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Vitamin D receptor genetic polymorphisms and the risk of multiple sclerosis: A systematic review and meta-analysis

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Running title: VDR gene and MS risk

Abstract

There are conflicting results regarding the exact effect of the vitamin D receptor (VDR) gene polymorphisms on the susceptibility to multiple sclerosis (MS). Therefore, we aimed to investigate the impact of four major studied VDR gene polymorphisms consisting of ApaI, BsmI, FokI, and TaqI on the risk of MS in the Iranian population. A literature search was performed in various databases to find case-control studies evaluating the association between VDR gene polymorphisms and MS risk in Iran. Data were extracted and odds ratios (OR) with 95% confidence intervals (CI) were calculated. Subgroup analyze was performed to detect potential sources of heterogeneity. A total of 1206 cases and 1402 controls in nine case-control studies were included. ApaI was the only variant which showed statistically significant relation in allelic (OR=0.54 (95% CI: 0.37–0.79); $P=0.00$), homozygote (OR=3.48 (95% CI: 1.7–6.9); $P=0.00$), dominant (OR=0.56 (95% CI: 0.3–0.79); $P=0.01$), and recessive (OR=0.35 (95% CI: 0.18–0.66); $P=0.00$) models. The TaqI polymorphism showed a significant negative association with MS only in the homozygote model (OR= 0.28 (95% CI: 0.08–0.9); $P=0.04$). The BsmI polymorphism also showed significant relation in allelic (OR= 0.69 (95% CI: 0.51–0.94); $P=0.01$), homozygote (OR= 0.46 (95% CI: 0.25–0.86); $P=0.01$), and recessive OR= 0.56 (95% CI: 0.39–0.8); $P=0.00$) models after performing sensitivity analysis. FokI polymorphism showed no significant association with MS risk. ApaI and TaqI TT genotype were found contributing to MS susceptibility and BsmI and FokI showed no relation with MS susceptibility in the Iranian population.

Keywords: Multiple Sclerosis; Vitamin D receptor; Iranian population; Meta-analysis.

Introduction

Multiple sclerosis (MS) is known as a chronic demyelinating disease of the central nervous system (CNS), an inflammatory neurodegenerative disorder associated with loss of motor and sensory function and major clinical disabilities (1). As the most common immune-mediated disorder, MS has complex pathophysiology which involves both genetic susceptibility and environmental factors (2). In many countries, it is one of the most common causes of non-traumatic neurological disability in young adults and more than two million people worldwide suffer from MS, but the exact etiology of the disease is still unknown (3).

Vitamin D (1,25- dihydroxy vitamin D₃) receptor (VDR), an intracellular receptor belonging to the steroid/thyroid nuclear receptor family, is expressed on various cells such as skeletal, intestine, bone marrow, brain, colon, breast, malignant cells, and immune cells (4). Given the expression of vitamin D receptor on the majority of immune cells (B cells, T cells, and antigen-presenting cells such as macrophages), the biologically active metabolite of vitamin D, 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) has shown a vital role as an immune modulator; therefore, it can modulate the innate and adaptive immune responses which result in an ability to maintain tolerance and to promote protective immunity (4-6). Vitamin D deficiency has been observed to be related to increased risk of autoimmunity, progression of existing autoimmune diseases, such as multiple sclerosis (MS), rheumatoid arthritis (RA), diabetes mellitus (DM), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and higher susceptibility to infectious diseases including influenza, bacterial vaginosis, tuberculosis, and human immunodeficiency virus (HIV) (7-11).

The VDR gene is located on human chromosome 12q13.1 (**Figure 1**). With the help of case-control and Genome-wide association study (GWAS), a large variety of the genetic susceptibility elements has been revealed in many multifactorial diseases. Despite over 30 polymorphisms discovered within the VDR gene, four polymorphisms have more been studied as the major variants involved in autoimmune diseases such as MS, including Apa-I (rs7975232) and BsmI (rs1544410) which are located on intron between exon 8–9, Fok-I (rs10735810) located in the translation initiation site in exon 2, and Taq-I (rs731236) which is presented in exon 9 (12).

The interaction between vitamin D and the immune system might be influenced by different VDR gene polymorphisms, is still the subject of interest, and has been investigated in different case-

control studies. This systematic review and meta-analysis were aimed to comprehensively evaluate all the current literature on the association between four different VDR gene polymorphisms and susceptibility to MS in the Iranian population for the first time.

Materials and Methods

Search Strategy

The review process followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. A comprehensive literature search was performed using the PubMed and Scopus databases to retrieve the related studies that examined the associations between four VDR polymorphisms of ApaI, BsmI, FokI, and TaqI with MS in the Iranian population. The search was performed in February 2019 and obtained studies were searched with no date and language restrictions. Two independent reviewers performed searching in duplicate. The combination keywords used as the medical subject heading (MeSH) and text words in the mentioned database were as follows: vitamin D receptor, VDR, vitamin D, multiple sclerosis, MS, VDR gene polymorphism, and association study. The reference lists of the recruited articles were hand-searched to prevent missing any relevant article. Google Scholar was also searched to find articles that are not indexed in PubMed or Scopus.

Inclusion and Exclusion Criteria

Inclusion criteria were all the case-control, cohort or cross-sectional studies with minimum of two comparison groups (MS group and control group) and detailed genotype data to calculate the odds ratio (OR) and corresponding 95% CI of the relation between VDR polymorphisms and risk of MS. Review articles, editorials, and case reports could not be included. Articles with no control group or genotype data to calculate the odds ratio (OR) and corresponding 95% CI were excluded. The article with the larger sample size was selected to be included in systematic review and meta-analysis for publications on the same topic performed by one research group.

Data Extraction and Synthesis

The following information was extracted from each eligible article: first author's last name, publication year, ethnicity, age, gender, and sample size, criteria for MS diagnosis, genotyping methods, and the number of cases and controls for the VDR ApaI, BsmI, FokI, and TaqI genotype.

The major and minor alleles frequency and different genetic models of each polymorphism were calculated for both the case and control groups from the corresponding genotype distribution. For each polymorphism, three different including the homozygote (FF vs ff), dominant (FF+Ff vs ff), and recessive (FF vs Ff+ff) genetic models were assessed.

Statistical analysis

The strength of the association between polymorphisms and increase or decrease of the MS risk was assessed and compared between cases and controls by calculation of Odds ratio (ORs) and corresponding 95% confidence intervals (CIs) in all different genetic models on a forest plot. A comprehensive meta-analysis (CMA) version 2 and the random-effects model (Dersimonian and Laird method) (13) was used for pooling data and obtaining the ORs.

Asymptotic Pearson's χ^2 test based on an Excel program was used to show if genotype distribution of all single nucleotide polymorphisms (SNPs) in controls and patients exhibited Hardy–Weinberg equilibrium (HWE) in the control group (HWE; $p < 0.05$ was considered significant).

Heterogeneity was evaluated based on the Cochrane Q-test ($P < 0.05$ was considered statistically significant) and I^2 index statistics, I^2 where values of 25, 50, and 75 % were defined as low, moderate, and high estimates, respectively. The publication biases among the studies were assessed using the Eggers regression intercept.

Results

Eligible studies

The process of study selection is shown in **Figure 2**. Although the search results led to a retrieve of 60 references, 10 studies were selected as the most relevant researches based on the described inclusion criteria. However one study was omitted because it was accessible only as an abstract (14); therefore, only 9 case-control studies comprising 1206 cases and 1402 controls reporting genotypic frequencies in cases and in controls were included in the meta-analysis (**Figure. 2**) (15-23). Appropriate diagnostic criteria and proper genotyping methods were used in all included studies. Searching the reference list of the included studies did not result in any additional relevant article.

Table 1 shows the allele distribution of each VDR variant extracted from eligible studies for including in meta-analysis. The detail characteristics of the eligible studies are summarized in **Table 2**.

Included studies were heterogeneous for study characteristics and contained patients enrolled between 2008-2018, from different cities of Iran including Tehran (15, 18, 20), Rafsanjan (17), Zahedan (16, 22), Arak (19), Shiraz (23) and Khuzestan (21). Case and control groups were matched for gender, age, and ethnicity and no significant differences were reported in any of the publications.

FokI (rs2228570) VDR gene polymorphism was evaluated in five studies (Tehran:3 (15, 18, 20), Arak:1(19), and Zahedan:1) including 576 cases and 738 controls; VDR BsmI gene polymorphism was also assessed in five of the included studies (Tehran:2, Arak:1, Zahedan:1, and Shiraz:1) comprising 738 cases and 738 controls. Six studies with 721 cases and 696 controls explored ApaI (rs7975232) gene polymorphism and VDR TaqI (rs731236) gene polymorphism was investigated in six studies containing 721 cases and 696 controls.

MS patients including relapsing-remitting (RR), secondary progressive (SP), and primary progressive (PP) were diagnosed based on the clinical and paraclinical symptoms according to McDonald's criteria in all the studies (24).

Heterogeneity and publication bias

The results of the HWE test are presented in **Table 2**. The genotype distributions of all single nucleotide polymorphisms in the control group of each study were exhibited with Hardy–Weinberg equilibrium except for studies of Ghaemi et al (21), and Sadeghi et al (19), which showed significant deviation from HWE in control groups for ApaI and TaqI, respectively.

Based on the Eger regression intercept, there was no important publication bias among the studies (**Table 3**). According to the I^2 index, there is significant heterogeneity between the publication (**Table 3**). The sensitivity analysis was performed to omit the outlier study which could drastically change the results of data analysis. A random-effects model was used for meta-analysis instead of the fixed-effects model due to high heterogeneity between researches.

Data analysis

The main results of the meta-analysis are summarized in **Table 3**. The pooled ORs were estimated for each VDR gene polymorphism based on the allele contrast, homozygote model, dominant and recessive genetic model.

For FokI VDR polymorphism, the wild-type allele of F showed no statistically significant association with risk of MS (OR=1.17 (95% CI: 0.7-1.7); $P=0.4$). Similarly, none of the obtained ORs showed any relation between different genetic models of FokI and risk of MS, as follows: homozygote model: (OR=0.76 (95% CI: 0.28- 2.03); $P=0.5$), recessive model: (OR= 0.84 (95% CI: 0.5 – 1.3); $P=0.4$), and dominant model: (OR=0.82 (95% CI: 0.35-1.9); $P=0.6$), **Table 3**.

Sensitivity analysis and omitting the outlier study of Narooie-Nejad et al (16), did not change the ORs obtained for FokI polymorphism (**Table 3**).

Analyses showed that the wild-type B allele of BsmI polymorphism was no statistically significant related to the risk of MS in the Iranian population. In the same way, the evaluated genetic models of BsmI polymorphism revealed no significant relation with MS in Iran as follows: homozygote model: (OR=0.63 (95% CI: 0.29 – 1.3); $P=0.2$), recessive model: (OR= 0.7 (95% CI: 0.4 – 1.2); $P=0.2$), and dominant model: (OR=0.77 (95% CI: 1.38 – 0.8); $P=0.3$), which are presented in **Table 3** and **Figure 3**.

The sensitivity analysis was performed for BsmI polymorphism and omitting the study by Narooie-Nejad et al (16) resulted in a significant association for allelic comparison B vs. b (OR= 0.69 (95% CI: 0.51 – 0.94); $P=0.01$), homozygote model comparison (OR= 0.46 (95% CI: 0.25 – 0.86); $P=0.01$), and the recessive model OR= 0.56 (95% CI: 0.39 – 0.8); $P=0.00$) and risk of MS in Iran (**Table 3**).

For TaqI VDR gene polymorphism, the allelic comparison showed no statistical association between allele t and risk of MS in Iran. Only the homozygote genetic model revealed a statistically significant negative relation between TaqI polymorphism and risk of MS (OR= 0.28 (95% CI: 0.08 – 0.9); $P=0.04$). The sensitivity analysis was performed by omitting the outlier study of Narooie-Nejad et al (16), however, it did not influence the overall result: (OR=0.51 (95% CI: 0.26 – 0.97); $P=0.04$).

The forest plot of the homozygote model of TaqI is presented in **Figure 4**. The obtained ORs for recessive model (OR=0.49 (95% CI: 0.17-1.48); $P=0.1$) and dominant model (OR= 0.44 (95% CI: 0.17 – 1.17); $P=0.1$) of TaqI polymorphism did not show any statistically significant relation with MS in the Iranian patients.

For ApaI polymorphism, the allelic comparison showed a statistically significant relationship between the wild A allele with decreased risk of MS in Iran, (OR=0.54 (95% CI: 0.37 – 0.79); $P=0.00$). A similar statistically significant association was also found between ApaI homozygote genetic model of AA vs aa and risk of MS (OR=3.48 (95% CI: 1.7 – 6.9); $P=0.00$), **Table 3**.

The overall association found between the recessive and dominant genetic models of ApaI polymorphism was also significant. As shown in **Table 3**, ApaI genetic models showed a protective effect against MS in Iranian population based on the obtained ORs by random-effects model: the dominant model: (OR=0.56 (95% CI: 0.3 – 0.79); $P=0.01$), and the recessive model: (OR= 0.35 (95% CI: 0.18 – 0.66); $P=0.00$). The Forest plots regarding allele contrast and all the genetic models of ApaI polymorphism are presented in **Figure 5**.

Discussion

Different VDR polymorphisms might affect the structure and function of the Vitamin D and consequently the risk of several diseases such as type 1 (25, 26) and type 2 diabetes mellitus (27, 28), RA (29, 30), and several types of cancers (31-33). VDR gene is considered as a pleiotropic gene and in spite of the evaluation of the effects of VDR gene polymorphisms in predisposition to the autoimmune disease of MS (34-38), the results have not been conclusive and this issue is still the subject of investigations. Small sample sizes, differences in ethnicities, lifestyle, and extensive geographical variations might be the origin of this disparity. Therefore, the current meta-analysis was performed in order to overcome the limitations of individual studies.

Accordingly, we pooled and analyzed all the data extracted from published case-control studies on the association of four well-characterized VDR polymorphisms of ApaI, BsmI, FokI, and TaqI with the development of MS in the Iranian population. Iranian population is a diverse nation with various ethnic groups including Persian, Azeri, Kurd, Gliaki and Mazandarani, Arab, Turkoman, Lor, Baloch and Zabolies (39). Iran is located in south-western Asia and borders the Republic of Armenia, Azerbaijan, and Turkmenistan, as well as the Caspian Sea at the north; Turkey and Iraq at the west; the Persian Gulf and the Gulf of Oman at the south; and Pakistan and Afghanistan at the east (40).

Our analyses suggested that MS was only significantly associated with the ApaI polymorphism in all genetic models in the Iranian population; wherein the relation was obtained by allelic comparison and also all the related genetic models. TaqI homozygote model was negatively associated with MS risk and sensitivity analysis showed that when one study was

removed, the BsmI polymorphism was significantly associated with MS risk. These results suggested that ApaI VDR polymorphisms might directly or indirectly be involved in mechanisms related to MS disease. Effectively, the etiology for many of the common complex diseases such as MS derives from permutations and combinations of common variants. Each variant may only confer a small risk. DNA sequence variations such as polymorphisms exert both modest and subtle biological effects. Therefore, the allele and genetic models of ApaI within intron 8 of the VDR in the Iranian MS patients might have regulatory effects on expression level and function of the VDR which has immunoregulatory functions.

Similar to our results, the protective effect of the homozygous dominant of AA has previously been shown for Asian groups (34, 36) as well as the Caucasian population (35) following subgroup analysis. However, in another study, no relation between ApaI polymorphism and MS in Asian or Caucasian groups has been reported (38).

For FokI polymorphism, pooling five studies (3 from Tehran, one from Arak, and one from Zahedan) performed on the Iranian MS patients did not show any statistically significant relationship between any genetic models or allelic comparison. Sensitivity analysis even showed that when the study of Narooie-Nejad et al (16), which conducted in Sistan and Baluchistan province, was removed the association of FokI polymorphism with MS risk was not significant. Sistan and Baluchistan province is bordering Afghanistan and Pakistan and inhabited mainly by Balouch people as a different ethnic group of Iran (40, 41). Baloch people have mostly populated Iran, Pakistan and Afghanistan, which show a close relatedness but have genetic differences with the other Iranian populations (40, 41). The previous meta-analyses analyzing the Asian and Caucasian groups have obtained no significant relation for FokI polymorphism with the predisposition to MS (34, 37, 38). However, inconsistent results were reported by one other meta-analysis which showed a significant relationship between the dominant and codominant models of FokI and MS pathogenesis and they proposed the FF genotype as a risk factor of MS development (35).

The overall evaluation of 5 studies (two in Tehran, one in Arak, one in Zahedan, and one in Shiraz), revealed no significant association between any genetic models of BsmI polymorphism and MS in Iran. The sensitivity analysis by omitting the study of Narooie-Nejad et al with different results for the Zahedan population changed the results of the allelic comparison, homozygote, and recessive genetic models between cases and controls. Accordingly, our finding showed that the wild allele

of B and BB genotype would have a significant protective effect on MS development, on the other side, the allele b and bb genotype would increase the risk of MS in Iran. Previous studies showed no significant association based on the pooled ORs except for the BsmI recessive model of an Asian group which was significantly associated with MS (34). Other previously published meta-analysis revealed similar results with ours and showed no relation between BsmI polymorphism and MS pathogenesis, even in the Asian population (35, 36, 38).

In the case of TaqI polymorphism, the allele of t showed no significant effect on the risk of MS in Iran, however, the homozygote genetic model of TT versus tt showed a significant protective effect. Previous meta-analyses were similar about the allelic comparison and proposed no significant relation between allele T and the risk of MS (34-38). Although the homozygous model of (TT+ tt vs. Tt) and a recessive genetic model of TaqI polymorphism have shown a relation with the development of MS in Caucasian and Asian patients in a research (34), no associations have been reported in other similar studies for TaqI polymorphism (35-38).

Limitations that could be addressed for the present study are the high heterogeneity observed between the researches which might be due to differences in sample size and statistical power, geographic and ethnic variations, and methodological and clinical dissimilarities. Findings from the present meta-analysis should be interpreted with caution for several reasons.

We gathered all the published articles regarding the MS in the Iranian population in English or Persian languages for the first time; however, more investigation on Iranian are needed to obtain a reliable conclusion. In conclusion, VDR ApaI polymorphism and homozygous dominant of TT genotype for TaqI were only observed to be associated with MS in the Iranian population and BsmI and FokI showed no relation with risk of MS; however, the conclusion should be interpreted with caution due to the low number of studies and relatively small sample size.

Conflict of Interests

The authors have no conflicts.

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Figure Legends

Figure 1. The encoding vitamin D receptor (VDR) gene is located on human chromosome 12q13.1, which contains 100 kb and divided into 8 introns and 9 exons. The first exon contains the gene promoter, exon 2–3 code for the DNA binding domain, and exon 6–9 for the ligand-binding domain. Over 30 polymorphisms within the VDR gene have been identified which only a few of these polymorphisms have been studied in relation to immune regulation, autoimmune diseases, and MS. Four polymorphisms that are most widely studied includes Apa-I (rs7975232), Bsm-I (rs1544410), Fok-I (rs10735810), and Taq-I (rs731236).

Figure 2. The flow chart of the included articles.

Figure 3. Forest plot of the relation between BsmI polymorphism and multiple sclerosis risk with the random effects model before sensitivity analysis (A) and after sensitivity analysis (B). The forest plot shows the odds ratio (ORs) and respective 95 % confidence intervals (CIs) for the different studies included in the meta-analysis. For each study in the forest plot, the area of the black square is proportional to study weight and the horizontal bar represents the 95 % CI. Z score: the standardized expression of value in terms of its relative position in the full distribution of values.

Figure 4. Forest plot of the relation between TaqI polymorphism and multiple sclerosis risk with the random-effects model: TT vs. tt. The forest plot shows the odds ratio (ORs) and respective 95 % confidence intervals (CIs) for the different studies included in the meta-analysis. For each study in the forest plot, the area of the black square is proportional to study weight and the horizontal bar represents the 95 % CI. Z score: the standardized expression of value in terms of its relative position in the full distribution of values.

Figure 5. Forest plot of the association between ApaI polymorphism and multiple sclerosis risk with the random-effects model before sensitivity analysis (A) and after sensitivity analysis (B). The forest plot shows the odds ratio (ORs) and respective 95 % confidence intervals (CIs) for the different studies included in the meta-analysis. For each study in the forest plot, the area of the black square is proportional to study weight and the horizontal bar represents the 95 % CI. Z score: the standardized expression of value in terms of its relative position in the full distribution of values.

Table 1. Distribution of *VDR* allele frequency in the selected studies (cases vs controls).

References	FokI				BsmI				TaqI				Apal			
	<i>F</i>		<i>f</i>		<i>B</i>		<i>b</i>		<i>T</i>		<i>t</i>		<i>A</i>		<i>a</i>	
Mirzaei et al, 2012(15)	156	428	54	156												
Mosavi et al, 2013(17)									63	71	132	129	69	90	130	110
Narooie-Nejad et al, 2015(16)									62	214	164	30	142	178	84	66
Narooie-Nejad et al, 2015(22)	178	215	48	29	168	155	58	89								
Sadeghi et al, 2015(19)	126	66	34	34	75	61	85	39	117	62	43	38	97	68	63	32
Abdollahzadeh et al, 2016(18)	224	219	96	81	171	205	149	95	156	195	164	105	217	249	103	51
Abdollahzadeh et al, 2018(20)	156	194	80	54	137	161	99	87	127	173	109	75	154	177	82	77
Ghaemi et al, 2017(21)									209	209	91	91	156	244	144	56
Nikseresht et al, 2015(23)					232	262	302	322								

*The shaded columns represent cases and the unshaded columns represent controls.

Table 2. Characteristics of reviewed studies on BsmI, ApaI, TaqI, and FokI VDR polymorphisms and MS risk.

References	VDR Polymorphisms	City	Case	Control	Age (mean±SD) (case/control)	Female	Genotyping method	HWE
Mirzaei et al, 2012(15)	FokI	Tehran	105	292	36.16±8.7 36.16±10.25	83/231	PCR-RFLP	
Mosavi et al, 2013(17)	ApaI, TaqI	Kerman	100	100	40±9 40±7	59/60	PCR-RFLP	ApaI (0.18), TaqI (0.68)
Narooie-Nejad et al, 2015(16)	ApaI, TaqI	Zahedan	113	122	32.4±8.9 30.8±10.2	88/94	PCR-RFLP	ApaI (0.07), TaqI (0.8)
Narooie-Nejad et al, 2015(22)	FokI, BsmI	Zahedan	113	122	32.4±8.9 30.8±10.2	88/94	PCR-RFLP	FokI (0.13), BsmI (0.09)
Sadeghi et al, 2015(19)	FokI, BsmI, ApaI, TaqI	Arak	80	50	18-60 18-60	63/39	PCR-RFLP	FokI (0.2), BsmI (0.1), ApaI (0.9), TaqI (0.0)
Abdollahzadeh et al, 2016(18)	FokI, BsmI, ApaI, TaqI	Tehran	160	150	36.9±2.3 36.8±1.8	120/112	PCR-RFLP	FokI (0.9), BsmI (0.9), ApaI (0.8), TaqI (0.9)
Abdollahzadeh et al, 2018(20)	FokI, BsmI, ApaI, TaqI	Tehran	118	124	37.8 ± 2.5 38.2 ± 3.6	82/85	PCR-RFLP	FokI (0.5), BsmI (0.6), ApaI (0.9), TaqI (0.4)
Ghaemi et al, 2017(21)	ApaI, TaqI	Khuzestan	150	150	22-52 >40	108/94	PCR-RFLP	ApaI (0.0), TaqI (0.4)
Nikseresht et al, 2015(23)	BsmI	Shiraz	267	292	NR	203/292	PCR-RFLP	BsmI (0.8)

*BsmI (rs1544410 G>A), ApaI (rs7975232 A>C), TaqI (rs731236 T>C), FokI (rs2228570 C>T).

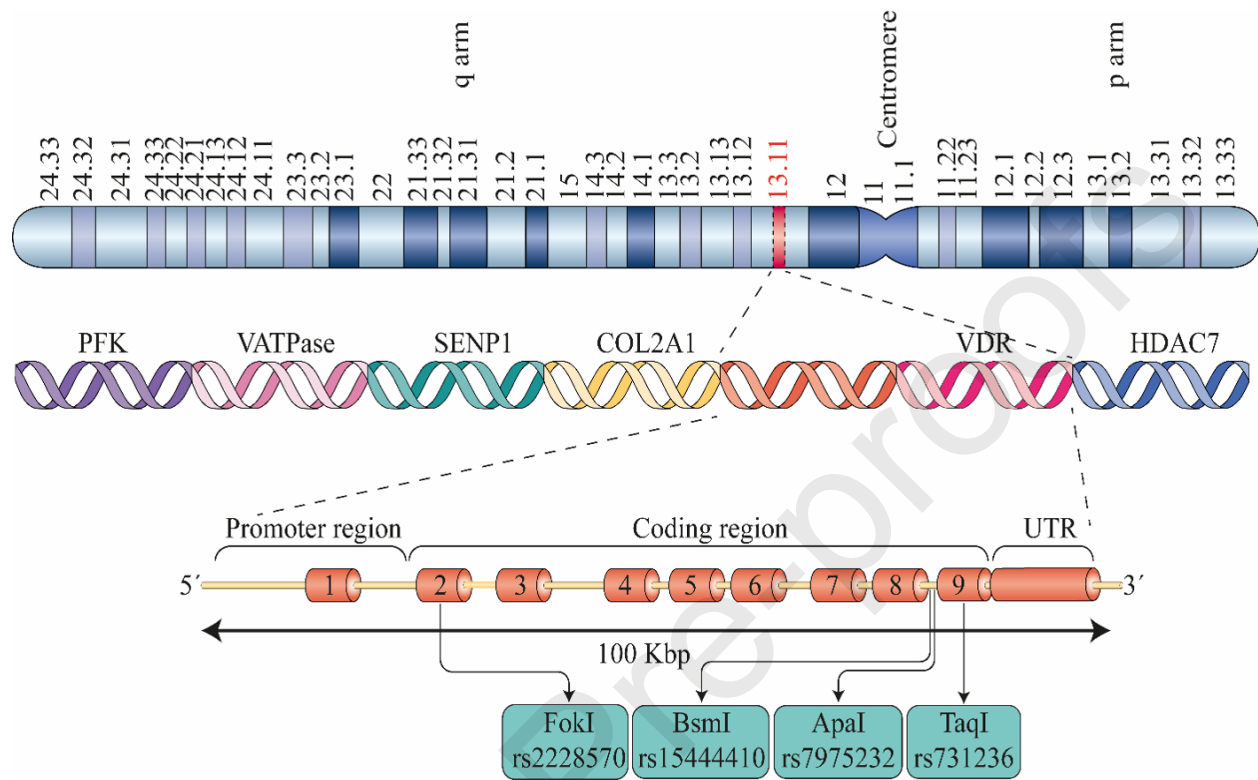
**PCR; Polymerase chain reaction, RFLP; restriction fragment length polymorphism, HWE; Hardy–Weinberg equilibrium test.

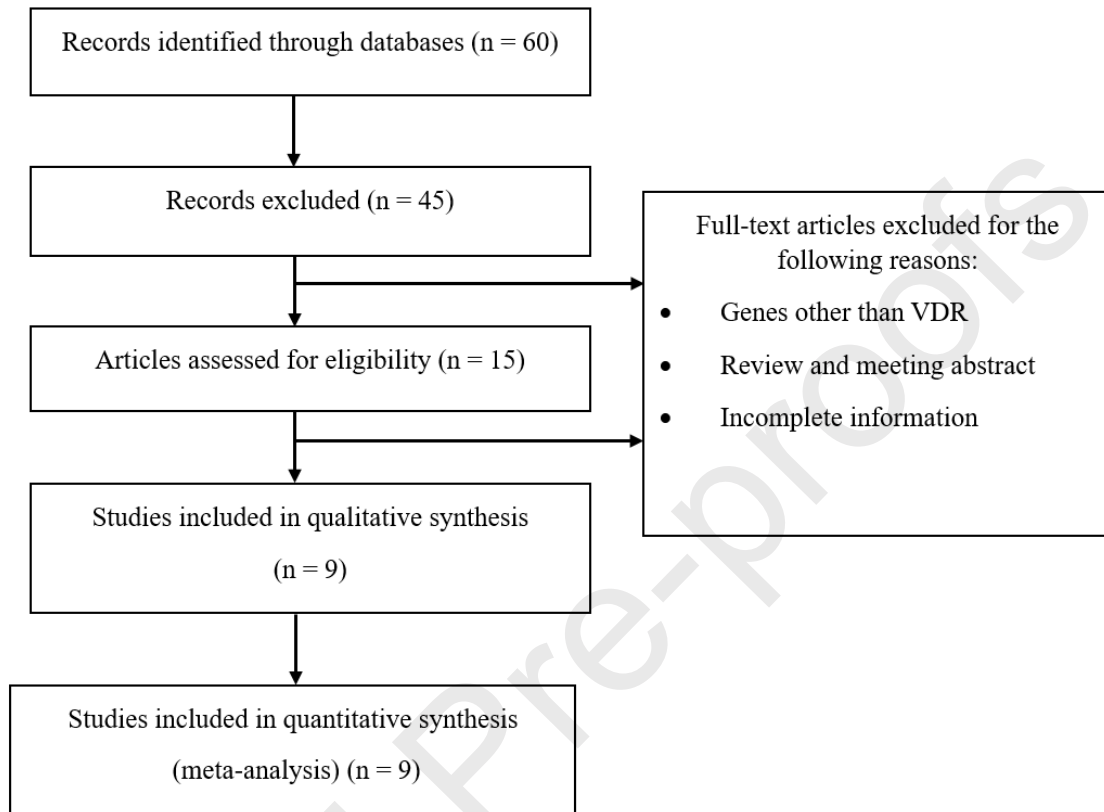
Table 3. Results obtained by meta-analysis, heterogeneity, and sensitivity analysis.

Comparisons		Random effects model		Heterogeneity			Eggers regression intercept	Sensitivity analysis
		OR (95%CI)	P-value	Q-value	P-value	I-squared		
<i>FokI</i>								
F vs f	Allele	0.84(0.56-1.27)	0.4	18.34	0.00	78	0.82	0.95(0.61- 1.47)
FF vs ff	Homozygote	0.76 (0.28-2.03)	0.5	11.8	0.01	66.3	0.94	0.95(0.39-2.34)
FF+Ff vs ff	Dominant	0.82 (0.35-1.9)	0.6	9.2	0.05	56.64	0.85	0.96(0.47-1.96)
FFvs Ff+ff	Recessive	0.84 (0.5, 1.3)	0.4	13.99	0.00	71.42	0.58	0.92(0.55-1.56)
<i>BsmI</i>								
B vs b	Allele	0.81(0.56 - 1.18)	0.2	22.56	0.00	82.27	0.8	0.69(0.51-0.94)
BB vs bb	Homozygote	0.63 (0.29 – 1.3)	0.2	17.94	0.00	77.7	0.98	0.46(0.25-0.86)
BB+Bb vs bb	Dominant	0.77 (1.38 – 0.8)	0.3	13.01	0.01	69.26	0.77	0.64(0.37-1.08)
BB vs Bb+bb	Recessive	0.7 (0.4 – 1.2)	0.2	20.9	0.00	80.87	0.73	0.56(0.39-0.8)
<i>TaqI</i>								
T vs t	Allele	0.52 (0.23- 1.19)	0.12	125.5	0.00	96.01	0.72	0.81(0.54-1.2)
TT vs tt	Homozygote	0.28 (0.08- 0.94)	0.04	46	0.00	89	0.71	0.54(0.26-0.97)
TT+Tt vs tt	Dominant	0.44(0.17 – 1.17)	0.1	38.6	0.00	87	0.4	0.73(0.39-1.36)
TT vs Tt+tt	Recessive	0.49(0.17-1.48)	0.1	84.7	0.00	94	0.7	0.86(0.44-1.6)
<i>ApaI</i>								
A vs a	Allele	0.54 (0.37 – 0.79)	0.00	26.17	0.00	80.89	0.44	NP
AA vs aa	Homozygote	0.28 (0.14 – 0.59)	0.00	12.3	0.03	59.36	0.88	NP
AA+Aa vs aa	Dominant	0.56 (0.3 – 0.79)	0.01	8.7	0.12	42.77	0.92	NP
AA vs Aa+aa	Recessive	0.35(0.18 – 0.66)	0.00	31.5	0.00	84.14	0.55	NP

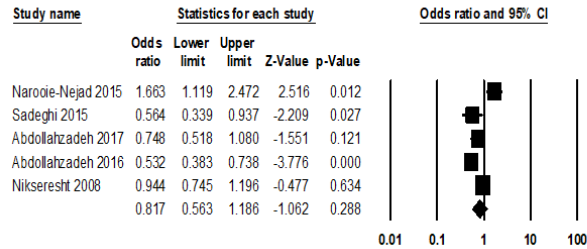
NP: Not performed

Sensitivity analysis was performed by omitting the study of Narooie-Nejad et al, as the outlier study which could drastically change the results of data analysis.

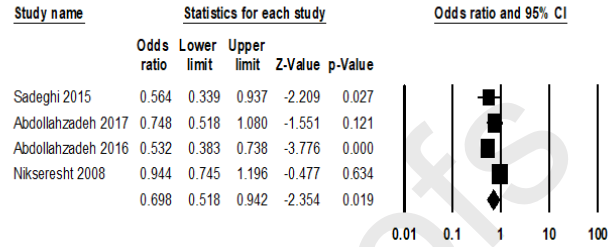




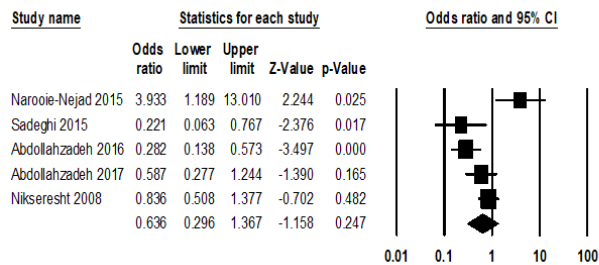
BsmI B vs. b



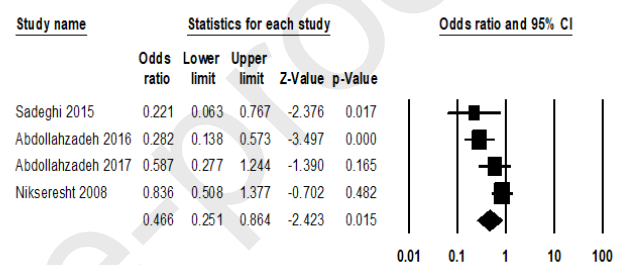
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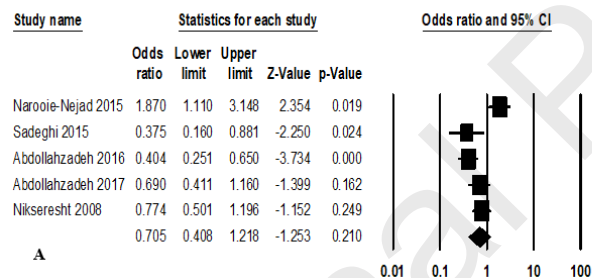
BsmI BB vs. bb



BsmI BB vs. bb

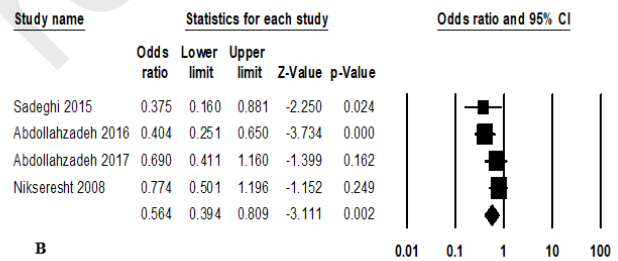


BsmI BB vs. Bb+bb



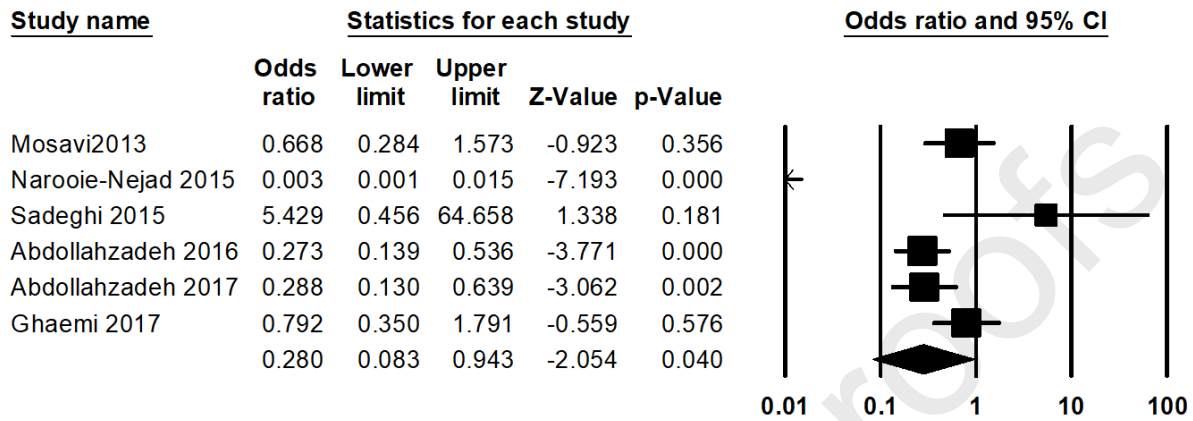
A

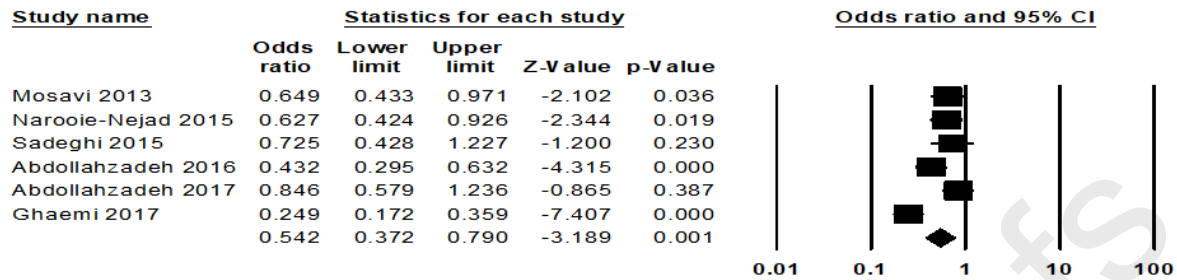
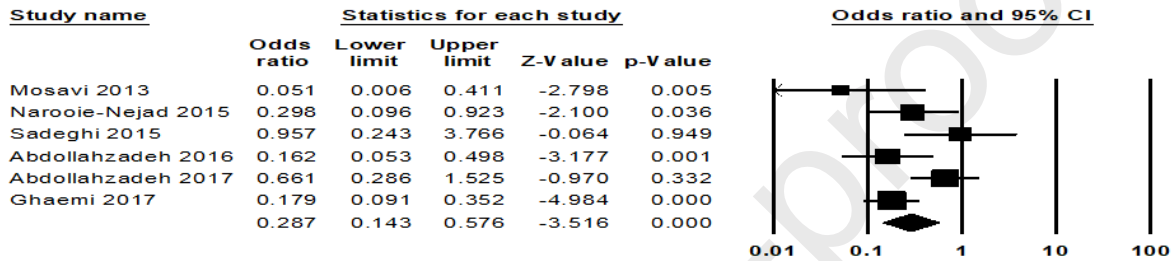
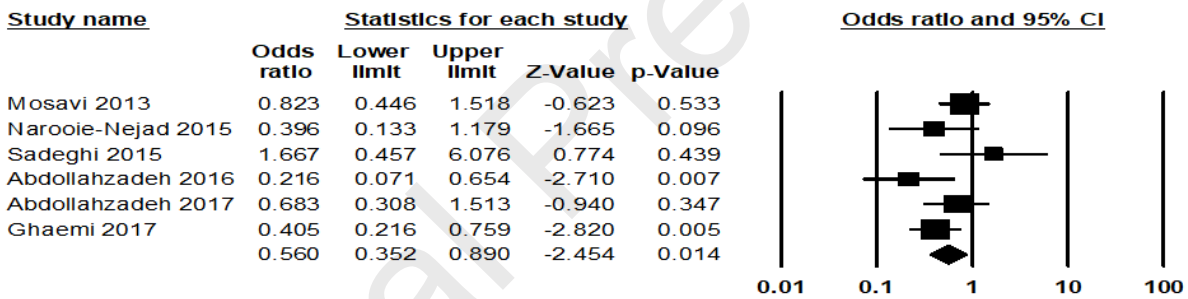
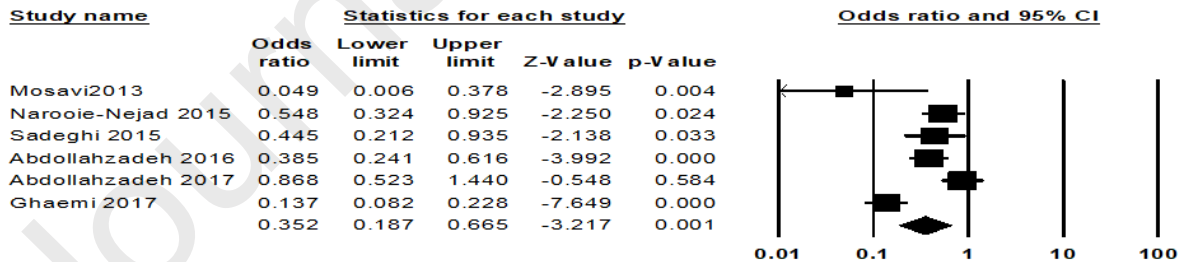
BsmI BB vs. Bb+bb



B

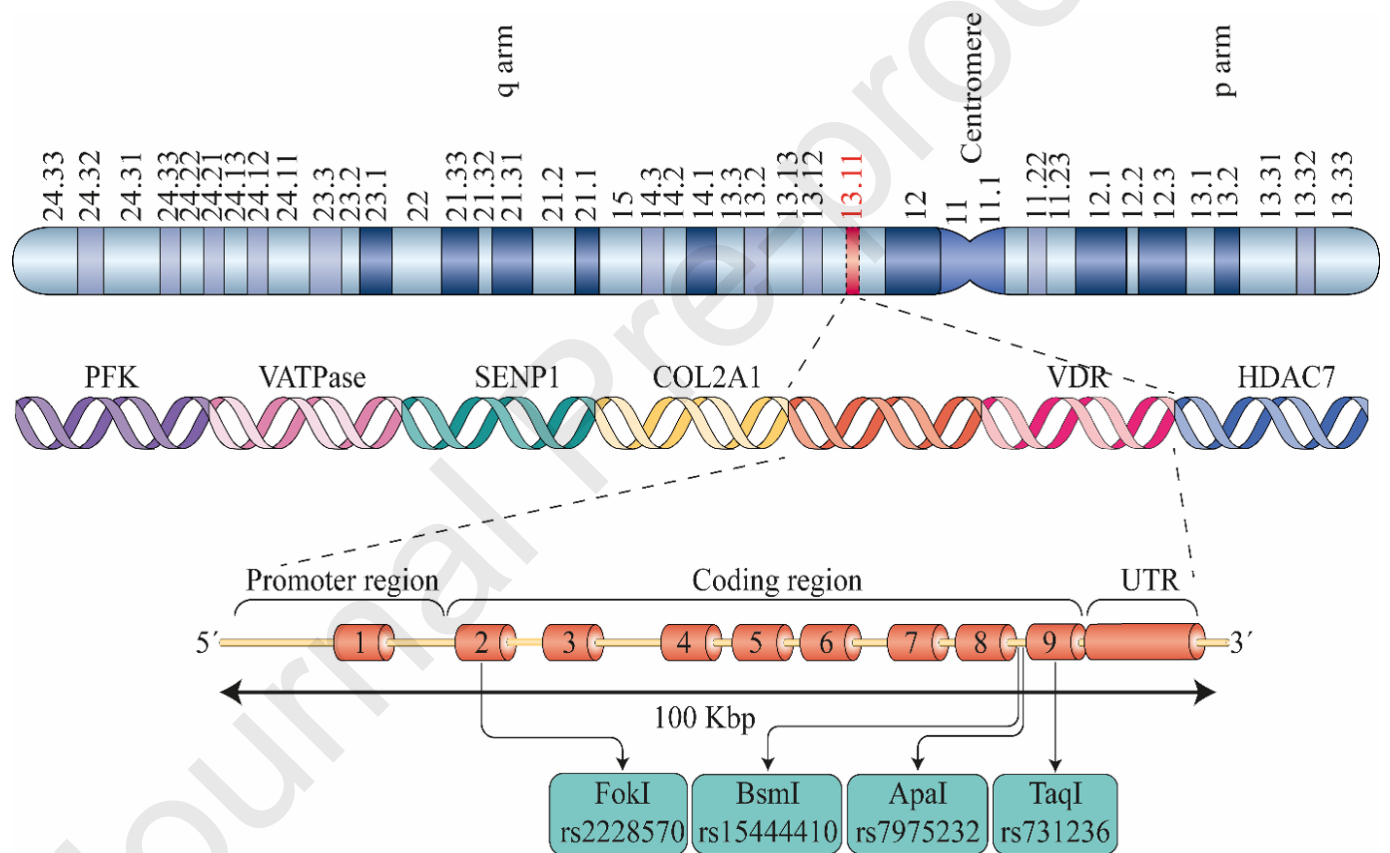
Taqi tt vs TT



Apal A vs. a**Apal AA vs. aa****Apal AA + Aa vs. aa****Apal AA vs. Aa + aa**

Vitamin D receptor genetic polymorphisms and the risk of multiple sclerosis: A systematic review and meta-analysis

Asadollah Mohammadi, Asaad Azarnezhad, Hashem Khanbabaei, Esmael Izadpanah, Rasoul Abdollahzadeh, George E. Barreto, Amirhossein Sahebkar



We analyzed the vitamin D polymorphisms on the susceptibility to multiple sclerosis

ApaI was the only VDR variant which showed statistically significant relation in allelic

The TaqI polymorphism showed significant negative association with MS only in homozygote model