Vitamin D receptor gene polymorphisms and the risk of the type 1 diabetes: a meta-analysis based on 40 case–control studies

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Abstract

Objective

The association between the vitamin D receptor (VDR) gene polymorphisms and the risk of Type 1 diabetes mellitus (T1DM) has been evaluated in several studies. However, the findings were inconclusive. Thus, we conducted a meta-analysis to comprehensively evaluate the effect of VDR gene polymorphisms on the risk of T1DM.

Methods

All relevant studies reporting the association between VDR gene polymorphisms and susceptibility to T1DM published up to July 2019 were identified by comprehensive systematic database search in Web of Science, Scopus, and PubMed. Strength of association were assessed by calculating of pooled odds ratios (ORs) and 95% confidence intervals (CIs). The methodological quality of each study was assessed according to the Newcastle-Ottawa Scale. Subgroup analysis stratified by ethnicity was also conducted.

Results

A total of 40 case-control studies were included in this meta-analysis. The results of overall population rejected any significant association between VDR gene polymorphisms and T1DM risk. However, the pooled results of subgroup analysis revealed significant negative and positive associations between FokI and BsmI genes polymorphism and T1DM in African and American populations, respectively.

Conclusions

This meta-analysis suggested a significant association between VDR gene polymorphism and T1DM susceptibility in ethnic-specific analysis.

Background

Type 1 diabetes mellitus (T1DM) is a globally-recognized disease characterized by a
reduction in insulin production or the production of ineffective insulin [1]. It is generally believed that the immune-associated destruction of beta cells of the islets of Langerhans causes the disease, resulting in lower insulin levels (type 1a diabetes mellitus). In a smaller T1DM subset, no evidence of autoimmunity can be found (type 1b) [2]. T1DM constitutes roughly 5 to 10% of all diabetes, and its prevalence is still rising [3]. With more than half a million children living with T1DM, and almost 90000 children diagnosed each year, T1DM inflicts mostly children of under 15 years of age [4]. It is well known that T1DM is a multi-factorial autoimmune disorder caused by interactions between both genetic and environmental factors[5].

Vitamin D (VitD) is a steroid molecule which has many roles in the body, one of which is regulating the immune cells. In addition to immune responses, VitD is also involved in cancer, autoimmune disorders, cardiovascular disorders, asthma, and diabetes [6-8]. In animal model of T1DM, VitD suppresses the occurrence of diabetes, by regulating the T helper (Th) 1/Th2 cytokine balance in the local pancreatic lesion [9, 10]. Moreover, VitD inhibits T cell activation and secretion of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-12, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, which are involved in the pathogenesis of T1DM [11-13]. Mostly, VitD exerts its function through vitamin D receptor (VDR), which is found in the nuclei of target cells such as lymphocytes, macrophages, and pancreatic cells. VDR is a member of the nuclear hormone receptors superfamily and is linked to insulin sensitivity and secretion [14]. Genetic polymorphisms have been studied as a factor for T1DM pathogenesis, specifically VDR gene polymorphisms. Four common single nucleotide polymorphisms (SNPs) of VDR gene are FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232). Among them polymorphisms of ApaI, BsmI, and TaqI are located in the 3'-end of VDR gene which lead to silent mutation associated with increased VDR mRNA stability. In contrast, FokI SNP is
located in the start codon resulting protein with shorter size, the shorter form of the protein (424 amino acid) is more active than the long form (427 amino acid) [15, 16]. In recent years, several epidemiological studies have investigated the association between VDR gene SNPs and T1DM in all over the world which yielded conflicting results [17, 18]. The reasons for these discrepancies might be small sample sizes, clinical heterogeneity, and low statistical power. Therefore, a comprehensive meta-analysis might be the best way to solve these problems. Two previous meta-analyses performed by Tizaouia et al. [19] and Guo et al. [20] reported that VDR gene polymorphisms were not associated with the susceptibility to T1DM. However, Zhang et al. [21] demonstrated that Bsml polymorphism is significantly associated with the risk of the T1DM. Since several articles published after the last meta-analysis, here we conducted an updated meta-analysis with the aim of providing a much more reliable finding on the significance of the association.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, including search strategy, inclusion and exclusion criteria, data extraction and quality assessment, and statistical analysis [22].

Search Strategy

Three English databases (PubMed, Scopus, and Web of Science) were systematically searched for studies regarding the association of VDR gene polymorphisms, including FokI (rs2228570) and/or TaqI (rs731236) and/or Bsml (rs1544410) and/or Apal (rs7975232), and T1DM susceptibility, which were published before July of 2019. The following combinations of search terms were used: (“T1D” OR “type 1 diabetes” OR “diabetes”) AND (“VDR” OR “vitamin D receptor”) AND (“polymorphisms” OR “SNP” OR “variation” OR “mutation”). As a complementary approach, the reference lists of retrieved articles and
review articles were also manually searched to identify possible missing literatures. Original data in English language and human population studies were collected.

**Inclusion and exclusion criteria**

Eligible studies must meet the following criteria: a) studies which assess the association of VDR gene polymorphisms and T1DM risk; b) studies presenting sufficient data to calculate the odds ratio (OR) and its 95% confidence intervals (CIs); c) studies with case-control design. The exclusion criteria were: a) studies that their genotype or allele frequency could not be extracted; b) letters, case reports, reviews, comments, book chapters, and abstracts; c) duplicated reports and republished studies. The application of these criteria recognized 40 studies eligible for the meta-analysis.

**Data extraction and quality assessment**

According to a standardized extraction form, the following data were independently extracted by two reviewers: 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. The third reviewer finalized the extracted data, and potential discrepancies were resolved by consensus. For quality assessment of the included publications, the Newcastle-Ottawa Scale (NOS) was applied [23]. In this respect, studies with 0–3, 4–6 or 7–9 scores were respectively low, moderate, and high-quality.

**Statistical analysis**

Deviation from Hardy–Weinberg equilibrium (HWE) for distribution of the allele frequencies was analyzed by χ²-test in control groups. The strength of association between VDR gene polymorphisms and T1DM susceptibility was estimated by calculating pooled OR and its 95% CI. Different comparison model for FokI, TaqI, BsmI, and Apal were as follows: **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): 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): 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). The heterogeneity among studies was measured by the χ² test-based Q statistic, and I² value which quantify the degree of heterogeneity [24]. Accordingly, heterogeneity was considered significant if I² values exceeded 50% or the Q statistic had a p-value of less than 0.1 and random-effects model (DerSimonian–Laird approach) was carried out [25]. Otherwise, the fixed-effects model (Mantel–Haenszel approach) was performed for combination of data [26]. In order to show the stability of our results, sensitivity analysis was performed. Potential publication bias was estimated by Egger’s linear regression test, and also Begg’s test was employed to estimate the funnel plot asymmetry (p-value<0.05 considered statistically significant) [27, 28]. 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).

Results

Study characteristics

Regarding to aforementioned keywords, a total of 1116 studies were initially retrieved. Of these studies, 456 publications were duplicate, 559 and 61 publications excluded by title & abstract and full text examination, respectively. Finally, 40 studies qualified for quantitative analysis Figure 1. The eligible studies were published from 1998 to 2019 and had an overall good methodological quality with NOS scores ranging from 6 to 8. Polymerase chain reaction-restriction fragment length polymorphism (PCR- RFLP) and Taq-
man were used by majority of included studies as genotyping method. Table 1 and 2 summarized the characteristics and genotype frequency of the included studies.

Quantitative synthesis

Meta-analysis of the association between FokI (rs2228570) gene polymorphism and T1DM risk

Overall, 29 case-control studies with 3723 cases and 5578 controls were analyzed for assessment of FokI gene polymorphism and T1DM risk. Of 29 studies, 15 studies were conducted in European countries [14, 29-39], 9 studies were in Asian countries [40-48], 3 studies were in African population [49-51] and eventually one study in Australia [52] and one study in American population [53]. Among studies were performed in Europe, Audi et al. [32] conducted an association study in different city of Spain (Barcelona and Navarra) and reported all data separately including genotype and allele frequency; thus we considered each population as a separate study. The pooled results revealed no significant association in overall population across all genotype models, meanwhile subgroup analysis according to ethnicity showed decreased risk of T1DM susceptibility in European population [dominant model (OR= 0.86, 95% CI, 0.74-1.00, P=0.05) and heterozygote contrast (OR= 0.86, 95% CI, 0.75-0.99, P=0.04)] and increased risk of T1DM susceptibility in African population under all genotype models; dominant model (OR= 2.06, 95% CI, 1.20 - 3.53, P=0.008), recessive model (OR= 2.14, 95% CI, 1.03 – 4.43, P=0.04), allelic model (OR= 1.17, 95% CI, 1.06 – 2.97, P=0.02), ff vs. FF model (OR= 3.11, 95% CI, 1.44 -6.69, P=0.004), and Ff vs. FF model (OR= 1.81 , 95% CI, 1.13 – 2.91, P=0.01). Besides, susceptibility to T1DM in Asians compared to Africans and Europeans were not affected by FokI gene polymorphism (Figure 3). The results of pooled ORs, heterogeneity tests and publication bias tests in different analysis models are shown in Table 3.

Meta-analysis of the association between TaqI (rs731236) gene polymorphism and T1DM
There were 21 case-control studies with 1973 cases and 1995 controls concerning TaqI gene polymorphism and T1DM risk. Studies were performed in different population, 8 studies were in Europeans [14, 29, 30, 33, 36, 37, 54, 55], 9 studies in Asians [41, 43, 44, 48, 56-60], 2 studies in Africans [51, 61] and one study each was in Australia [52] and Americans [17]. Meta-analysis rejected any significant association between TaqI SNP and the risk of T1DM susceptibility. Moreover, the results of subgroup analysis by ethnicity were not significant under five genotype models. In subgroup analysis, since there was only one study for the Australians [52], Americans [17], and two studies for Africans [51, 61], these studies were excluded from the analysis. The results of pooled ORs, heterogeneity tests and publication bias tests in different analysis models are shown in Table 3.

Meta-analysis of the association between BsmI (rs1544410) gene polymorphism and T1DM risk

To examining the association between BsmI gene polymorphism and T1DM risk, 35 case-control studies with 4926 cases and 7259 controls subjects were included. It was detected that 15 studies with 1938 cases and 4450 controls were performed in European countries [14, 29-33, 35-37, 39, 54, 55] which among these 15 studies, Turpeinen et al. [31] conducted an association study in different city of Finland (Turku, Tampere and Oulu) and reported all data separately, including genotype and allele frequency; thus we considered each population as a separate study. Moreover, 14 studies out of 35 eligible studies were carried out in Asian populations [18, 41, 43, 44, 47, 48, 56-60, 62-64], 3 studies were in Americans [17, 53, 65] and three studies were in Africans [49, 51, 61]. No significant association between BsmI polymorphism and T1DM risk were found under all genotype models for the overall population. However, pooled results of subgroup analysis indicated
markedly significant negative associations between BsmI SNP and the risk of T1DM susceptibility in American populations across all genotype models; dominant model (OR= 0.57, 95% CI, 0.39 – 0.84, P=0.004), recessive model (OR= 0.62, 95% CI, 0.41 – 0.94, P=0.02), allelic model (OR= 0.66, 95% CI, 0.54 – 0.81, P<0.001), bb vs. BB model (OR= 0.52, 95% CI, 0.34 -0.80, P=0.003), except Bb vs. BB model (OR= 0.66, 95% CI, 0.41 – 1.05, P=0.08) (Figure 2). No significant association was detected for European, Asian and African population. The results of pooled ORs, heterogeneity tests and publication bias tests in different analysis models are shown in Table 3.

Meta-analysis of the association between Apal (rs7975232) gene polymorphism and T1DM risk

24 Case-control studies with 2436 cases and 4074 controls were identified eligible for quantitative synthesis of the association between Apal polymorphism and T1DM risk. Overall, 10 studies were conducted in Europe [14, 30, 31, 33, 36, 37, 54, 55], 10 studies were in Asia [41, 43-46, 48, 56-59], 2 studies in Africa [51, 61] and one study each was in Australia [52] and America[17]. Because of limited number of studies performed in Australia, America and Africa these studies were excluded from subgroup analysis. The results demonstrated no significant association between the Apal gene polymorphism and risk of T1DM in the overall population and ethnic-specific analysis (Figure2). The results of pooled ORs, heterogeneity tests and publication bias tests in different analysis models are shown in Table 3.

Evaluation of heterogeneity and publication bias

During the meta-analysis of VDR gene polymorphism evidence of substantial to moderate heterogeneity was detected. However, partial heterogeneity was resolved while the data were stratified by ethnicity. Publication bias was evaluated by funnel plot, Begg’s test and Egger’s test. There was no obvious evidence of asymmetry from the shapes of the funnel
plots (Figure 4), and all $p$-values of Begg’s test and Egger’s test were >0.05, which showed no evidences of publication biases.

**Sensitivity analysis**

The leave-one-out method was used in the sensitivity analysis to explore the effect of individual data on the pooled ORs. The significance of ORs was not altered through omitting any single study in the dominant model for FokI, TaqI, BsmI and ApaI SNPs, indicating that our results were statistically robust (Figure 5).

**Discussion**

In this study, we performed a systematic review and meta-analysis to approach with a vivid and exact approximation of the associations between the VDR gene polymorphisms, including FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232) and proneness to T1DM. The findings of meta-analysis on 40 case-control studies indicated no significant association of VDR gene polymorphisms with T1DM risk in overall population. That notwithstanding, the subgroup analysis resulted in identification of significant associations between FokI and BsmI genes polymorphism and T1DM in African and American population.

Over the course of past years, a bulk of studies has addressed the association of VDR gene polymorphisms and risk of T1DM throughout various populations, resulting in conflicting findings [17, 18]. Such discrepancies might stem from diversity in detection methods, differences in diagnostic criterions, clinical heterogeneity, small sample sizes, low statistical power, and interactions between genetic and environmental contributing factors according to variations in the geo-epidemiological factors. As a consequence, three previous meta-analyses by Guo et al. [20] in 2006, Zhang et al. [21] in 2012, and Tizaouia et al. [19] in 2014 were carried out to resolved the conundrum and attain an exact approximation. They indicated that VDR gene SNPs were not associated with T1DM
risk, except than BsmI polymorphism association with T1DM predisposition that was observed in Zhang et al. [21] study. Upon the latest meta-analysis published in 2014, several original association studies evaluated the role of VDR gene polymorphisms with T1DM risk. As a result, the necessity for performing an updated meta-analysis is sensed to come up with resolution of the limitations of individual association studies and to gain a much more valid and comprehensive pooled estimation on the association of VDR gene polymorphisms with T1D risk.

Previous meta-analysis by Tizaouia et al. [19] in 2014 reported no significant association of VDR gene FokI polymorphism with risk of T1D. According to our meta-analysis, the pooled results in overall population across all genotype models demonstrated no significant association of VDR gene FokI polymorphism; nonetheless, subgroup analysis according to ethnicity showed a marginally-significant decreased susceptibility to T1DM in European population according to dominant genetic model and heterozygote comparison, while an increased risk of T1DM in African population according to all genotype models. In addition, our meta-analysis did not support any significant association between TaqI SNP and susceptibility to T1DM. Furthermore, the results of subgroup analysis according to ethnicity did not show any significant association in all genetic models. However, in the subgroup analysis, given that there was only one study in the Australian [52] and American [17] populations, and two studies in the African [51, 61] population, the subgroup analysis was not performed in these populations. In line with our findings, previous meta-analysis by Tizaouia et al. [19] also did not show significant association of VDR gene TaqI polymorphism with risk of T1D. According to the previous meta-analysis, BsmI SNP was not the risk factor for T1D susceptibility. However, after excluding one study, a marginal significant \( P = 0.051 \) association was found in the homozygous model. On the other side, our meta-analysis also revealed that BsmI polymorphism was not a risk
for T1DM in all genetic models when all of the population were analyzed. Nonetheless, subgroup analysis demonstrated a strong negative significant association between Bsml SNP and the risk of T1DM in American population in all of the genetic model comparisons. Finally neither our meta-analysis nor the previous one by Tizaouia et al. [19] found any significant association of Apal polymorphism and T1DM risk in overall as well as subgroup analyses. Taken together, although our meta-analysis included further studies compared to the previous study, the overall analysis was almost the same. Nonetheless, our subgroup analysis indicated association of VDR genetic polymorphisms with T1DM risk in different ethnical groups.

A combination of common variants might play a critical role in the genetic etiopathogenesis of the complex diseases. Genetic polymorphisms seem to confer mild to harsh biological impression given the protein they codify [66]. It has been reported that VDR genetic polymorphisms, including Apal, Bsml and TaqI, do not affect on the VDR protein structure, while they might influence on the stability of the protein, translation quality, or splicing of the RNA. However, it was observed that the FokI SNP impress the VDR protein structure as well as its RAN transcriptional efficacy [67]. As a result, VDR gene Apal, Bsml and TaqI polymorphisms may be associated with T1D pathogenesis as markers in linkage disequilibrium with the bona fide disease-associating genes [36].

Ethnicity as well as environmental interactions may play a role in determining the expression and the function of VDR to stimulate target genes [68], which are considered as confounding factors in evaluating disease association.

A number of animal as well as in vitro studies have indicated supporting evidence for the protective function of VitD in T1DM. VitD has been reported to be involved in the glucose metabolism. Furthermore, active form of VitD has been associated with several important immune-modulatory properties. In addition, several animal models of autoimmune
disorders have shown a protective or preventing role for VitD. That notwithstanding, little has been disclosed with respect to the therapeutic role of VitD in the therapy of autoimmune disorders and further clinical trials are required to this end.

Conclusion

In consideration of all, this was a systematic review and meta-analysis of 40 case-control association studies to come up with the clear estimation of the associations between the VDR gene SNPs [FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and Apal (rs7975232)] and susceptibility to T1DM. The findings of meta-analysis revealed no significant association of VDR gene SNPs with T1DM risk in overall population. However, the subgroup analysis indicated significant associations between FokI and BsmI genes polymorphism and T1DM in African and American population. As a limitation, we did not evaluate a number of VDR gene SNPs that might act in interaction with environmental factors to determine the fate of T1DM pathogenicity. Further investigations on the VDR, above and beyond the genetic as well as traditional risk factors may confer a possibility for identification of critical susceptibility factors in the disease development, which might be applicable in the personalized medicine for better and optimized therapy of T1DM patients.

Abbreviations

VDR: vitamin D receptor

SNP: Single nucleotide polymorphisms

IL: Interleukin

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

NOS: Newcastle-Ottawa Scale

RXR: Retinoid X receptor
Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
DI generated the idea. MH analyzed and interpreted the data. PM and SA prepared the original draft. MH, BR, and SA critically revised the paper. DI supervised the project. All authors read and approved the final manuscript.

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Disclosure of conflict of interest
None.

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**Tables**

Due to technical limitations, the tables are only available as a download in the supplemental files section.

**Figures**
Figure 1

Flow diagram of study selection process.
### Pooled OR and 95% CI of individual studies and pooled data for the association between Apal gene polymorphism and T1DM risk in heterozygote contrast (Aa vs. AA).

#### Study ID

| Study ID                                | Aa Vs. AA (Apa1) | OR (95% CI) %Weight |
|-----------------------------------------|------------------|---------------------|
| Chang et al. (2000)                     | 0.56 (0.24, 1.39)| 2.35                |
| Gyory et al. (2002)                     | 0.86 (0.39, 1.87)| 2.96                |
| Skrabic et al. (2003)                   | 0.60 (0.35, 1.05)| 6.02                |
| Turpeinen(Turku) et al. (2003)          | 1.04 (0.67, 1.64)| 9.07                |
| Turpeinen(Tampere) et al. (2003)        | 0.53 (0.24, 1.21)| 2.78                |
| Turpeinen(Oulu) et al. (2003)           | 1.13 (0.75, 1.72)| 10.54               |
| Bianco et al. (2004)                    | 0.33 (0.10, 1.08)| 1.28                |
| San Pedro et al. (2005)                 | 1.60 (0.70, 3.74)| 3.90                |
| Garcia et al. (2007)                    | 0.73 (0.44, 1.20)| 7.22                |
| Lemos et al. (2008)                    | 1.22 (0.76, 1.97)| 8.01                |
| Israni et al. (2009)                    | 0.85 (0.55, 1.32)| 9.48                |
| Papanastakis et al. (2009)              | 0.61 (0.30, 1.20)| 3.78                |
| Yavuz et al. (2011)                     | 0.80 (0.43, 1.50)| 4.65                |
| Bonakdaran et al. (2012)                | 2.79 (1.08, 7.13)| 2.41                |
| Mohamadnejad et al. (2012)              | 0.84 (0.41, 1.71)| 3.56                |
| Greer et al. (2012)                     | 0.60 (0.21, 1.66)| 1.70                |
| Abol-Allah et al. (2014)                | 0.78 (0.43, 1.41)| 5.15                |
| Cheon et al. (2015)                     | 1.69 (0.44, 6.47)| 0.94                |
| Khalid et al. (2016)                    | 1.11 (0.51, 2.39)| 3.04                |
| Nasreen et al. (2016)                   | 1.07 (0.38, 3.05)| 1.73                |
| Sy et al. (2017)                        | 1.05 (0.36, 3.07)| 1.58                |
| Resoul et al. (2019)                    | 0.70 (0.40, 1.22)| 5.84                |
| Ahmed et al. (2019)                     | 2.60 (1.00, 6.70)| 2.01                |
| Overall (I-squared = 25.5%, p = 0.130)  | 0.91 (0.80, 1.04)| 100.00              |

#### Figure 2

Pooled OR and 95% CI of individual studies and pooled data for the association between Apal gene polymorphism and T1DM risk in heterozygote contrast (Aa vs. AA).

### Study ID

| Study ID                                | Dominant (Fok1) | OR (95% CI) %Weight |
|-----------------------------------------|-----------------|---------------------|
| Asian                                   |                 |                     |
| Ban et al. (2001)                       | 0.56 (0.34, 0.92)| 4.47                |
| Israni et al. (2009)                    | 0.94 (0.63, 1.42)| 5.17                |
| Yokota et al. (2012)                    | 0.42 (0.25, 0.70)| 4.35                |
| Bonakdaran et al. (2012)                | 0.54 (0.23, 1.24)| 2.54                |
| Mohamadnejad et al. (2012)              | 0.94 (0.50, 1.76)| 3.60                |
| Nasreen et al. (2016)                   | 0.49 (0.18, 1.31)| 2.02                |
| Ali et al. (2018)                       | 1.93 (0.99, 3.77)| 3.37                |
| Rasoul et al. (2019)                    | 0.90 (0.58, 1.36)| 5.08                |
| Subtotal (I-squared = 60.0%, p = 0.015) | 0.76 (0.56, 1.05)| 30.59               |

#### European

| Study ID                                | OR (95% CI) %Weight |
|-----------------------------------------|---------------------|
| Fassbender et al. (2002)                | 0.57 (0.26, 1.23)| 2.82                |
| Gyory et al. (2002)                     | 1.15 (0.61, 2.15)| 3.59                |
| Turpeinen(Turku) et al. (2003)          | 0.64 (0.44, 0.95)| 5.34                |
| Turpeinen(Tampere) et al. (2003)        | 1.05 (0.44, 2.69)| 2.18                |
| Turpeinen(Oulu) et al. (2003)           | 0.76 (0.41, 1.47)| 4.04                |
Figure 3

Pooled odds ratio (OR) and 95% confidence interval of individual studies and pooled data for the association between FokI, BsmI gene polymorphism and T1DM risk in different ethnicity subgroups and overall populations for A; dominant model (FokI), B; Ff vs. FF Model (FokI), 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 Apal. Each point represents a separate study for the indicated association.
Figure 5

Sensitivity analysis in present meta-analysis investigates the single nucleotide polymorphisms of Vitamin D Receptor contribute to risk for T1DM (A, FokI; B, TaqI; C, BsmI; D, ApaI).

Supplementary Files

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