Association between Vitamin D receptor gene polymorphism and the risk of Multiple Sclerosis: Systematic review and meta-analysis

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Abstract

Background The association between the vitamin D receptor (VDR) gene polymorphism and the risk of Multiple sclerosis (MS) has been evaluated in several studies. However, the findings were inconsistent and inconclusive.

Methods All relevant studies reporting the association between the FokI (rs2228570) or/and TaqI (rs731236) or/and BsmI (rs1544410) or/and Apal (rs7975232) polymorphisms of the VDR and susceptibility to multiple sclerosis published up to September 2019 were identified by comprehensive systematic database search in web of science, Scopus, and PubMed.

Results A total of 30 case-control studies were included in this meta-analysis. The overall results suggested a significant association between TaqI gene polymorphism and MS risk under heterozygote contrast (OR = 1.27, 95%CI = 1.01-1.59, REM). Moreover, the pooled results of subgroup analysis decline presence of significant association under all defined genotype model. In subgroup analysis, BsmI gene polymorphism was associated with increased risk of MS under the recessive model in Asian population. In other hand, Apal gene polymorphism was associated with decreased risk of MS under recessive and homozygote contrast (aa vs AA) models in Asian population.

Conclusions This meta-analysis suggested a significant association between TaqI gene polymorphism and MS susceptibility. Furthermore, BsmI gene polymorphism was associated with an increased risk of MS in Asian population. In contrast, Apal gene polymorphism was associated with a decreased risk of MS in Asian population. Future large scale studies on gene-environment and gene- gene interactions are required to estimate related risk factors and assist early diagnosis of patients at high risk for MS.

1. Background
Multiple sclerosis (MS) is a chronic, demyelinating disorder of the brain and spinal cord that mainly develops in young individuals [1]. Autoantibodies and reactive T cells against the myelin are recognized as implicit pathogenic function in the tissue damage and development of CNS inflammation [2]. The main etiology of the disease remains to be elusive, but it has been demonstrated genetic and environmental factors play important roles in susceptibility to the disease [3]. Vitamin D is a group of fat-soluble secosteroids that have functional and regulatory effects in the body. Vitamin D has been implicated in the development of the brain and spinal cord. Alternatively, the active form of vitamin D, 1,25-dihydroxyvitamin D has a wide anti-inflammatory and immunomodulatory properties [4, 5]. Vitamin D exerts its immunomodulatory functions within the immune system by decreasing the presentation of major histocompatibility complex II (MHC-II) on T cells and monocytes. Vitamin D also reduces T cell proliferation and pro-inflammatory cytokine release [6]. The lower serum vitamin D levels compared to healthy controls have been reported in MS patients. Moreover, Vitamin D has positive effects on regulating MS risk development [7, 8]. The effects of Vitamin D on the immune system are exerted by binding to the nuclear vitamin D receptor (VDR) [9]. Particular variants of the VDR gene are related to changes in vitamin D metabolism and function [10]. Taken together, these results suggested that VDR may play an important role in the pathogenesis of MS.

The human VDR gene is located on chromosome 12q12-14 and series of restriction fragment length polymorphisms (RFLP) in the human VDR gene have been reported, containing BsmI (rs1544410), Apal (rs7975232), FokI (rs2228570), TaqI (rs731236) restriction sites [11]. Apal, BsmI, and TaqI are localized near the 3’ end of the VDR gene in the intron between exons 8 and 9, and shown to be in strong linkage disequilibrium (LD) [12]. The 3’UTR of the VDR gene involved in the regulation of gene expression by regulation of mRNA stability and expression level [13]; Polymorphism FokI is located at
the translation starting codon [14].

The association between MS and VDR single nucleotide polymorphisms (SNPs) has been investigated in several studies. Particularly, studies have evaluated associations between the most common SNPs of the VDR gene (the TaqI, ApaI, FokI, and BsmI polymorphisms) and MS. While studies in Australia [15], Kuwait [16], and Southeast Iran [17], reported a significant association between Taq I, Apa I, and Fok I gene polymorphisms and MS, other studies in Tunisia [18], Slovakia [19], and Greece [20] failed to find such an association. The reasons for this disparity may be small sample sizes, low statistical power, clinical heterogeneity, or a combination of the above factors. To offset these limitations, this meta-analysis was performed to investigate whether VDR gene polymorphisms contribute to MS or not. Up to now, there are four meta-analysis studies, which investigated the association between VDR polymorphisms and MS. The two studies performed by Huang et al. [21], and Garcia-Martin et al. [22] have indicated that there was no association between VDR gene polymorphism and MS risk. Nevertheless, the other meta-analysis by Zhang et al. [23], and Tizaoui et al. [24] demonstrated a significant association between ApaI and FokI VDR gene polymorphisms and MS susceptibility. Since the publication of the last meta-analysis, seven new studies have been founded in electronic databases. Therefore, we set out a meta-analysis of all eligible published case-control studies to obtain an exact evaluation of the association between MS and VDR gene polymorphisms.

2. Methods

The current meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [25].

2.1 Literature review

All relevant studies reporting the association between the FokI (rs2228570) or/and TaqI (rs731236) or/and BsmI (rs1544410) or/and ApaI (rs7975232) polymorphisms of the
Vitamin D receptor and susceptibility to multiple sclerosis published up to September 2019 were identified by comprehensive systematic electronic database search in web of science, Scopus, and PubMed. The following search terms were applied: (VDR” OR “vitamin D receptor”) AND (“multiple sclerosis” OR “MS”) AND (“polymorphisms” OR “single nucleotide” OR “polymorphism” OR “SNP” OR “variation” OR “mutation”). As a complementary approach, in order to detect additional relevant studies, manual references evaluation of the included studies was performed. In this meta-analysis, the strategy of the search was restricted solely to the English-language publications and human population.

2.2 Study selection

Two reviewers independently assessed titles and abstracts of all studies retrieved in the initial search. Articles not following the eligibility criteria were excluded by applying a hierarchical approach based on study design. The full-text examination was applied if we could not decide include or exclude based on title and abstract. In particular conditions, if an author has published more than one study by the same case series, the most recently published study was included. Any disagreements were discussed and resolved by consensus.

2.3 Eligibility criteria

Studies considered eligible if met the following criteria: 1) all eligible case-control studies that evaluate the relationship between the VDR SNPs and the risk of MS as the main outcome; 2) sufficient data are available to extract or calculate odds ratios (ORs) and 95% confidence intervals; 3) contained genotype or allele distributions of case and healthy individuals for VDR gene polymorphism in the studies. The exclusion criteria were as
follows: 1) studies which genotype or allelic frequency could not be extracted; 2) letter, case report, review, comment, book chapter, and abstract; 3) duplicated reports and studies with repetitive subjects. The application of these criteria recognized 30 case-control studies eligible for the meta-analysis.

2.4 Data extraction

Two reviewers independently extracted all data according to standardized extraction form for the following data: the author's name, journal and year of publication, country of origin, ethnicity, number of case and control for each gender separately, mean or range of age, genotyping method, total sample size of cases and controls, and the number of cases and controls for each genotype. For quality assessment of the included publications, the Newcastle-Ottawa Scale (NOS) was applied[26]. Studies with scores 0-3, 4-6 or 7-9 were of low, moderate or high-quality, respectively.

2.5 Statistical analysis

Deviation from Hardy-Weinberg equilibrium (HWE) for distribution of the allele frequencies was analyzed using Chi-Square test in the control group. Sensitivity analysis was conducted to evaluate the stability of the results by removing the studies not in HWE. The strength of association between the FokI and/or TaqI and/or BsmI and/or ApaI polymorphisms of the Vitamin D Receptor and susceptibility to multiple sclerosis was calculated by OR and their 95 % CI. Defined model for FokI, TaqI, BsmI, ApaI were: FokI: dominant model (ff+Ff vs FF), recessive model (ff vs Ff+FF), allelic model (f vs F), homozygote (ff vs FF), and heterozygote (Ff vs FF); TaqI: dominant model (tt+Tt vs TT), recessive model (tt vs Tt+TT), allelic model (t vs T), homozygote (tt vs TT), and
heterozygote (Tt vs TT):\textit{BsmI}; dominant model (bb+Bb vs BB), recessive model (bb vs Bb+BB), allelic model (b vs B), homozygote (bb vs BB), and heterozygote (Bb vs BB):\textit{ApaI}; dominant model (aa+Aa vs AA), recessive model (aa vs Aa+AA), allelic model (a vs A), homozygote (aa vs AA), and heterozygote (Aa vs AA).. For each genetic contrast, subgroup analysis was applied to evaluate ethnicity effects. In consideration of the possible heterogeneity (between-study variability) across included studies chi-square based Q-test was used[27]. Additionally, to show heterogeneity quantitatively, the other index ($I^2$) calculated. There was significant heterogeneity if an $I^2$ values exceeded 50% or the Q statistic had a p-value less than 0.1. In the presence of significant heterogeneity, the random-effects model (DerSimonian–Laird approach) was performed. Otherwise, the fixed-effects model (Mantel–Haenszel approach) was performed for combination of data[28, 29]. Visual inspection of asymmetry in funnel plots asymmetry, Begg's and Egger's tests were conducted to evaluate publication bias (p value< 0.05 considered statistically significant)[30, 31]. The data analyses were carried out using STATA (version 14.0; Stata Corporation, College Station, TX) and SPSS (version 23.0; SPSS, Inc. Chicago, IL).

3. Results

3.1 Study characteristics

The primary search yielded a total of 636 publications from web of science, Scopus, and PubMed databases. After the removal of duplicates and title abstract review, only 76 studies remained for full-text examination. Eventually, 30 studies have met inclusion criteria and included for quantitative synthesis. The search workflow is shown in Figure 1. Study characteristics are summarized in Table 1. Among 30 eligible studies, 16 Studies investigate \textit{FokI} SNP, 23 Studies \textit{TaqI} SNP, 16 studies \textit{BsmI} SNP and 20 Studies \textit{ApaI} SNP.
The studies were published between 1999 and 2019. Taq-Man and PCR-RFLP genotyping method were used by most studies.

3.2 Quantitative synthesis

The distributions of Fokl, TaqI, BsmI and Apal genotypes of the included studies are shown in Table 2. FF for Fokl SNP, TT for TaqI SNP, BB for BsmI SNP and AA for Apal were used as the reference category. The heterogeneities in the comparisons ($I^2 \leq 50\%$, fixed-effects models; $I^2 > 50\%$, random-effects models) ascertain the application of Fixed-effects or random-effects models.

3.3 Meta-analysis for Fokl (rs2228570) polymorphism and MS

Overall 16 case-control studies with 3057 cases and 2852 controls were analyzed for assessment of Fokl gene polymorphism and MS risk. Of 16 studies, 9 studies carried out in Europe continent [19, 22, 32-38] 4 studies in Asia continent [16, 17, 39, 40] One study in America continent [41] and finally 2 studies in Australia [15, 42] (Table 1). No significant association was observed between Fokl gene polymorphism and MS risk across all genetic models. Additionally, subgroup analysis based on geographical location was performed which the pooled results rejected any association between Fokl gene polymorphism and risk of MS in European and Asian population. Since there was only one study for American, and two studies for Australian populations, these studies were excluded from the subgroup analysis. The results of pooled ORs, heterogeneity tests and publication bias tests for different analysis models are shown in Table 3. (Supplementary file Figure 1 and 2).

3.4 Meta-analysis for TaqI (rs731236) polymorphism and MS
There were 23 Case-control studies with 3758 cases and 3992 controls concerning TaqI gene polymorphism and MS risk. Among them, 13 studies were conducted in European countries [19, 20, 22, 32, 34, 35, 37, 38, 43-47] 5 studies in Asian countries [16, 39, 40, 48, 49] 2 studies in each Australian [15, 42] and American [41, 50] countries and one study in Tunisia [18]. The TaqI gene polymorphism was demonstrated to associate with MS risk under heterozygote contrast (OR = 1.27, 95%CI = 1.01–1.59, random effect) (Figure 2) whilst, No significant association was detected across other genotype models (Table3). In addition, the pooled results of subgroup analysis decline presence of significant association under all defined genetic model (Supplementary file Figure 3 and 4). The group with less than three studies were removed from the subgroup analysis. The results of pooled ORs, heterogeneity tests and publication bias tests for different analysis models are shown in Table 3.

3.5 Meta-analysis for BsmI (rs1544410) polymorphism and MS

16 case-control studies with 1793 cases and 1815 controls subjects examined the association between BsmI polymorphism and MS risk. Among 16 studies, Six studies were performed in Europe [19, 20, 34, 38, 46, 47], eight studies in Asia [16, 39, 48, 49, 51-53] and only two studies in America continent [41, 50]. The pooled results demonstrate no significant association between BsmI polymorphism and MS risk under all genotype model but subgroup analysis revealed that BsmI gene polymorphism across recessive model increase risk of Multiple sclerosis in Asian population (OR = 1.78 , 95%CI = 1.01–2.93, random effect) compared to European population (OR = 0.84, 95%CI = 0.66–1.06, random effect) Figure 3 . The results of pooled ORs, heterogeneity tests and publication bias tests for different analysis models are shown in (Table 3) (Supplementary file Figure 5 and
3.6 Meta-analysis for Apa1 (rs7975232) polymorphism and MS

20 Case-control studies with 2306 cases and 2669 controls were identified eligible for quantitative synthesis of the association between Apa1 polymorphism and MS risk. Overall, 9 studies were conducted in Europe [19, 34, 35, 37, 38, 43, 44, 46, 47], 8 studies in Asia [16, 39, 40, 48, 49, 52-54] and one study in Africa [18], America [41] and Australia [15], respectively. There was no evidence of association between Apa1 gene polymorphism and MS risk in the pooled results. However, subgroup analysis detected significant association between presence of Apa1 SNP and risk of MS under Recessive model (OR = 0.61, 95%CI = 0.42–0.89, random effect) and homozygote contrast model (OR = 0.52, 95%CI = 0.32–0.86, random effect) in Asian population in comparison with European population (OR = 1.01, 95%CI = 0.78–1.33, Recessive) and (OR = 1.11, 95%CI = 0.76–1.63, homozygote contrast) Figure 3. The results of pooled ORs, heterogeneity tests and publication bias tests for different analysis models are shown in Table 3 (Supplementary file Figure 7 and 8).

3.7 Evaluation of heterogeneity

Significant heterogeneity existed for FokI, TaqI, BsmI and Apa1 gene polymorphism in all of the genetic models. Furthermore, in subgroup analysis, there was significant heterogeneity for studies were carried out in Asian and European countries (Table 3).

3.8 Publication bias

Publication bias was estimated by using funnel plot, Begg's and Egger's tests. No evidence of Publication bias was seen for all four SNP and subgroup analysis under all genetic
models. Additionally, the shape of the funnel plot appeared to be symmetrical which demonstrated that there was no significant publication bias (Figure 4).

**3.9 Sensitivity analysis**

Sensitivity analysis was conducted after sequentially removing each eligible study. This approach is to enumerate as an inevitable step for analyzing multiple criteria. The significance of the pooled ORs was not affected by any single study in the dominant model for *FokI, TaqI, BsmI* and *ApaI* SNPs (Figure 5), indicating that our results were statistically robust.

**4. Discussion**

The *VDR* gene, as a pleiotropic gene, has been associated with several diseases. In the previous studies, the relationship between *VDR* gene SNPs and autoimmune disorders was evaluated in several meta-analyses. The study of Feng *et al.* [55] described that *TaqI* or *BsmI* gene polymorphism in the *VDR* gene was significantly connected with autoimmune thyroid diseases. Mao *et al.* [56] represented that the *BsmI* B allele may act as a risk factor for the onset of systemic lupus erythematosus (SLE) among Asians and overall populations and also the *FokI* FF genotype act as a potential risk factor for SLE predisposition in Asians. Furthermore, Tizaoui *et al.* [57] showed that the *VDR TaqI* and *FokI* gene polymorphisms may increase the risk of rheumatoid arthritis (RA) in European population. And finally, Wang *et al.* [58] reported that the *ApaI* and *BsmI* gene polymorphisms were related with elevated susceptibility to type 1 diabetes (T1D) in Asian population. Collectively, it could be assumed that *VDR* gene polymorphisms act as a potential risk factor in the development or progression of autoimmune disorders. Although four meta-analyses have been conducted over the course of past 10 years to
evaluate the association between the VDR gene polymorphisms and MS, these findings were inconclusive due to the variations of the literature and selected databases. Hence, for resolving these inconsistencies, and to decrease the heterogeneity and the probability of random errors, we set out an updated meta-analysis. In this meta-analysis, 30 studies met the inclusion criteria and included quantitative synthesis. No evidence of publication bias for all four SNP in subgroup analysis and overall populations under five genetic models was observed. Regarding the essential role of genetic factors in the pathogenesis of MS, we categorized our results according to ethnicity. Our meta-analysis revealed that BsmI, ApaI, and TaqI VDR gene polymorphisms may play a significant role in the pathogenesis of MS in overall and Asian population, respectively. The results of this study indicated that TaqI polymorphism was associated with MS susceptibility under heterozygote contrast in the overall population. Moreover, BsmI gene polymorphism was associated with an increased risk of MS under a recessive model in Asian population. In other hand, ApaI gene polymorphism was associated with decreased risk of MS under recessive and aa vs. AA models in Asian population. These findings are inconsistent with the results of Huang et al.. [21] and Garcia-Martin et al.. [22] studies. In the study of Huang et al, they included 11 case-control studies with 2599 cases and 2816 controls for assessing the association between VDR gene polymorphisms and the MS susceptibility, but no significant association was found. Another study by Garcia-Martin et al.. that analyzed ten studies with 2944 MS patients and 3166 healthy subjects reported that TaqI and FokI gene polymorphisms are not associated with the MS risk. In accordance with our study, the study of Zhang et al.. [23] and Tizaoui et al.. [24] showed a significant association between VDR gene polymorphisms and MS susceptibility. However, there are some obvious differences in the findings of these studies in comparison with our study. Meta-analysis of Tizaoui et al.. reported an association of the FF FokI and AA ApaI genotypes with an
elevated susceptibility to MS in a total of 3300 MS patients and 3194 healthy subjects from 13 case-control studies. In contrast, our analysis consists of 20 case-control studies showed that Apal gene polymorphism was associated with decreased risk of MS in Asian population. In addition, the study of Zhang et al. reported that the A allele was related to the onset of disease in Asian population. Nevertheless, the sensitivity analysis removing the studies not in HWE, rejected any association between the A allele and risk of MS, which was dissimilar from the results of the overall analysis. Moreover, they failed to find any association between TaqI, BsmI, and Apal gene polymorphisms and MS susceptibility in overall populations, Asians, and Caucasians. The main reasons that VDR gene polymorphism plays a diverse function across different studies or in different ethnic populations may be due to the following hints. Firstly, in many cases, controls in included studies deviated from HWE. Secondly, the differences in the ethnic contextual characteristics of the patients may be an important factor for these variations. Thirdly, VDR gene SNPs were suggested to be related with the basal levels of 1,25(OH)2D3 and vitamin D structure and function [59], which in turn could influence MS predisposition. Finally, MS is regarded to be a polygenic disorder, and therefore it is expected that various gene loci have interacted in the pathogenesis of MS.

Permutations and combinations of common variants account as predisposition factors in the etiology of several complex diseases. Variations of DNA sequences such as single nucleotide polymorphisms exert modest biological impacts [9]. Three polymorphisms of VDR including TaqI, Apal, and BsmI do not influence the structure of VDR protein. Their effect may be associated with alterations in translation efficiency and/or stability of the RNA. On the other hand, the FokI polymorphism has related to changes in both transcriptional activity and VDR protein structure [60]. The wild-type short transcript of FokI is related to the elevated transcriptional activity [60]. One potential exception is the
differential effect of the \textit{FokI} gen polymorphism on the immune system \cite{14}. Our data suggested that the \textit{ApaI} gene polymorphism has a significant functional effect on MS. Furthermore, the \textit{TaqI} gene polymorphism was associated with MS risk. However, there are some other factors have not examined in the current meta-analysis that might affect the \textit{TaqI} expression. At this point, the expression and function of VDR in transactivating target genes are indicated by environment, genetics, and ethnicity due to its complex interactions \cite{61}. Thus, three essential environmental risk factors for MS have been determined: vitamin D insufficiency, cigarette smoking, and Epstein–Barr virus infection \cite{62, 63}. Moreover, sun exposure interacts with VDR gene functional variants in childhood to affect MS predisposition.

Some limitations of this meta-analysis should be considered. First, inaccessibility to the original data of the included studies restricted our further assessment of potential interactions, since the interactions between and even various polymorphic regions of the same gene may affect the risk. Moreover, this study was solely focused on the articles published in the English language. We detected significant heterogeneity in all of the genetic models, which could be derived by various factors such as variations in ethnicities. In the current study, ethnicities were Caucasians from Asians, Caucasians from Europe and Australia. Additionally, heterogeneity may be created by the publication year of included studies, which extended between 1999 to 2018. There are several other possible reasons which may be regarded as a source of heterogeneity. Firstly, the criteria for MS diagnosis are inconsistent between studies. While some of them employed Poser's criteria, other studies used McDonald's criteria for MS diagnosis. Secondly, gender may act as a potential source for heterogeneity. Although both male and female subjects were enrolled in most studies, two studies were not sex-matched and one study only included women subjects \cite{33, 41, 43}. Thirdly, genotyping methods were not consistent. While half
of the included studies used RFLP-PCR approximately the other half employed Taqman assay and one study used PCR-SPP. Fourthly, geographical and ethnic factors may also participate in heterogeneity, because studies with the same ethnic source were accompanied in various geographical regions.

The results from the studies examined in this meta-analysis should be interpreted with cautious for some reasons. Our findings suggest that to afford accurate estimates of the relation between VDR gene polymorphisms and MS risk, several factors should be regarded. Although there are many functional VDR gene polymorphisms in the promoter region of the VDR gene, only four single nucleotide polymorphisms in the VDR gene have been evaluated. The interaction of the HLA genes with the VDR gene has been demonstrated to be important in MS [64, 65]. Remarkably, various environmental factors may interact with VDR gene SNPs to alter MS susceptibility. The current meta-analysis could not assess all interactions between VDR gene polymorphisms and study characteristics because of insufficient data from the original publications.

Conclusion

Taken all together, the current meta-analysis affords a comprehensive investigation of the available information for the association between the VDR gene polymorphisms and MS susceptibility. This meta-analysis of 30 case-control studies revealed a significant association between TaqI gene polymorphism and MS susceptibility. In subgroup analysis, BsmI gene polymorphism was associated with increased risk of MS in Asian population. On the other hand, ApaI gene polymorphism was associated with decreased risk of MS in Asian population. However, neither in the overall population nor in subgroup analysis, the significant association between FokI gene polymorphism and MS susceptibility was found.
Future large scale studies on gene–environment and gene–gene interactions are required to estimate related risk factors and assist early diagnosis of patients at high risk for MS.

Abbreviations

VDR: Vitamin D receptor polymorphism
MS: Multiple sclerosis
MHC-II: major histocompatibility complex II
CNS: central nervous system
RFLP: restriction fragment length polymorphisms
LD: linkage disequilibrium
UTR: untranslated region
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
SNP: Single Nucleotide Polymorphisms
OR: Odd Ratio
CI: Confidence Interval
SLE: systemic lupus erythematosus
T1D: type 1 diabetes
PCR-SPP: Polymerase chain reaction - Sequence Specific
HLA: human leukocyte antigen

Declarations

Ethics approval and consent to participate

This study has been approved by ethic committee of Tehran University of Medical Sciences.

Consent for publication

Not applicable.
Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Conceived and designed the experiments: DI and BR. Extracted data: DI and MA. Performed the data analysis: BR. Writing original draft: RR and BR. All authors read and approved the final manuscript.

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Tables

**Table 1:** Characteristics of studies included in Meta-analysis of overall MS.

| Study author     | Year | Country   | Ethnicity  | Sex cases/controls |
|------------------|------|-----------|------------|--------------------|
| FokI (rs2228570) |      |           |            |                    |
| Partridge et al. | 2004 | UK        | European   | M=NR F=NR          |
| Tajouri et al.   | 2005 | Australia | Australian | M=NR F=NR          |
| Smolders et al.  | 2009 | Netherlands | European | M=62/142 F=150/147 |
| Dickinson et al. | 2009 | Australia | Australian | M=NR               |
| Study                        | Year | Country    | Ethnicity | M (Range) | F (Range) |
|------------------------------|------|------------|-----------|-----------|-----------|
| Simon et al.                 | 2010 | USA        | American  | M=NR      | F=NR      |
| Garcia-Martin et al.         | 2013 | Spain      | European  | M=94/98   | F=209/212 |
| Al-Temaimi et al.            | 2015 | Kuwait     | Asian     | M=17/19   | F=33/31   |
| Narooie-Nejad et al.         | 2015 | Iran       | Asian     | M=25/28   | F=88/94   |
| Cierny et al.                | 2015 | Slovakia   | European  | M=66/74   | F=204/229 |
| Luisa Agnello et al.         | 2016 | Italy      | European  | M=24/30   | F=80/42   |
| Abdollahzadeh et al.         | 2016 | Iran       | Asian     | M=40/38   | F=120/112 |
| Yucel et al.                 | 2017 | Turkey     | European  | M=NR      | F=NR      |
| Bettencourt et al.           | 2017 | Portugal   | European  | M=185/198 | F=348/248 |
| Kamisli et al.               | 2018 | Turkey     | European  | M=46/58   | F=121/88  |
| Sadeghi et al.               | 2018 | Iran       | Asian     | M=17/11   | F=63/39   |
| Křenek et al.                | 2018 | Czech Republic | European  | M=80/49   | F=216/86  |
| TaqI (rs731236)              |      |            |           |           |           |
| Partridge et al.             | 2004 | UK         | European  | M=NR      | F=NR      |
| Tajouri et al.               | 2005 | Australia  | Australian | M=NR    | F=NR      |
| Smolders et al.              | 2009 | Netherland | European  | M=62/142  | F=150/147 |
| Dickinson et al.             | 2009 | Australia  | Australian | M=NR    | F=NR      |
| Simon et al.                 | 2010 | USA        | American  | M=NR      | F=NR      |
| Sioka et al.                 | 2011 | Greece     | European  | M=23/23   | F=46/58   |
| Agliardi et al.              | 2011 | Italy      | European  | M=NR      | F=NR      |
| Irizar et al.                | 2012 | Spain      | European  | M=NR      | F=NR      |
| Garcia-Martin et al.         | 2013 | Spain      | European  | M=94/98   | F=209/212 |
| Selma et al.                 | 2015 | Tunisia    | African   | M=22/47   | F=38/67   |
| Narooie-Nejad et al.         | 2015 | Iran       | Asian     | M=25/28   | F=88/94   |
| Al-Temaimi et al.            | 2015 | Kuwait     | Asian     | M=17/19   | F=33/31   |
| Yamout et al.                | 2016 | Lebanon    | Asian     | M=NR      | F=NR      |
| Cierny et al.                | 2016 | Slovakia   | European  | M=66/74   | F=204/229 |
| Luisa Agnello et al.         | 2016 | Italy      | European  | M=24/30   | F=80/42   |
| Terzi et al.                 | 2016 | Turkey     | European  | M=NR      | F=NR      |
| Abdollahzadeh et al.         | 2016 | Iran       | Asian     | M=40/38   | F=120/112 |
| Yucel et al.                 | 2017 | Turkey     | European  | M=NR      | F=NR      |

| TaqI (rs731236)              |      |            |           |           |           |
|------------------------------|------|------------|-----------|-----------|-----------|
| Partridge et al.             | 2004 | UK         | European  | M=NR      | F=NR      |
| Tajouri et al.               | 2005 | Australia  | Australian | M=NR    | F=NR      |
| Smolders et al.              | 2009 | Netherland | European  | M=62/142  | F=150/147 |
| Dickinson et al.             | 2009 | Australia  | Australian | M=NR    | F=NR      |
| Simon et al.                 | 2010 | USA        | American  | M=NR      | F=NR      |
| Sioka et al.                 | 2011 | Greece     | European  | M=23/23   | F=46/58   |
| Agliardi et al.              | 2011 | Italy      | European  | M=NR      | F=NR      |
| Irizar et al.                | 2012 | Spain      | European  | M=NR      | F=NR      |
| Garcia-Martin et al.         | 2013 | Spain      | European  | M=94/98   | F=209/212 |
| Selma et al.                 | 2015 | Tunisia    | African   | M=22/47   | F=38/67   |
| Narooie-Nejad et al.         | 2015 | Iran       | Asian     | M=25/28   | F=88/94   |
| Al-Temaimi et al.            | 2015 | Kuwait     | Asian     | M=17/19   | F=33/31   |
| Yamout et al.                | 2016 | Lebanon    | Asian     | M=NR      | F=NR      |
| Cierny et al.                | 2016 | Slovakia   | European  | M=66/74   | F=204/229 |
| Luisa Agnello et al.         | 2016 | Italy      | European  | M=24/30   | F=80/42   |
| Terzi et al.                 | 2016 | Turkey     | European  | M=NR      | F=NR      |
| Abdollahzadeh et al.         | 2016 | Iran       | Asian     | M=40/38   | F=120/112 |
| Yucel et al.                 | 2017 | Turkey     | European  | M=NR      | F=NR      |
| Study                              | Year | Country     | Region     | M (♀) | F (♂)    |
|-----------------------------------|------|-------------|------------|-------|----------|
| Kamisli et al.                    | 2018 | Turkey      | European   | M=46  | F=58     |
| Morales et al.                    | 2018 | Mexico      | American   | M=39  | F=57     |
| Sadeghi et al.                    | 2018 | Iran        | Asian      | M=17  | F=111/123|
| Cakina et al.                     | 2018 | Turkey      | European   | M=19  | F=22/48  |
| Křenek et al.                     | 2018 | Czech Republic | European | M=80  | F=49/216 |

**BsmI (rs1544410)**

| Study                              | Year | Country     | Region     | M (♀) | F (♂)    |
|-----------------------------------|------|-------------|------------|-------|----------|
| Fukazawa et al.                   | 1999 | Japan       | Asian      | M=21  | F=56/62  |
| Qinli Sun et al.                  | 2004 | China       | Asian      | M=NR  | F=NR     |
| Bing Wu et al.                    | 2009 | China       | Asian      | M=NR  | F=NR     |
| Simon et al.                      | 2010 | USA         | American   | M=NR  | F=NR     |
| Sioka et al.                      | 2011 | Greece      | European   | M=23  | F=46/58  |
| Al-Temaimi et al.                 | 2015 | Kuwait      | Asian      | M=17  | F=33/31  |
| Narooie-Nejad et al.              | 2015 | Iran        | Asian      | M=25  | F=88/94  |
| Abdollahzadeh et al.              | 2016 | Iran        | Asian      | M=40  | F=120/112|
| Yamout et al.                     | 2016 | Lebanon     | Asian      | M=NR  | F=NR     |
| Cierny et al.                     | 2016 | Slovakia    | European   | M=66  | F=204/229|
| Luisa Agnello et al.              | 2016 | Italy       | European   | M=24  | F=80/42  |
| Terzi et al.                      | 2016 | Turkey      | European   | M=NR  | F=NR     |
| Morales et al.                    | 2017 | Mexico      | American   | M=39  | F=81/123 |
| Sadeghi et al.                    | 2018 | Iran        | Asian      | M=17  | F=63/39  |
| Cakina et al.                     | 2018 | Turkey      | European   | M=19  | F=51/48  |
| Křenek et al.                     | 2018 | Czech Republic | European | M=80  | F=49/216 |

**Apal (rs7975232)**

| Study                              | Year | Country     | Region     | M (♀) | F (♂)    |
|-----------------------------------|------|-------------|------------|-------|----------|
| Niino et al.                      | 2000 | Japan       | Asian      | M=21  | F=56/62  |
| Qinli Sun et al.                  | 2004 | China       | Asian      | M=NR  | F=NR     |
| Tajouri et al.                    | 2005 | Australia   | Australian | M=NR  | F=NR     |
| Smolders et al.                   | 2009 | Netherland  | European   | M=62  | F=150/147|
| Bing Wu et al.                    | 2009 | China       | Asian      | M=NR  | F=NR     |
| Simon et al.                      | 2010 | USA         | American   | M=NR  | F=NR     |
| Irizar et al.                     | 2012 | Spain       | European   | M=NR  | F=NR     |
| Narooie-Nejad et al.              | 2015 | Iran        | Asian      | M=25  | F=88/94  |
NR, not reported; M, male; F, female; MS, Multiple Sclerosis.

Table 2. Distribution of genotype and allele among MS patients and controls.

| Study author          | 2015 | 2016 | 2016 | 2016 | 2016 | 2017 | 2018 | 2018 | 2018 | 2018 | 2018 | 2018 | 2018 | 2018 |
|----------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Al-Temaimi et al.    | Kuwait | Asian | M=17/19 F=33/31 | | | | | | | | | | | |
| Selma et al.         | Tunisia | African | M=22/47 F=38/67 | | | | | | | | | | | |
| Yamout et al.        | Lebanon | Asian | M=NR F=NR | | | | | | | | | | | |
| Luisa Agnello et al. | Tunisia | European | M=24/30 F=80/42 | | | | | | | | | | | |
| Abdollahzadeh et al. | Iran | Asian | M=40/38 F=120/112 | | | | | | | | | | | |
| Cierny et al.        | Slovakia | European | M=66/74 F=204/229 | | | | | | | | | | | |
| Terzi et al.         | Turkey | European | M=NR F=NR | | | | | | | | | | | |
| Yucel et al.         | Turkey | European | M=NR F=NR | | | | | | | | | | | |
| Kamisli et al.       | Turkey | European | M=46/58 F=121/88 | | | | | | | | | | | |
| Sadeghi et al.       | Iran | Asian | M=17/11 F=63/39 | | | | | | | | | | | |
| Cakina et al.        | Turkey | European | M=19/22 F=51/48 | | | | | | | | | | | |
| Křenek et al.        | Turkey | European | M=80/49 F=216/86 | | | | | | | | | | | |

NR, not reported; M, male; F, female; MS, Multiple Sclerosis.

Table 2. Distribution of genotype and allele among MS patients and controls.

| Study author          | MS cases | Healthy control |
|----------------------|----------|-----------------|
|                       | FF       | Ff              | ff   | F   | f   | FF  | Ff  |
| FokI (rs2228570)      |          |                 |
| Partridge et al.      | 155      | 196             | 55   | 506 | 306 | 83  | 105 |
| Tajouri et al.        | 47       | 40              | 11   | 134 | 62  | 34  | 48  |
| Smolders et al.       | 79       | 103             | 30   | 261 | 163 | 113 | 134 |
| Dickinson et al.      | 58       | 61              | 17   | 177 | 95  | 86  | 110 |
| Simon et al.          | 36       | 45              | 19   | 117 | 83  | 41  | 44  |
| Garcia-Martin et al.  | 130      | 141             | 32   | 401 | 205 | 144 | 124 |
| AI-Temaimi et al.     | 33       | 14              | 3    | 80  | 20  | 33  | 16  |
| Narooie-Najad et al.  | 73       | 32              | 8    | 178 | 48  | 93  | 29  |
| Cierny et al.         | 96       | 143             | 31   | 335 | 205 | 118 | 143 |
| Luisa Agnello et al.  | 34       | 52              | 18   | 120 | 88  | 29  | 36  |
| Abdollahzadeh et al.  | 14       | 67              | 79   | 95  | 225 | 11  | 59  |
| Yucel et al.          | 22       | 6               | 1    | 50  | 8   | 72  | 34  |
| Bettencourt et al.    | 223      | 227             | 83   | 673 | 393 | 204 | 197 |
| Kamisli et al.        | 75       | 77              | 15   | 227 | 107 | 94  | 46  |
| Sadeghi et al.        | 47       | 32              | 1    | 126 | 34  | 20  | 26  |
| Křenek et al.         | 102      | 145             | 49   | 349 | 243 | 37  | 74  |

TaqI (rs731236)

| Study author          | MS cases | Healthy control |
|----------------------|----------|-----------------|
|                       | TT       | Tt              | tt   | T   | t   | T   | Tt  | tt  |

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| Study author          | MS cases | Hef |
|-----------------------|----------|-----|
|                       | BB | Bb | bb | B  | b  | BB | Bb |
| **BsmI (rs1544410)**  |   |    |    |    |    |    |    |
| Fukazawa et al.       | 0  | 11 | 66 | 11 | 143| 3  | 24 |
| Qinli Sun et al.      | 0  | 7  | 56 | 7  | 119| 0  | 11 |
| Bing Wu et al.        | 0  | 5  | 78 | 5  | 161| 0  | 26 |
| Simon et al.          | 39 | 49 | 13 | 127| 75 | 34 | 47 |
| Study author            | MS cases | Healthy control |  |
|------------------------|----------|-----------------|---|
| Sioka et al.           | 28       | 41              | 0 |
| Al-Temaimi et al.      | 20       | 30              | 0 |
| Narooie-Nejad et al.   | 59       | 50              | 4 |
| Abdollahzadeh et al.   | 46       | 79              | 35|
| Yamout et al.          | 10       | 21              | 19|
| Cierny et al.          | 43       | 139             | 88|
| Luisa Agnello et al.   | 23       | 48              | 33|
| Terzi et al.           | 19       | 40              | 28|
| Morales et al.         | 60       | 38              | 22|
| Sadeghi et al.         | 12       | 51              | 17|
| Cakina et al.          | 14       | 36              | 20|
| Křenek et al.          | 114      | 153             | 29|

| Study author | MS cases | Healthy control |  |
|--------------|----------|-----------------|---|
| Apal (rs7975232) | | | |
| Niino et al.  | 21       | 23              | 33|
| Qinli Sun     | 9        | 17              | 37|
| Tajouri et al.| 35       | 55              | 14|
| Smolders et al.| 58      | 99              | 55|
| Bing Wu et al.| 14      | 39              | 30|
| Simon et al.  | 29       | 45              | 26|
| Irizar et al. | 39       | 60              | 35|
| Narooie-Nejad et al.| 40 | 62              | 11|
| Al-Temaimi et al.| 20     | 25              | 5 |
| Selma et al.   | 14       | 36              | 10|
| Yamout et al.  | 19       | 22              | 9 |
| Luisa Agnello et al.| 31   | 58              | 15|
| Abdollahzadeh et al.| 18   | 67              | 75|
| Cierny et al.   | 78       | 132             | 60|
| Terzi et al.    | 28       | 46              | 13|
Table 3. Main results of pooled ORs in meta-analysis of Vitamin D Receptor Gene Polymorphisms.

| Test of publication bias (Egger’s test) | Test of publication bias (Begg’s test) | Test of heterogeneity | Test of association |
|----------------------------------------|----------------------------------------|-----------------------|---------------------|
| P                                      | Z                                      | I² (%)                | 95% CI              | Odds               |
| FokI (rs2228570)                       |                                        |                       |                     |                    |
| 0.29                                   | -1.09                                  | 0.15                  | -1.44               | 0.02               | 45.7               | 0.94 - 1.19        | 1.06               |
| 0.90                                   | 0.13                                   | 0.45                  | 0.78                | 0.14               | 23.8               | 0.81 - 1.13        | 0.56               |
| 0.65                                   | 0.46                                   | 0.52                  | 0.63                | ≤0.001             | 66.6               | 0.93 - 1.26        | 1.08               |
| 0.54                                   | -0.63                                  | 0.96                  | 0.05                | 0.01               | 48.4               | 0.80 - 1.16        | 0.56               |
| 0.20                                   | -1.33                                  | 0.15                  | -1.44               | 0.16               | 26.4               | 0.93 - 1.19        | 1.06               |
| 0.55                                   | -0.62                                  | 0.24                  | -1.16               | 0.08               | 41.7               | 0.97 - 1.26        | 1.10               |
| 0.84                                   | 0.20                                   | 0.24                  | 1.16                | 0.10               | 38.1               | 0.80 - 1.16        | 0.56               |

P-HWE, p-value for Hardy–Weinberg equilibrium; MAF, minor allele frequency of control group.
|                |       |       |       |       |       | 1.1 | 5 |
|----------------|-------|-------|-------|-------|-------|-----|---|
| 0.75           | -0.32 | 0.78  | 0.27  | 0.01  | 56.5  | 0.9 | 0–1.20 |
| 0.86           | -0.17 | 0.78  | 0.27  | 0.07  | 42.8  | 0.7 | 5–1.30 |
| 0.81           | 0.24  | 0.78  | 0.27  | 0.21  | 24.9  | 0.7 | 7–1.28 |
| 0.54           | -0.86 | 0.60  | -0.52 | 0.03  | 70.9  | 0.6 | 8–1.61 |
| *              | *     | 0.31  | -1    | 0.12  | 57.9  | 0.2 | 1–7.61 |
| 0.77           | -0.36 | 0.60  | -0.52 | ≤0.001 | 80.9  | 0.4 | 6–2.45 |
| *              | *     | 0.31  | 1     | 0.01  | 84    | 0.0 | 2–14.1 |
| 0.42           | -1.02 | 0.60  | -0.52 | 0.17  | 43.5  | 0.6 | 0–1.45 |

**TaqI (rs731236)**

|                |       |       |       |       |       | 1.1 | 5 |
|----------------|-------|-------|-------|-------|-------|-----|---|
| 0.71           | 0.38  | 0.89  | -0.13 | ≤0.001 | 80.5  | 0.9 | 9–1.60 |
| 0.16           | 1.46  | 0.08  | 1.75  | ≤0.001 | 63    | 0.9 | 1–1.57 |
| 0.81           | 0.24  | 0.38  | -0.87 | ≤0.001 | 87.2  | 0.9 | 4–1.42 |
| 0.34           | 0.98  | 0.58  | 0.54  | ≤0.001 | 65.9  | 0.9 | 3–1.71 |
| 0.67           | 0.43  | 0.61  | -0.50 | ≤0.001 | 74.5  | 1.0 | 1–1.59 |
| 0.94           | 0.08  | 0.42  | -0.80 | 0.90  | 0     | 0.9 | 1.1  |

31
|    |    | 0.27 | 0.14 | 0.24 | 1.17 | 0.63 | 0 | 0.8 | 0.4 |
|----|----|------|------|------|------|------|---|----|----|
|    |    | 0.96 | 0.05 | 0.12 | -1.55 | 0.76 | 0 | 0.9 | 1.6 |
|    |    | 0.34 | 0.98 | 0.52 | 0.63 | 0.82 | 0 | 0.9 | 1.4 |
|    |    | 0.94 | -0.08 | 0.47 | -0.72 | 0.79 | 0 | 0.9 | 1.2 |
|    |    | 0.82 | -0.24 | 0.32 | -0.98 | ≤0.001 | 95 | 0.3 | 1.5 |
|    |    | 0.84 | 0.22 | 1 | 0 | ≤0.001 | 84.4 | 0.5 | 2.5 |
|    |    | 0.59 | -0.59 | 0.05 | -1.96 | ≤0.001 | 96.9 | 0.4 | 3.4 |
|    |    | 0.87 | 0.18 | 1 | 0 | ≤0.001 | 90.5 | 0.4 | 4.3 |
|    |    | 0.81 | -0.25 | 0.32 | -0.98 | ≤0.001 | 91.7 | 0.3 | 1.8 |

**Bsml(rs1544410)**

|    |    | 0.09 | 1.81 | 0.80 | -0.24 | ≤0.001 | 91.3 | 0.4 | 1.3 |
|----|----|------|------|------|------|-------|-----|----|----|
|    |    | 0.12 | 1.67 | 0.35 | 0.93 | ≤0.001 | 62.9 | 0.9 | 1.0 |
|    |    | 0.82 | 0.23 | 0.85 | 0.18 | ≤0.001 | 69.7 | 0.8 | 1.0 |
|    |    | 0.59 | -0.55 | 0.05 | -1.95 | ≤0.001 | 64.9 | 0.7 | 1.4 |
|      |      |      |      |      |      |      |      |      |
|------|------|------|------|------|------|------|------|------|
| 0.12 | -1.65 | 0.14 | -1.46 | 0.02 | 49.6 | 0.9 | 6 - 1.3 | 7 |
| 0.2  | 1.50  | 0.85 | -0.19 | ≤0.001 | 93.3 | 0.2 | 5 - 1.5 | 2 |
| 0.16 | 1.84  | 0.14 | 1.47  | 0.66  | 0    | 0.6 | 5 - 1.0 | 9 |
| 0.22 | -1.45 | 0.34 | -0.94 | 0.51  | 0    | 0.8 | 5 - 1.1 | 6 |
| 0.28 | -1.29 | 0.05 | -1.96 | 0.46  | 0    | 0.7 | 6 - 1.5 | 0 |
| 0.07 | -2.34 | 0.34 | -0.94 | 0.05  | 54.1 | 0.7 | 2 - 1.6 | 2 |
| 0.78 | -0.30 | 1    | 0    | ≤0.001 | 78.5 | 0.5 | 4 - 2.2 | 2 |
| 0.35 | -1.01 | 0.17 | -1.35 | 0.09  | 44.2 | 1.0 | 8 - 2.9 | 3 |
| 0.80 | 0.26  | 0.69 | -0.49 | ≤0.001 | 79   | 0.8 | 1 - 2.0 | 2 |
| 0.43 | -0.97 | 0.17 | -1.36 | ≤0.001 | 76.3 | 0.4 | 6 - 4.8 | 8 |
| 0.91 | -0.12 | 0.62 | -0.49 | 0.01  | 66.9 | 0.5 | 9 - 1.9 | 6 |
|      |      |      |      |      |      |      |      |      |
| Apal (rs7975232) |
|      |      |      |      |      |      |      |      |      |
| 0.26 | -1.14 | 0.21 | -1.23 | ≤0.001 | 58   | 0.8 | 2 - 1.3 | 1 |
| 0.57 | -0.57 | 0.55 | -0.58 | ≤0.001 | 51   | 0.6 | 6 - 1.0 | 5 |
| 0.32 | -1.02 | 0.58 | -0.55 | ≤0.001 | 68.2 | 0.8 | 0 - 1.1 | 0 |
| 0.22 | -1.26 | 0.43 | -0.78 | ≤0.001 | 55.1 | 0.6 | 3 - 1.6 | 6 |
| 0.53 | -0.64 | 0.33 | -0.97 | ≤0.001 | 72.2 | 0.8 | 8 - 1.6 | 4 |
| 0.84 | 0.21  | 1    | 0    | 0.04  | 49.8 | 0.8 | 7 - 1.4 | 7 |
| 0.64 | -0.49 | 0.67 | -0.42 | 0.11  | 38.7 | 0.7 | 8 - 1.3 | 1 |
|      |      |      |      |      |      |      |      |      |

ApaI (rs7975232)
|      |      |      |      |      |      |      |
|------|------|------|------|------|------|------|
| 0.59 | -0.56| 1    | 0    | 0.02 | 53.6 | 3    |
| 0.95 | 0.06 | 0.40 | 0.83 | 0.01 | 56.9 | 0.76|
| 0.61 | 0.52 | 0.40 | 0.83 | ≤0.001 | 81.4 | 0.86-
| 0.03 | -2.67| 0.08 | -1.73| ≤0.001 | 70.9 | 0.49-
| 0.54 | 0.64 | 0.32 | 0.99 | 0.11 | 40.4 | 0.42-
| 0.51 | 0.69 | 0.17 | 1.37 | ≤0.001 | 76.1 | 0.57-
| 0.72 | 0.37 | 0.80 | 0.25 | 0.20 | 28   | 0.32-
| 0.07 | -2.17| 0.02 | -2.23| ≤0.001 | 64.5 | 0.59-

**Figures**
Figure 1. Flow diagram of study selection process

1. Identification
   - Records identified through database searching (n = 636)
   - Records after duplicates removed (n = 450)

2. Screening
   - Records screened (n = 450)
   - Records excluded (n = 374)
     - Full-text articles excluded, with reasons (n = 46)
       - Reviews (29)
       - Editorial, Letter, comments and meeting abstracts (7)
       - Studies of no control (3)
       - Other SNP of VDR (4)
       - Insufficient data (3)

3. Eligibility
   - Full-text articles assessed for eligibility (n = 76)
   - Studies included in qualitative synthesis (n = 30)

4. Included
   - Studies included in meta-analysis (n = 30)
     - Studies on FokI SNP (16)
     - Studies on TaqI SNP (23)
     - Studies on Bsml SNP (16)
     - Studies on Apal SNP (20)
Figure 2: Pooled OR and 95% CI of individual studies and pooled data for the association between TaqI gene polymorphism and MS risk in Tt vs. TT Model (TaqI).

Figure 2
Pooled OR and 95% CI of individual studies and pooled data for the association between TaqI gene polymorphism and MS risk in Tt vs. TT Model (TaqI).
Figure 3

Pooled odds ratio (OR) and 95% confidence interval of individual studies and pooled data for the association between BsmI, Apal gene polymorphism and MS risk in different ethnicity subgroups and overall populations for A; Recessive Model (Apal), B; aa vs. AA Model (Apal), and C; Recessive Model (BsmI).
Figure 4

Begg’s funnel plot for publication bias test. A; Dominant Model FokI . B; Dominant Model TaqI. C; Dominant Model BsmI. D; Dominant Model ApaI . Each point represents a separate study for the indicated association.
Sensitivity analysis in present meta-analysis investigates the single nucleotide polymorphisms of Vitamin D Receptor contribute to risk for multiple sclerosis susceptibility (A, FokI; B, TaqI; C, BsmI; D, Apal).

Supplementary Files

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Supplementary figure.docx