Vitamin D Receptor Gene FokI Polymorphism Contributes to Increasing the Risk of Tuberculosis: Evidence from a Meta-Analysis

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Abstract

Purpose In the present study, we explored the link between vitamin D receptor (VDR) FokI gene polymorphisms with tuberculosis (TB).

Methods Based on a comprehensive search of PubMed, Embase, Web of Science, Elsevier Science Direct, Cochrane Library, CNKI, Wanfang, and Chongqing VIP databases, we searched case-control study on FokI gene polymorphism and TB susceptibility. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature and extracted data, and R 4.0.5 software was used for the meta-analysis.

Results: Among the 243 selected articles, 35 in the meta analysis. The meta-analysis showed that the FokI gene polymorphism allele gene model (f vs F, Odds ratio=1.22, 95% confidence interval: 1.11-1.36); dominant model (ff+fF vs F, Odds ratio=1.29, 95% confidence interval: 1.13-1.47); recessive model (ff vs fF+FF, Odds ratio=1.31, 95% confidence interval: 1.09-1.56); codominant (ff vs FF, Odds ratio=1.48, 95% confidence interval: 1.19-1.83); codominant (fF vs FF, Odds ratio=1.23, 95% confidence interval: 1.09-1.39). The meta-analysis indicates a high level of heterogeneity between the VDR FokI gene polymorphism and TB and the race is a source of heterogeneity in the results.

Conclusion The present update meta-analysis suggest that FokI gene polymorphism is significantly associated with an increased risk of TB.

Introduction

Tuberculosis (TB) is an ancient disease for millennia and has always been a serious public health problem in history. Pulmonary tuberculosis (PTB) caused by Mycobacterium is one of the leading 10 causes of death globally currently. People are generally all susceptible to Mycobacterium, about 90% of adults could possibly develop TB [1]. The probability of developing TB disease is much higher among people infected with HIV and those with other risk factors of malnutrition, diabetes, smoking and alcohol consumption and so on. With the rapid development of molecular biology, the impact of host genetic variation in susceptibility of tuberculosis attracts much attention and regarding studies have shown it plays a critical role in increasing susceptibility to TB. At present, human leukocyte antigens (HLA) gene, natural resistance associated macrophage protein 1 (NRAMP1) gene, vitamin D receptor (VDR) gene has become a focus of scholars at home and abroad.

The main role of vitamin D is regulating calcium and phosphorus metabolism. 1,25-Dihydroxyvitamin D₃ is the most active metabolite of Vit D, and it has been proven to have an important role in regulating the immune system and humoral regulation. Macrophages play many essential roles in the immune responses through 1,25-Dihydroxyvitamin D₃ activation. The active form of vitamin D₃, 1,25-Dihydroxyvitamin D₃ exerts inhibition of growth of a tubercle bacillus in macrophages. People usually study VDR to study role of Vit D. Recently, polymorphisms in the VDR gene, their polymorphism affects receptor activity and has been determined to be related to the pathogenesis of tuberculosis. Although multiple studies have confirmed the relationship with VDR gene polymorphism and TB, however, the

findings of these studies have been contradictory. How can we explain the relevant contradictory results? Hence, we using meta-analysis to carry out comprehensive quantitative analysis and draw stable and reliable conclusions.

Materials And Methods

2.1 Literature search strategy

A literature search was carried out via computer and hand searches. We used vitamin D receptor or VDR or rs2228570 or FokI and tuberculosis and pulmonary search published articles in Chinese and English database. We use these databases: SinoMed data-base, CNKI, Wanfang, VIP, PubMed, Cochrane Library, Elsevier ScienceDirect, Embase, Web of Science and SpringLink.

2.2 Literature inclusion and exclusion criteria

The literature inclusion criteria: (1) type of study: case-control studies; (2) content of study: FokI gene polymorphisms and TB susceptibility; (3) research object: cases of inclusion were diagnosed TB, and exclusion autoimmune diseases, diseases of the endocrine system, long time use of adrenal cortical hormones or immunosuppressive drugs, and HIV infection[2, 3]; (4) control of inclusion were healthy control group: X-ray chest showed no abnormalities, PPD test less than 5mm³; (5) the studies with enough data to calculate odds ratio(OR) and 95% confidence interval(CI)[4, 5]; (6) there were no restrictions on race and gender, and aged ≥ 16 years.

Literature exclusion criteria: (1) the studies with incomplete data or required data cannot be calculated OR and 95%CI; (2) there were reporting the clinical consequences; (3) repeated research; (4) controls were healthy subjects with no history of contact with TB patients.

2.3 Data extraction

All data were extraction independently by 2 investigators. The data were extraction included: the first author's name, publication year, the area of research, case group and control group sample.

2.4 Literature quality evaluation

We evaluated the literature with 2 investigators using Newcastle-Ottawa Scale(NOS). The scale includes a total of 8 items including the selection, comparability and exposure. The highest score is 9 points, and the score more than 7 points as high-quality literature[6].

2.5 Statistical analysis

In this study, we considered the f allele is a gene that increases risk. Therefore, we use the five models: allele contrast(f vs. F), dominant model(ff + fF vs. FF), recessive model(ff vs. fF + FF), co-dominant model(ff vs. FF, fF vs. FF) to calculate OR and 95%CI. The het-erogeneity between studies was assessed with a based Q test and I² statistics. If there is no significant heterogeneity (I² < 50%, Q test P > 0.05),

select the fixed effect model; otherwise, choose random Effect model. Sensitivity analysis to verify the stability and reliability of meta-analysis results[4, 5, 7]. The Begg rank correlation method was used to statistically assess publication bias. All the statistical tests were conducted with R software(version 4.0.5), and the statistical significance was defined as $p < 0.05$. All p values were two-sided.

Results

3.1 Characteristics of inclusion studies

Two hundred and forty-three studies were identified after database and manual literature searches. According to the inclusion and exclusion criteria, 35 relevant studies[8–42] were considered in this meta-analysis. A flow chart of the study selection process is shown in Fig. 1. And detailed characteristics of the enrolled studies were listed in Table 1.

Table 1
Main characteristics of included studies summarized for the meta-analysis

First author	Year	County	patients	controls	Genotyping method	HWE	NOS
Liu Wei[8]	2003	China	76	171	PCR	N	7
Liu Wei[9]	2003	China	110	180	PCR-RFLP	N	8
P Selvaraj[10]	2004	India	46	64	PCR	Y	9
Liu Wei[11]	2005	China	152	259	PCR	Y	8
Zane Lombard[12]	2006	South Africa	104	117	ARMS-PCR	Y	8
Gao Yujing[13]	2008	China	108	154	PCR-RFLP	Y	7
Liu Yidian[14]	2008	China	30	30	PCR	Y	7
P. Selvaraj[15]	2009	India	65	60	PCR	N	9
M. Vidyarani[16]	2009	India	40	49	PCR	N	8
Feng Fumin[17]	2009	China	122	248	PCR-RFLP	N	7
Banoei MM[18]	2010	Iran	60	62	PCR	N	8
Wang Xi[19]	2011	China	213	211	PCR-RFLP	Y	7
Wang Xi[20]	2011	China	224	225	PCR-RFLP	Y	8
J. Rathored[21]	2012	India	692	205	PCR-RFLP	N	8
Maijuan Ma[22]	2012	China	543	544	PCR	Y	9
Ying Xiang[23]	2013	China	198	195	PCR	Y	7
Dai Yaoyao[24]	2013	China	1584	1566	PCR	Y	9
Chen Dandan[25]	2013	China	993	880	PCR	Y	7
Sinaga BY[26]	2014	Indonesia	76	76	PCR-RFLP	Y	8
Mahmoud AA[27]	2014	Egypt	40	25	PCR	N	8
Jalil Rashedi[28]	2014	Iran	84	90	PCR-RFLP	N	8
Wu Linlin[29]	2015	China	151	453	PCR-RFLP	Y	9
Saeedeh Salimi[30]	2015	Iran	120	131	PCRRFLP	Y	8
Zhang Juan[31]	2015	China	300	300	HRM-PCR	Y	7

HWE = Hardy Weinberg Equilibrium; NOS = Newcastle-Ottawa Scale; Y = calculate HWE; N = no calculate HWE.

First author	Year	County	patients	controls	Genotyping method	HWE	NOS
Mohammad Jafari[32]	2016	Iran	96	122	ARMS-PCR	N	8
Shih-Wei Lee[33]	2016	China Taiwan	198	170	PCR	Y	7
Ke Xiao[34]	2016	China	61	49	PCR-RFLP	Y	7
Wu Jin[35]	2017	China	180	100	PCR	N	6
Shi Jie[36]	2017	China	260	260	PCR-SSCP	Y	9
Shi Jie[37]	2017	China	260	258	PCR	Y	9
Devi KR[38]	2018	India	169	227	PCR-RFLP	Y	8
Zhang Ye[39]	2018	China	180	59	PCR	N	7
Silva-Ramírez B[40]	2019	Mexico	257	457	RT-PCR	Y	8
Yang Kaixuan[41]	2019	China	205	435	TaqMan	Y	8
Liu Xing[42]	2020	China	300	300	PCR	Y	7
HWE = Hardy Weinberg Equilibrium; NOS = Newcastle-Ottawa Scale; Y = calculate HWE; N = no calculate HWE.							

3.2 Characteristics of inclusion studies

We pooled all 35 studies together for the assessment of the relationship between the VDR FokI polymorphism and TB risk. In this study used four models for meta-analysis. The pooled forest plot of effect estimates(ORs) from 35 studies estimated OR1 (f vs. F), OR2 (ff + fF vs. FF), OR3 (ff vs. fF + FF), OR4 (ff vs. FF) and OR5 (fF vs. FF) were 1.22(95%CI: 1.11–1.36), 1.29(95%CI: 1.13–1.47), 1.31(95%CI: 1.09–1.56), 1.48(95%CI: 1.19–1.83), 1.23(95%CI: 1.09–1.39). These indicated that OR1, OR2, OR3, OR4, and OR5 were significant ($P \leq 0.05$). The meta-analysis results association between VDR FokI gene polymorphism and TB risk was showed in Table 2, and Supplementary Fig. 1.

Table 2
meta-analysis of FokI polymorphism and TB

Model	Polymorphism	test of association			test of heterogeneity		
		OR	95%CI	p	Model	P	I^2 (%)
Allele	f vs F allele	1.22	1.11–1.36	< 0.0001	R	< 0.0001	76.1
Dominant	ff + fF vs FF	1.29	1.13–1.47	0.0002	R	< 0.0001	69.8
Recessive	ff vs fF + FF	1.31	1.09–1.56	0.0031	R	< 0.0001	68.3
Co-dominant A	ff vs FF	1.48	1.19–1.83	0.0004	R	< 0.0001	74.2
Co-dominant B	fF vs FF	1.23	1.09–1.39	0.0011	R	< 0.0001	59.9
OR = odds ratio; CI = confidence interval; R = random effect model.							

3.3 Sensitivity analysis

In the sensitivity analysis, each study was deleted one at a time to evaluate the im-pact of each individual data set on the combined OR. Results showed no significant dif-ferences in the corresponding combined ORs, suggesting the stability of this me-ta-analysis (Supplementary Fig. 2).

3.4 Subgroup meta-analysis

In order to assess the possible impact of different ethnic groups on the overall esti-mate, we will divide the analysis into three subgroups according to ethnicity, namely Asian ethnic group, African ethnic group and Caucasian ethnic group. The results of the comparison of the five models are shown in Table 3 and Supplementary Fig. 3.

Table 3
subgroup meta-analysis of FokI polymorphism and TB

Model	Subgroup	test of association	
		OR	95%CI
Allele(f vs F allele)	Asian	1.20	1.08–1.35
	African	1.42	0.89–2.28
	Caucasian	1.34	1.07–1.68
Dominant(ff + fF vs FF)	Asian	1.26	1.09–1.46
	African	1.70	0.94–3.06
	Caucasian	1.40	1.05–1.86
Recessive(ff vs fF + FF)	Asian	1.28	1.06–1.56
	African	1.08	0.38–3.11
	Caucasian	1.75	1.30–2.37
Co-dominant A(ff vs FF)	Asian	1.45	1.14–1.84
	African	1.40	0.44–4.39
	Caucasian	2.00	1.42–2.81
Co-dominant B(fF vs FF)	Asian	1.21	1.05–1.38
	African	1.75	0.94–3.25
	Caucasian	1.30	0.99–1.71
OR = odds ratio; CI = confidence interval.			

3.5 Publication bias

The meta-analysis results of the four models were through Begg's rank correlation test and showed no evidence confirmed of publication bias($p \geq 0.05$). The results showed in Table 4.

Table 4
statistics to test the publication bias

Model	Polymorphism	Begg's correlation test	
		Z	p
Allele	f vs F allele	0.10	0.921
Dominant	ff + fF vs FF	-0.07	0.943
Recessive	ff vs fF + FF	0.27	0.787
Co-dominant A	ff vs FF	0.10	0.921
Co-dominant B	fF vs FF	0.21	0.831

Discussion

Tuberculosis is one of the major causes of tuberculosis morbidity and mortality, and the VDR gene may play an important role in regulating host susceptibility to tuberculosis due to the potential role of VDR in tuberculosis morbidity and mortality. Many scholars believe that the deficiency of vitamin D3 in the human body will increase the susceptibility to tuberculosis, and the change of the VDR gene will have a certain impact on its cytological function. However, many studies have produced contradictory association data between VDR FokI gene polymorphism and tuberculosis risk. This shows that TB infection situation will be affected by environmental and genetic factors interact.

We conducted a meta-analysis based on 35 literatures that met the inclusion and exclusion criteria as of November 2020, and confirmed that VDR FokI gene polymorphism was associated with tuberculosis. We found that the f allele was a risk factor for pulmonary tuberculosis in the allele model, dominant, recessive, and co-dominant model. This meta-analysis found that f gene mutations in Asian and Caucasian populations were associated with tuberculosis in different models. However, an insignificant association was found in Africans for all comparison models. To some extent, this finding reflects the existence of ethnic differences, suggesting that this polymorphism may play a multi-functional role in the pathogenesis of tuberculosis, or interact with other genetic and environmental factors. Previous studies, including the WHO TB report, have shown that yellow people are more likely to develop TB than blacks and whites.

The present study has some advantages over the previous ones. First of all, this is an updated meta-analysis, adding many new research results compared with the two meta-analyses in 2015. We use different models to compare. Second, we evaluated the quality of each literature included in this study. Thirdly, we carried out sensitivity analysis on the results of this study, and the results were all stable. However, there are some limitations to consider in this study, and I should pay attention to the potential publication bias when interpreting the results, although no significant publication bias was found in this study. Second, patient heterogeneity and potential confounders may have distorted the analysis. Third,

VDR polymorphism may be related to the clinical characteristics of PTB. Due to the lack of raw data from the authors, we performed subgroup analysis by ethnicity, while we did not stratify or analyze other factors, such as gender or clinical and environmental variables, but the limited data available did not allow us to study this correlation.

Conclusions

In summary, this meta-analysis shows that VDR FokI polymorphism is associated with PTB susceptibility, suggesting that this polymorphism may play an important role in the risk of PTB. There are differences in the degree of susceptibility among different populations. Asian and Caucasian populations are more susceptible to f allele mutations, but no correlation has been found in African populations.

Declarations

Author Contributions: W.ZF project administration, L.YX. and W.F.contributed to the study screening and data extraction, L.B. contributed to writing original draft preparation. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict interest.

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Figures

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study identification process