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Comprehensive Evaluation of Polymorphism in SLC11A1 and its Association with Susceptibility to Tuberculosis: A Meta-Analysis

Sneha Chhonkar
Department of Zoology, Miranda House, University of Delhi
Priyanka
Texas Biomedical Research Institute, San Antonio, Texas, United States
Sadhna Sharma
DSKC BioDiscovery Laboratory and Department of Zoology, Miranda House, University of Delhi
Monika Sharma
monika.sharma@mirandahouse.ac.in

DSKC BioDiscovery Laboratory and Department of Zoology, Miranda House, University of Delhi

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Abstract

Background

Tuberculosis (TB) remains the deadliest infectious disease, with about 8 million new cases annually. Since only 10% of the exposed individuals develop active disease, host genetics play a significant role. The SLC11A1 (NRAMP1) gene encodes a macrophage phagosomal iron transporter, central to innate immunity. D543N, 3'UTR TGTG ins/del, INT4 and $(GT)_n$ polymorphisms have been extensively studied for associations with TB susceptibility, but findings remain inconsistent across populations.

Objectives

To evaluate associations between these four major SLC11A1 polymorphisms and TB susceptibility with ethnicity-stratified subgroup analyses.

Methods

Case-control studies published to year 2025 were systematically retrieved from PubMed/MEDLINE and Scopus. DerSimonian-Laird random effects model was used to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs). Publication bias was assessed using the Harbord-Egger test, with trim-and-fill analysis applied where indicated.

Result

In total, 43, 38, 30 and 12 studies were included for D543N, 3'UTR TGTG ins/del, INT4 and $(GT)_{n,}$ respectively. All four polymorphisms were significantly associated with TB susceptibility. D543N showed significant dominant model (OR = 1.247, 95% CI = 1.064–1.461, p = 0.006). The 3'UTR deletion allele showed significant allelic association (OR = 1.406, 95% CI = 1.234–1.601). The INT4 achieved significance across all five models (OR = 1.223–1.770), demonstrating a codominant dose-response pattern. The (GT)n non-allele 3 carriers showed increased TB risk (OR = 1.350, 95% CI = 1.136–1.605). Ethnicity- stratified subgroup analysis revealed significant risk in Asian populations, with protective effects in Middle eastern populations.

Conclusion

All four SLC11A1 polymorphisms significantly contribute to TB susceptibility. Population-specific effects underline the importance of ethnicity-stratified analyses for identifying high-risk populations.

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (Mtb) and has been a leading cause of worldwide mortality and morbidity. Annually, it is estimated that 8–9 million new cases are reported worldwide [1]. It remains a global health threat resulting in 1.23 million deaths in 2024. Only 10% of infected individuals develop the clinical disease during their lifetime, even when one third of the population of the world is infected with Mtb[2]. This suggests the involvement of host's genetics, including polymorphisms, to be a contributing factor in TB pathogenesis along malnutrition, immunosuppressive treatments, human immunodeficiency virus and other environmental factors. This makes TB a multifactorial disease[3] .

During the onset of the disease, the immune system of the host recruit phagocytic cells like macrophages which produce large number of defensive proteins, which help in eliminating the pathogen. Solute-carrier family 11 proton coupled divalent metal ion transporter membrane 1 (SLC11A1) is also called Natural resistance associated macrophage protein 1 (NRAMP1). It plays an essential role against mycobacterial infections, like TB by encoding a metal transporter for divalent transition metals like Fe and Mn which then localises on the membrane of the lysososme [2]. It regulates divalent cation levels that promotes the formation of toxic hydroxyl radicals as shown in Fig. 1. This in turns contribute to the killing of intracellular pathogens [4]. Iron is an important mycobacterial nutrient, playing a significant role in reactive oxygen species (ROS) and nitrogen intermediate generation in immune cells like macrophages [5]. Therefore, SLC11A1 is involved in the innate immune response against intracellular pathogens like Mycobacteria. Several polymorphisms have been extensively studied across the globe as risk factors to TB, which includes D543N (single base substitution of G to A at codon 543 of exon 15), 3'UTR TGTG ins/del (TGTG deletion in the 3' untranslated region), INT4 (single nucleotide change from G to C in intron 4) and (GT)n in the 5'promoter region. A large number of control-based case studies have been published and evaluated for the association between SCL11A1 polymorphisms and TB risk in different regions, but the results have been inconclusive and inconstant due to differences in study population, sample sizes and study type.

A meta-analysis approach is needed for the comprehensive evaluation of SLC11A1 polymorphisms and TB risk, as single studies have low power to detect overall effects. Meta-analysis is a powerful tool which includes synthesising data from different studies on the same topic. The last meta-analysis which evaluated these four major SLC11A1 polymorphisms comprehensively with TB risk was published in 2012 [6]. In the past few years, several case studies have been published which are yet to be included in the analysis. None of the past meta-analyses reported results for all four polymorphisms across five genetic patterns of inheritance, along with sub-group analysis based on ethnicity. This, to our knowledge is the most comprehensive meta-analysis of SLC11A1 polymorphisms and TB risk to date.

Methods

Study identification and selection

A comprehensive computerized literature search was conducted on electronic databases including PubMed/MEDLINE and Scopus to identify studies for association of SLC11A1 polymorphisms and TB susceptibility on 10th January 2026. Boolean operators such as "AND" and "OR", combined with search subjects in the advanced search builder were used. The search terms used were 'tuberculosis' or 'TB' with 'SLC11A1' or 'solute carrier family 11 member 1' or 'NRAMP1' or 'natural resistance associated macrophage protein 1' in combination with 'polymorphism' or 'mutation' or 'variant' or 'SNP'. Previous meta-analyses were included in citation chasing. A total of 50 abstracts were retrieved for further analysis after those that overlapped the databases were removed.

Selection criteria

INCLUSION CRITERIA

1.Case-control studies of unrelated individuals; 2. Studies evaluating the association between SLC11A1 polymorphisms and TB risk; 3. Studies with extractable and sufficient data like genotypic distribution for controls and cases to calculate odds ratio (OR) with 95% confidence interval (CI).

EXCLUSION CRITERIA

1. Family-based or linkage studies; 2. Genotypic numbers not reported; 3. Studies with no control group; 4. Genotypic distribution not consistent with Hardy-Weinberg equilibrium (HWE); 5. Review articles and concept notes; 6. Study on any other polymorphism or on animals; 7. Studies not in English.

Data extraction

Based on the inclusion criteria, investigator collected data. Any inconsistency was verified with the co-authors until a consensus was reached. The following items were extracted from each study if provided: Last name of the first author, Year of publication, Country of origin, ethnicity, sample size, TB definition, and genotypic numbers in cases and controls.

Statistical Analysis

The strength of association between SLC11A1 polymorphism and tuberculosis risk was assessed using odds ratio (ORs) with 95% confidence interval (CIs). Five genetic inheritance models were evaluated for D543N, 3'UTR TGTG ins/del and INT4 polymorphism as follows: for D543N, the allelic model (A vs G), dominant model (AA + GA vs GG), recessive model (AA vs GA + GG), heterozygous model (GA vs GG) and homozygous model (AA vs GG); for 3'UTR TGTG in/del, the allelic model (TGTG- vs TGTG+), dominant model (TGTG+/- + TGTG-/- vs TGTG+/+), recessive model (TGTG-/- vs TGTG+/- + TGTG+/+)' heterozygous model (TGTG+/- vs TGTG+/+) and homozygous model (TGTG-/- vs TGTG+/+); for INT4, the allelic model (C vs G), dominant model (CC + CG vs GG), recessive model (CC v CG + GG), heterozygous model (CG vs GG) and homozygous model (CC vs GG); and for (GT)n polymorphism, only the allelic model (other alleles vs allele 3) was evaluated. All pooled ORs were calculated using the DerSimonian-Laird random effects model.

Heterogeneity between studies was assessed using χ^2-based Cochran Q statistics and the I^2 statistics. The I^2 value quantifies the total variation which attributes to genuine between-study heterogeneity with values 25%, 50% and 75% representing low, moderate and substantial heterogeneity respectively. The Breslow-Day test was additionally used to assess homogeneity of odds ratio across studies. The between-study variance component τ^2 was estimated using the moment-based DerSimonian-Laird method. The significance of pooled OR was determined by Z-test and $P < 0.05$ was considered statistically significant.

Hardy-Weinberg equilibrium (HWE) was assessed in control populations of each included study using χ^2 goodness of fit test. Studies in which control group genotypic frequencies were deviating significantly from HWE ($P < 0.05$) were excluded. Studies with zero cell genotype counts in one or both groups were automatically excluded from the relevant models by the statistical software.

Subgroup analyses were performed by ethnic group to evaluate population specific effects. Five ethnic subgroups were used: Asian, Middle Eastern, African, Latin American and European. Studies were assigned to the subgroups based on the country of origin and ethnicity of the participants in the study. A minimum of three studies per group were required for pooled analysis.

Publication bias was assessed using three complementary methods: the Begg-Mazumdar rank correlation test, Egger's weighted regression test, and the Harbord- Egger test. The Harbord-Egger test was considered the primary indicator of publication bias as it is specifically designed for binary outcome data and is less susceptible to false positive results for odds ratio meta-analysis. Publication bias was considered statistically significant where $P < 0.05$. For models where significant funnel plot asymmetry was detected, trim and fill analysis was performed using DerSimonian-Laird random effects model to estimate the number of potentially missing studies and recalculate bias-adjusted pooled ORs.

Sensitivity analyses were performed by excluding individual studies identified an influential outliers based on extreme odds ratios or data quality concerns.

All statistical analyses were performed using StatsDirect Version 4 as the primary software platform. Trim and Fill analyses were performed using the meta package in R statistical software. All tests were two sided and $P < 0.05$ was considered statistically significant.

Results

Studies included in the meta-analysis

The flow chart of the literature search with number of included and excluded studies is shown in Fig.S.1 and the characteristics of each article have been listed in table 1. A total of 204 and 262 records were identified from databases and citation searching. After removal of 225 duplicates, 241 articles were screened by title and abstract. Based on the exclusion criteria, 158 articles were removed. 83 full text articles were accessed for eligibility, where 33 articles were removed due to various reasons as listed in Fig.S.1. Therefore, a total of 130 case-control studies in 50 articles were identified and included in the meta-analysis. The characteristics of these studies are reported in Table.1. The genotypic frequencies of cases and controls are reported in Table.S.1.

Overall, 43 case-control studies on D543N polymorphism, 38 for 3'UTR TGTG ins/del polymorphism, 30 for INT4 polymorphism and 12 for (GT)n polymorphism were included in the meta-analyses study.

Association of SLC11A1 polymorphisms with TB susceptibility

D543N polymorphism

A total of 6625 TB cases and 7805 controls in 43 case-control studies were included in the Meta-analysis. Overall, D543N polymorphism was found to be significantly associated with the risk of TB in three models. A allele carriers showed significantly increased TB risk (OR=1.247, 95% CI 1.064-1.461, p=0.006 across dominant model (AA+GA vs GG) as shown in Fig.2. It showed substantial heterogeneity (I^2=64.3). All three bias tests were non-significant (Begg p=0.330, Egger p=0.457, Harbord p=0.558), which explains the symmetry of the funnel plot in Fig.3. So, trim-and-fill analysis was not required.

Allelic (OR=1.254, 95%CI= 1.090-1.443, p=0.002) and heterozygous (OR= 1.208, 95% CI= 1.028-1.420, p=0.022) models showed significant association of this polymorphism with TB susceptibility. However, Recessive (OR=1.244, 95%CI= 0.886-1.745, p= 0.207) and homozygous model (OR=1.295, 95% CI= 0.924-1.816, p= 0.133) models were non-significant, as mentioned in Table.2. Sensitivity analysis was performed by removing outlier studies, which resulted in no major shift in the OR, confirming the robustness of the results.

3'UTR TGTG ins/del

A total of 38 case-control studies were included for the 3'UTR TGTG ins/del polymorphism. We observed that the deletion allele was significantly associated with increased TB risk in all five models. Fig. 4 shows forest plot for deletion allele in allelic model where OR= 1.506, 95% CI=1.234-1.610, p<0.0001, with substantial heterogeneity (I^2=65.2%). Egger's (p=0.023) and Harbord-Egger (p=0.025) test indicated significant publication bias as indicated in the funnel plot in Fig.5, so trim and fill analysis was conducted. The trim-and-fill analysis identified no missing studies i.e. k=0, which confirms robustness. The dominant (OR=1.433, 95% CI= 1.247-1.648, p<0.0001), recessive (OR=1.423, 95% CI= 1.092-1.854, p<0.009), heterozygous (OR=1.374 95% CI= 1.200-1.573, p<0.0001) and homozygous (OR=1.550, 95% CI= 1.169-2.056, p=0.002) models also confirmed that deletion allele is risk conferring as mentioned in Table.2. Sensitivity analyses for 3'UTR TGTG polymorphism excluded Medapati et al. 2017 [7] with OR=5.45 and Kim et.al 2003 [8]with OR=5.18 as extreme outlier studies. For allelic model, a OR changed to 1.353, with a resolved asymmetry (Egger p=0.088, Harbord p=0.081). This confirms the robustness of the primary findings.

INT4

A total of 30 case-control studies were included for the INT4 polymorphism in genotype models, with Shahzad et al. 2022[9] excluded from dominant, recessive, heterozygous and homozygous models due to data inconsistencies. The

study was included only in allelic model.

Across all five genetic models, the C allele was significantly associated with increased TB susceptibility. The forest plot for dominant model, represented by Fig.6, showed increased TB odds (OR=1.294, 95% CI= 1.083-1.547, p= 0.005) with substantial heterogeneity (I^2=64.4%,). All bias tests were non-significant (Begg p=0.214, Egger p=0.333 and Harbord p=0.401) which reflects the symmetry of the funnel plot in Fig.7. Therefore, Trim-and-fill analysis was not required. The allelic model (OR=1.297, 95% CI= 1.095-1.536, p=0.003), recessive (OR=1.671, 95% CI= 1.152-2.423, p=0.007), heterozygous model (OR=1.223, 95% CI= 1.041-1.437, p=0.014) and homozygous model (OR=1.770, 95% CI= 1.157-2.707, p=0.009) also showed significant risk associated with C allele.

Sensitivity analysis excluding Shahzad et al. 2022[9] from the INT4 allelic model substantially reduced heterogeneity (I^2=83.6% to 66.4%; τ^2=0.291 to 0.124) which confirms the disproportionate influence of this study on the outcome. The direction and significance of the INT4 allelic association remain unchanged which indicates robustness.

(GT)n

A total of 12 case-control studies were included for (GT)n polymorphism. The allelic model demonstrated substantial between study heterogeneity (I^2=66.4%, 95% CI 56.1–79.0%; Q=99.38, p<0.0001), with non-allele 3 carriers showing increased TB risk (OR=1.350, 95% CI 1.136–1.605, p=0.001) as shown in Fig.8. All three bias tests were clean, so no asymmetry was detected in the funnel plot (Fig. 9).

Table.1 Characteristics of the studies included in the Meta-analysis :

Author	Year	Country	Ethnicity	Case /Control	Type of TB	HIV status	Polymorphisms
Abe [10]	2003	Japan	Asian	95/90	PTB	NA	D543N, 3'UTR TGTG ins/del, INT4
Asai [11]	2008	Japan	Asian	57/51	PTB and EPTB	HIV-negative	D543N, INT4
Ates [12]	2009	Turkey	European	112/80	PTB and EPTB	NA	D543N, 3'UTR TGTG ins/del, INT4, (GT)n
Bellamy[13]	1998	Gambia	African	41[14]0/417	PTB	HIV-negative	D543N, INT4, (GT)n
Ben-Selma[15]	2012	Tunisia	Caucasian	223/150	PTB and EPTB	HIV negative	D543N, 3'UTR TGTG ins/del,
Chen [16]	2009	China	Asian	140/139	PTB	HIV-negative	D543N, 3'UTR TGTG ins/del, INT4, (GT)n
De Wit[17]	2010	South African	African	505/318	TB	HIV-negative	3'UTR TGTG ins/del, (GT)n
Delgado [14]	2002	Cambodia	Asian	358/106	PTB	HIV-negative	D543N, 3'UTR TGTG ins/del,
Duan [18]	2003	China	Asian	147/145	PTB and EPTB	NA	3'UTR TGTG ins/del
Fernandez[19]	2015	Venezuela	South American	92/100, 89/100, 89/98	TB	HIV-negative	D543N, 3'UTR TGTG ins/del, INT4
Fitness [20]	2004	Malawi	African	546/1043	TB	HIV-negative	(GT)n, 3'UTR TGTG ins/del
Freidin[21]	2006	Russia	European	238/263,304/140	TB and EPTB	NA	D543N, INT4
Farnia[22]	2008	Iran	Asian	71/39	TB	HIV-negative	D543N, 3'UTR TGTG ins/del, INT4
Gao[23]	2000	Japan	Asian	202/267	PTB	HIV-negative	D543N, (GT)n
Hanta[24]	2012	Turkey	Asian	127/116	PTB+EPTB		D543N, INT4
Hatta[25]	2010	Indonesia	Asian	58/198	TB	NA	D543N, 3'UTR TGTG ins/del, INT4
Hsu[26]	2006	China	Asian	110/92, 105/95	TB	NA	D543N, INT4, (GT)n 3'UTR TGTG ins/del
Jafari[27]	2016	Iran	Asian	96/122	PTB	NA	D543N, 3'UTR TGTG ins/del, INT4
Jin[2]	2009	China	Asian	136/435	PTB	HIV-negative	INT4, 3'UTR TGTG ins/del

Kim[8]	2003	Korea	Asian	56/45	TB	HIV-negative	D543N, 3'UTR TGTG ins/del, INT4
Leung[8]	2007	China	Asian	278/282	EPTB	NA	(GT)n, 3'UTR TGTG ins/del, D543N
Li[28]	2022	China	Asian	227/516	PTB	NA	D543N
Liaw[29]	2002	China	Asian	49/48	EPTB	HIV-negative	D543N, 3'UTR TGTG ins/del
Liu[30]	2008	China	Asian	60/30	TB	HIV-negative	3'UTR TGTG ins/del
Liu[31]	2004	China	Asian	120/240	PTB	NA	D543N, 3'UTR TGTG ins/del, INT4
Medapati[7]	2017	India	Asian	91/88	PTB	HIV-negative	3'UTR TGTG ins/del
Merza[32]	2009	Iran	Asian	117/60	PTB	NA	D543N, 3'UTR TGTG ins/del, INT4
Meng[33]	2009	China	Asian	224/225	PTB	HIV-negative	3'UTR TGTG ins/del
Ma[34]	2002	USA	European	113/108	PTB	HIV-negative	(GT)n
Nino-Moreno[4]	2007	Mexican	South American	94/100	PTB and EPTB	NA	D543N
Nugraha[35]	2011	Indonesia	Asian	69/43	PTB	HIV negative	D543N, 3'UTR TGTG ins/del, INT4
Puzyrev[36]	2002	Russia	European	58/127	PTB	NA	INT4
Ryu[37]	2000	Korea	Asian	192/192	PTB and EPTB	NA	D543N, 3'UTR TGTG ins/del
Qu[38]	2007	China	Asian	61/122	TB	HIV-negative	D543N, INT4
Sahiratmadja [39]	2007	Indonesia	Asian	494/519	PTB	HIV-positive NA in cases; 2 in controls	D543N, 3'UTR TGTG ins/del
Selvaraj[40]	2002	India	Asian	157/112	PTB	NA	D543N
Singh[41]	2011	India	Asian	101 / 225	PTB and EPTB	HIV-negative	D543N, 3'UTR TGTG ins/del, INT4
Soborg[42]	2007	Tanzania	African	443/426	PTB	HIV-negative	D543N, 3'UTR TGTG ins/del, INT4, (GT)n
Soborg[43]	2002	Denmark	European	104/176	PTB	HIV-negative	D543N, 3'UTR TGTG ins/del,

							INT4, (GT)n
Solgun[44]	2011	Turkey	Caucasian	50/50 (but 3'UTR: 49/50)	PTB and EPTB	NA	D543N, 3'UTR TGTG ins/del, INT4
Stagas[45]	2011	Greek	European	142/144	TB	NA	D543N, 3'UTR TGTG ins/del, INT4
Shahzad[9]	2022	Pakistan	Asian	164 / 85	PTB	HIV-negative	D543N, INT4
Taype[46]	2006	Peru	South American	630/513	PTB	HIV-negative	D543N, 3'UTR TGTG ins/del, INT4
Tiksnadi[47]	2013	Indonesia	Asian	164/123	PTB and EPTB	NA	D543N, 3'UTR TGTG ins/del
Vejbaesya[48]	2007	Thailand	Asian	149/147	PTB and EPTB	HIV-negative	D543N, 3'UTR TGTG ins/del, INT4
Wu[49]	2015	China	Asian	151/453	TB	HIV-negative	D543N, 3'UTR TGTG ins/del, INT4
Wu F[50]	2013	China	Asian	213/211	TB	HIV-negative	3'UTR TGTG ins/del
Waworuntu [51]	2023	Indonesia	Asian	35 / 35	TB	HIV-negative	D543N
Zaida Araujo[52]	2023	Venezuela	Caucasian	13/90	TB	HIV-negative	D543N
Zhang W[1]	2005	China	Asian	127/91	TB	NA	D543N, INT4

Table.2 Summary of results from different comparative genetic models

A. **D543N**

Model	Ethnicity	Number of studies	Test of association			Model	Test of heterogeneity		Publication bias
			OR	95% CI	P		P	I^2	
Dominant	Overall	43	1.247	1.064–1.461	0.006	Random Effects	<0.0001	64.3%	0.558
	Asian	26	1.402	1.189–1.654	<0.0001	Random Effects	0.0014	51.4%	0.418
	Middle Eastern	6	0.358	0.183-0.701	0.0027	Random Effects*	0.1433	39.3%	0.115
	Latin American	5	1.252	0.763-2.059	0.372	Random Effects	0.0029	75.1%	0.657
	African	3	1.54	1.150-8.330	0.0039	Random effects*	0.224	33.2%	0.506
	European	3	0.93	0.456-1.925	0.861	Random effects*	0.218	34.3%	0.663
Allelic	Overall	43	1.254	1.090–1.443	0.002	Random Effects	<0.0001	63.6%	0.786
Recessive	Overall	43	1.244	0.886–1.745	0.207	Random Effects*	0.174	19.1%	0.056 (k=2)
Heterozygous	Overall	43	1.208	1.028–1.420	0.022	Random Effects	<0.0001	63.5%	0.241
Homozygous	Overall	43	1.295	0.924–1.816	0.133	Random Effects*	0.116	18.0%	0.074

B. **3'UTR TGTG ins/del**

Model	Ethnicity	Number of studies	Test of association			Model	Test of heterogeneity		Publication bias
			OR	95% CI	P		P	I^2	
Allelic	Overall	38	1.406	1.234–1.601	<0.0001	Random Effects	<0.0001	65.2%	0.025 (k=0)
	Asian	23	1.615	1.390-1.875	<0.0001	Random Effects	0.006	55.9%	0.114
	Middle eastern	5	0.925	0.482-1.775	0.816	Random Effects*	0.772	0%	0.192
	Latin American	3	1.227	0.795-1.893	0.3535	Random Effects	0.018	74.8%	0.866
	African	5	0.995	0.791-1.253	0.972	Random Effects	0.0577	56.2%	0.195
	European	2	1.129	0.873-1.458	0.353	Random Effects*	0.850	0%	**
Dominant	Overall	38	1.433	1.247–1.648	<0.0001	Random Effects	<0.0001	58.6%	0.075
Recessive	Overall	38	1.423	1.092–1.854	0.009	Random Effects*	0.031	34.4%	0.090 (k=4)
Heterozygous	Overall	38	1.374	1.200–1.573	<0.0001	Random Effects	0.0001	52.1%	0.285
Homozygous	Overall	38	1.550	1.169–2.056	0.002	Random Effects* *	0.031	39.5%	0.041 (k=0)

C. INT4

Model	Ethnicity	Number of studies	Test of association			Model	Test of heterogeneity		Publication bias
			OR	95% CI	P		P	I^2	
Dominant	Overall	30	1.294	1.083–1.547	0.005	Random Effects	<0.0001	64.4%	0.075
	Asian	16	1.308	1.003-1.704	0.047	Random Effects	0.0016	58.6%	0.032
	Middle Eastern	6	1.094	0.838-1.428	0.505	Random Effects*	0.957	0%	0.934
	Latin American	2	0.935	0.513-1.704	0.828	Random Effects	0.051	73.7%	**
	African	2	1.503	1.059-2.132	0.0224	Random Effects*	0.206	37.4%	**
	European	2	1.309	0.946-1.812	0.1032	Random Effects*	0.825	0%	**
Allelic	Overall	31	1.297	1.095–1.536	0.003	Random Effects	<0.0001	66.4%	0.025 (k=0)
Recessive	Overall	30	1.671	1.152–2.423	0.007	Random Effects*	0.116	26.4%	0.090 (k=4)
Heterozygous	Overall	30	1.223	1.041–1.437	0.014	Random Effects	0.0001	53.8%	0.285
Homozygous	Overall	30	1.770	1.157–2.707	0.009	Random Effects*	0.026	39.4%	0.041 (k=0)

D. (GT)n

Model	Ethnicity	Number of studies	Test of association			Model	Test of heterogeneity		Publication bias
			OR	95% CI	P		P	I^2	
Allelic	Overall	12	1.350	1.136–1.605	0.001	Random Effects	0.004	60.2%	0.025 (k=0)

** Fixed effects estimates are presented in supplementary material (Table.S.2) for datasets with low heterogeneity. Results were consistent with random effects findings which confirms that conclusions were not sensitive to the choice of statistical model.*

*** Bias was not calculated due to not enough sample size.*

Discussion

One of the deadliest infectious diseases in the world is TB, causing a worldwide mortality of 1.5 million people annually. Only approximately 10% of the infected individual develop active TB infection, whereas the remaining 90% maintain latent infection or clear the pathogen. This variability in the clinical outcome is a result of differences in the host genes which control the defence against *Mtb* [53]. Many host genes like SLCC11A1 [6, 54, 55]Interferon gamma[56, 57]Interleukin-10[57]Vitamin-D receptor [58, 59]and Mannose-binding lectin [60, 61]have been studied in relation with TB.

The human SLC11A1 gene, located on chromosome region 2q35, is made up of 15 exons that form an mRNA encoding a 550 amino acid polypeptide[62]. It encodes for a cation transporter which forms a crucial part of host immune response. The association between SLC11A1 polymorphisms and the risk of TB has been widely investigated by many epidemiological studies. Li et al, in 2006, reported significant association between all four SLC11A1 polymorphisms and Pulmonary TB in the population [63]. In 2012, Meilang et al. also reported the association of SLC11A1 polymorphisms with Pulmonary Tuberculosis (PTB) and Extra-Pulmonary Tuberculosis (EPTB) but, pervious analyses by Yuan et al. in 2017 suggested that SLC11A1 D543N polymorphism had no association with PTB risk in general population [6] [64]. Bellamy et al. reported that SLC11A1 variants were associated with active TB infection in African populations in 1998, but these results have been remarkably different among studies [13]. Taype et al. reported no such association in Peruvian populations [46]. These inconsistencies in results explain the need for an updated meta-analysis, with ethnicity-stratified subgroup analysis to explain population-specific effects.

Meta-analyses play a crucial role in identifying genetically vulnerable groups and allow us to move beyond generalized approach and adopt targeted, population specific strategies for disease management and prevention. From a disease management perspective, individuals carrying high-risk SLC11A1 genotypes, may benefit from enhanced surveillance programmes, more frequent screening, and earlier initiation of preventive therapy. Genotyping of SLC11A1 variants in high-burden countries, especially across Asia and sub-Saharan Africa, could therefore serve as a cost-effective tool for stratifying individuals at higher TB risk. Such individuals can benefit from personalised preventive interventions.

To establish a statistically significant risk among SLC11A1 polymorphisms and TB susceptibility, quantitative synthesis of data was done in this meta-analysis. Previously reported meta-analyses comprehensively studied the link between the two by including case-control studies up to year 2011 only. In the past 14 years, many individual studies have been published which addressed the effect of SLC11A1 polymorphisms and TB risk, so, we extended the analysis by including case-control studies up to year 2025.

Our findings are consistent with three prior meta-analyses which studied the association between SLC11A1 polymorphisms and TB susceptibility. Li et al. demonstrated significant associations between all 4 polymorphism and TB susceptibility across 14 case-control studies [54]. Li et al. updated this analysis with incorporating data from 36 case-control studies [65]. Meilang et al. further extended this analysis to 82 case control studies and reported dominant ORs- 1.31 for D543N, 1.45 for 3'UTR, 1.27 for INT4 and 1.35 for (GT)n [6]. The present analysis incorporated additional published studies in the recent years and yielded allelic model ORs- 1.254, 1.406, 1.297 and 1.350 for the previously mentioned polymorphisms which is consistent in magnitude and direction with previous analyses. The result for (GT)n is identical to Meilang et al. which validates our methodological approach [6].

A key difference in the present analyses is the systematic evaluation of all five genetic inheritance models. Previous studies only evaluated the dominant model as primary model for D543N, 3'UTR and INT4, which did not reveal the complete picture. Our approach reveals inheritance patterns for each polymorphism, which are essential to understand the biological mechanisms underlying SLC11A1-mediated susceptibility.

Between-study heterogeneity was substantial across most models with I^2 ranging from 19% to 84%. This reflects genuine biological diversity, including ethnic diversity, Mtb strains, variation in study design and sample sizes. So, the use of Random effects models throughout the analysis accounts for between-study variations.

The D543N G/A polymorphism demonstrated significant association with TB susceptibility under allelic (OR = 1.254), dominant (OR = 1.247) and heterozygous (OR = 1.208) models, with non-significant recessive and homozygous models. This pattern is consistent with dominant inheritance where a single risk allele (A allele) is sufficient to confer increased TB susceptibility. The non-significant recessive and homozygous models are due to zero-cell exclusions which results into decreased statistical power. The A allele confers 24% increased TB susceptibility in general population. Since D543N results into G-to-A substitution which results in change of aspartic acid to asparagine at 543 codon position, it may alter the protein conformation in a way that reduces the efficiency of the divalent cation transporter. This would make a person more susceptible to TB.

The subgroup analysis for D543N polymorphism identified significant increased TB risk in Asian populations (OR = 1.402, 95% CI = 1.189–1.654, p < 0.0001) and African populations (OR = 1.54, 95% CI = 1.150–8.330, p = 0.0039). In contrast, Middle Eastern populations demonstrated a significant protective effect (OR = 0.358, 95% CI = 0.183–0.701, p = 0.0027), suggesting a population-specific divergence in the role of this polymorphism. Latin American and European subgroups showed non-significant trends (OR = 1.252, p = 0.372 and OR = 0.93, p = 0.861, respectively). The non-significant findings in these subgroups likely reflect insufficient study numbers (n = 3 to 5) rather than a true absence of effect, as individual studies in these groups showed wide CIs.

The 3'UTR TGTG del allele is significantly associated with increased TB risk under allelic (OR = 1.406), dominant (OR = 1.433), recessive (OR = 1.423), heterozygous (OR = 1.374) and homozygous (OR-1.550) models, which suggests dominant mode of inheritance. The deletion allele results into 40% more risk in the general population under allelic model. Since 3'UTR TGTG ins/del polymorphism is located in the 3' untranslated region of SLC11A1, it may affect mRNA stability and translation efficiency. The deletion allele destabilises the mRNA which might affect protein expression and result into impaired function of the divalent cation transporter. Funnel plot analysis revealed significant asymmetry for allelic and homozygous models by Harbord-Egger tests. So, trim-and-fill analysis was performed which identified no missing studies for either model i.e. k = 0. This confirms that the asymmetry was between-study heterogeneity from population-specific effects, not because of missing negative and non-significant studies.

The subgroup analysis for 3'UTR polymorphism identified significant increased TB risk in Asian populations (OR = 1.615, 95% CI 1.390–1.875, p < 0.0001) and Latin American populations (OR = 1.227, 95% CI 0.795–1.893). African, Middle Eastern, and European subgroups showed non-significant trends.

The INT4 polymorphism demonstrated the most compelling genetic pattern. The INT4 C allele is significant with increased TB risk across Allelic (OR = 1.29), Dominant (OR = 1.29), Recessive (OR = 1.67), Heterozygous (OR = 1.22) and Homozygous (OR = 1.77) models. This finding reveals a codominant dose-response pattern that GC heterozygotes show 22% increased risk, while CC homozygotes show 77% increased risk. Since INT4 G-to-C substitution in intron 4, it potentially affects mRNA processing efficiency and results into altered protein efficiency.

The subgroup analysis for INT4 demonstrated significant risk in Asian populations (OR = 1.308, 95% CI 1.003–1.704, p = 0.047) with moderate heterogeneity (I^2=58.6%). Middle Eastern populations showed non-significant trends (OR = 1.094, p = 0.505).

The (GT)n promoter microsatellite demonstrates significant allelic association with TB susceptibility (OR = 1.350). The non-allele 3 carriers show 35% increased TB odds compared to allele 3 carriers. Allele 3 is associated with higher promoter activity which results into increased SLC11A1 efficiency. So, non-allele 3 carriers would be at a higher TB risk as promoter activity is compromised.

The sub-group analyses revealed that Asian populations, which formed the largest subgroup, showed an increased TB risk across D543N, 3'UTR TGTG ins/del and INT4 polymorphisms. The D543N dominant model revealed 40% increased TB odds for Asian population (including East-Asian subgroups) i.e. OR = 1.402 and 54% increased risk for African populations

(OR = 1.54). In contrast, Middle eastern population show protective effects (OR = 0.358). 3'UTR TGTG ins/del reported 61% and 22% increased TB risk for Asian population and Latin American populations respectively. INT4 also reported 30% increased TB odds in Asian populations.

Despite the strengths of the findings in the present study, some limitations must be acknowledged. One of the limitations of this study is that majority of the studies included were conducted for Asian populations, which formed our largest subgroup. This is because the Asian populations are often the focus of meta-analyse as they have a disproportionately high burden of TB infection worldwide, making them an important target for epidemiological research [66]. These under-represented other ethnic groups which did not reach significant statistical power, particularly European, Latin American, African and Middle Eastern populations. This study did not include subgroup analysis to analyse TB types, HIV status and other gene-environment interactions because many primary studies did not report these variables. Lastly, publication bias cannot be fully eliminated, even after trim-and-fill analysis due to small sample size of some subgroups. Therefore, more case-control studies need to be published to overcome these limitations.

In conclusion, this updated and most comprehensive meta-analysis confirms that all four SLC11A1 polymorphisms are significantly associated with TB susceptibility. The consistent risk for Asian subgroups across all three polymorphisms indicates that Asian populations carry a genetic risk profile for SLC11A1. This also explains the high TB burden in Asian countries. Large-scale epidemiological studies with larger sample sizes are required to verify the present findings.

Declarations

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Author Contributions

M.S. contributed to the study conception and design. Material preparation, data collection and analysis were performed by S.C. The first draft of the manuscript was written by S.C. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

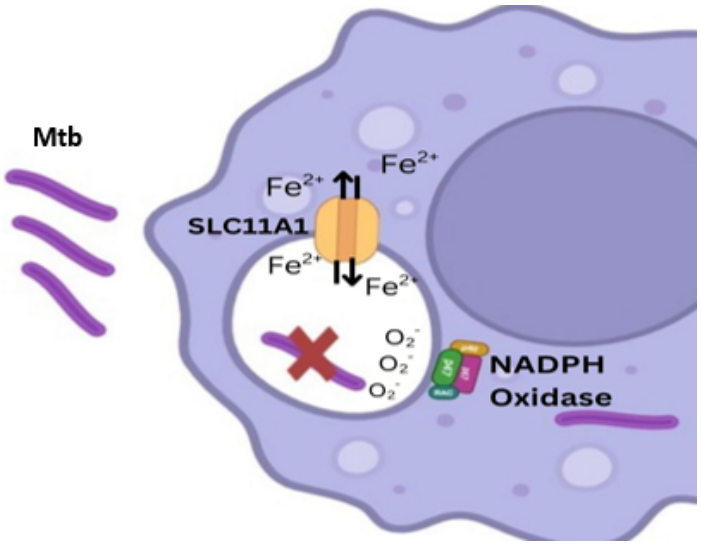


Figure 1

Function of SLC11A1: SLC11A1 gene encodes for a divalent metal cation ,which translocates to the phagolysosome membrane. It assists transport of metal ions, particularly Fe which catalyses the formation of ROS by NADPH oxidase.

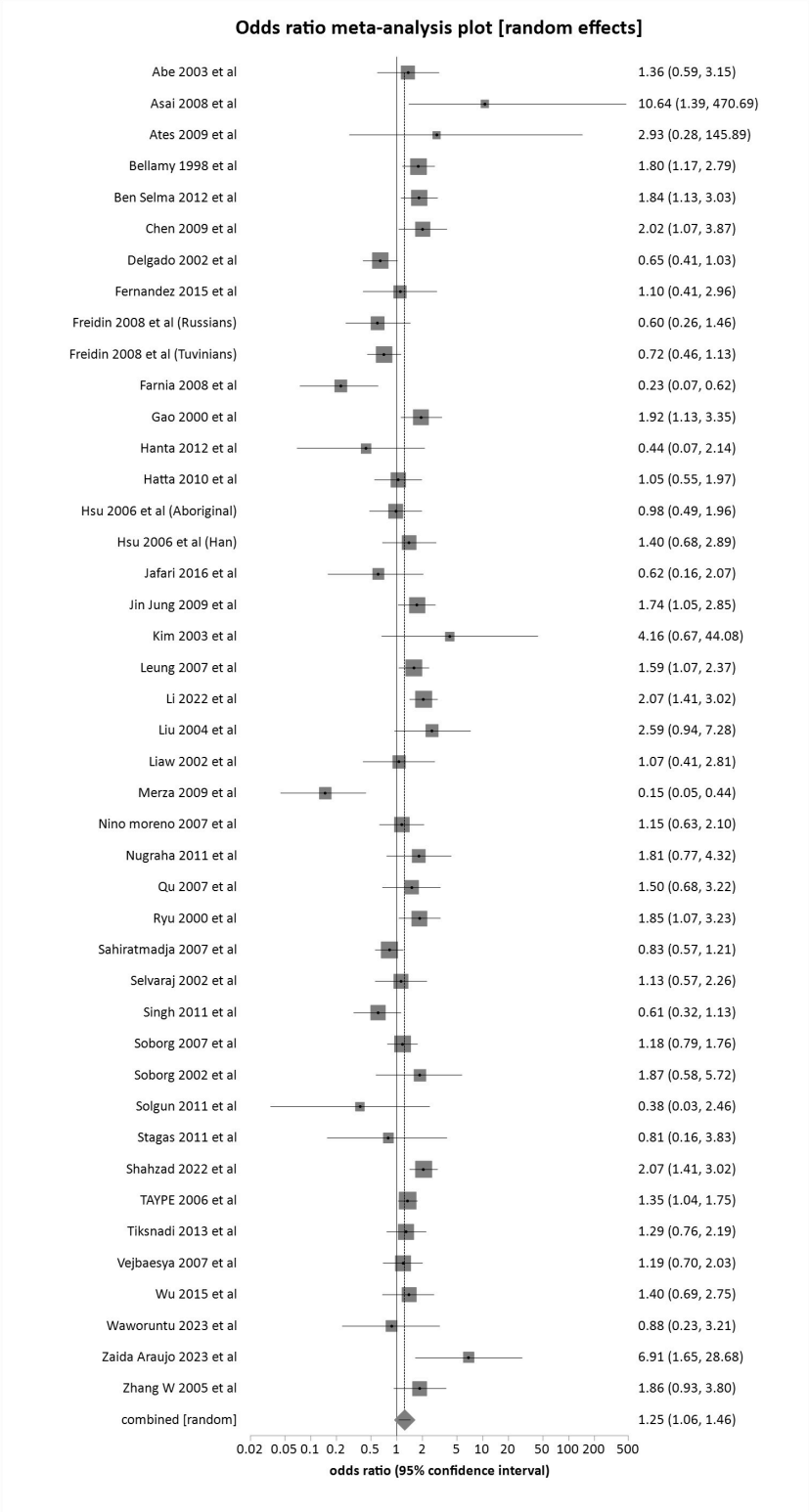


Figure 2

Forest Plot of D543N Polymorphism and Tuberculosis Susceptibility under the Dominant Model (GC+CC vs. GG): Each horizontal line represents an individual study, with the central square indicating the odds ratio (OR) and its 95% confidence interval (CI). Square size reflects the statistical weight of each study. The diamond at the bottom represents the pooled OR, with its lateral points denoting the CI boundaries. The vertical line at OR=1.0 is the line of no effect. Pooled analysis using the DerSimonian-Laird random-effects model demonstrated a statistically significant increased TB susceptibility among carriers of at least one D543N variant allele (OR=1.247, 95% CI=1.064–1.461, p=0.006).

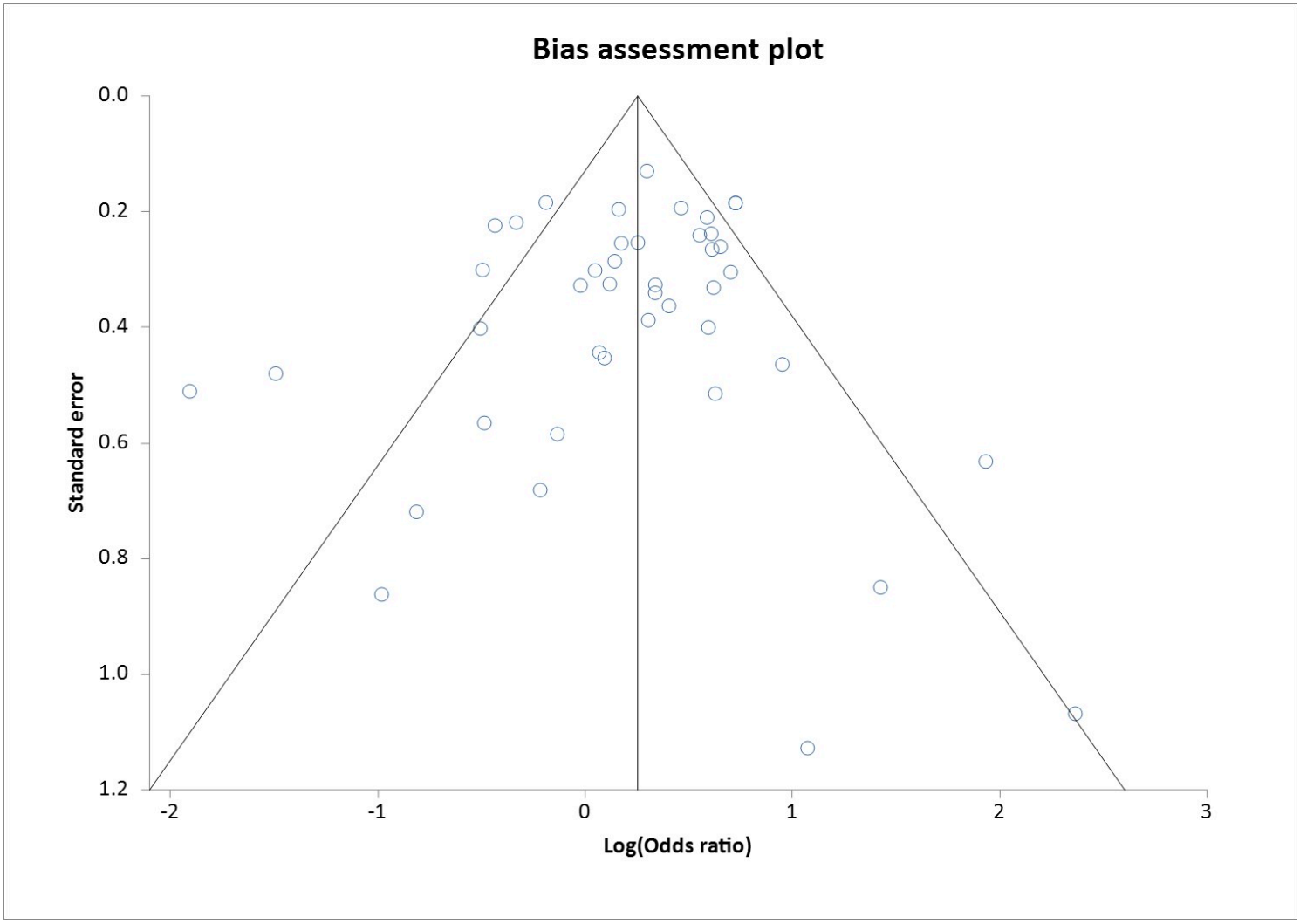


Figure 3

Funnel Plot for Publication Bias Assessment of D543N Polymorphism under the Dominant Model: The funnel plot displays the standard error of each study plotted against its log odds ratio (OR) to assess publication bias. In the absence of publication bias, studies are expected to be symmetrically distributed around the pooled effect estimate, forming an inverted funnel shape. Each circle represents an individual study. The plot appears largely symmetrical, consistent with the Harbord-Egger test result (p=0.558), indicating no significant publication bias in the dominant model.

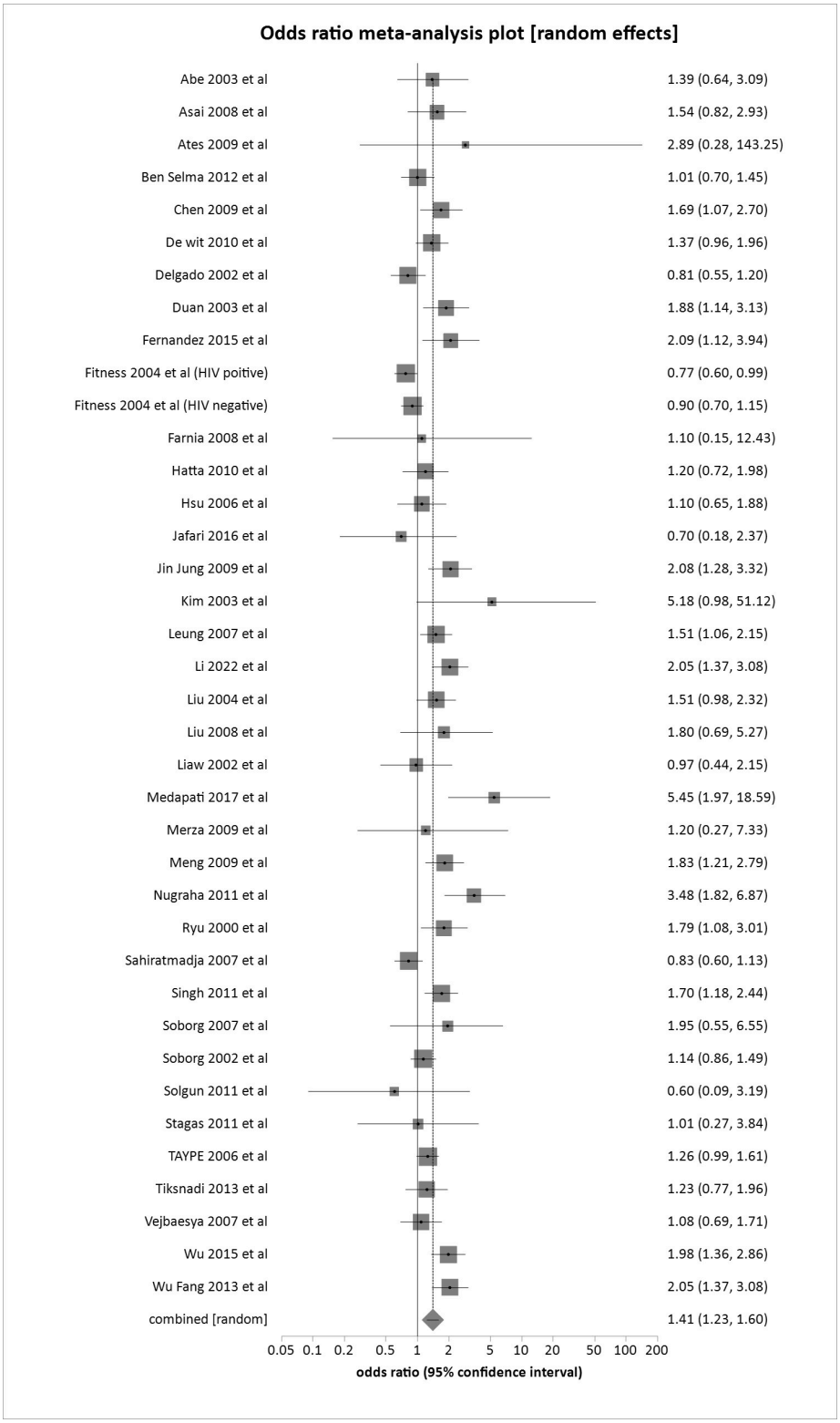


Figure 4

Forest Plot of 3'UTR TGTG ins/del Polymorphism and Tuberculosis Susceptibility under the Allelic Model (del vs. ins): Each horizontal line represents an individual study, with the central square indicating the odds ratio (OR) and its 95% confidence interval (CI). Square size reflects the statistical weight of each study. The diamond at the bottom represents the pooled OR, with its lateral points denoting the CI boundaries. The vertical line at OR=1.0 is the line of no effect. Pooled analysis using the DerSimonian-Laird random-effects model demonstrated a statistically significant association, with the deletion allele conferring increased TB susceptibility (OR=1.406, 95% CI=1.234–1.601).

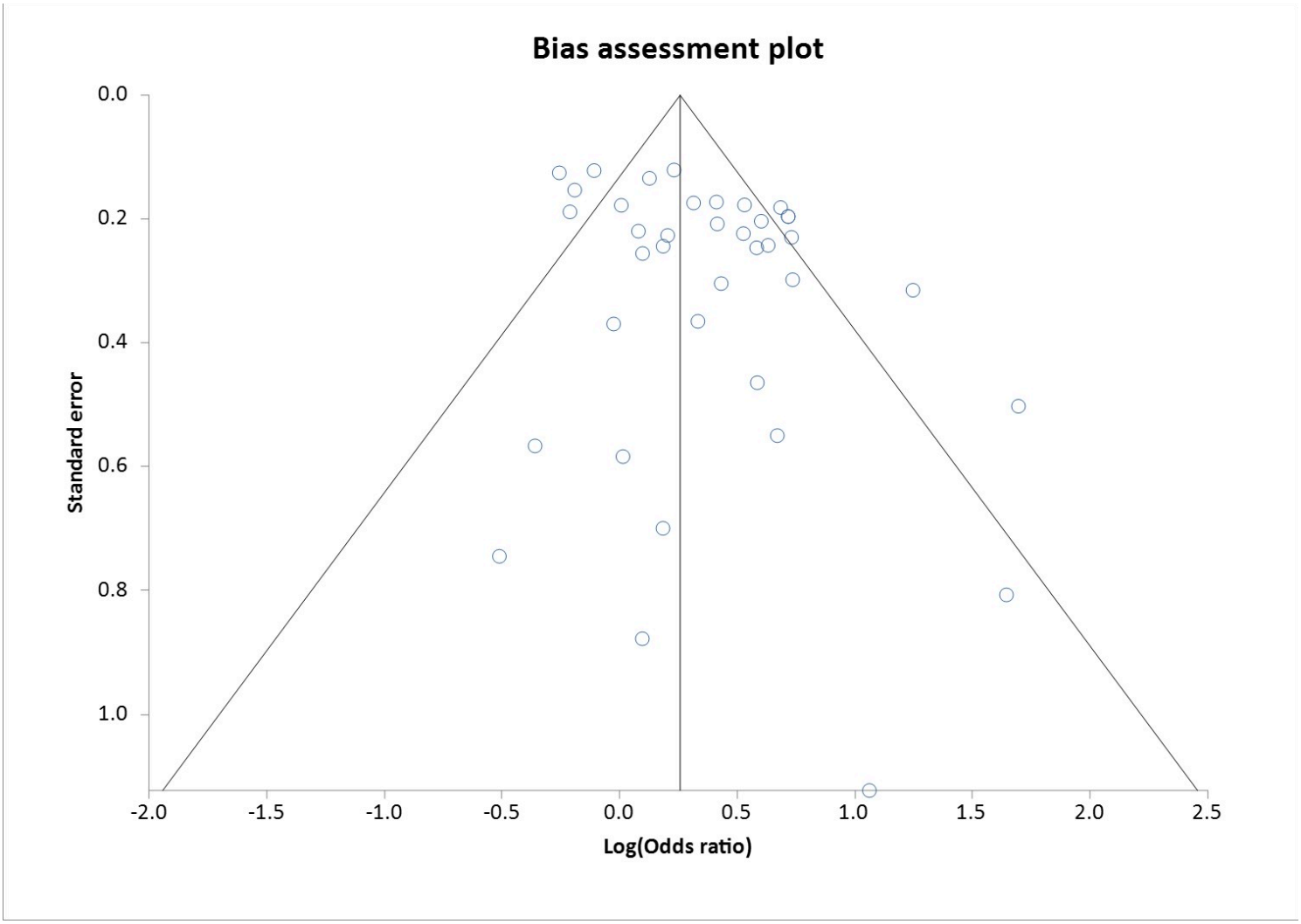


Figure 5

Funnel Plot for Publication Bias Assessment of 3'UTR TGTG ins/del Polymorphism under the Allelic Model: The funnel plot displays the standard error of each study plotted against its log odds ratio (OR) to assess publication bias. Each circle represents an individual study. The Harbord-Egger test revealed significant publication bias (p=0.025). Trim-and-fill analysis was subsequently applied, however no studies required imputation (k=0), suggesting that despite the statistically significant Egger's test, the pooled effect estimate remains robust and is unlikely to be materially influenced by missing studies.

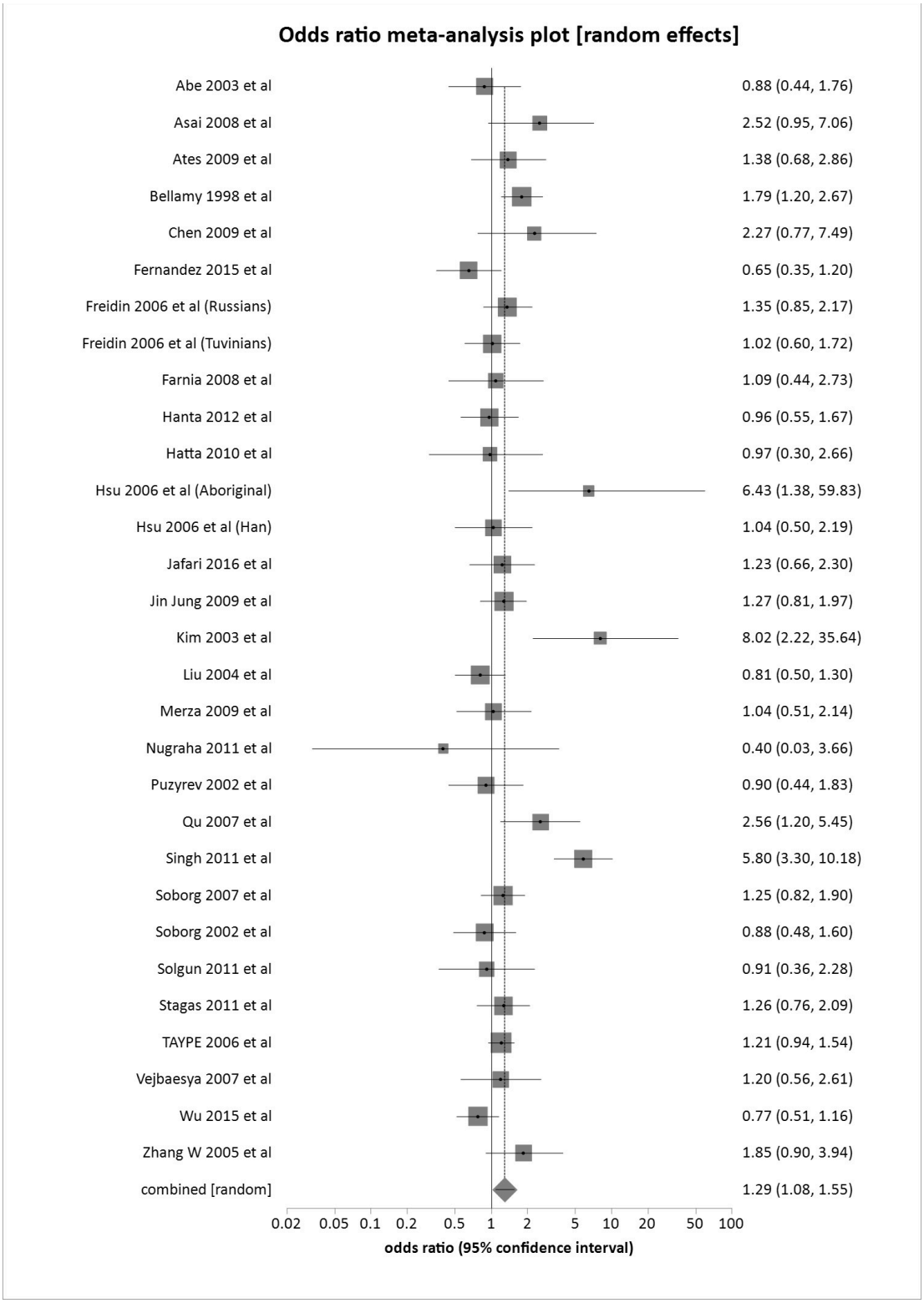


Figure 6

Forest Plot of INT4 Polymorphism and Tuberculosis Susceptibility under the Dominant Model (GC+CC vs. GG): Each horizontal line represents an individual study, with the central square indicating the odds ratio (OR) and its 95% confidence interval (CI). Square size reflects the statistical weight of each study. The diamond at the bottom represents the pooled OR, with its lateral points denoting the CI boundaries. The vertical line at OR=1.0 is the line of no effect. Pooled analysis using the DerSimonian-Laird random-effects model demonstrated a statistically significant association, with carriers of at least one INT4 C allele showing increased TB susceptibility.

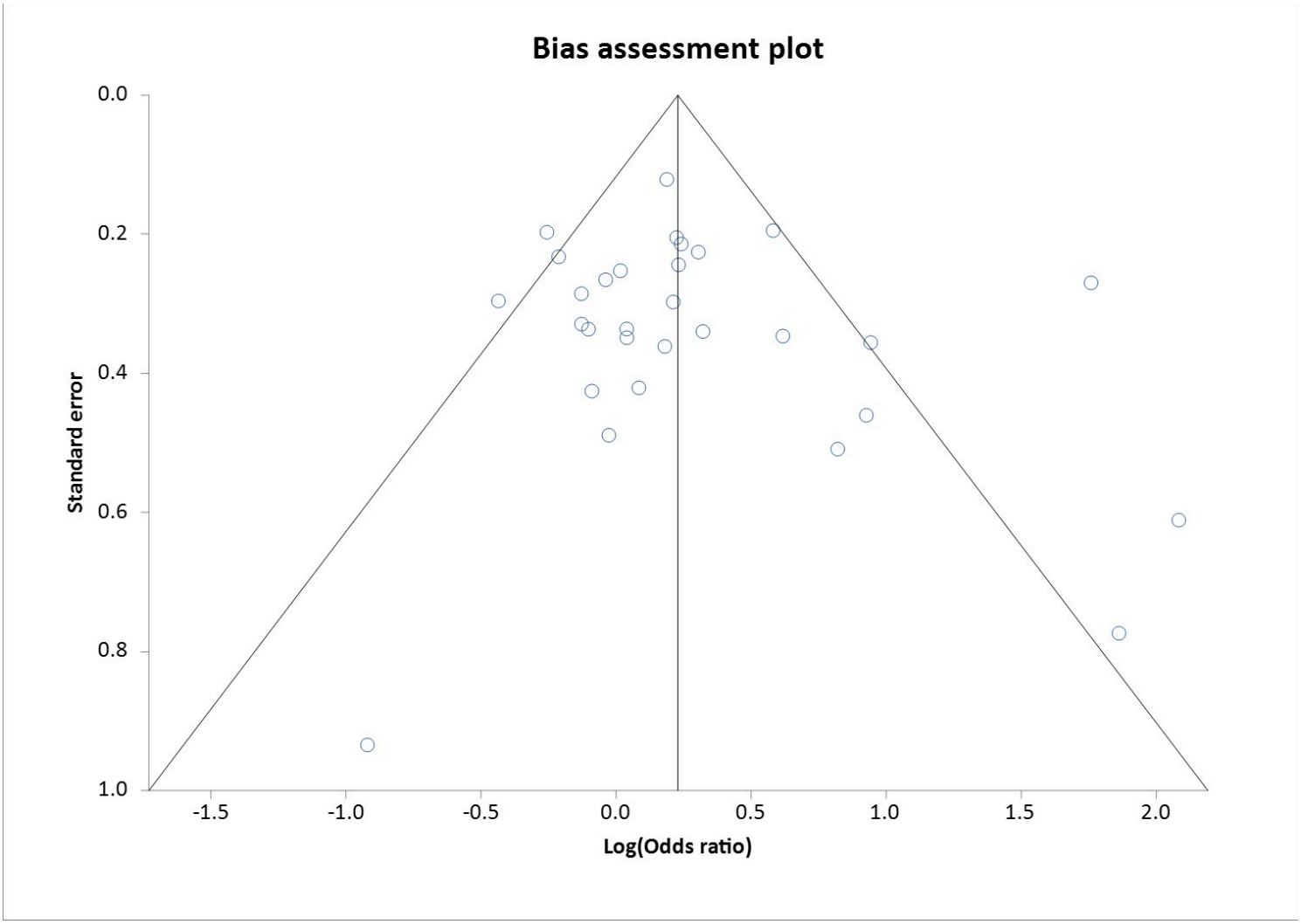


Figure 7

Funnel Plot for Publication Bias Assessment of INT4 Polymorphism under the Dominant Model: The funnel plot displays the standard error of each study plotted against its log odds ratio (OR) to assess publication bias. Each circle represents an individual study. The Harbord-Egger test revealed no statistically significant publication bias (p=0.075), indicating that the pooled effect estimate for the INT4 dominant model not influenced by publication bias.

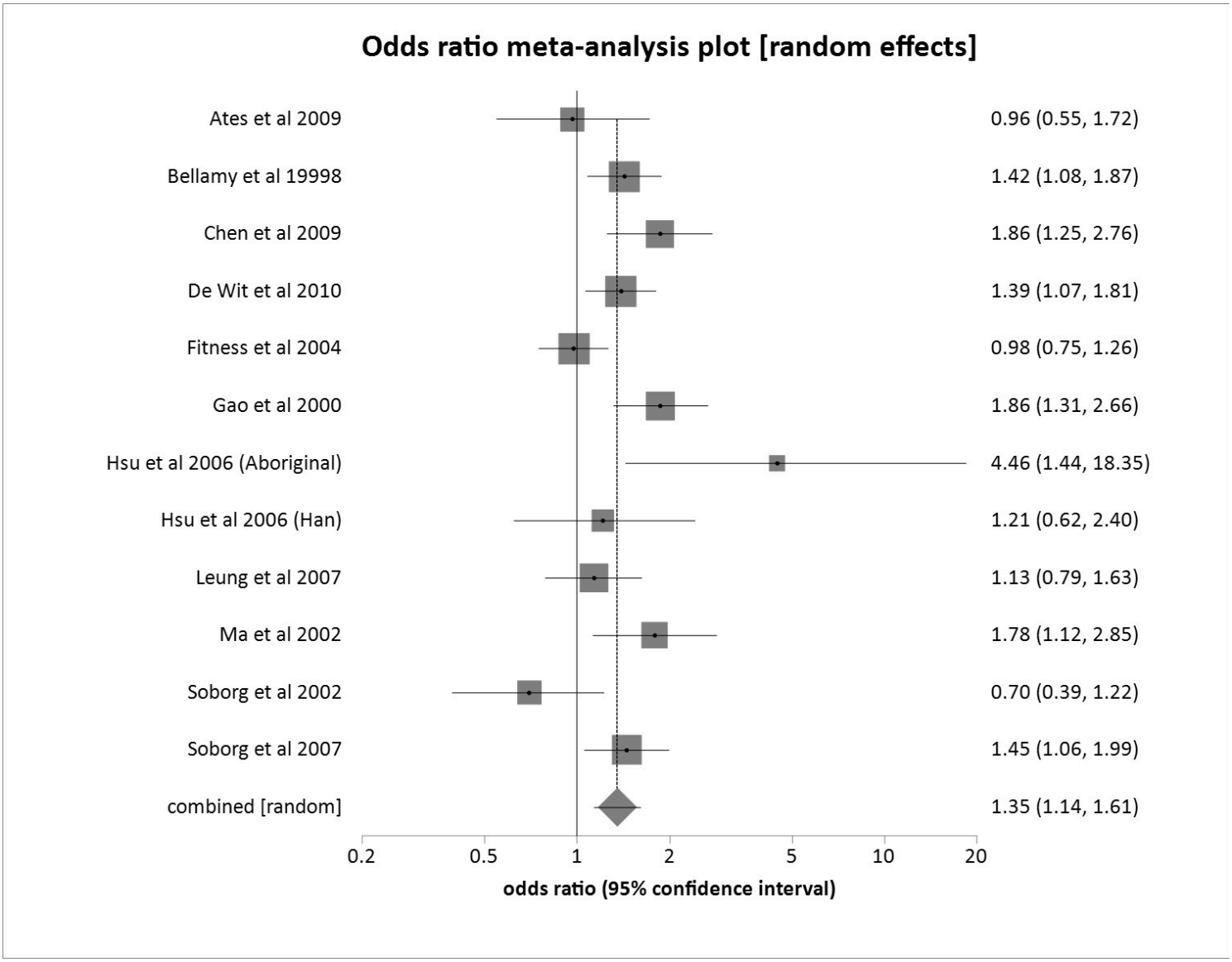


Figure 8

Forest Plot of (GT)n Polymorphism and Tuberculosis Susceptibility under the Allelic Model (non-allele 3 vs. allele 3): Each horizontal line represents an individual study, with the central square indicating the odds ratio (OR) and its 95% confidence interval (CI). Square size reflects the statistical weight of each study. The diamond at the bottom represents the pooled OR, with its lateral points denoting the CI boundaries. The vertical line at OR=1.0 is the line of no effect. Pooled analysis using the DerSimonian-Laird random-effects model demonstrated a statistically significant association, with non-allele 3 carriers showing increased TB susceptibility (OR=1.350, 95% CI=1.136–1.605).

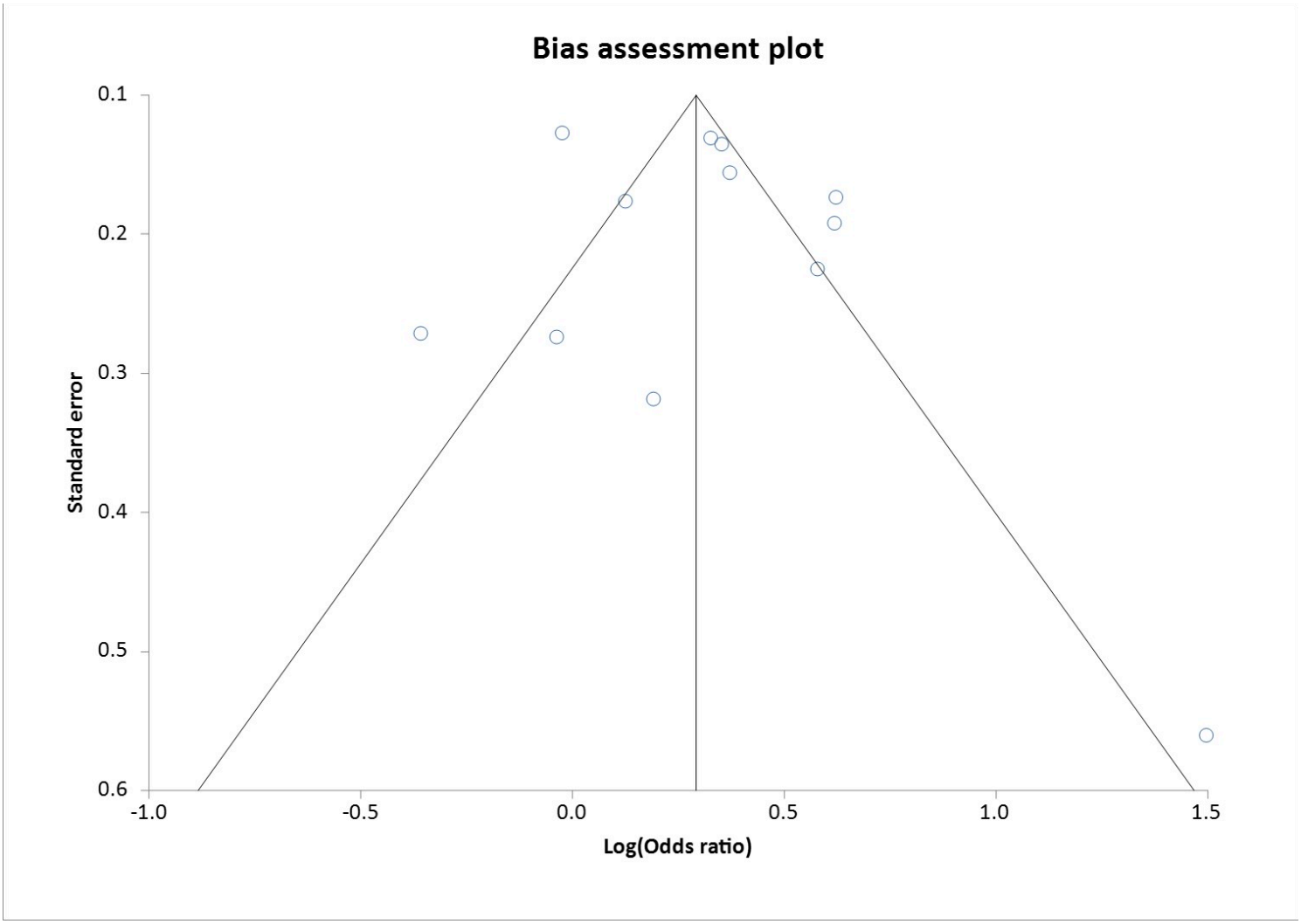


Figure 9

Funnel Plot for Publication Bias Assessment of (GT)n Polymorphism under the Allelic Model: The funnel plot displays the standard error of each study plotted against its log odds ratio (OR) to assess publication bias. Each circle represents an individual study. The Harbord-Egger test indicated significant publication bias (p=0.025); however, trim-and-fill analysis required no study imputation (k=0), confirming that the pooled effect is not affected by missing studies.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfile.docx