FokI polymorphism of the vitamin D receptor (VDR) gene and susceptibility to tuberculosis: evidence through a meta-analysis

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Abstract

Background: Tuberculosis is one of the top ten causes of deaths worldwide. The deficiency of vitamin D was reported to be associated with the increased susceptibility of tuberculosis. Various previous reports were published to check the association of *FokI* polymorphism of the vitamin D receptor gene with tuberculosis risk. But their results were inconsistent so, we performed a meta-analysis to know the exact relation of the two.

Methods: Different databases were screened up to November, 2020 with the keywords “Vitamin D receptor”, “VDR”, and “*FokI*”, along with “Tuberculosis” and “TB” to find the suitable articles. All the statistical analyses were performed by the Open Meta-Analyst program and all p-values were two-tailed with a significance level of 0.05.

Results: No statistically significant association was observed in the allele contrast model ($OR_{fv.s.F} = 1.11$, 95%CI= 0.99-1.24, $p = 0.05$, $I^2 = 73.46\%$), in the dominant model ($OR_{ff+ffvs.FF} = 1.11$, 95%CI= 0.96-1.28, $p = 0.14$, $I^2 = 71.39\%$), and in the co-dominant model ($OR_{Fffvs.FF} = 1.05$, 95%CI= 0.92-1.21, $p = 0.41$, $I^2 = 65.97\%$). However, a significant association was found in the homozygote model ($OR_{ffvs.FF} = 1.32$, 95%CI= 1.03-1.69, $p = 0.02$, $I^2 = 67.02\%$) and in the recessive model ($OR_{FF+FF vs. ff} = 1.26$, 95%CI= 1.03-1.54, $p = 0.02$, $I^2 = 58.01\%$). Further analysis was performed on the bases of the ethnicity. In Asian population a significant association was found in the homozygote model ($OR_{ffvs.FF} = 1.57$, 95%CI= 1.12-2.21, $p = 0.008$, $I^2 = 70.37\%$) and in the recessive model ($OR_{FF+FF vs. ff} = 1.43$, 95%CI= 1.08-1.89, $p = 0.01$, $I^2 = 63.13\%$).

Conclusion: In conclusion, a significant association of *FokI* with tuberculosis susceptibility was found in the overall analysis and in the Asian population.

Background

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*. TB is one of the top 10 causes of death globally. In the year 2019 an estimated 10 million people fell ill with TB worldwide and nearly 1.4 million people were died worldwide due to TB [1]. Although, one third of the population of the world is infected with the bacillus but only a tiny percentage of the people may progress to active TB disease [2]. A number of factors are associated with the susceptibility of TB such as- environmental [3], genetic [4], and HIV infection [5,6] etc. A number of studies were performed to determine the role of single nucleotide polymorphisms (SNPs) in the susceptibility of TB like- natural resistance-associated macrophage protein 1 (NRAMP1) gene [7], interleukin (IL) genes [8,9], vitamin D receptor (VDR) genes [10], and tumor necrosis factor (TNF) genes [11].

Among them the VDR gene is most studied and it has been considered as a risk factor for the TB development process as it may affect the host immunity. The vitamin D receptor interacts with the 1,25-dihydroxyvitamin D3 and activates the monocytes, stimulate cell mediated immunity and suppress the proliferation of lymphocytes [12], so the susceptibility to TB may be increased by deficiency of 1,25-

dihydroxyvitamin D3. The VDR gene is located on chromosome 12 that spans approximately 75 kb of genomic DNA and contains 11 exons [13]. One of the most studied polymorphism of the VDR gene is *FokI*. A polymorphic variant (FF) is generated from a change of T to C in the start codon sequence that is shortened by three amino acids and shows increased transcriptional efficiency of the VDR protein as compared to the long ff allele form [14].

Several studies were performed to check the association of *FokI* polymorphism with the susceptibility of TB. The results of these studies were inconclusive so we designed this study to determine the role of *FokI* in the TB susceptibility.

Materials And Methods

Study selection

The studies for the present meta-analysis were searched through four databases *viz.* PubMed, Google scholar, SpringerLink and Elsevier. These databases were searched with the keywords “Vitamin D receptor”, “VDR”, and “*FokI*”, along with “Tuberculosis” and “TB”. The articles were selected up to November, 2020.

Inclusion and exclusion criteria

We included the studies if they met following criteria- i) case-control study; ii) provided data of alleles and genotypes for the case and control groups. At the same time, we excluded those studies which were i) reported case only; ii) performed on the animal models; iii) other than English language; iv) review and meta-analyses.

Data extraction

From all the selected articles the authors extracted following information- i) first author's last name; ii) year of publication; iii) ethnicity; iv) number of alleles and/or genotypes. All these information's were retrieved by the authors independently and if any inconsistency was found it was resolved by the mutual discussion.

Meta-analysis

For the present study, we constructed five genetic models through the data extracted from different included studies. The five genetic models are allele contrast, dominant, homozygote, co-dominant and recessive. We calculated odds ratio (OR) and 95% confidence interval (CI) for all the individual studies

and then pooled OR and 95% CI was calculated by the method of Mantel and Haenszel [15] for the fixed effect model and by the method of DerSimonian and Laird [16] for the random effect model. The choice of the best fit model was determined by the between study heterogeneity, which was calculated by the Q-statistics (a p-value of less than 0.05 was considered as statistically significant) and I^2 statistics was used to quantify the inconsistency of between study estimates. Sub-group analysis based on ethnicity was also performed. Potential publication bias was identified by the evaluation of the funnel plot. The linear regression method of Egger et al. [17] was used for further evaluation of the publication bias. All the statistical analyses were performed in the Open Meta-Analyst program [18]. All p-values were two-tailed with a significance level of 0.05.

Results

Eligible studies

With our search criteria we identified 1098 articles from different databases. After application of our study selection criteria we identified a total of 44 articles suitable for inclusion in the present meta-analysis [10, 19-61]. Out of 44 studies, 29 studies were belong to Asia, eight studies were from Africa, one from Europe and 6 studies were from South America.

Meta-analysis

In the overall analysis the heterogeneity was very high and no statistically significant association was observed in the allele contrast model ($OR_{fvs.F} = 1.11$, 95%CI= 0.99-1.24, $p = 0.05$, $I^2 = 73.46\%$) (Fig. 1). Similar results were found in the dominant model ($OR_{ff+Ffvs.FF} = 1.11$, 95%CI= 0.96-1.28, $p = 0.14$, $I^2 = 71.39\%$) (Fig. 2) and co-dominant model ($OR_{Ffvs.FF} = 1.05$, 95%CI= 0.92-1.21, $p = 0.41$, $I^2 = 65.97\%$). A significant association was found in the homozygote model ($OR_{ffvs.FF} = 1.32$, 95%CI= 1.03-1.69, $p = 0.02$, $I^2 = 67.02\%$) (Fig. 3) and in the recessive model ($OR_{FF+Ff vs. ff} = 1.26$, 95%CI= 1.03-1.54, $p = 0.02$, $I^2 = 58.01\%$) (Fig. 4). High heterogeneity was found in all the genetic models so the random effect model was applied (Table 1).

Further analysis was performed on the bases of the ethnicity. In Asian population high heterogeneity was found in all the genetic models so the random effect model was applied. No significant association was found in the allele contrast model ($OR_{fvs.F} = 1.15$, 95%CI= 0.98-1.34, $p = 0.06$, $I^2 = 77.48\%$), dominant model ($OR_{ff+Ffvs.FF} = 1.15$, 95%CI= 0.93-1.41, $p = 0.18$, $I^2 = 77.47\%$) and co-dominant model ($OR_{Ffvs.FF} = 1.06$, 95%CI= 0.86-1.31, $p = 0.53$, $I^2 = 74.73\%$). However, a significant association was found in the homozygote model ($OR_{ffvs.FF} = 1.57$, 95%CI= 1.12-2.21, $p = 0.008$, $I^2 = 70.37\%$) and in the recessive model ($OR_{FF+Ff vs. ff} = 1.43$, 95%CI= 1.08-1.89, $p = 0.01$, $I^2 = 63.13\%$) (Table 1).

Furthermore, no association was found in any genetic models in the African and South American populations. In the African studies no heterogeneity was observed but in the South American studies high between study heterogeneity was found (Table 1).

Sensitivity analysis

The sensitivity analysis was performed by the exclusion of the studies that were deviated from the Hardy-Weinberg equilibrium (HWE). Total seven studies [30, 32, 34, 51, 52, 54, 61] were deviated from the HWE. After removal of these studies we again performed the overall meta-analysis and sub-group meta-analysis. The overall heterogeneity was increased while the odds ratio marginally increased ($OR_{ffvs,FF}=1.34$; 95%CI= 1.03-1.73; $p=0.02$, $I^2=69.22\%$).

Publication bias

The symmetry in the funnel plots showed absence of publication bias (Fig. 5). The p-value of Egger's test were more than 0.05 in all models which showed no publication bias statistically (Table 1).

Discussion

The present study was designed to evaluate the role of the *FokI* polymorphism in the etiology of the TB because a number of studies were published before with inconclusive results. In this study we found that the homozygote model ($OR_{ffvs,FF}=1.32$, 95%CI= 1.03-1.69, $p=0.02$, $I^2=67.02\%$) and recessive model ($OR_{FF+Ffvs,ff}=1.26$, 95%CI= 1.03-1.54, $p=0.02$, $I^2=58.01\%$) of the overall studies was significantly associated with the TB. Again, we performed the sub-group analysis on the basis of the ethnicity and found that the Asian population is at risk of developing TB in the homozygote model ($OR_{ffvs,FF}=1.57$, 95%CI= 1.12-2.21, $p=0.008$, $I^2=70.37\%$) and recessive model ($OR_{FF+Ffvs,ff}=1.43$, 95%CI= 1.08-1.89, $p=0.01$, $I^2=63.13\%$).

The susceptibility of developing TB in different populations is different that may be due to the genetic variations among the populations. In the various previous studies, a number of gene polymorphisms have been found to be associated with the TB risk. One such gene polymorphism is *FokI* of the VDR gene. Vitamin D suppresses the proliferation of lymphocytes and activates monocytes. It also suppresses the cytokine synthesis and production of immunoglobulins; thus, it plays a crucial role in human innate immunity to the infectious agents including *M. tuberculosis* [62]. How vitamin D suppresses the infection of *M. tuberculosis* is not clear but one of the suggested mechanism is the production of cathelicidin. Vitamin D induces the production of cathelicidin, an antimicrobial peptide, which restricts the growth of *M. tuberculosis* in the macrophages [63] so it provides defense against the development of TB. The macrophages convert circulating 25(OH) vitamin D to 1,25(OH) vitamin D during bacterial infection,

which stimulates the expression of the genes encoding the antimicrobial peptides like cathelicidin [64]. This peptide is secreted by peripheral immune cells and respiratory epithelial cells [65]. Cathelicidin is a molecule that is essential for normal immune responses to infection. It has many properties like- cytokine release, tissue regeneration and also inhibits apoptosis of neutrophil [66].

Meta-analysis is a powerful tool in evaluating the risk of a disease with a particular gene. It combines the low powered studies to make a pooled study with more statistical power. In recent years by using this technique a number of studies were published which clarifies the relationship between a gene polymorphisms and some disease/or disorder like- Down syndrome [67, 68], glucose-6-phosphate dehydrogenase deficiency [69] neural tube defects [70], male infertility [71], osteoporosis [72], cancer [73-78] etc.

So far nine meta-analyses were published, which evaluated the role of VDR *FokI* gene polymorphism in the etiology of the TB [79-87]. In few meta-analyses no significant association was found in between the *FokI* polymorphism and TB [79, 86, 87]. In a study conducted by Gao et al. [80] a significant association in the homozygote model ($OR_{ffvs,FF} = 1.5$, 95%CI= 1.1-2.0, $p < 0.1$) was found. Chen et al. [81] found association in the recessive model ($OR = 1.36$, 95%CI= 1.14-1.62, $p = 0.002$) only. Low heterogeneity was found in the study of Sun and Cai [82] and they found significant association ($OR_{ffvs,FF} = 1.36$, 95%CI= 1.11-1.66). Similar results with low heterogeneity was found in the study of Huang et al. [83] ($OR_{ffvs,FF+ff} = 1.34$, 95%CI= 1.09-1.64, $p = 0.005$). Significant association was also reported in the studies of Cao et al. [84] ($OR_{ffvs,FF} = 1.37$, 95%CI= 1.17-1.60) and Wang and Li [85] ($OR_{FF+Ffvs,ff} = 1.30$, 95%CI= 1.06-1.59, $p = 0.01$).

There are few limitations in our meta-analysis which we want to acknowledge here- First, in our meta-analysis we included only those studies which were published in English, which might introduce potential bias. Second, based on our calculations we found a significant deviation from the HWE in the control population for seven studies. So, we performed sensitivity analysis after exclusion of these studies but no significant improvement in the results were found. Third, in some sub-groups only a few studies were present for sub-group analyses which might not represent the entire population so more studies are needed to confirm the association of *FokI* polymorphisms and risk of TB.

Conclusions

VDR *FokI* gene polymorphism is found to be associated with the increased susceptibility to the TB in overall the analysis. While no such association was found in the sub-group analyses.

Declarations

Declaration of conflict of interest: All the authors declare that there is no conflict of interest.

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Table

Table 1. Summary estimates for the odds ratio (OR) of *FokI* in various allele/genotype contrasts, the significance level (p value) of heterogeneity test (Q test), and the I² metric: overall analysis, and subgroup analyses.

Genetic Contrast		Fixed effect OR (95% CI), p	Random effect OR (95% CI), p	Heterogeneity p-value (Q test)	I ² (%)	Publication Bias (p of Egger's test)
All (44 studies)	Allele Contrast (f vs. F)	1.16 (1.10-1.22), <0.001	1.11 (0.99-1.24), 0.05	<0.001	73.46	0.10
	Dominant (ff+Ff vs. FF)	1.14 (1.06-1.22), <0.001	1.11 (0.96-1.28), 0.14	<0.001	71.39	0.45
	Homozygote (ff vs. FF)	1.46 (1.29-1.66), <0.001	1.32 (1.03-1.69), 0.02	<0.001	67.02	0.22
	Co-dominant (Ff vs. FF)	1.08 (1.00-1.17), 0.02	1.05 (0.92-1.21), 0.41	<0.001	65.97	0.48
	Recessive (FF+Ff vs. ff)	1.39 (1.24-1.55), <0.001	1.26 (1.03-1.54), 0.02	<0.001	58.01	0.15
Asian (29 studies)	Allele Contrast (f vs. F)	1.25 (1.16-1.34), <0.001	1.15 (0.98-1.34), 0.06	<0.001	77.48	0.75
	Dominant (ff+Ff vs. FF)	1.23 (1.12-1.36), <0.001	1.15 (0.93-1.41), 0.18	<0.001	77.47	0.65
	Homozygote (ff vs. FF)	1.76 (1.50-2.07), <0.001	1.57 (1.12-2.21), 0.008	<0.001	70.37	0.91
	Co-dominant (Ff vs. FF)	1.14 (1.03-1.26), 0.008	1.06 (0.86-1.31), 0.53	<0.001	74.73	0.32
	Recessive (FF+Ff vs. ff)	1.59 (1.37-1.84), <0.001	1.43 (1.08-1.89), 0.01	<0.001	63.13	0.68
African (8 studies)	Allele Contrast (f vs. F)	1.01 (0.91-1.12), 0.81	1.01 (0.91-1.12), 0.81	0.76	0	0.27
	Dominant (ff+Ff vs. FF)	1.02 (0.89-1.16), 0.77	1.01 (0.89-1.16), 0.77	0.59	0	0.07
	Homozygote	1.01 (0.75-	1.01 (0.75-	0.99	0	0.45

	(ff vs. FF)	1.34), 0.94	1.34), 0.94			
	Co-dominant (Ff vs. FF)	1.02 (0.89-1.17), 0.74	1.02 (0.89-1.17), 0.75	0.51	0	0.06
	Recessive (FF+Ff vs. ff)	0.99 (0.75-1.32), 0.97	0.99 (0.75-1.32), 0.97	0.99	0	0.62
South American (6 studies)	Allele Contrast (f vs. F)	1.11 (0.97-1.28), 0.12	0.99 (0.72-1.35), 0.96	<0.001	76.22	0.66
	Dominant (ff+Ff vs. FF)	1.06 (0.86-1.30), 0.57	0.95 (0.66-1.35), 0.78	0.02	61.24	0.61
	Homozygote (ff vs. FF)	1.24 (0.92-1.67), 0.14	0.87 (0.41-1.84), 0.72	<0.001	76.41	0.35
	Co-dominant (Ff vs. FF)	1.01 (0.81-1.26), 0.89	0.97 (0.74-1.27), 0.84	0.24	25.68	0.77
	Recessive (FF+Ff vs. ff)	1.28 (1.00-1.63), 0.04	1.02 (0.61-1.72), 0.92	0.008	67.96	0.28

Figures

Figure 1

Random effect forest plot of allele contrast model of VDR FokI polymorphism. Results of individual and summary OR estimates, and 95% CI of each study were shown. Horizontal lines represented 95% CI, and dotted vertical lines represent the value of the summary OR.

Figure 2

Random effect forest plot of dominant model of VDR FokI polymorphism.

Figure 3

Random effect forest plot of homozygote model of VDR FokI polymorphism.

Figure 4

Random effect forest plot of recessive model of VDR FokI polymorphism.

Figure 5

Funnel plots of standard error by log odds ratio for a) allele contrast model; b) dominant model; c) homozygote model; and d) recessive model.