1.07–1.54)	58.7%	1.18 (0.93–1.50)	14.7%

CI = confidence interval.

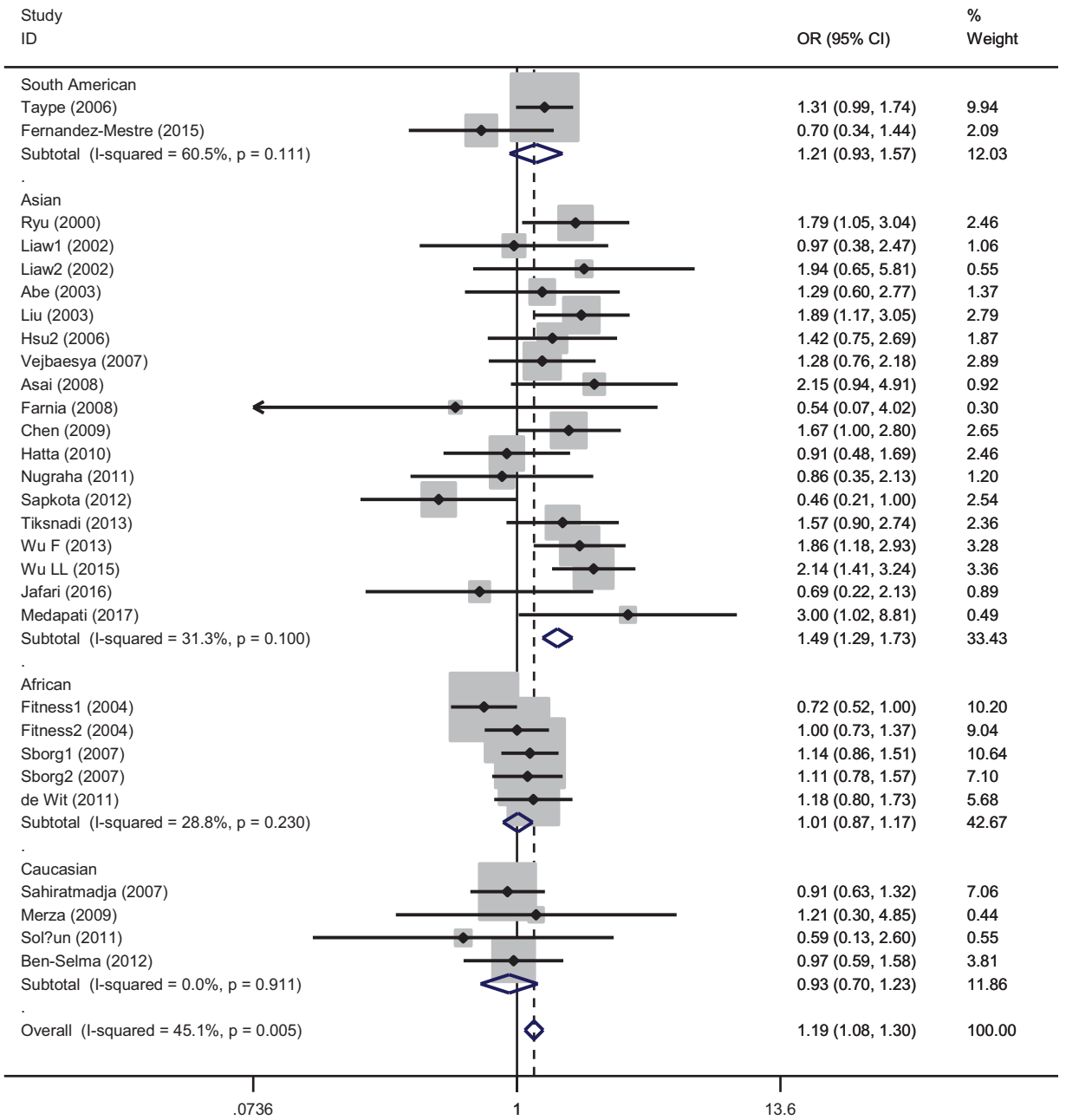

Figure 2. Forest plot for the association between 3'UTR polymorphism and pulmonary tuberculosis risk for the Ins/del genotype compared with the ins/ins genotype In a stratified analysis by ethnicity. CI = confidence interval, OR = odds ratio.

establish an actual association. Second, publication bias was detected in the del/del versus ins/ins models and the recessive model in overall analysis; hence, the present results should be considered with caution. Third, PTB is a complex disease; however, we did not carry out subgroup analysis to analyze potential gene-gene and gene-environment interactions because of insufficient data. Fourth, this meta-analysis was performed with a candidate gene strategy. Genome-wide association studies (GWAS) scanning entire genomes for genetic variation include immense amounts of SNPs and have been designed for the same ethnic background and study design. A GWAS by Zheng et al[36] reported that 2 loci 14q24.3 (rs12437118, Pcombined = $1.72 \times 10-11$, OR = 1.277, ESRRB) and 20p13(rs6114027, Pcombined = 2.37×10.11, OR = 1.339, TGM6) were significantly associated with TB in Han Chinese individuals. Miao et al[37] reported that rs9272461 is significantly associated with the risk of PTB in various genetic models. Hence, GWAS are required to further validate the present results.

In conclusion, the present results indicate that the *NRAMP1* 3'UTR polymorphism may be associated with an increased risk of PTB in the Asian population, but not in the Caucasian, African, and South American populations. Well-designed epidemiological studies with larger sample sizes are needed to verify the present findings.

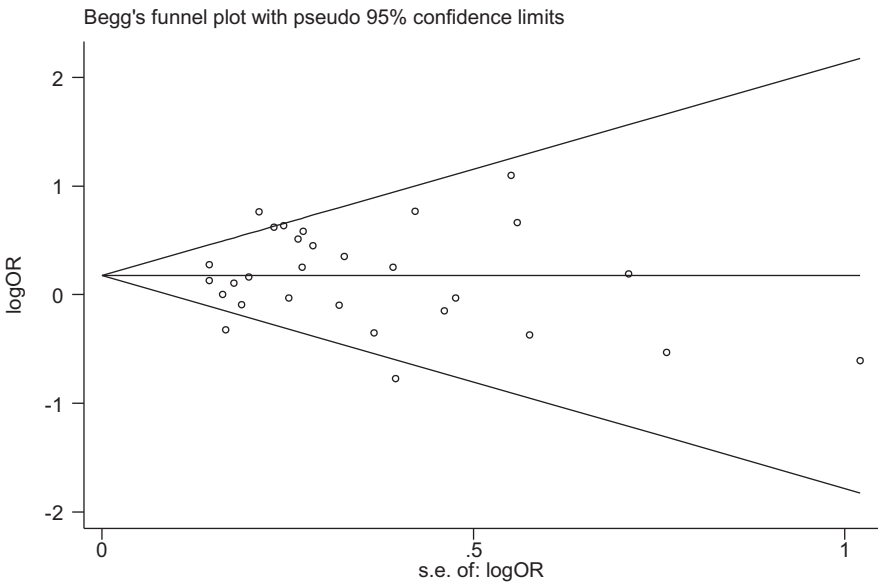

Figure 3. Funnel plot of the association 3'UTR polymorphism and pulmonary tuberculosis risk for the del/del genotype compared with the ins/ins genotype in overall populations. OR = odds ratio, se = standard error.

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