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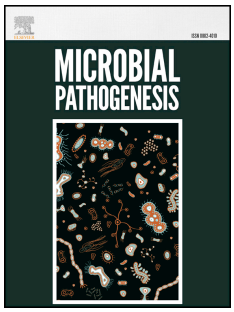

A meta-analysis on associations between vitamin D receptor genetic variants and tuberculosis

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A meta-analysis on associations between vitamin D receptor genetic variants and tuberculosis

Running head: VDR variants and TB

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Abstract

Objectives: We aimed to analyze potential associations between vitamin D receptor (*VDR*) genetic variants and tuberculosis (TB) through a meta-analysis.

Methods: Systematic literature research of PubMed, Web of Science, Embase and CNKI was performed to identify eligible articles. Statistical analyses were conducted by using Review Manager**.**

Results: Totally 54 studies were enrolled for analyses. Pooled overall analyses suggested that *VDR* rs1544410 (dominant model: p=0.02; allele model: p=0.04), rs2228570 (recessive model: p=0.01; allele model: p=0.03) and rs731236 (recessive model: p=0.02; allele model: p=0.02) variants were significantly associated with TB. Further subgroup analyses by ethnicity revealed that rs1544410 variant was significantly associated with TB in South Asians (dominant and allele models) and Caucasians (dominant, recessive and allele models), rs2228570 variant was significantly associated with TB in East Asians (recessive model), and rs731236 variant was significantly associated with TB in South Asians (dominant, recessive and allele models).

Conclusions: Our meta-analysis suggested that *VDR* rs1544410, rs2228570 and rs731236 variants might serve as genetic biomarkers of TB in certain populations.

Keywords: Vitamin D receptor (*VDR*); Gene variants; Tuberculosis (TB); Pulmonary tuberculosis (PTB); Extrapulmonary tuberculosis (EPTB); Meta-analysis

1. Introduction

Tuberculosis (TB) is a commonly seen chronic infectious disorder, and it could manifest as pulmonary tuberculosis (PTB) or extrapulmonary tuberculosis (EPTB) [1]. Despite rapid advancements achieved in early diagnosis and pharmacological therapy over the past few decades, TB remains a serious public health problem. According to a recent investigation, over 30% of the general population is currently infected with mycobacterium tuberculosis (MTB), and around 5%-10% of these infected individuals will eventually develop active TB [2]. The course of MTB infection depends on a complex interaction of pathogen, host and environmental factors, and the fact that only a small portion of infected individuals finally develop active TB suggests that host genetic background may play a crucial role in its development [3-4].

Recently, some of evidences supported that vitamin D metabolic pathway might be involved in the pathogenesis of TB. First, previous epidemical investigations found that vitamin D deficiency was much more prevalent in patients with TB, and the serum level of vitamin D was reversely correlated with disease severity [5-7]. Second, it was evident that vitamin D supplement gained from food intake or exposure to sunlight would benefit the treatment of TB [8]. Previous experimental studies showed that vitamin D could be activated by 1α-hydoxylase that was expressed by macrophages and other immune cells, and the active form of vitamin D,

1,25-dihydroxyvitamin D 3, could activate macrophages and promote elimination of MTB by binding with vitamin D receptor (VDR), which could subsequently lead to induction of the antimicrobial peptide cathelicidin and killing of intracellular MTB [9-11]. ~~It is well acknowledged that vitamin D exerts its biological functions by binding with vitamin D receptor (VDR).~~ Consequently, it is possible that *VDR* variants, which may result in diminished function of vitamin D, might also be involved in the development of TB.

To date, numerous studies already investigated potential associations between *VDR* variants and TB. However, the results of these studies were not consistent, especially when they were conducted in different populations. Previous studies failed to reach a consensus regarding associations between *VDR* variants and TB partially because of their relatively small sample sizes. Thus, we performed the present meta-analysis to explore the relationship between *VDR* variants and TB in a larger pooled sample size. Additionally, we also aimed to elucidate the potential effects of ethnic background on associations between *VDR* variants and TB. ~~To date, some pilot studies already investigated potential associations between *VDR* variants and TB. But the results of these studies were conflicting. Thus, we performed the present meta-analysis to obtain a more conclusive result.~~

2. Materials and Methods

2.1 Literature search and inclusion criteria

This meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [12]. Potentially related literatures published prior to January 2019 were retrieved from PubMed, Web of Science, Embase and CNKI using the following searching strategy: (Vitamin D receptor OR VDR) AND (polymorphism OR variant OR mutation OR genotype OR allele) AND (tuberculosis OR TB). We also checked the references of enrolled articles to identify other potentially relevant studies.

To test the research hypothesis of this meta-analysis, included studies must meet all the following criteria: 1. case-control study on associations between *VDR* variants and TB; 2. provide genotypic and/or allelic frequency of investigated *VDR* variants in cases and controls; 3. full text in English or Chinese available. Studies were excluded if one of the following criteria was fulfilled: 1. not relevant to *VDR* variants and TB; 2. case reports or case series; 3. abstracts, reviews, comments, letters and conference presentations. For repeated reports, we only included the study with the largest sample size for analyses.

2.2 Data extraction and quality assessment

We extracted following data from included studies: (1) the name of the first author; (2) publication time; (3) country and ethnicity; (4) sample size; and (5) genotypic distribution of *VDR* variants in cases and controls. The probability value (*p* value) of Hardy-Weinberg equilibrium (HWE) was also calculated. When necessary, we wrote to the corresponding authors for raw data. We used the Newcastle-Ottawa scale (NOS)

to assess the quality of eligible studies [13]. This scale has a score range of zero to nine, and studies with a score of more than seven were thought to be of high quality. Data extraction and quality assessment were performed by two independent reviewers. Any disagreement between two reviewers was solved by discussion until a consensus was reached.

2.3 Statistical analyses

We used Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update) to conduct statistical analyses. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) to estimate strength of associations in all possible genetic models, and p values ≤ 0.05 were considered to be statistically significant. Q test and I^2 statistic were employed to assess between-study heterogeneities. If p value of Q test was less than 0.1 or I^2 was greater than 50%, random-effect models (REMs) would be used to pool the data. Otherwise, fixed-effect models (FEMs) would be applied for synthetic analyses. Subgroup analyses by ethnicity of participants and type of disease were performed. Stabilities of synthetic results were evaluated with sensitivity analyses, and publication biases were evaluated with funnel plots.

3. Results

3.1 Characteristics of included studies

We found 421 potential relevant articles. Among these articles, totally 54 eligible

studies were finally included for pooled analyses (see Fig. 1). The NOS score of eligible articles ranged from 7 to 8, which indicated that all included studies were of high quality. Baseline characteristics of included studies were shown in Table 1.

3.2 Overall and subgroup analyses

Pooled overall analyses suggested that *VDR* rs1544410 (dominant model: p = 0.02, OR = 0.79, 95%CI 0.65-0.96; allele model: p = 0.04, OR = 0.87, 95%CI 0.76-0.99), rs2228570 (recessive model: p = 0.01, OR = 1.30, 95%CI 1.06-1.59; allele model: p = 0.03, OR = 0.88, 95%CI 0.78-0.99) and rs731236 (recessive model: p = 0.02, OR = 1.39, 95%CI 1.06-1.81; allele model: p = 0.02, OR = 0.87, 95%CI 0.77-0.98) variants were significantly associated with TB.

Further subgroup analyses by ethnicity revealed that rs1544410 variant was significantly associated with TB in South Asians (dominant and allele models) and Caucasians (dominant, recessive and allele models), rs2228570 variant was significantly associated with TB in East Asians (recessive model), and rs731236 variant was significantly associated with TB in South Asians (dominant, recessive and allele models). When we stratified data by type of disease, positive results were detected for rs2228570 variant in PTB (dominant, recessive and allele models) and EPTB (recessive, over-dominant and allele models) subgroups, and for rs731236 variant in PTB (recessive model) subgroup. No any other positive findings were observed in overall and subgroup analyses (see Table 2 and Supplementary figure 1).

3.3 Sensitivity analyses

We performed sensitivity analyses to test stabilities of pooled results by excluding studies that violated HWE. No any altered results were observed in overall and subgroup comparisons, which indicated that our findings were statistically stable.

3.4 Publication biases

We used funnel plots to assess publication biases. We did not find obvious asymmetry of funnel plots in any comparisons, which suggested that our findings were unlikely to be impacted by severe publication biases.

4. Discussion

To the best of our knowledge, this is so far the most comprehensive meta-analysis on roles of *VDR* variants in TB, and our pooled analyses suggested that *VDR* rs1544410, rs2228570 and rs731236 variants were all significantly associated with TB in certain ethnicities. There are two possible explanations for our positive findings. First, genetic variations of the *VDR* gene may lead to alternations in gene expression or changes in VDR protein structure, which may subsequently affect biological functions of vitamin D and ultimately impact individual susceptibility to TB. Second, it is also possible that *VDR* variants may be linked to each other or even linked to other unidentified genes, which could also impact individual susceptibility to TB.

~~There are~~ Several points are worth noting when interpreting our findings ~~that~~

~~need to be addressed about this meta-analysis~~. Firstly, although the investigated *VDR* variants were intensively analyzed with regard to their potential associations with TB, the functional significances of these variants were still not well established [14-15], and thus future investigations are warranted to explore the underlying molecular mechanisms of our positive findings. Secondly, the pathogenic mechanism of TB is highly complex, and therefore it is unlikely that a single genetic variant could significantly contribute to their development. So to better illustrate potential associations of certain genetic variants with TB, we strongly recommend further studies to perform haplotype analyses and explore potential gene-gene interactions. Thirdly, it should be noted that two recent meta-analyses conducted by Huang et al [16] and Cao et al [17] also tried to explore potential associations between *VDR* variants and TB. However, our findings are more conclusive than that of previous meta-analyses, and the current meta-analysis is also much more comprehensive than these two works because the following two points, 1) many related studies were published in the last three years. Therefore, an update meta-analysis is warranted and the sample sizes of our analyses were also significantly larger than previous meta-analyses, which could significantly reduce the risk of obtaining false positive or false negative results; 2) These two previous meta-analyses only focused on one common investigated *VDR* variant in TB (FokI rs2228570), while our meta-analysis explored associations between four common *VDR* variants and TB. So our work should be considered as a valuable supplementary work to these two previous meta-analyses, and it should also be considered as a significant improvement over

pre-existing literatures.

As with all meta-analysis, this study certainly has some limitations. First, our results were based on unadjusted analyses, and lack of further adjusted analyses for potential confounding factors might impact the reliability of our findings [18]. Second, associations between *VDR* variants and TB might also be modified by gene-gene and gene-environmental interactions. However, most eligible studies ignore these potential interactions, which impeded us to perform relevant analyses accordingly [19-20]. Third, only retrospective case-control studies were included in this meta-analysis, and thus direct causal relation between investigated variants and TB could not be established [21]. On account of above mentioned limitations, our findings should be cautiously interpreted.

In conclusion, our meta-analysis suggested that *VDR* rs1544410, rs2228570 and rs731236 variants might serve as genetic biomarkers of TB in certain populations. However, further well-designed studies are still warranted to confirm our findings. Moreover, future investigations also need to explore potential roles of other *VDR* variants in the development of TB.

Authors' contributions

Yan Wang and Hong-jie Li conceived of the study, participated in its design. Yan Wang and Hong-jie Li conducted the systematic literature review. Yan Wang and Hong-jie Li data analyses. Yan Wang and Hong-jie Li drafted the manuscript. All

gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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None.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study formal consent is not required.

References

1. Sgaragli G, Frosini M. Human Tuberculosis I. Epidemiology, Diagnosis and Pathogenetic Mechanisms. Curr Med Chem 2016; 23: 2836-73.
2. Trébucq A, Schwoebel V. Numbers of tuberculosis cases: dreams and reality. Int J Tuberc Lung Dis 2016; 20: 1288-92.
3. Abel L, Casanova JL. Genetic predisposition to clinical tuberculosis: bridging the gap between simple and complex inheritance. Am J Hum Genet 2000; 67: 274-7.
4. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP. The immune response in tuberculosis. Annu Rev Immunol 2013; 31: 475-527.
5. Gou X, Pan L, Tang F, Gao H, Xiao D. The association between vitamin D status and tuberculosis in children: A meta-analysis. Medicine (Baltimore) 2018; 97: e12179.
6. Brighenti S, Bergman P, Martineau AR. Vitamin D and tuberculosis: where next? J Intern Med 2018; doi: 10.1111/joim.12777.
7. Joo MH, Han MA, Park SM, Shin HH. Vitamin D Deficiency among Adults with History of Pulmonary Tuberculosis in Korea Based on a Nationwide Survey. Int J Environ Res Public Health 2017; 14: E399.
8. Desai NS, Tukvadze N, Frediani JK, Kipiani M, Sanikidze E et al. Effects of sunlight and diet on vitamin D status of pulmonary tuberculosis patients in Tbilisi, Georgia. Nutrition 2012; 28: 362-366.

9. Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, Hormone, and Immunomodulator. Nutrients 2018; 10: E1656.

10. Kim EW, Teles RMB, Haile S, Liu PT, Modlin RL. Vitamin D status contributes to the antimicrobial activity of macrophages against Mycobacterium leprae. PLoS Negl Trop Dis 2018; 12: e0006608.

11. Vanherwegen AS, Gysemans C, Mathieu C. Regulation of Immune Function by Vitamin D and Its Use in Diseases of Immunity. Endocrinol Metab Clin North Am 2017; 46: 1061-94.

12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-9.

13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-5.

14. Uitterlinden AG, Fang Y, Van Meurs JB, Pols HA, Van Leeuwen JP. Genetics and biology of vitamin D receptor polymorphisms. Gene 2004; 338: 143-56.

15. Valdivielso JM, Fernandez E. Vitamin D receptor polymorphisms and diseases. Clin Chim Acta 2006; 371: 1-12.

16. Huang L, Liu C, Liao G, Yang X, Tang X, Chen J. Vitamin D Receptor Gene FokI Polymorphism Contributes to Increasing the Risk of Tuberculosis: An Update Meta-Analysis. Medicine (Baltimore). 2015; 94: e2256.

17. Cao Y, Wang X, Cao Z, Cheng X. Vitamin D receptor gene FokI polymorphisms

and tuberculosis susceptibility: a meta-analysis. Arch Med Sci. 2016; 12: 1118-1134.

18. Xie X, Shi X, Liu M. The Roles of TLR Gene Variants in Atherosclerosis: A Systematic Review and Meta-Analysis of 35,317 Subjects. Scand J Immunol 2017; 86: 50-8.
19. Shi X, Xie X, Jia Y, Li S. Associations of insulin receptor and insulin receptor substrates genetic variants with polycystic ovary syndrome: A systematic review and meta-analysis. J Obstet Gynaecol Res 2016; 42: 844-54.
20. Zhu Y, Zheng G, Hu Z. Association between SERT insertion/deletion polymorphism and the susceptibility of irritable bowel syndrome: A meta-analysis based on 7039 subjects. Gene 2018; 679: 133-7.
21. Sun H, Li Q, Jin Y, Qiao H. Associations of tumor necrosis factor-α variants with the susceptibility of asthma: a meta-analysis. Exp Mol Pathol 2018; 105: 411-6.

Figure legends

Fig. 1. Flowchart of study selection for the present study.

Table 1. The characteristics of included studies.

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P*-value for HWE	NOS score
					Cases	Controls		
ApaI rs7975232					AA/AC/CC			
Alagarasu 2009	India	South Asian	PTB	185/146	77/79/29	44/81/21	0.096	7
Arji 2014	Morocco	Caucasian	PTB	274/203	NA	NA	NA	7
Babb 2007	South Africa	African	PTB	249/352	101/108/40	116/173/63	0.914	7
Bornman 2004	UK	African	PTB	343/634	152/153/38	266/292/76	0.762	8
Devi 2018	India	South Asian	PTB	169/227	50/83/36	75/103/49	0.225	8
Fernández-Mestre 2015	Venezuela	African	PTB	89/101	27/42/20	29/54/18	0.062	7
Fitness 2004	UK	African	PTB	328/543	150/145/33	287/210/46	0.391	7
Hu 2016	China	East Asian	PTB	217/383	NA	NA	NA	7
Jafari 2016	Iran	South Asian	PTB	96/122	33/44/19	36/55/31	0.285	7
Lee 2016	Taiwan	East Asian	PTB	198/170	103/78/17	89/65/16	0.416	8
Lombard 2006	South Africa	African	PTB	95/117	78/16/1	84/29/4	0.455	7
Olesen 2007	Gambia	African	PTB	320/345	150/145/25	161/150/34	0.913	8
Panwar 2016	India	South Asian	PTB	106/106	74/23/9	88/15/3	0.033	8
Panwar 2016	India	South Asian	EPTB	106/106	47/43/16	88/15/3	0.033	8
Rashedi 2014	Iran	South Asian	TB	84/90	29/42/13	30/48/12	0.292	8
Rizvi 2016	India	South Asian	PTB	130/130	96/25/9	102/23/5	0.021	7
Rizvi 2016	India	South Asian	EPTB	130/130	69/44/17	102/23/5	0.021	7
Selvaraj 2004	India	South Asian	EPTB	64/103	20/35/9	39/49/15	0.951	7
Selvaraj 2009	India	South Asian	PTB	65/60	25/29/11	23/25/12	0.286	7
Sharma 2011	India	South Asian	PTB	478/857	191/255/32	395/401/61	0.002	7
Søborg 2007	Tanzania	African	PTB	438/426	224/186/28	211/170/45	0.223	7

Vidyarani 2009	India	South Asian	PTB	40/49	17/16/7	14/25/10	0.849	8
Zhang 2017	China	East Asian	EPTB	100/100	51/41/8	33/55/12	0.132	7
Zhang 2018	China	East Asian	PTB	180/59	94/67/19	36/21/2	0.613	8
BsmI rs1544410						AA/AT/TT		
Alagarasu 2009	India	South Asian	PTB	179/146	42/73/64	45/62/39	0.071	7
Arji 2014	Morocco	Caucasian	PTB	274/203	NA	NA	NA	7
Ates 2011	Turkey	Caucasian	TB	128/80	32/68/28	37/38/5	0.241	7
Banoei 2010	Iran	South Asian	PTB	60/62	13/27/20	31/26/5	0.889	8
Bornman 2004	UK	African	PTB	343/634	215/108/20	387/208/39	0.125	8
Devi 2018	India	South Asian	PTB	169/227	45/100/24	58/113/56	0.948	8
Fitness 2004	UK	African	PTB	345/545	212/123/10	314/192/39	0.201	7
Jafari 2016	Iran	South Asian	PTB	96/122	43/42/11	55/52/15	0.620	7
Joshi 2014	India	South Asian	PTB	110/115	35/58/17	55/37/23	0.001	8
Junaid 2016	Pakistan	South Asian	PTB	235/106	NA	NA	NA	7
Kang 2011	Korea	East Asian	PTB	150/83	135/13/2	75/8/0	0.644	8
Lee 2016	Taiwan	East Asian	PTB	198/170	183/14/1	146/24/0	0.322	8
Lombard 2006	South Africa	African	PTB	95/117	55/35/5	76/32/9	0.044	7
Merza 2009	Iran	South Asian	PTB	117/60	43/67/7	26/21/13	0.039	7
Olesen 2007	Gambia	African	PTB	320/342	146/141/33	152/152/38	1.000	8
Rashedi 2014	Iran	South Asian	TB	84/90	30/27/27	33/31/26	0.004	8
Rathored 2012	India	South Asian	PTB	692/205	192/346/154	51/108/46	0.437	8
Salimi 2015	Iran	South Asian	PTB	120/131	31/66/23	39/70/22	0.319	8
Selvaraj 2004	India	South Asian	EPTB	64/103	15/36/13	40/38/25	0.012	7
Selvaraj 2009	India	South Asian	PTB	51/60	12/16/23	27/17/16	0.001	7
Sharma 2011	India	South Asian	PTB	488/1062	144/215/129	274/577/211	0.003	7
Sinaga 2014	Indonesia	South Asian	PTB	76/76	24/52/0	56/18/2	0.705	8

Singh 2011	India	South Asian	PTB	101/225	32/52/17	57/134/34	0.002	7
Vidyarani 2009	India	South Asian	PTB	40/49	10/14/16	21/13/15	0.001	8
Zhang 2018	China	East Asian	PTB	180/59	159/19/2	54/4/1	0.022	8
FokI rs2228570					TT/TA/AA			
Acen 2016	Uganda	African	PTB	41/41	36/3/2	38/2/1	0.002	7
Alagarasu 2009	India	South Asian	PTB	187/144	116/58/13	81/59/4	0.077	7
Arji 2014	Morocco	Caucasian	PTB	274/203	NA	NA	NA	7
Ates 2011	Turkey	Caucasian	TB	128/80	58/60/10	35/37/8	0.695	7
Babb 2007	South Africa	African	PTB	248/352	132/103/13	203/129/20	0.934	7
Banoei 2010	Iran	South Asian	PTB	60/62	30/21/9	29/27/6	0.938	8
Bornman 2004	UK	African	PTB	416/718	258/138/20	444/242/32	0.893	8
Chen 2006	China	East Asian	PTB	140/139	60/56/24	70/60/9	0.414	7
Chen 2013	China	East Asian	PTB	976/861	316/468/192	245/459/157	0.023	7
Devi 2018	India	South Asian	PTB	169/227	59/106/4	119/90/18	0.865	8
Fernández-Mestre 2015	Venezuela	African	PTB	93/102	34/47/12	26/60/16	0.058	7
Gao 2008	China	East Asian	PTB	108/154	34/54/20	38/94/22	0.004	8
Guo 2006	China	East Asian	EPTB	42/64	6/15/21	15/35/14	0.452	8
Jafari 2016	Iran	South Asian	PTB	96/121	41/50/5	55/61/5	0.018	7
Jin 2017	China	East Asian	PTB	180/100	51/104/25	42/51/7	0.104	8
Joshi 2014	India	South Asian	PTB	110/115	51/46/13	63/41/11	0.266	8
Kang 2011	Korea	East Asian	PTB	103/105	30/58/15	41/43/21	0.124	8
Lee 2016	Taiwan	East Asian	PTB	198/170	44/104/50	51/87/32	0.634	8
Li 2011	China	East Asian	PTB	213/211	72/96/45	101/88/22	0.664	8
Liu 2003	China	East Asian	PTB	76/171	29/34/13	90/70/11	0.593	8
Lombard 2006	South Africa	African	PTB	95/117	62/30/3	90/24/3	0.373	7
Medapati 2017	India	South Asian	PTB	89/83	5/76/8	12/61/10	<0.001	7

Merza 2009	Iran	South Asian	PTB	117/60	67/46/4	35/25/0	0.042	7
Olesen 2007	Gambia	African	PTB	320/344	198/106/16	207/118/19	0.686	8
Rashedi 2014	Iran	South Asian	TB	84/90	44/33/7	50/32/8	0.388	8
Rathored 2012	India	South Asian	PTB	692/205	319/298/75	118/80/7	0.136	8
Roth 2004	Peru	African	PTB	200/201	119/60/21	109/78/14	0.993	7
Salimi 2015	Iran	South Asian	PTB	120/131	65/44/11	93/31/7	0.054	8
Selvaraj 2004	India	South Asian	EPTB	64/103	47/15/2	55/39/9	0.583	7
Selvaraj 2009	India	South Asian	PTB	65/60	33/29/3	33/26/1	0.102	7
Sharma 2011	India	South Asian	PTB	258/924	133/95/30	585/311/28	0.081	7
Sinaga 2014	Indonesia	South Asian	PTB	76/80	27/42/7	30/34/12	0.650	8
Singh 2011	India	South Asian	PTB	101/225	55/40/6	96/110/19	0.107	7
Søborg 2007	Tanzania	African	PTB	435/416	288/128/19	267/128/21	0.273	7
Vidyarani 2009	India	South Asian	PTB	40/49	23/14/3	20/29/0	0.003	8
Wang 2017	China	East Asian	EPTB	150/149	75/53/22	42/68/39	0.289	8
Wilbur 2007	USA	African	PTB	91/290	64/26/1	165/120/5	0.001	7
Wilkinson 2000	USA	South Asian	PTB	91/116	52/31/8	74/39/3	0.418	8
Wu 2015	China	East Asian	PTB	151/453	57/70/24	226/181/46	0.277	8
Xiang 2013	China	East Asian	PTB	238/215	37/157/44	49/140/26	<0.001	7
Xiao 2016	China	East Asian	PTB	61/49	22/33/6	14/25/10	0.849	7
Zhang 2010	China	East Asian	EPTB	110/102	51/43/16	29/47/26	0.433	7
Zhang 2018	China	East Asian	PTB	180/59	21/80/79	21/25/13	0.294	8
TaqI rs731236					AA/AG/GG			
Alagarasu 2009	India	South Asian	PTB	184/146	71/80/33	70/62/14	0.960	7
Arji 2014	Morocco	Caucasian	PTB	274/203	NA	NA	NA	7
Ates 2011	Turkey	Caucasian	TB	128/80	49/65/14	30/39/11	0.766	7
Babb 2007	South Africa	African	PTB	249/356	136/94/19	190/144/22	0.442	7

Banoei 2010	Iran	South Asian	PTB	60/62	8/33/19	33/24/5	0.829	8
Bellamy 2000	UK	African	PTB	408/414	204/177/27	188/177/49	0.460	7
Bornman 2004	UK	African	PTB	343/634	174/132/37	331/253/50	0.864	8
Chen 2006	China	East Asian	PTB	140/139	137/3/0	134/5/0	0.829	7
Chen 2013	China	East Asian	PTB	982/872	815/149/18	739/128/5	0.831	7
Delgado 2002	USA	East Asian	PTB	358/106	325/30/3	96/10/0	0.610	7
Devi 2018	India	South Asian	PTB	169/227	86/73/10	116/86/25	0.143	8
Fernández-Mestre 2015	Venezuela	African	PTB	86/97	51/33/2	58/38/1	0.053	7
Fitness 2004	UK	African	PTB	397/672	261/118/18	384/241/47	0.279	7
Harishankar 2016	India	South Asian	PTB	90/89	36/39/15	42/39/8	0.805	7
Jafari 2016	Iran	South Asian	PTB	96/120	38/46/12	56/58/6	0.063	7
Junaid 2016	Pakistan	South Asian	PTB	230/100	NA	NA	NA	7
Kang 2011	Korea	East Asian	PTB	149/94	134/14/1	85/8/1	0.133	8
Lee 2016	Taiwan	East Asian	PTB	198/170	186/12/0	149/20/1	0.715	8
Li 2011	China	East Asian	PTB	213/211	191/19/3	183/23/5	<0.001	8
Lombard 2006	South Africa	African	PTB	95/117	56/33/6	67/49/1	0.013	7
Medapati 2017	India	South Asian	PTB	91/85	27/56/8	5/74/6	<0.001	7
Olesen 2007	Gambia	African	PTB	320/345	150/145/25	161/150/34	0.913	8
Panwar 2016	India	South Asian	PTB	106/106	66/28/12	90/14/2	0.122	8
Panwar 2016	India	South Asian	EPTB	106/106	58/34/14	90/14/2	0.122	8
Rashedi 2014	Iran	South Asian	TB	84/90	44/33/7	50/32/8	0.388	8
Rathored 2012	India	South Asian	PTB	692/205	319/298/75	118/80/7	0.135	8
Rizvi 2016	India	South Asian	PTB	130/130	92/27/11	104/22/4	0.051	7
Rizvi 2016	India	South Asian	EPTB	130/130	66/49/15	104/22/4	0.051	7
Roth 2004	Peru	African	PTB	200/201	119/60/21	109/78/14	0.993	7
Salimi 2015	Iran	South Asian	PTB	120/131	52/54/14	67/50/14	0.318	8

Selvaraj 2004	India	South Asian	EPTB	64/102	27/28/9	40/48/14	0.947	7
Selvaraj 2009	India	South Asian	PTB	65/60	24/33/8	27/21/12	0.050	7
Sharma 2011	India	South Asian	PTB	275/659	138/95/42	358/275/26	0.002	7
Shi 2017	China	East Asian	PTB	260/258	214/42/4	225/33/0	0.273	8
Singh 2011	India	South Asian	PTB	101/225	61/30/10	132/60/33	<0.001	7
Søborg 2007	Tanzania	African	PTB	438/425	247/172/19	233/162/30	0.799	7
Vidyarani 2009	India	South Asian	PTB	40/49	15/18/7	27/18/4	0.686	8
Wilbur 2007	USA	African	PTB	156/496	61/85/10	251/218/27	0.020	7
Wilkinson 2000	USA	South Asian	PTB	91/116	39/46/6	45/58/13	0.375	8
Wu 2015	China	East Asian	PTB	151/453	138/13/0	403/50/0	0.213	8
Xiang 2013	China	East Asian	PTB	198/195	157/37/4	140/49/6	0.504	7
Zhang 2018	China	East Asian	PTB	180/59	160/19/1	52/7/0	0.628	8

Abbreviations: TB, Tuberculosis; PTB, Pulmonary tuberculosis; EPTB, Extrapulmonary tuberculosis; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-ottawa scale; NA, Not available.

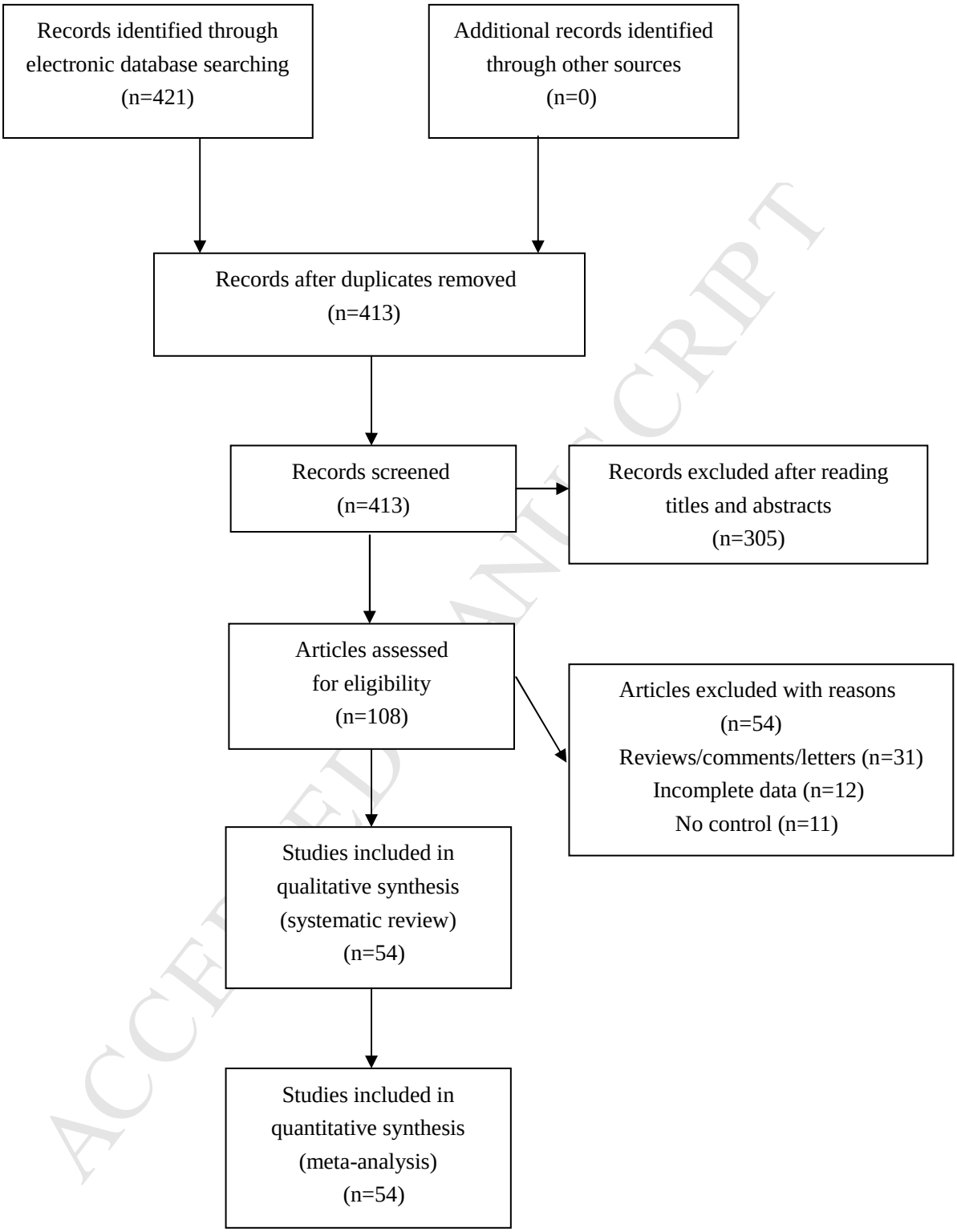
Table 2. Results of overall and subgroup analyses.

Polymorphisms	Population	Sample size	Dominant comparison		Recessive comparison		Over-dominant comparison		Allele comparison	
			P value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)
ApaI rs7975232	Overall	4484/5559	0.36	0.92 (0.76-1.11)	0.96	1.00 (0.87-1.15)	0.39	1.07 (0.92-1.24)	0.23	0.92 (0.80-1.05)
	South Asian	1653/2126	0.10	0.75 (0.54-1.06)	0.17	1.16 (0.94-1.42)	0.12	1.24 (0.95-1.61)	0.06	0.78 (0.60-1.01)
	East Asian	695/712	0.68	0.88 (0.49-1.59)	0.91	1.03 (0.62-1.71)	0.43	0.89 (0.66-1.19)	0.82	0.96 (0.68-1.35)
	African	1862/2518	0.46	1.05 (0.93-1.18)	0.20	0.88 (0.72-1.07)	0.94	1.00 (0.89-1.14)	0.25	1.06 (0.96-1.16)
	PTB	4000/5030	0.65	0.98 (0.89-1.07)	0.43	1.06 (0.92-1.23)	0.35	1.05 (0.95-1.15)	0.82	0.99 (0.93-1.06)
	EPTB	400/439	0.26	0.53 (0.18-1.60)	0.25	1.83 (0.66-5.07)	0.25	1.64 (0.71-3.78)	0.22	0.56 (0.23-1.41)
BsmI rs1544410	Overall	4715/5072	**0.02**	**0.79 (0.65-0.96)**	0.82	1.03 (0.81-1.30)	0.09	1.18 (0.97-1.43)	**0.04**	**0.87 (0.76-0.99)**
	South Asian	2682/2839	**0.01**	**0.70 (0.53-0.92)**	0.71	1.05 (0.81-1.37)	0.07	1.31 (0.98-1.75)	**0.02**	**0.81 (0.68-0.96)**
	East Asian	528/312	0.29	0.78 (0.49-1.23)	0.59	1.56 (0.32-7.64)	0.19	0.73 (0.45-1.17)	0.43	0.84 (0.54-1.30)
	African	1103/1638	0.42	1.07 (0.91-1.25)	0.06	0.74 (0.55-1.01)	0.85	1.02 (0.87-1.19)	0.15	1.10 (0.97-1.24)
	Caucasian	402/283	**0.002**	**0.39 (0.21-0.70)**	**0.005**	**4.20 (1.55-11.39)**	0.43	1.25 (0.72-2.19)	**0.0002**	**0.46 (0.30-0.69)**
	PTB	4439/4799	0.06	0.83 (0.68-1.01)	0.88	1.02 (0.79-1.30)	0.16	1.16 (0.94-1.43)	0.13	0.90 (0.79-1.03)
FokI rs2228570	Overall	7686/8661	0.11	0.89 (0.78-1.03)	**0.01**	**1.30 (1.06-1.59)**	0.91	1.01 (0.90-1.12)	**0.03**	**0.88 (0.78-0.99)**
	South Asian	2419/2795	0.18	0.86 (0.69-1.07)	0.15	1.40 (0.89-2.20)	0.50	1.08 (0.86-1.34)	0.13	0.88 (0.74-1.04)
	East Asian	2926/3002	0.15	0.81 (0.61-1.08)	**0.03**	**1.41 (1.04-1.91)**	0.26	0.94 (0.85-1.05)	0.07	0.83 (0.67-1.02)
	African	1739/2380	0.66	0.94 (0.70-1.25)	0.56	1.04 (0.91-1.18)	0.70	0.97 (0.85-1.11)	0.56	0.90 (0.65-1.27)
	Caucasian	402/283	0.83	1.07 (0.61-1.87)	0.59	0.76 (0.29-2.02)	0.93	1.03 (0.59-1.80)	0.82	1.03 (0.81-1.31)
	PTB	7108/8073	**0.007**	**0.83 (0.73-0.95)**	**0.0007**	**1.42 (1.16-1.73)**	0.42	1.05 (0.94-1.17)	**0.0009**	**0.83 (0.74-0.93)**
	EPTB	366/418	0.60	0.77 (0.28-2.08)	**0.01**	**1.89 (1.14-3.15)**	**0.001**	**1.62 (1.20-2.17)**	0.26	0.70 (0.39-1.30)
TaqI rs731236	Overall	8847/9535	0.05	0.87 (0.76-1.00)	**0.02**	**1.39 (1.06-1.81)**	0.50	1.04 (0.93-1.16)	**0.02**	**0.87 (0.77-0.98)**
	South Asian	2924/2938	**0.002**	**0.68 (0.53-0.87)**	**0.004**	**1.79 (1.20-2.65)**	0.07	1.22 (0.99-1.51)	**0.0005**	**0.69 (0.55-0.85)**
	East Asian	2829/2557	0.63	0.96 (0.82-1.14)	0.14	1.51 (0.87-2.64)	0.32	0.92 (0.78-1.09)	0.99	1.00 (0.86-1.16)
	African	2692/3757	0.19	1.07 (0.97-1.18)	0.79	0.96 (0.69-1.32)	0.40	0.96 (0.86-1.06)	0.50	1.04 (0.92-1.17)

Caucasian	402/283	0.91	1.03 (0.58-1.84)	0.54	0.77 (0.33-1.79)	0.78	1.08 (0.62-1.90)	0.93	0.99 (0.79-1.24)
PTB	8335/9027	0.23	0.92 (0.81-1.05)	**0.04**	**1.35 (1.02-1.80)**	0.63	0.98 (0.91-1.06)	0.09	0.91 (0.81-1.02)
EPTB	384/428	0.08	0.48 (0.21-1.09)	0.13	2.13 (0.81-5.61)	0.08	1.75 (0.93-3.28)	0.08	0.51 (0.24-1.08)

Abbreviations: OR, Odds ratio; CI, Confidence interval; NA, Not available; PTB, Pulmonary tuberculosis; EPTB, Extrapulmonary tuberculosis.

The values in bold represent there is statistically significant differences between cases and controls.



Highlights

1. This is so far the most comprehensive evidence-based meta-analysis on *VDR* variants and TB.
2. Our pooled analyses suggested that *VDR* rs1544410, rs2228570 and rs731236 variants were all significantly associated with TB in certain ethnicities.
3. Future investigations need to explore potential roles of other *VDR* variants in TB.