Vitamin D receptor gene FokI polymorphisms and tuberculosis susceptibility: a meta-analysis

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Abstract

Introduction: The association between FokI polymorphism of vitamin D receptor (VDR) and tuberculosis (TB) susceptibility has been investigated previously; however, the results were inconsistent and conflicting. In the present study, a meta-analysis was performed to assess the relationship between VDR FokI gene polymorphism and the risk of TB.

Material and methods: Databases including PubMed and Embase were searched for genetic association studies of FokI polymorphism of vitamin D receptor (VDR) and TB. Data were extracted by two independent authors and the pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to assess the strength of the association between VDR FokI gene polymorphism and TB risk. Meta-regression and subgroup analyses were performed to identify the source of heterogeneity.

Results: Thirty-four studies with a total of 5669 cases and 6525 controls were reviewed in the present meta-analysis. A statistically significant correlation was found between VDR FokI gene polymorphism and increased TB risk in two comparison models: the homozygote model (ff vs. FF: OR = 1.37, 95% CI: 1.17–1.60; \(P_{\text{heterogeneity}} = 0.001\)) and the recessive model (ff vs. Ff + FF: OR = 1.32, 95% CI: 1.14–1.52; \(P_{\text{heterogeneity}} = 0.006\)). Meta-regression found no source contributing to heterogeneity. However, sub-group analyses revealed that there was a statistically increased TB risk in the East and Southeast Asian population.

Conclusions: Synthesis of the available studies suggests that homozygosity for the FokI polymorphism of the VDR gene might be associated with an increased TB risk, especially in the East and Southeast Asian population. Additional well-designed, larger-scale epidemiological studies among different ethnicities are needed.

Key words: vitamin D receptor, FokI polymorphisms, tuberculosis susceptibility.

Introduction

Tuberculosis (TB) is one of the most important infectious diseases, with an estimated 9.0 million new cases and 1.5 million deaths worldwide in 2013, and more than half were in the South-East Asia and Western Pacific Regions [1]. It is suggested that the susceptibility to disease after infection with Mycobacterium tuberculosis is influenced by many risk factors, such as malnutrition, HIV infection, and environmental and host genetic factors [2–5]. Host genetic factors implicated in human susceptibility
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Material and methods

Data extraction and quality assessment

Statistical analysis

Results

Characteristics of enrolled studies

A flow chart of the study selection process is shown in Figure 1. According to the inclusion crite-
ria, 34 qualified case-control studies were selected in the final analysis after the literature search from the PubMed (Medline), Web of Science and Embase web databases [8, 10–15, 19–45]. Twenty-four studies were based on Asian populations [8, 10–13, 19–37], seven were based on African populations [14, 15, 38–42] and the remaining three were conducted in Europe and America [43–45]. The eligible studies contained 4 “large” studies [19, 29, 40, 42] and 30 “small” studies [8, 10–15, 21–28, 30–39]. Thirty studies were genotyped by restriction fragment length polymorphism (RFLP) analysis and five were conducted by other methods [19, 23, 38, 40, 41]. The detailed characteristics of the enrolled studies are listed in Table I. A total of 5669 TB cases were obtained in the 34 studies, including 5126 (92.3%) with pulmonary TB and 426 (7.7%) with extra-pulmonary TB. The corresponding controls for the TB cases numbered 6525. Distribution of genotypes and HWE p-values in the controls are shown in Table II. Among the controls, the genotype distribution for 31 studies of the assessed polymorphisms was in HWE, except for 3 studies from India and Iran [31, 32, 35].

Sensitivity analyses and publication bias

In the sensitivity analysis, the influence of each individual data set on the pooled OR was assessed by deleting one single study each time. The results showed that the corresponding pooled ORs were not materially varied, suggesting stability of this meta-analysis (data not shown). Begg’s funnel plot and Egger’s test were used to evaluate the publication bias of the selected studies for the meta-analysis (Figure 2). Begg’s funnel plot seemed symmetrical in all genetic models. Furthermore, the statistical results from Egger’s test supported the result of Begg’s funnel plot indicating that there was no publication bias among all genetic models (p > 0.05) (Table III).

Meta-analysis results

We pooled all 34 studies together for the assessment of the relationship between the VDR FokI polymorphism and the risk of TB. The pooled ORs from overall studies indicated a significantly increased risk of TB in the homozygote model (ff vs. FF: OR = 1.37, 95% CI: 1.17–1.60; P heterogeneity = 0.001, Figure 3) and recessive model (ff vs. Ff + FF: OR = 1.32, 95% CI: 1.14–1.52; P heterogeneity = 0.006, Figure 4). However, no significant association was found in the allele model (f vs. F: OR = 1.09, 95% CI: 0.97–1.21; P heterogeneity = 0.000, Figure 5) and in the dominant model (ff + Ff vs. FF: OR = 1.08, 95% CI: 0.99–1.17; P heterogeneity = 0.000, Figure 6). The heterozygote model (Ff vs. FF: OR = 1.03, 95% CI: 0.95–1.13; P heterogeneity = 0.001, Figure 7) failed to show any association with the risk of TB. The strength of the association between VDR FokI gene polymorphism and TB risk is shown in Table IV.

To account for the sources of heterogeneity, we performed meta-regression by publication years, ethnicity, sample size, genotyping methods, as well as source of controls and type of TB. However, no significant source was found to substantially contribute to heterogeneity (Table V).

To further investigate the heterogeneity, we performed subgroup analyses (Table IV). To evaluate the possible effect of the geographical differences on the variability of overall estimates, we classified the studies conducted in Asia into two groups: East and Southeast Asia (China, Indonesian and South Korean) and South and West Asia (India and Iran). As a result, the enrolled studies were divided into five subgroups including Africans, East and Southeast Asians, South and West
### Table I. Main characteristics of included studies summarized for the meta-analysis

| Year | First author | Country | Ethnicity | Study design | Tuberculosis Part of the body | Sample size Cases/controls | Diagnosis method | Genotyping method | Controls source | HIV status | Age, gender | Diabetes status |
|------|--------------|---------|-----------|--------------|-----------------------------|---------------------------|-------------------|------------------|-----------------|-------------|--------------|----------------|
| 2014 | Arji         | Morocco | Arab or Berber | PB | Pulmonary tuberculosis | 274/203 | AFB smear and culture | PCR-RFLP | Healthy persons | Negative | Matched | Negative |
| 2014 | Mahmoud      | Egypt   | Egyptian  | PB | Pulmonary tuberculosis | 40/25 | AFB smear and culture | PCR-RFLP | Healthy persons | Not available | Matched | Negative |
| 2014 | Sinaga       | Indonesia | Indonesian Batak | PB | Pulmonary tuberculosis | 76/76 | Clinical evaluation, AFB smear and chest radiography | PCR-RFLP | Healthy health workers, tuberculin skin test positivity (61.7%) | Negative | Matched | Negative |
| 2013 | Wu           | China   | Chinese Kazakh | PB | Pulmonary tuberculosis | 213/211 | Clinical symptoms bacteriology, X-ray | PCR-RFLP | Healthy persons | Negative | Matched | Negative |
| 2013 | Joshi        | India   | Indian    | PB | Pulmonary tuberculosis | 110/225 | AFB smear | PCR-RFLP | Household contacts (110) and healthy persons (115) | Negative | Matched | Negative |
| 2012 | Rathored     | India   | Indian    | PB | MDR tuberculosis and drug-sensitive pulmonary tuberculosis | 692/205 | AFB smear and culture | PCR-RFLP | Healthy persons | Negative | Matched | Negative |
| 2011 | Kim          | South Korean | Korean | PB | Pulmonary tuberculosis (98) and extra-pulmonary tuberculosis (62) | 160/156 | AFB smear and culture | Pyro sequencing | Healthy persons | Not available | Matched | Not available |
| 2011 | Kang         | South Korean | Korean | PB | Pulmonary tuberculosis | 103/105 | AFB smear and culture | PCR-RFLP | Healthy persons | Not available | Matched | Not available |
| 2011 | Singh        | India   | Indo-Caucasian Brahmin caste | HB, PB | Pulmonary tuberculosis | 101/225 | AFB smear or culture | PCR-RFLP | Healthy persons | Negative | Not matched | Not available |
| 2011 | Sharma       | India   | Indian    | PB | Pulmonary tuberculosis | 474/607 | AFB smear or culture | PCR-RFLP | Healthy persons | Not available | Matched | Not available |
| Year | First author | Country | Ethnicity | Study design | Tuberculosis Part of the body | Sample size | Diagnosis method | Genotyping method | Controls source | HIV status | Age, gender | Diabetes status |
|------|--------------|---------|-----------|--------------|-----------------------------|-------------|-----------------|------------------|----------------|------------|-------------|----------------|
| 2011 | Ates         | Turkey  | Anatolian | PB           | Pulmonary (98) and extra-pulmonary tuberculosis (30) | 128/80      | AFB smear or culture | PCR-RFLP        | Healthy persons | Not available | Matched     | Not available |
| 2010 | Marashian    | Iran    | Iranian   | HB           | Pulmonary tuberculosis     | 164/50      | AFB smear and X-ray | PCR-RFLP        | Contacts        | Not available | Matched     | Not available |
| 2010 | Zhang        | China   | Chinese Han | PB           | Spinal tuberculosis       | 110/102     | Postoperative pathology | PCR-RFLP | Unrelated contacts | Negative | Matched     | Negative |
| 2009 | Banoel       | Iran    | Iranian   | PB           | Pulmonary tuberculosis     | 60/62       | Confirmed in Massih Daneshvar | PCR-RFLP | Healthy subjects | Negative | Matched     | Negative |
| 2009 | Merza        | Iran    | Iranian   | HB           | Pulmonary tuberculosis     | 117/60      | AFB smear and X-ray | PCR-RFLP        | Contacts        | Not available | Matched     | Not available |
| 2009 | Vidyarani    | India   | Dravidian | PB           | Pulmonary tuberculosis     | 40/49       | AFB smear and culture | PCR-RFLP        | Normal healthy subjects | Not available | Matched     | Not available |
| 2009 | Selvaraj     | India   | Indian    | HB           | Pulmonary tuberculosis     | 65/60       | Clinical symptom, AFB smear and culture | PCR-RFLP | Healthy subjects | Negative | Matched     | Not available |
| 2009 | Alagarasu    | India   | Dravidian | HB           | Pulmonary (187) and extra-pulmonary tuberculosis (30) | 217/144     | AFB smear, clinical criteria and X-ray | PCR-RFLP | Healthy controls | Cases (51%), controls (0) | Matched     | Not available |
| 2008 | Selvaraj     | India   | Dravidian | HB           | Pulmonary tuberculosis     | 51/60       | AFB smear and culture | PCR-RFLP        | Normal healthy subjects | Negative | Matched     | Not available |
| 2008 | Liu          | China   | Chinese Han | PB           | Pulmonary tuberculosis     | 60/30       | AFB smear and culture | SNaPshot       | Normal healthy subjects | Negative | Matched     | Negative |
| 2007 | Wilbur       | Paraguay | Ache, Chiripa, Guarani | PB           | Pulmonary tuberculosis     | 54/124      | Clinical symptoms, PPD test | PCR-RFLP | No symptoms | Not available | Not available | Not available |
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| Year | First author | Country | Ethnicity | Study design | Tuberculosis Part of the body | Sample size Cases/controls | Diagnosis method | Genotyping method | Controls source | HIV status | Age, gender | Diabetes status |
|------|--------------|---------|-----------|--------------|-------------------------------|-----------------------------|------------------|------------------|----------------|------------|-------------|----------------|
| 2007 | Olesen        | Guinea-Bissau | Papel, Manjaco, Mancanha, Balanta, Fulani, Mandinka and others | PB | Pulmonary tuberculosis | 320/344 | AFB smear and clinical criteria | TaqMan | Healthy controls | HIV positive in 33% of cases and negative in controls | Gender not matched | Not available |
| 2007 | Babb          | South Africa | South African | HB | Pulmonary tuberculosis | 249/352 | AFB smear and X-ray | PCR-RFLP | No clinical history or symptoms of TB | Negative | Not available | Not available |
| 2007 | Soborg        | Tanzania | Tanzanian | HB | Pulmonary tuberculosis | 435/416 | Culture | PCR-SSP | Culture negative | HIV positive in 44% of cases and 18% of controls | Gender not matched | Not available |
| 2006 | Chen XR       | China | Chinese Tibetans | PB | Pulmonary tuberculosis | 140/139 | Clinical symptoms, AFB smear and X-ray | PCR-RFLP | House hold contacts | Negative | Matched | Negative |
| 2006 | Lombard       | Venda | Venda | HB | Pulmonary and meningeal tuberculosis | 66/86 | AFB smear | ARMS-PCR | Healthy controls with no history of TB | Negative | Not available | Not available |
| 2004 | Bornman       | Gambia, Guinea-Bissau, Guinea | Gambia, Guinea-Bissau, Guinea | HB | Pulmonary tuberculosis | 416/718 | AFB or culture | PCR-RFLP | Healthy community control subjects | Cases (12.5%), controls (6.8%) | Matched | Not available |
| Year | First author | Country | Ethnicity | Study design | Tuberculosis Part of the body | Sample size Cases/controls | Diagnosis method | Genotyping method | Controls source | HIV status | Age, gender | Diabetes status |
|------|--------------|---------|-----------|--------------|-----------------------------|----------------------------|-------------------|-------------------|----------------|------------|-------------|----------------|
| 2004 | Selvaraj a   | India   | Indian    | HB           | Spinal tuberculosis patients | 64/103                     | X-ray and clinical criteria | PCR-RFLP         | 77 were contacts and 26 were normal healthy subjects | Not available | Matched    | Not available |
| 2004 | Selvaraj b   | India   | Indian    | HB           | Pulmonary tuberculosis      | 46/64                      | AFB smear, culture and radiographic abnormalities | PCR-RFLP         | Clinically normal | Negative    | Matched    | Not available |
| 2004 | Roth         | Peru     | Amerindian | PB           | Pulmonary tuberculosis      | 100/201                    | AFB smear         | PCR-RFLP         | Two healthy controls, 1 PPD + and 1 PPD– | Negative    | Matched    | Not available |
| 2004 | Liu          | China    | Chinese Han| PB           | Pulmonary tuberculosis      | 120/240                    | AFB smear, culture and X-ray | PCR-RFLP         | Normal controls | Negative    | Not available | Negative |
| 2004 | Liu          | China    | Chinese Han| PB           | Pulmonary tuberculosis      | 76/171                     | Culture and X-ray | PCR-RFLP         | Normal controls | Not available | Matched    | Negative |
| 2004 | Selvaraj     | India    | Indian    | HB           | Pulmonary tuberculosis      | 120/80                     | Culture           | PCR-RFLP         | Patient contacts | Not available | Matched    | Not available |
| 2000 | Wilkinson    | India    | Gujarati  | HB           | Pulmonary tuberculosis (27) and military tuberculosis (64) | 91/116                     | Biopsy or culture Tuberculosis | PCR-RFLP         | Contacts with no TB | Negative    | Gender not matched | Not available |

PB – population-based, HB – hospital-based, AFB – acid-fast bacilli, HIV – human immunodeficiency virus, MDR – multi-drug resistance for isoniazid and rifampicin, PPD – purified protein derivative, SNPs – single nucleotide polymorphism, TB – tuberculosis, PCR-RFLP – polymerase chain reaction–restriction fragment length polymorphism.
Asians, Americans and Europeans. As for ethnicities, an increased TB risk was found in the East and Southeast Asia population in five comparison models: allele model (f vs. F: OR = 1.42, 95% CI: 1.20–1.69; \( P_{\text{heterogeneity}} = 0.055 \)), homozygote model (ff vs. FF: OR = 1.98, 95% CI: 1.53–2.56; \( P_{\text{heterogeneity}} = 0.012 \)), recessive model (ff vs. Ff + FF: OR = 1.64, 95% CI: 1.31–2.06; \( P_{\text{heterogeneity}} = 0.003 \)), heterozygote model (Ff vs. FF: OR = 1.37, 95% CI: 1.13–1.65; \( P_{\text{heterogeneity}} = 0.853 \)) and dominant model (ff + Ff vs. FF: OR = 1.52, 95% CI: 1.27–1.82; \( P_{\text{heterogeneity}} = 0.695 \)). In South and West Asians, however, no significant association was found in the heterozygote model (ff vs. Ff + FF: OR = 1.33, 95% CI: 1.00–1.78; \( P_{\text{heterogeneity}} = 0.045 \)).

Further subgroup analyses were stratified by the source of the controls. Studies were divided into healthy persons-based and patient

| Year | First author | Case | Control |
|------|--------------|------|---------|
|      | Genotype Minor allele | Genotype Minor allele | HWE |
|      | FF | Ff | ff | MAF | FF | Ff | ff | MAF | P-value |
| 2014 | Arji | 151 | 103 | 20 | 0.26 | 109 | 82 | 12 | 0.26 | 0.5038 |
| 2014 | Mahmoud | 12 | 20 | 8 | 0.45 | 10 | 10 | 5 | 0.4 | 0.404 |
| 2014 | Sinaga | 27 | 42 | 7 | 0.37 | 30 | 34 | 12 | 0.38 | 0.6497 |
| 2013 | Fang | 72 | 96 | 45 | 0.44 | 101 | 88 | 22 | 0.31 | 0.6642 |
| 2013 | Joshi | 51 | 46 | 13 | 0.33 | 118 | 85 | 22 | 0.29 | 0.252 |
| 2012 | Rathored | 319 | 298 | 75 | 0.32 | 118 | 80 | 7 | 0.23 | 0.1356 |
| 2011 | Kim | 47 | 75 | 38 | 0.47 | 46 | 73 | 37 | 0.47 | 0.4463 |
| 2011 | Kang | 30 | 58 | 15 | 0.43 | 41 | 43 | 21 | 0.40 | 0.1240 |
| 2011 | Singh | 55 | 40 | 6 | 0.26 | 96 | 110 | 19 | 0.33 | 0.1069 |
| 2011 | Sharma | 77 | 67 | 10 | 0.28 | 395 | 197 | 36 | 0.21 | 0.0880 |
| 2011 | Ates | 58 | 60 | 10 | 0.31 | 35 | 37 | 8 | 0.33 | 0.6945 |
| 2010 | Marashian | 97 | 57 | 10 | 0.23 | 15 | 30 | 5 | 0.40 | 0.0771 |
| 2010 | Zhang | 16 | 43 | 51 | 0.66 | 26 | 47 | 29 | 0.51 | 0.4330 |
| 2009 | Banoei | 30 | 21 | 9 | 0.33 | 29 | 27 | 6 | 0.31 | 0.9375 |
| 2009 | Merza | 67 | 46 | 4 | 0.23 | 35 | 25 | 0 | 0.21 | 0.0415 |
| 2009 | Vidyarani | 23 | 14 | 3 | 0.25 | 20 | 29 | 0 | 0.30 | 0.0033 |
| 2009 | Selvarani | 33 | 29 | 3 | 0.27 | 33 | 26 | 1 | 0.23 | 0.1019 |
| 2009 | Alagarasu | 138 | 66 | 13 | 0.21 | 81 | 59 | 4 | 0.23 | 0.0766 |
| 2008 | Selvaraj | 31 | 16 | 4 | 0.24 | 27 | 33 | 0 | 0.28 | 0.0033 |
| 2008 | Liu | 16 | 25 | 19 | 0.53 | 11 | 17 | 2 | 0.35 | 0.1789 |
| 2007 | Wilbur | 35 | 19 | 0 | 0.18 | 81 | 42 | 1 | 0.18 | 0.0740 |
| 2007 | Olesen | 198 | 106 | 16 | 0.22 | 207 | 118 | 19 | 0.23 | 0.6862 |
| 2007 | Babb | 132 | 104 | 13 | 0.26 | 203 | 129 | 20 | 0.24 | 0.9337 |
| 2007 | Soborg | 288 | 128 | 19 | 0.19 | 267 | 128 | 21 | 0.20 | 0.2734 |
| 2006 | Chen | 60 | 56 | 24 | 0.37 | 70 | 60 | 9 | 0.28 | 0.4144 |
| 2006 | Lombard | 43 | 21 | 2 | 0.19 | 64 | 18 | 2 | 0.13 | 0.5917 |
| 2004 | Bornman | 258 | 138 | 20 | 0.21 | 444 | 242 | 32 | 0.21 | 0.8932 |
| 2004 | Selvaraj | 47 | 15 | 2 | 0.15 | 55 | 39 | 9 | 0.28 | 0.5834 |
| 2004 | Selvaraj^a | 28 | 15 | 3 | 0.23 | 38 | 23 | 3 | 0.23 | 0.8388 |
| 2004 | Roth | 9 | 32 | 59 | 0.75 | 14 | 78 | 109 | 0.74 | 0.9928 |
| 2004 | Liu | 29 | 63 | 28 | 0.50 | 85 | 120 | 35 | 0.40 | 0.4821 |
| 2004 | Liu W | 29 | 34 | 13 | 0.39 | 90 | 70 | 11 | 0.27 | 0.5930 |
| 2003 | Selvaraj | 78 | 36 | 6 | 0.20 | 43 | 29 | 8 | 0.28 | 0.3551 |
| 2000 | Wilkinson | 52 | 31 | 8 | 0.26 | 74 | 39 | 3 | 0.19 | 0.4178 |

HWE – Hardy-Weinberg equilibrium, MAF – minor allele frequency, ^a the different articles by the same author in the same year.
contacts-based studies, and importantly the association in healthy persons-based studies was reinforced in the allele model (f vs. F: OR = 1.13, 95% CI: 1.01–1.27; $P_{\text{heterogeneity}} = 0.001$), the homozygote model (ff vs. FF: OR = 1.42, 95% CI: 1.18–1.70; $P_{\text{heterogeneity}} = 0.019$) and the recessive model (ff vs. Ff + FF: OR = 1.31, 95% CI: 1.10–1.56; $P_{\text{heterogeneity}} = 0.028$), which conferred a significantly increased risk of TB, whereas this risk was reversed in patient contacts-based studies with no significance in each model (Table IV).

In addition, when categorized by the sample size with a cutoff of 500 individuals, 30 out of 34 studies had sample sizes less than 500 and conferred an increased risk of TB for two comparison models: the homozygote model (ff vs. FF: OR = 1.38, 95% CI: 1.15–1.64; $P_{\text{heterogeneity}} = 0.002$) and the recessive model (ff vs. Ff + FF: OR = 1.33, 95% CI: 1.14–1.56; $P_{\text{heterogeneity}} = 0.012$). For the subgroup analysis by the genotyping methods, the homozygote model (ff vs. FF: OR = 1.47, 95% CI: 1.23–1.75; $P_{\text{heterogeneity}} = 0.001$), recessive genetic model (ff vs. Ff + FF: OR = 1.39, 95% CI: 1.19–1.63; $P_{\text{heterogeneity}} = 0.010$) and dominant model (ff + Ff vs. FF: OR = 1.10, 95% CI: 1.00–1.20; $P_{\text{heterogeneity}} = 0.000$) remained statistically significant in PCR-RFLP studies (Table IV).

Table III. Statistics to test the publication bias and heterogeneity in the meta-analysis

| Comparisons | Begg’s regression analysis | Egger’s regression analysis | Heterogeneity analysis | Model used for the meta-analysis |
|-------------|----------------------------|----------------------------|-----------------------|---------------------------------|
|             | $P$-value | 95% confidence interval  | $P$-value | Q-value | $I^2$ (%) |
| f vs. F     | 0.614     | (–1.133)–0.404            | 0.341     | 88.47    | 0.000     | 62.7       | Random |
| ff vs. FF   | 0.441     | (–0.327)–0.574            | 0.580     | 65.90    | 0.001     | 49.9       | Random |
| Ff vs. FF   | 0.313     | (–0.949)–0.241            | 0.234     | 66.35    | 0.001     | 50.3       | Random |
| ff + Ff vs. FF | 0.459 | (–0.918)–0.409 | 0.440 | 79.44 | 0.000 | 58.5 | Random |
| ff vs. Ff + FF | 0.495 | (–0.327)–0.640 | 0.514 | 57.01 | 0.006 | 42.1 | Random |

Discussion

Tuberculosis is one of the leading causes of morbidity and mortality, and the VDR gene might be important in modulating host susceptibility to TB because of the potential roles of VDR in the immune response to TB. However, many studies generated conflicting association data concerning the association between VDR FokI gene polymorphism and the risk of TB.

Our present meta-analysis, based on 34 eligible studies until January 2015, provides evidence to propose a consistent effect of VDR FokI polymorphism. We found that the f allele was associated with a significantly increased risk of TB in the East and Southeast Asian population, whereas this risk was reversed in patient contacts-based studies with no significance in each model (Table IV).
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**Figure 3.** Forest plot of homozygote model for overall comparison (ff vs. FF) (TIF)

| Study ID          | OR (95% CI) | Weight (%) |
|-------------------|-------------|------------|
| African           |             |            |
| Arji 2014         | 1.20 (0.56–2.56) | 4.35       |
| Mahmoud 2014      | 1.33 (0.33–5.39) | 1.28       |
| Olesen 2007       | 0.88 (0.44–1.76) | 5.20       |
| Babb 2007         | 1.00 (0.48–2.08) | 4.66       |
| Saborg 2007       | 0.84 (0.44–1.59) | 6.04       |
| Lombard 2006      | 1.49 (0.20–10.97) | 0.63      |
| Bomman 2004       | 1.08 (0.60–1.92) | 7.43       |
| Subtotal (I² = 0.0%, p = 0.985) | 1.01 (0.75–1.35) | 29.59   |
| SW Asian          |             |            |
| Joshi 2013        | 3.96 (1.78–8.85) | 3.87       |
| Rathored 2012     | 0.55 (0.21–1.46) | 2.62       |
| Singh 2011        | 1.42 (0.68–2.99) | 4.53       |
| Sharma 2011       | 0.31 (0.09–1.03) | 1.72       |
| Marashian 2010    | 1.45 (0.46–4.59) | 1.88       |
| Banoei 2009       | 4.73 (0.25–90.42) | 0.29       |
| Merza 2009        | 6.11 (0.30–125.35) | 0.27      |
| Vidyarani 2009    | 3.00 (0.30–30.35) | 0.47       |
| Selvaraj 2009     | 1.91 (0.60–6.05) | 1.87       |
| Alagarasu 2009    | 7.86 (0.40–152.57) | 0.28      |
| Selvaraj 2008     | 0.26 (0.05–1.26) | 1.00       |
| Selvaraj 2004a    | 1.36 (0.25–7.23) | 0.89       |
| Selvaraj 2004b    | 0.41 (0.13–1.27) | 1.98       |
| Selvaraj 2003     | 3.79 (0.96–14.99) | 1.32      |
| Wilkinson 2000    | 1.28 (0.95–1.74) | 27.27      |
| Subtotal (I² = 54.0%, p = 0.007) |            |            |
| ES Asian          |             |            |
| Wu 2013           | 0.64 (0.22–1.86) | 2.22       |
| Sinaga 2014       | 1.01 (0.55–1.85) | 6.74       |
| Kim 2011          | 0.98 (0.43–2.20) | 3.78       |
| Kang 2011         | 2.86 (1.32–6.18) | 4.19       |
| Zhang 2010        | 6.53 (1.26–33.90) | 0.92     |
| Liu 2008          | 3.11 (1.34–7.21) | 3.53       |
| Chen 2006         | 2.34 (1.22–4.50) | 5.88       |
| Liu 2004          | 3.67 (1.48–9.07) | 3.04       |
| Liu W 2004        | 1.98 (1.53–2.56) | 37.39      |
| Subtotal (I² = 59.1%, p = 0.012) |            |            |
| European          |             |            |
| Ates 2011         | 0.75 (0.27–2.09) | 2.40       |
| Subtotal          | 0.75 (0.27–2.09) | 2.40       |
| American          |             |            |
| Wilbur 2007       | 0.77 (0.03–19.24) | 0.24       |
| Roth 2004         | 0.84 (0.34–2.06) | 3.11       |
| Subtotal (I² = 0.0%, p = 0.955) | 0.84 (0.35–1.98) | 3.35     |
| Heterogeneity between groups: p = 0.005 |           |            |
| Overall (I² = 49.9%, p = 0.001) | 1.37 (1.17–1.60) | 100.00     |

Additionally, it was reported that the f allele frequency was higher in Asians than Africans [17]. Thus, the finding of this meta-analysis might be attributed to the racial differences.

There are some limitations to this systematic review. First, some individual information such as age, sex, HIV status and environmental factors could not be obtained, which makes the detailed sub-grouping analyses and interpretation of the results difficult. Second, considering that diabetes, hypertension and any other medical problem may affect vitamin D level, the confounding effect should be taken into account. VDR FokI polymorphisms have been suggested to be related to diabetes in Asians [46]. Diabetes status in the study population may therefore influence the association observed for VDR polymorphisms and TB incidence. Therefore, the stratification of diabetes status would further reveal the relationship between VDR gene SNPs and TB. However, diabetes status was not reported in two-thirds of the enrolled studies. Therefore, it was not possible to
Figure 4. Forest plot of recessive model for overall comparison (ff vs. Ff + FF) (TIF)

apply stratification according to diabetes status. Third, the small sample sizes in some subgroup analyses may not comprehensively represent the population. More studies are needed to confirm the association of FokI polymorphisms and TB risk, especially in different ethnic populations. Fourth, the different experimental designs and diagnostic standards make the analyses prone to bias. Fifth, included studies were restricted to those published in English or Chinese in our study, which might introduce potential bias into data analysis as well. Sixth, based on the data provided by the articles and our own calculations, significant deviations from HWE (p < 0.05) in controls were observed for three studies based on Asians [31, 32, 35]. Thus, their results should be interpreted with more caution. We therefore repeated the meta-analyses after exclusion of these studies. However, this exclusion did not materially affect the results (Table VI). Although genome-wide association studies (GWAS) are important for the discovery of genetic variations, we did not identify
any published GWAS on this subject. In conclusion, the results from this meta-analysis demonstrate that VDR FokI polymorphism is associated with increased TB risk, especially in East and Southeast Asians, which supports the hypothesis that VDR might play an important role in the host defense against TB. However, due to the moderate strength of the associations, their values to be used for risk prediction should be considered cautiously, and future large scale case-control studies are required to validate these findings.

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Conflict of interest

The authors declare no conflict of interest.
### Figure 6

Forest plot of dominant model for overall comparison (ff + Ff vs. FF) (TIF)

| Study ID     | OR (95% CI) | Weight (%) |
|--------------|-------------|------------|
| African      |             |            |
| Aji 2014     | 0.89 (0.62–1.27) | 5.07       |
| Mahmoud 2014 | 1.56 (0.55–4.43) | 0.60       |
| Olesen 2007  | 0.93 (0.68–1.27) | 6.78       |
| Babb 2007    | 1.21 (0.87–1.67) | 6.20       |
| Soborg 2007  | 0.91 (0.69–1.21) | 8.30       |
| Lombard 2006 | 1.71 (0.84–3.49) | 1.30       |
| Bornman 2004 | 0.99 (0.77–1.27) | 10.68      |
| Subtotal     | 1.01 (0.88–1.15) | 38.94      |
| SW Asian     |             |            |
| Joshi 2013   | 1.06 (0.67–1.69) | 3.07       |
| Rathored 2012| 1.59 (1.16–2.17) | 6.67       |
| Singh 2011   | 1.70 (0.19–2.42) | 5.25       |
| Sharma 2011  | 0.30 (0.15–0.58) | 1.43       |
| Marashian 2010| 0.88 (0.43–1.79) | 1.31       |
| Banoei 2009  | 1.04 (0.56–1.96) | 1.66       |
| Merza 2009   | 0.51 (0.22–1.19) | 0.92       |
| Vidyarani 2009| 1.19 (0.59–2.40) | 1.34       |
| Selvaraj 2009| 0.74 (0.48–1.13) | 3.58       |
| Alagarasu 2009| 0.53 (0.25–1.13) | 1.15       |
| Selvaraj 2008| 0.41 (0.21–0.82) | 1.44       |
| Selvaraj 2004a| 0.94 (0.43–2.04) | 1.10       |
| Selvaraj 2004b| 0.63 (0.35–1.12) | 1.98       |
| Selvaraj 2003| 1.32 (0.75–2.32) | 2.09       |
| Wilkinson 2000| 0.97 (0.85–1.11) | 35.96      |
| Subtotal     | 1.80 (1.22–2.66) | 4.31       |
| ES Asian     |             |            |
| Wu 2013      | 1.18 (0.62–2.25) | 1.59       |
| Sinaga 2014  | 1.01 (0.62–1.63) | 2.82       |
| Kim 2011     | 1.56 (0.87–2.78) | 1.98       |
| Kang 2011    | 2.01 (1.01–4.02) | 1.38       |
| Zhang 2010   | 1.59 (0.62–4.07) | 0.75       |
| Liu 2008     | 1.35 (0.84–2.17) | 2.97       |
| Chen 2006    | 1.72 (1.05–2.82) | 2.70       |
| Liu 2004     | 1.80 (1.04–3.13) | 2.17       |
| Liu W 2004   | 1.52 (1.27–1.82) | 20.67      |
| Subtotal     | 0.94 (0.53–1.65) | 2.09       |
| European     |             |            |
| Ates 2011    | 0.94 (0.53–1.65) | 2.09       |
| Subtotal     | 0.94 (0.53–1.65) | 2.09       |
| American     |             |            |
| Wilbur 2007  | 1.02 (0.52–2.00) | 1.47       |
| Roth 2004    | 0.76 (0.32–1.81) | 0.87       |
| Subtotal     | 0.91 (0.54–1.56) | 2.34       |
| Heterogeneity between groups: $p = 0.001$ | 1.08 (0.99–1.17) | 100.00  |
| Overall      |             |            |

Overall ($I^2 = 58.5\%, p < 0.001$)
Vitamin D receptor gene FokI polymorphisms and tuberculosis susceptibility: a meta-analysis

Figure 7. Forest plot of heterozygote model for overall comparison (Ff vs. FF) (TIF)
### Table IV. Meta-analysis results

| Variable       | f vs. F   | ff vs. FF | ff vs. F + FF | ff vs. FF | ff + Ff vs. FF |
|----------------|-----------|-----------|---------------|-----------|---------------|
|                | N         | OR        | P-h           | OR        | P-h           | OR        | P-h           | OR        |
| Total          | 34        | 1.09 (0.97–1.21) | 0.000 | 1.37 (1.17–1.60)* | 0.001 | 1.32 (1.14–1.52)* | 0.006 | 1.03 (0.95–1.13) | 0.001 | 1.08 (0.99–1.17) | 0.000 |
| **Ethnicities:** |           |           |               |           |               |           |           |               |
| ES Asians      | 9         | 1.42 (1.20–1.69)* | 0.055 | 1.98 (1.53–2.56)* | 0.012 | 1.64 (1.31–2.06)* | 0.003 | 1.37 (1.13–1.65) | 0.853 | 1.52 (1.27–1.82)* | 0.695 |
| SW Asians      | 15        | 0.92 (0.75–1.13) | 0.000 | 1.28 (0.95–1.74) | 0.007 | 1.33 (1.00–1.78)* | 0.045 | 0.91 (0.79–1.05) | 0.000 | 0.97 (0.85–1.11) | 0.000 |
| Africans       | 7         | 1.01 (0.91–1.12) | 0.731 | 1.01 (0.75–1.35) | 0.985 | 0.10 (0.75–1.32) | 0.990 | 1.02 (0.89–1.17) | 0.533 | 1.01 (0.88–1.15) | 0.525 |
| Americans      | 2         | 1.05 (0.76–1.45) | 0.821 | 0.84 (0.35–1.98) | 0.955 | 1.20 (0.74–1.94) | 0.775 | 0.88 (0.51–1.53) | 0.399 | 0.92 (0.54–1.56) | 0.592 |
| Europeans      | 1         | 0.92 (0.60–1.40) | –      | 0.75 (0.27–2.09) | –      | 0.76 (0.29–2.02) | –      | 0.98 (0.54–1.76) | –      | 0.94 (0.54–1.65) | –      |
| **Sample size:** |           |           |               |           |           |           |           |               |           |           |               |
| Largea         | 4         | 1.09 (0.97–1.21) | 0.003 | 1.34 (0.96–1.88) | 0.022 | 1.26 (0.90–1.76) | 0.048 | 1.15 (0.99–1.34) | 0.023 | 1.18 (1.02–1.36)* | 0.000 |
| Smallb         | 30        | 1.06 (0.94–1.20) | 0.000 | 1.38 (1.15–1.64)* | 0.002 | 1.33 (1.14–1.56)* | 0.012 | 0.98 (0.89–1.09) | 0.003 | 1.04 (0.94–1.14) | 0.006 |
| **Genotyping method:** | | | | | | | | | | | |
| PCR-RFLP       | 29        | 1.08 (0.95–1.22) | 0.000 | 1.47 (1.23–1.75)* | 0.001 | 1.39 (1.19–1.63)* | 0.010 | 1.05 (0.95–1.15) | 0.000 | 1.10 (1.00–1.20)* | 0.000 |
| Other methods  | 5         | 1.07 (0.86–1.33) | 0.114 | 1.02 (0.71–1.45) | 0.235 | 1.03 (0.74–1.44) | 0.196 | 0.99 (0.81–1.19) | 0.642 | 0.99 (0.83–1.19) | 0.447 |
| **Source of controls:** | | | | | | | | | | | |
| Contactsc      | 10        | 0.97 (0.75–1.26) | 0.000 | 1.24 (0.91–1.68) | 0.002 | 1.33 (1.03–1.71)* | 0.022 | 0.93 (0.78–1.11) | 0.012 | 0.99 (0.83–1.17) | 0.001 |
| Healthyd       | 24        | 1.13 (1.01–1.27)* | 0.001 | 1.42 (1.18–1.70)* | 0.019 | 1.31 (1.10–1.56)* | 0.028 | 1.07 (0.97–1.17) | 0.006 | 1.11 (1.01–1.21)* | 0.001 |

N – number of studies included; OR – odds ratio; P-h – p-value for heterogeneity; *OR with statistical significance; *studies with more than 500 participants; **studies with less than 500 participants; †studies with controls from patient contacts; ‡studies with controls from healthy persons.

### Table V. Meta-regression analysis results

| Variable       | f vs. F   | ff vs. FF | ff vs. F + FF | Ff vs. FF | ff + Ff vs. FF |
|----------------|-----------|-----------|---------------|-----------|---------------|
|                | N         | 95% CI    | P-value       | 95% CI    | P-value       | 95% CI    | P-value       | 95% CI    | OR | P-value |
| Publication years | 34 | (–52.14)–23.05 | 0.44 | (–92.13)–90.56 | 0.99 | (–76.13)–88.01 | 0.88 | (–65.78)–36.31 | 0.56 | (–61.78)–35.21 | 0.58 |
| Ethnicities     | 34 | (–0.48)–0.40 | 0.86 | (–1.17)–0.96 | 0.85 | (–1.13)–0.90 | 0.82 | (–0.62)–0.60 | 0.98 | (–0.61)–0.56 | 0.92 |
| Sample size     | 34 | (–0.06)–0.19 | 1.08 | (–0.24)–0.46 | 0.52 | (–0.25)–0.45 | 0.56 | (–0.10)–0.22 | 0.44 | (–0.08)–0.220 | 0.35 |
| Genotyping method | 34 | (–0.15)–0.15 | 0.96 | (–0.38)–0.37 | 0.98 | (–0.33)–0.36 | 0.94 | (–0.21)–0.19 | 0.95 | (–0.19)–0.19 | 0.97 |
| Source of controls | 34 | (–0.11)–0.15 | 0.76 | (–0.28)–0.37 | 0.78 | (–0.14)–0.39 | 0.36 | (–0.22)–0.15 | 0.74 | (–0.18)–0.17 | 0.95 |
| Type of tuberculosis | 34 | (–0.21)–0.99 | 0.97 | (–0.45)–0.51 | 0.90 | (–0.40)–0.46 | 0.89 | (–0.32)–0.25 | 0.79 | (–0.29)–0.25 | 0.87 |
Table VI. Sensitivity analyses of study with controls not in HWE excluded

| Study with controls not in HWE excluded | Summarized odds ratio (95% CI) | No. of included studies | I² (%) | P-value |
|----------------------------------------|-------------------------------|------------------------|--------|---------|
| f vs. F                                | 1.097 (0.978–1.229)           | 31                     | 65.3   | 0.113   |
| ff vs. FF                              | 1.323 (1.037–1.689)           | 31                     | 52.3   | 0.025   |
| ff vs. FF + FF                         | 1.320 (1.083–1.608)           | 31                     | 39.7   | 0.006   |
| Ff vs. FF                              | 1.042 (0.917–1.185)           | 31                     | 47.4   | 0.526   |
| ff vs. Ff + FF                         | 1.085 (0.945–1.246)           | 31                     | 58.8   | 0.246   |

CI – confidence interval.

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