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Review Article

Vitamin D receptor ApaI (rs7975232), BsmI (rs1544410), Fok1 (rs2228570), and TaqI (rs731236) gene polymorphisms and susceptibility to pulmonary tuberculosis in an Iranian population: A systematic review and meta-analysis

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KEYWORDS
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Abstract Polymorphisms of vitamin D receptors (VDRs), ApaI, BsmI, FokI, and TaqI might affect susceptibility to tuberculosis (TB). In this systematic review and meta-analysis, all published articles which investigated the effects of these polymorphisms on the risk of TB in the Iranian population were retrieved.

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Iranian population;
Meta-analysis

PubMed and Scopus were searched with no date or language restrictions. In this meta-analysis, the Comprehensive Meta-Analysis (CMA) version 2.0 and random effects model were applied. The association of polymorphisms with TB risk was assessed by measuring the odds ratio (ORs) at 95% CI. Heterogeneity was investigated based on Cochran Q-test and I2-index statistics. The significance level was set at 0.05. Also, Egger's regression intercept was determined to measure publication bias.

A total of six articles on Iranian populations were included. TaqI (5/6 included studies) showed a significant association with the increased risk of TB based on ORs (allele comparison: 1.57 (1.0, 2.3), p-value: 0.02; additive model of tt/TT: 1.57 (0.9, 2.5), p-value: 0.05; recessive model (tt/Tt + TT): 1.99 (1.2, 3.2), p-value: 0.00; dominant model (tt + Tt/TT): 1.98 (1.1, 3.5), p-value: 0.01). BsmI showed a significant positive effect on TB risk only in its dominant genotype (bb + bB/BB) (1.44 (1.0, 1.9); p-value: 0.02). FokI and ApaI did not show any significant effects on TB development in Iranian populations. Findings showed the significant effect of TaqI polymorphism in all genetic models and the dominant model of BsmI on the increased risk of TB. However, the effects of TaqI and BsmI should be further investigated in a larger sample size.

Introduction

Tuberculosis (TB), which is caused by *Mycobacterium tuberculosis*, is considered an important human health problem, associated with high morbidity and mortality in human populations worldwide.[1] TB is the ninth leading cause of mortality, accounting for 1.3 million deaths worldwide.[2,3] Its long-term latency can lead to the persistence of pathogen in the host, with no significant damage or transmission until the deterioration of host immune responses by coinfections or other factors.[4] The complex interaction of the host and pathogen leads to the progression of the disease, which is also influenced by environmental factors.

Several effector proteins control the intracellular survival of the pathogen and compromising of the host immunity.[5] Factors other than bacterial infection may be also responsible for disease development, such as environmental effects, lifestyle risk factors, and genetic susceptibility of the host, which might influence the outcomes of exposure to *M. tuberculosis* as an inter-individual difference.[6,7]

According to recent studies, vitamin D deficiency leads to musculoskeletal and chronic non-skeletal abnormalities, such as muscle weakness, bone pain, fragility fractures, diabetes, and autoimmune disorders.[8,9] Evidence suggests that 1,25-dihydroxyvitamin D3 is biologically active vitamin D, regulating its immunological activity by its vitamin D receptor (VDR). Human peripheral blood monocytes and activated lymphocytes are known to express VDR. Its immunomodulatory effects stimulate the activation of monocytes and suppress the proliferation of lymphocytes and the production of immunoglobulins and cytokines. This active metabolite and its receptor are involved in protecting the human body against certain infectious agents, such as *M. tuberculosis*. The higher risk of active TB might be associated with the low serum levels of vitamin D in comparison with healthy individuals with higher serum vitamin D levels.[10,11] Therefore, vitamin D deficiency, besides VDR gene polymorphisms, can contribute to pulmonary TB susceptibility.

Various host genes, such as VDR with several polymorphisms, might be involved in susceptibility or resistance to pulmonary TB development. The VDR gene, located on chromosome 12q13.11, encompasses various single nucleotide polymorphisms (SNPs), including ApaI (A/a), BsmI (B/b), FokI (F/f), and TaqI (T/t)[12](Fig. 1). These polymorphisms might affect the activity of VDR and subsequently downstream effects of vitamin D. Despite several studies evaluating the VDR gene polymorphisms and their effects on susceptibility to or resistance against TB in different ethnicities or populations, the exact effect is still unknown and inconsistent. In this systematic review, we pooled all the existing literature that evaluate the four common VDR gene polymorphisms, including ApaI, BsmI, FokI, and TaqI and susceptibility to or resistance against TB infection in Iranian populations using meta-analysis.

Methods

Search strategy

PubMed and Scopus were searched thoroughly using two keywords, i.e. "vitamin D" and "TB". The list of identified references was also evaluated and the retrieval from the literature by two independent reviewers. Search was done up to December 2018 with no date or language limitations; however, only articles that studied Iranian populations with TB were included. The title and abstract of the initial search results were screened to omit irrelevant articles. All case-control studies on Iranian patients, which explained the diagnosis of TB and included both case and control individuals with adequate data for measuring the odds ratio (OR), were included in this study. After reviewing the full-text of the remaining articles, the most relevant articles to

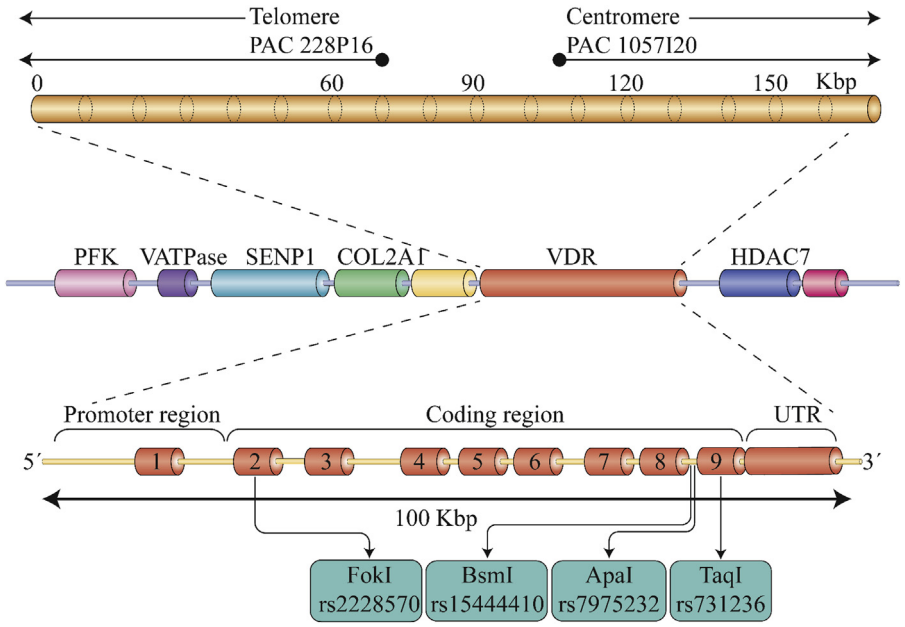

Fig. 1. Genomic region and exon-intron structure of the vitamin D receptor (VDR) gene. The VDR gene is placed on human chromosome 12q13.11, contains nine exons and encompasses various single nucleotide polymorphisms (SNPs) including ApaI (A/a), BsmI (B/b), FokI (F/f), and TaqI (T/t).

the aim of our study were included. For articles with overlapping data, the most recent article or the article with the largest sample size was selected. The selection scheme is based on the PRISMA flowchart presented in Fig. 2 and is explained in the following section.

Data collection

The required information was collected from the articles: first author, publication year, evaluated polymorphisms, mean age of subjects, population ethnicity, ratio of male to female, the source of recruiting healthy controls, and genotype distribution in the groups. For each article, data regarding allele frequency and four different genetic models of each VDR polymorphism were estimated. The evaluated genetic models were as follows: I) allele contrast model (a vs. A); II) recessive model, aa vs. (Aa + AA); III) dominant model (aa + Aa) vs. AA; and IV), homozygote contrast (additive) model (aa vs. AA).

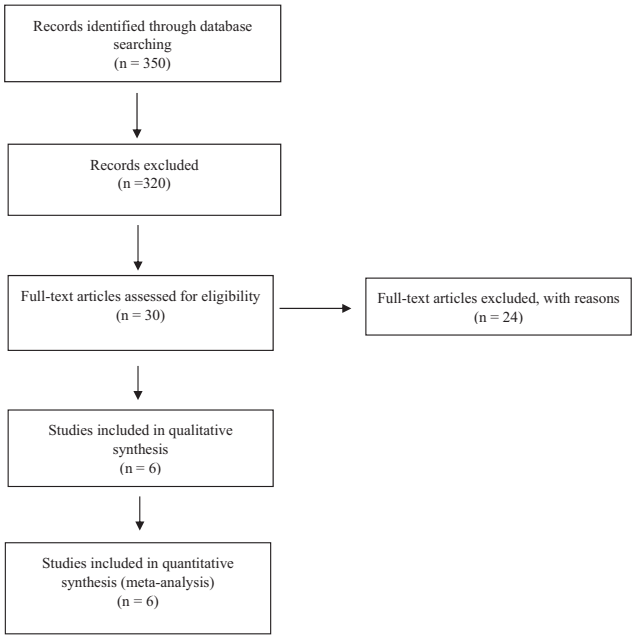

Fig. 2. PRISMA flow chart of included articles.

Data analysis

Using the Hardy–Weinberg equilibrium (HWE) method, polymorphisms were evaluated among the controls. The association between the polymorphisms and increase or decrease of TB risk was compared between the cases and controls by measuring the odds ratio (ORs) at 95% confidence intervals (CIs). In this study, for pooling data, Comprehensive Meta-Analysis (CMA v. 2.0) and the random effects model, based on the Dersimonian and Laird method, were applied. Cochran's Q-test and I2-index statistics were measured to determine heterogeneity, and the level of significance was set at 0.05. Also, Egger's regression method was used to determine publication bias.

Results

Sample selection

The initial search of PubMed and Scopus resulted in 350 articles, which were related to VDR and TB. In total, all related articles on Iranian TB cases were extracted following the review of titles and abstracts. Based on the inclusion and exclusion criteria, only six case-control studies from Iran, which evaluated the relationship

between TB susceptibility and VDR polymorphisms, were assessed in our meta-analysis.[13–18] In addition, the reference lists of the included studies were reviewed to prevent missing any relevant article; however, we did not find any additional articles by screening the reference lists. Table 1 shows the distribution of VDR allele frequency of each VDR variant extracted from eligible studies for the meta-analysis.

The population distribution and characteristics of studies (Table 2) showed the distribution of patients. Overall, four out of six investigating groups were from Tehran,[13–16] one from Tabriz,[17] and one from Zahedan.[18] In all the included studies, cases were matched with the controls regarding age, sex, and ethnicity.[13–18]

In all the included studies, a lower-case letter (e.g., f, b, a, and t) specified the restriction site, while an upper-case letter (e.g., F, B, A, and T) indicated its absence. FokI and BsmI polymorphisms were evaluated in all the included studies (641 cases and 515 controls)[13–18]; however, TaqI and ApaI polymorphisms were assessed in five (524 cases and 455 controls)[13–15,17,18] and three (344 cases and 262 controls) studies,[14,15,17] respectively.

HWE test was performed to demonstrate the genetic distribution of VDR polymorphisms in the control groups (Table 2); only the study of Banoei et al. was on HWE for all the evaluated polymorphisms.[13] Studies with significant deviation from HWE ($P < 0.05$) in the controls were as follows: 3 out of 6 studies focusing on FokI,[15,16,18] 3 out of 6 studies on BsmI,[15–17] 1 out of 5 studies on TaqI,[15] and 1 out of 3 studies on ApaI.[15]

Synthesis of quantitative data

Data from six included studies, comprising 641 TB cases and 515 healthy controls, were used in a random effects model to determine the possible correlation of VDR polymorphisms with susceptibility to TB.[13–18] Table 3 shows the associations between four VDR polymorphisms and TB by measuring OR and CI for each of the four genetic models evaluated for each polymorphism.

For VDR gene FokI polymorphism, the pooled analysis of six included studies using the random-effects model indicated no significant relationship in allelic or any of the studied genetic models with susceptibility to TB.[13–18]

The ApaI gene polymorphism was not significantly linked to TB susceptibility, based on its allelic model and different genetic models in three included studies.[14,15,17]

For VDR gene BsmI polymorphism, among different genetic models, which were compared between the case and control groups in six included studies, only (bb + Bb) versus BB comparison (the dominant model) showed a significant relationship with the increased rate of TB, using the random-effects model.[13–18]

VDR gene TaqI polymorphism was the only type of VDR polymorphism, which showed a significant relationship with increased susceptibility to TB in different genetic models and allelic comparisons of five included studies.[13–15,17,18] The ORs (95%CI) were as follows: allele comparison: 1.57 (1.0, 2.3) P-value 0.02; additive model of tt vs. TT: 1.57 (0.9, 2.5) P-value 0.05; recessive model of tt vs. (Tt + TT): 1.99 (1.2, 3.2) P-value 0.00; dominant model of (tt + Tt) vs.

Table 1 VDR allele frequency distribution of included studies (cases *vs* controls).

Reference	FokI				BsmI				TaqI				ApaI			
	F		f		B		b		T		t		A		a	
	Patient	Control	Patient	Control	Patient	Control	Patient	Control	Patient	Control	Patient	Control	Patient	Control	Patient	Control
Merza et al., 2009[16]	134	95	54	25	81	47	153	73								
Banoei et al., 2009[13]	81	85	39	39	53	88	67	36	49	90	71	34				
Salimi et al., 2014[18]	174	217	66	45	128	148	112	114	158	184	82	78				
Marashain et al., 2010[15]	251	60	77	40	132	29	196	71	219	76	109	24	237	75	91	25
Rashedi et al., 2013[17]	121	132	47	48	81	83	87	97	104	117	64	63	100	108	68	72
Jafari et al., 2016[14]	132	171	60	73	64	82	128	162	122	170	70	74	110	127	82	117

Table 2 Characteristics of the included studies.

References	Population	Sample size (N) Age F/M (case/control)	Diagnosis of cases	Selection of controls	Comparisons	HWE test FokI, BsmI, TaqI, ApaI
Merza et al., 2009[16]	Tehran	N:117/60 Age: NA F/M:NA	AFB, clinical symptoms confirmed PTB	nurses, doctors, and staffs; positive PPD test result; no symptoms	FokI, BsmI	0.04, 0.03,
Banoei et al., 2009[13]	Tehran	N:60/62 Age: 45.8 ± 11/41 ± 9 F/M: 30/30; 26/36	Confirmed in Massih Daneshvari Hospital	Randomly selected from blood donor centers; HIV(−); no history of TB	FokI, BsmI, TaqI	0.93, 0.88, 0.82
Salimi et al., 2014[18]	Zahedan	N:120/131 Age: 51.5 ± 19.7/48.1 ± 12.2 F/M:75/45; 93/38	Clinical symptoms, X-ray, sputum smear-confirmed PTB	normal healthy subjects who underwent the physical examination	FokI, BsmI, TaqI	0,05, 0.31, 0.31
Marashain et al., 2010[15]	Tehran	N:164/50 Age:NA F/M:79/85; 28/22	Clinical symptoms, X-ray, sputum smear-confirmed PTB	healthy people who worked in hospital	FokI, BsmI, TaqI, ApaI	0.07, 0.00, 0.02, 0.00
Rashedi et al., 2013[17]	Tabriz	N:84/90 Age:NA F/M:34/50; 41/49	Sputum smear confirmed PTB	healthy staff	FokI, BsmI, TaqI, ApaI	0.38, 0.00, 0.99, 0.73
Jafari et al., 2016[14]	Tehran	N:96/122 Age: 51 ± 31/48 ± 27 F/M:40/56; 54/68	sputum smear, culture, significant symptoms, chest radiography	Healthy individuals, no symptoms	FokI, BsmI, TaqI, ApaI	0,03, 0.62, 0.16, 0.53

Table 3 Summary of odds ratios (*ORs*) with confidence intervals (*CI*) for allele and genotype comparisons.

Comparisons	Random effects model		Heterogeneity			Egger's regression intercept
	OR (95%*CI*)	P value	Q- value	P-value	I-squared	
FokI						
f *vs* F	1.075 (0.7, 1.5)	0.7	19.8	0.00	74.7	0.86
ff *vs* FF	1.13 (0.6, 2.1)	0.6	7.41	0.19	32.54	0.74
ff *vs* (Ff + FF)	1.18 (0.7, 1.9)	0.4	3.36	0.6	0.00	0.46
(ff + Ff) *vs* FF	0.84 (0.4, 1.4)	0.5	23.39	0.00	78.6	0.44
BsmI						
b *vs* B	1.14 (0.7, 1.6)	0.4	21.48	0.00	76.7	0.53
bb *vs* BB	0.93 (0.41, 2.1)	0.8	19.32	0.00	74.12	0.90
bb *vs* (Bb + BB)	1.53 (0.67, 3.4)	0.3	54.65	0.00	90.85	0.33
(bb + Bb) *vs* BB	1.44 (1.0, 1.9)	0.02	18.26	0.00	72.6	0.76
TaqI						
t *vs* T	1.57 (1.0, 2.3)	0.02	18.78	0.00	72.95	0.12
tt *vs* TT	1.57 (0.9, 2.5)	0.05	3.09	0.54	0.00	0.23
tt *vs* (Tt + TT)	1.99 (1.2, 3.2)	0.00	6.137	0.18	34.81	0.31
(tt + Tt) *vs* TT	1.98 (1.1, 3.5)	0.01	12.48	0.01	67.97	0.03
ApaI						
a *vs* A	0.95 (0.7, 1.21)	0.69	1.33	0.5	0.00	0.26
aa *vs* AA	0.84 (0.5, 1.3)	0.5	1.11	0.57	0.00	0.95
aa *vs* (Aa + AA)	0.86 (0.5, 1.3)	0.5	0.83	0.65	0.00	0.53
(aa + Aa) *vs* AA	0.98 (0.6, 1,4)	0.9	1.44	0.4	0.00	0.24

TT: 1.98 (1.1, 3.5) P-value 0.01. The Forrest plots of allele comparison (t vs. T) and all four genetic models of VDR TaqI polymorphism are presented in Fig. 3. The Forrest plot of a dominant genetic model of BsmI polymorphism with TB susceptibility is presented in Fig. 4.

Test of heterogeneity

The Cochran Q test showed heterogeneity across all studies and all estimated polymorphisms, which was significant for all the evaluated polymorphisms (FokI, BsmI, and TaqI), except for ApaI, which showed no heterogeneity in its different genetic models. Table 3 presents the data regarding heterogeneity.

Bias diagnosis

To determine publication bias, the regression method proposed by Egger et al. was used[19]; the obtained results are presented in Table 3. Egger's regression intercept showed no significant publication bias among studies, except for the dominant genetic model of TaqI polymorphism, (tt + Tt) vs. TT, with the Egger's regression intercept P-value of 0.03. Therefore, it is supposed that bias from publications did not have significant effects on the association of all the studied VDR polymorphisms with TB susceptibility.

Discussion

The modulatory impact of vitamin D on the innate immune system, such as response to *M. tuberculosis* pathogen, remains uncertain. The relation between VDR polymorphism and TB susceptibility might be modulated by vitamin D status of the host; low body vitamin D might increase the risk of pulmonary TB.[11] This meta-analysis is the first review of case-control studies on Iranian populations regarding the contribution of the most widely studied VDR polymorphisms and their association with the development of TB.

Although various meta-analyses have been reported in this field of research,[11,20–24] no systematic review or meta-analysis has been conducted among all studies on Iranian TB patients. Despite various SNPs on VDR gene, only four polymorphisms were selected as the main variants in the included studies (FokI, BsmI, TaqI, and ApaI), considering the limited information about other VDR polymorphisms.

Based on the six included case-control studies which focused on VDR TaqI polymorphism, our meta-analysis showed the significant association of TaqI variant located near the 3′-untranslated region with an increase in susceptibility to TB in its allelic comparison and all different genetic models; however, FokI and ApaI polymorphisms showed no significant effects on increasing or decreasing the risk of TB. The BsmI polymorphism had a positive effect on increasing the risk of TB only in its dominant model (bb + bB/BB), which was statistically significant.

According to previous meta-analyses, TaqI had no role in TB development that is in contrast with our results, which showed the significant role of VDR TaqI polymorphism in increasing susceptibility to TB in an Iranian population. They also proposed FokI polymorphism as the main VDR variant, which results in a significant increase in TB risk[22,23,25]; however, we did not find any significant effect for FokI polymorphism on TB.

The inconsistent results proposed in different studies and different risky genotype proposed in each population might be due to the selection of patients from different

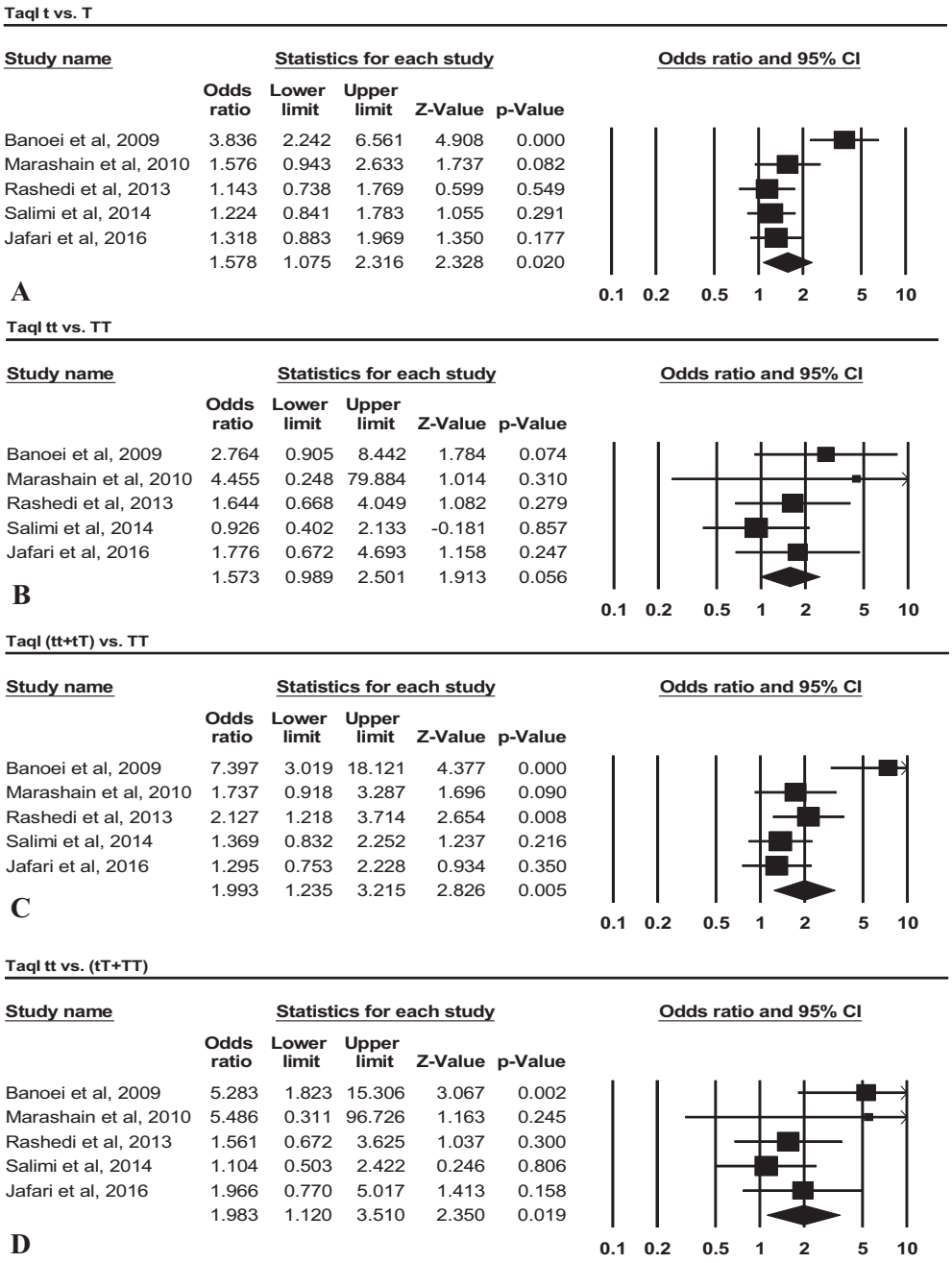

Fig. 3. Forrest plots of the TaqI polymorphism association with TB susceptibility; A) represents comparison of allele contrast model of t vs. T; B) represents comparison of dominant genetic model of tt vs. TT; C: represents comparison of the dominant genetic model of (tt + tT) vs. TT; D: represents a comparison of the recessive genetic model of tt vs. (tT + TT).

populations. VDR variants may play a different role in every population. Selection of a population from different environmental factors (nutritional status and sunlight intensity and hours) in each study, diversity of genetic background among cases of each ethnicity, and various genotypes and allele frequencies of VDR polymorphisms are other influential factors in inconsistent association with disease development and the observed heterogeneity.[26]

In other meta-analyses with ethnicity-specific subgroup assessments, FokI and BsmI polymorphisms have been proposed as the main risk factors for the increased and decreased risk of TB development among Asian patients, respectively; this was also in contrast with the present study, which indicated no significant association between FokI variant and TB progression in Iranian infected patients.[21,22,24] We only found a significant relationship between the dominant model (bb + bB/BB) of BsmI and TB susceptibility. By considering four different VDR polymorphisms, it has been shown that FokI SNP could significantly increase the risk of TB in Chinese people, and BsmI and ApaI polymorphisms showed protecting effects against TB among European populations.[20]

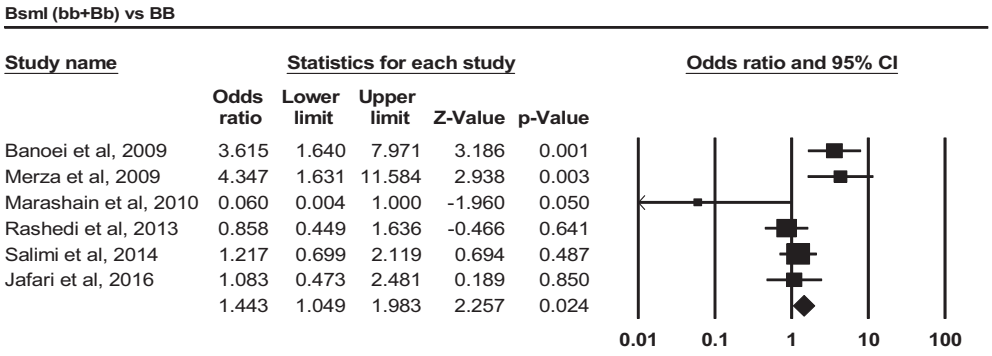

Fig. 4. Forrest plot of BsmI polymorphism (dominant model) association with TB risk.

The Caucasian, African, and South American populations did not show any significant association between FokI, BsmI (except the dominant model), and ApaI polymorphisms of VDR gene with TB susceptibility,[21,23] which agrees with our results on Iranian patients. The t allele of TaqI polymorphism has shown a marginally significant association with TB among Africans, which was similar to the effects we found between TaqI and TB among Iranian. Limitations that can be addressed in this study are related to HWE test in controls for each polymorphism, as some studies showed significant deviations from HWE ($P < 0.05$); therefore, the results of these studies should be interpreted cautiously.

In this meta-analysis, the role of four major VDR gene SNPs in the risk of TB was examined in Iranian populations, and the significant effect of TaqI polymorphism in all different genetic models and BsmI polymorphism dominant genotype on the increased risk of TB were confirmed. However, to validate the present results regarding the role of TaqI and BsmI in increasing susceptibility to TB, furthermore case-control and population-based studies with a larger sample size are needed.

Authors' contributions

Asadollah Mohammadi, Nader Tajik, Mohammad Jafari, and Rasoul Nasiri-Kalmarzi conceived and designed the experiments; Asadollah Mohammadi and Farzad Khademi performed the experiments, and Mohammad Jafari analyzed the data.

Declaration of Competing Interest

None.

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