Association of vitamin D receptor polymorphisms and type 1 diabetes susceptibility in children: a meta-analysis

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Abstract

Background: There have been studies focused on *Fok*I, *Bsm*I, *Apa*I and *Taq*I polymorphisms of the vitamin D receptor (VDR) gene and susceptibility to type 1 diabetes mellitus with controversial results.
Methods: This present study is a meta-analysis investigating the association between FokI, ApaI, TaqI and BsmI polymorphisms of VDR gene and type 1 DM in children. A literature search was performed using Medline, EMBASE, Cochrane and PubMed. Any study was considered eligible for inclusion if at least one of *Fok*I, *Apa*I, *Taq*I and *Bsm*I polymorphisms was determined, and outcome was type 1 DM at pediatric age.
Results: A total of 9 studies comprising 1053 patients and 1017 controls met the study inclusion criteria. The pooled odds ratios (ORs) of the *Fok*I, *Apa*I, *Taq*I and *Bsm*I polymorphisms were combined and calculated. Forest plots and funnel plots of the OR value distributions were drawn. Our meta-analysis has demonstrated statistically significant associations between DM1 and VDR genotypes, *Bsm*IBB ($P<0.05$), *Bsm*IBb, ($P<0.05$), *Bsm*Ibb ($P<0.05$), *Taq*ITT ($P<0.05$) and *Taq*Itt ($P<0.05$) in children.
Conclusion: The results indicated that *Bsm*IBB, *Bsm*IBb and *Taq*Itt polymorphisms were associated with an increased risk of type 1 DM, whereas *Bsm*Ibb and *Taq*ITT had protective effect for type 1 DM in children.

Key Words
- VDR
- diabetes mellitus
- polymorphisms
- meta-analysis

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Introduction

Type 1 diabetes (DM1) is a complex disease characterized by the autoimmune destruction of pancreatic β cells. Vitamin D is an immune regulatory hormone that exerts its effects through highly polymorphic VDR that belongs to steroid-receptor superfamily, and it is expressed in many cell types such as lymphocytes and antigen-presenting cells (APCs) (1). During the last decade, VDR gene polymorphisms have been shown to be associated with autoimmune pathologies (2). Vitamin D seems to downregulate type 1 helper (Th-1) cells, by decreasing their proliferation and inhibiting the production of cytokines such as IL-2, TNF-α and interferon-γ (3, 4). For many years, the strongest genetic contribution to DM1 susceptibility had been attributed to the presence of human leukocyte antigen region (HLA) on chromosome 6 (5, 6). Recently, single nucleotide polymorphisms (SNPs) in the VDR gene have been investigated namely *Fok*I $F>f$ (rs10735810), *Bsm*I $B>b$ (rs1544410), *Apa*I $A>a$

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(rs7975232) and *Taq*I t *T*>*t* (rs731236). Allele F of the *Fok*I SNP creates an alternative ATG initiation codon in exon 2 leading to a three amino acid longer VDR protein. The *Apa*I, *Bsm*I and *Taq*I polymorphisms take place near the 3′ end of the VDR gene; *Bsm*I and *Apa*I SNPs are located in intron 8, and the *Taq*I is a silent SNP in exon 9. Several studies with small data sets that suggested an association between these SNPs and type 1 DM had inconsistent results (7, 8, 9, 10). These inconclusive results had been attributed to ethnic diversities among populations or due to the environmental factors involved in type 1 DM pathogenesis. *Bsm*I is strongly linked with 3 poly(A) microsatellite repeat in the 3′ untranslated region, which may influence VDR mRNA stability (11). *Bsm*I, *Apa*I and *Taq*I polymorphisms were also designated as polymorphisms without functional effects in several studies (12, 13). There are some discrepancies in the literature with small data sets, regarding the relative importance of polymorphisms of VDR genes *Apa*I, *Bsm*I, *Fok*I and *Taq*I. In our meta-analysis, we included a total of 9 studies comprising 1053 patients and 1017 controls that indicated statistically significant associations between DM1 and VDR genotypes, *Bsm*IBB ($P<0.05$), *Bsm*IBb ($P<0.05$), *Bsm*Ibb ($P<0.05$), *Taq*ITT ($P<0.05$) and *Taq*Itt ($P<0.05$) in children. This present meta-analysis involves a large data set to investigate the associations between type 1 DM and VDR gene polymorphisms *Apa*I, *Bsm*I, *Fok*I and *Taq*I, accordingly demonstrate more reliable statistical results to rule out genotype–phenotype correlation of type 1 DM in children.

Methods

Search strategy criteria

For meta-analysis, all published studies evaluating the associations between type 1 DM and *Fok*I, *Apa*I, *Taq*I and *Bsm*I polymorphisms that are investigated in patients diagnosed as DM1 at pediatric age are included. A literature search for the MeSH terms 'type 1 Diabetes mellitus' or 'DM1' was performed by O A, D G and M S Medline, Cochrane and PubMed abstracts were reviewed for relevance. No language and date of study restriction were applied to search strategy. Search to include the eligible studies ended on 05/14/2016. Any study was considered to be eligible for inclusion if it met the following criteria: (1) the publication was an association study of the case control type, (2) at least one of the FokI, ApaI, TaqI and BsmI polymorphism was determined, (3) the outcome was DM in children and (4) there was at least one unrelated control group.

Data extraction

Study selection and data extraction were performed independently by three authors (O A, D G and M S) based on a customized database for extraction. For each study, the following information was collected: first author, year and location of the study, average age at the time of diagnosis, ethnicity, number of participants, number of cases and controls and number of the genotypes in cases and controls. The disagreements were resolved between the reviewers by consensus. For quality assessment, six domains were assessed. Those were representativeness of classes, representativeness of the controls, ascertainment of DM1, genotypic examination and association of assessment. The primary outcome considered in the meta-analysis was the association between DM1 and the presence of *Fok*I, *Apa*I, *Taq*I or *Bsm*I polymorphism at pediatric age. For the primary analysis and to allow appropriate comparison of all studies, cases and controls were classified based on *Fok*I, *Apa*I, *Taq*I and *Bsm*I genotypes.

Statistical analysis

The odds ratios (OR) with 95% confidence intervals, representativeness of controls, ascertainment of DM1, ascertainment of controls, genotypic examination and association assessments were done. The primary outcome considered in the meta-analysis was the association between DM1 and the presence of FokI, ApaI, TaqI or BsmI polymorphisms. MedCalc Software Acacialaan 22, 8400 (Ostend, Belgium) was used to perform meta-analysis. The odds ratios (OR) of the genetic polymorphisms were combined and calculated, and the funnel plots were drawn. All of the four studied SNPs (*FokI*, *ApaI*, *TaqI* and *BsmI*) were diallelic, and we calculated summary odds ratios incorporating both within- and between-study variation using a random effects model proposed by DerSimonian and Laird (14).

Results

Our search yielded a total of 50 references. After screening the titles and abstracts, 41 studies were excluded because they were not considered relevant to the study topic,

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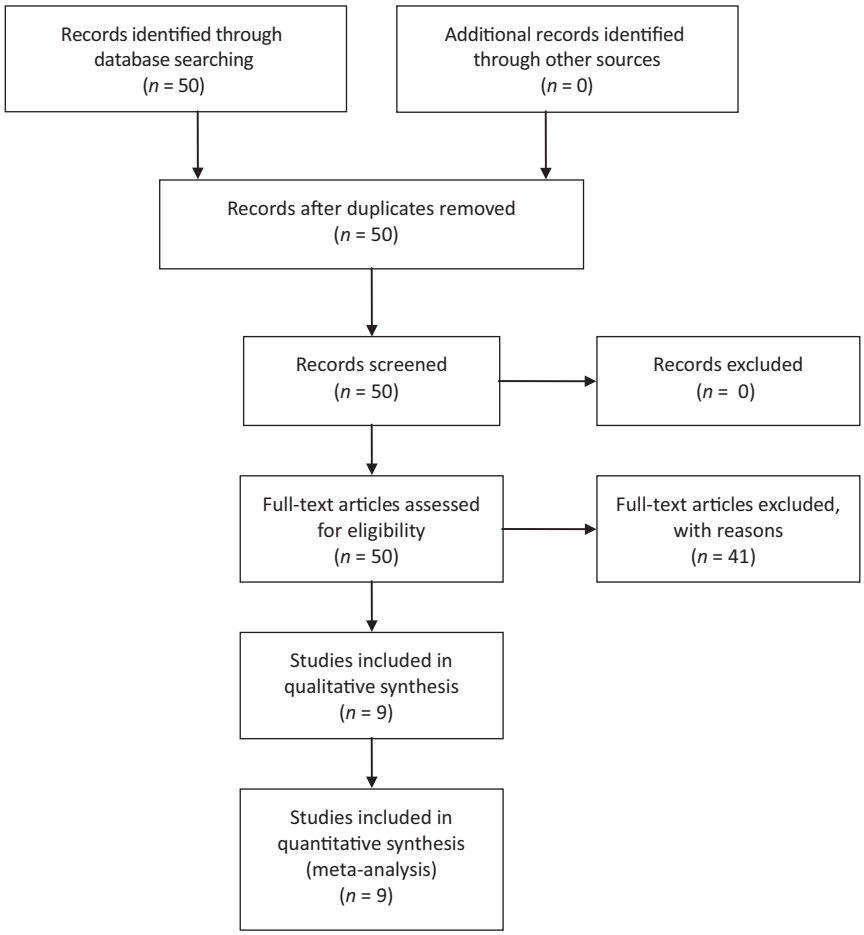

Figure 1
Flow chart for identification and selection of studies.

leaving 9 potentially eligible studies (Fig. 1) (15, 16, 17, 18, 19, 20, 21, 22, 23).

In the 9 published papers included in the meta-analysis, *Apa*I, *Bsm*I, *Fok*I and *Taq*I polymorphisms were investigated in pediatric population as case–control studies (Table 1).

Eight studies on the ApaI-type 1 diabetes association recruited 921 cases/patients and 1033 controls, whereas seven studies on the BsmI polymorphism recruited 866 cases and 983 controls. For the FokI polymorphism, five studies included 465 cases and 569 controls, whereas eight studies on the TagI polymorphism included 921 cases and 1033 controls. Individual and pooled odds ratio estimates of four single-nucleotide polymorphisms in the vitamin receptor gene, *P* values testing Hardy–Weinberg proportion, test for heterogeneity (Tables 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13) and funnels plots (Figs 2 and 3) are documented for BsmI and TaqI, respectively.

Table 1 Characteristics features of studies included in the meta-analysis of *Apa*I, *Bsm*I, *Fok*I and *Taq*I polymorphisms in the vitamin D receptor gene.

First author	Year	Region	Mean age of cases/diagnosis (years)	Cases	Source of controls	Mean age of controls (years)	Controls
Diego Garcia	2007	Santiago-Chile	9.3±4.2	216	Unrelated children	10.3±2.5	203
J I San Pedro	2005	Bilbao-Spain	14.5±9.9	71	Healthy blood donors		88
Tatijana Semunik	2005	Split-Croatia	8.6±4.3	132	Unrelated children	8.2±4.9	232
Vaselin Scrabic	2003	Split-Croatia	8.6±4.3	134	Unrelated children	8.24±4.9	132
Balazs Gyorffy	2002	Budapest-Hungary	5.8±3.2	107	Healthy blood donors		103
Tien-Jyung Chang	2000	Han Chinese-Taiwan	8.8±5.6	157	Healthy subjects		248
Charalambos Panierakis	2009	Crete-Greece	Children	100	Unrelated children		96
Greear R M	2013	Brisbane-Australia	<15	55	Healthy subjects	<15	50
Chong-Kun Cheon	2015	Pusan-South Korea	10.28±3.23	81	Healthy children	9.98±3.56	113

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Table 2 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for *ApaI* AA polymorphism respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
T J Chang 2000	16/157	13/248	2.051	0.958–4.391		
Balazs Gyorffy 2002	33/107	23/103	1.551	0.835–2.881		
Vaselin Scrabic 2003	66/134	51/132	1.542	0.947–2.509		
J J San Pedro 2005	15/71	28/88	0.574	0.278–1.185		
Diego Garcia 2007	54/216	43/203	1.240	0.786–1.957		
C Panierakis 2009	23/100	37/96	0.476	0.256–0.886		
Greear R M 2013	15/55	12/50	1.187	0.493–2.861		
Chung Cheon 2015	5/81	9/113	0.760	0.245–2.359		
Total (fixed effects)	227/921	216/1033	1.113	0.893–1.388	0.954	0.340
Total (random effects)	227/921	216/1033	1.081	0.755–1.547	0.425	0.671
Q	16.3471					
DF	7					
Significance level	$P=0.0221$					
I^2 (inconsistency)	57.18%					
95% CI for I^2	5.93–80.51					

Bias indicators: Begg–Mazumdar: Kendall's Tau = –0.142857 $P=0.5484$ (low power); Egger: bias = –1.369742 (95% CI = –6.646958 to 3.907474) $P=0.5488$; Harbord–Egger: bias = –1.179831 (92.5% CI = –5.949539 to 3.589877) $P=0.6138$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

Of the articles included in the study, investigators of all studies included in the meta-analysis specifically looked for the presence of autoantibodies to diagnose type 1 diabetes and all fulfilled World Health Organization and the American Diabetes Association criteria (24).

Selection of controls varied across studies. Groups of controls included healthy blood donors and unrelated children.

ApaI, BsmI, FokI and TaqI polymorphisms and the risk for type 1 diabetes

For ApaI-AA, the odds ratio ranged from 0.476 to 2.051 (Table 2). The random-effects model yielded a pooled odds ratio of 1.081 (95 percent confidence interval (CI): 0.755–1.547). There was indication of heterogeneitiy ($P=0.0221$).

Table 3 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for ApaI Aa polymorphism respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
T J Chang 2000	76/157	105/248	1.278	0.855–1.910		
Balazs Gyorffy 2002	45/107	54/103	0.659	0.382–1.136		
Vaselin Scrabic 2003	52/134	66/132	0.634	0.390–1.032		
J J San Pedro 2005	37/71	43/88	1.139	0.609–2.129		
Diego Garcia 2007	115/216	125/203	0.710	0.481–1.048		
C Panierakis 2009	58/100	57/96	0.945	0.535–1.669		
Greear R M 2013	24/55	32/50	0.435	0.198–0.956		
Chung Cheon 2015	32/81	34/113	1.517	0.833–2.765		
Total (fixed effects)	439/921	516/1033	0.873	0.729–1.046	–1.473	0.141
Total (random effects)	439/921	516/1033	0.866	0.664–1.131	–1.054	0.292
Q	14.2512					
DF	7					
Significance level	$P=0.0469$					
I^2 (inconsistency)	50.88%					
95% CI for I^2	0.00–78.02					

Bias indicators: Begg–Mazumdar: Kendall's Tau = 0 $P=0.9049$ (low power); Egger: bias = –0.928241 (95% CI = –7.113964 to 5.257482) $P=0.7261$; Harbord–Egger: bias = –0.806491 (92.5% CI = –6.321591 to 4.708608) $P=0.7638$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

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Table 4 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for ApaI aa polymorphism respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
T J Chang 2000	65/157	130/248	0.641	0.428–0.960		
Balazs Gyorffy 2002	27/107	26/103	1.000	0.536–1.863		
Vaselin Scrabic 2003	16/134	15/132	1.058	0.500–2.238		
J J San Pedro 2005	19/71	17/88	1.526	0.724–3.217		
Diego Garcia 2007	44/216	35/203	1.228	0.751–2.009		
C Panierakis 2009	15/100	6/96	2.647	0.982–7.139		
Greear R M 2013	11/55	11/50	0.886	0.346–2.270		
Chung Cheon 2015	44/81	70/113	0.731	0.409–1.304		
Total (fixed effects)	241/921	310/1033	0.956	0.772–1.182	–0.419	0.675
Total (random effects)	241/921	310/1033	1.005	0.754–1.339	0.0349	0.972
Q	11.2531					
DF	7					
Significance level	$P=0.1280$					
I^2 (inconsistency)	37.79%					
95% CI for I^2	0.00–72.53					

Bias indicators: Begg–Mazumdar: Kendall's Tau = 0.428571 $P=0.1789$ (low power); Egger: bias = 2.766246 (95% CI = –0.351565 to 5.884058) $P=0.073$; Harbord–Egger: bias = 2.78392 (92.5% CI = –0.118976 to 5.686817) $P=0.0847$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

For ApaI-Aa, the odds ratio ranged from 0.435 to 1.517 (Table 3). The random-effects model yielded a pooled odds ratio of 0.866 (95 percent confidence interval (CI): 0.664–1.131). There was indication of heterogeneity ($P=0.0469$).

For ApaI-aa, the odds ratio ranged from 0.641 to 2.647 (Table 4). The fixed-effects model yielded a pooled odds ratio of 0.956 (95 percent confidence interval (CI): 0.772–1.182). There was indication of homogeneity ($P=0.1280$). In view of these estimates, there is no evidence that any of the three alleles alone is associated with type 1 diabetes.

For BsmI-BB, the odds ratio ranged from 0.460 to 6.458 (Table 5). The fixed-effects model yielded a pooled odds ratio of 1.397 (95 percent confidence interval (CI): 1.034–1.888, $P=0.030$). There was indication of homogeneity ($P=0.4531$).

For BsmI-Bb, the odds ratio ranged from 0.598 to 5.210 (Table 6). The random-effects model yielded a pooled odds ratio of 1.534 (95 percent confidence interval (CI): 1.001–2.350, $P=0.049$). There was indication of heterogeneity ($P=0.0014$).

For BsmI-bb, the odds ratio ranged from 0.242 to 1.407 (Table 7). The random-effects model yielded a

Table 5 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for *BsmI BB* polymorphism, respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
T J Chang 2000	4/157	1/248	6.458	0.715–58.314		
Balazs Gyorffy 2002	17/107	19/103	0.835	0.407–1.713		
Vaselin Scrabic 2003	24/134	17/132	1.476	0.752–2.896		
J J San Pedro 2005	15/71	17/88	1.119	0.514–2.435		
Diego Garcia 2007	21/216	14/203	1.454	0.718–2.943		
C Panierakis 2009	38/100	23/96	1.945	1.048–3.611		
Chung Cheon 2015	0/81	1/113	0.460	0.0185–11.440		
Total (fixed effects)	119/866	92/983	1.397	1.034–1.888	2.174	0.030
Total (random effects)	119/866	92/983	1.386	1.021–1.880	2.092	0.036
Q	5.7387					
DF	6					
Significance level	$P=0.4531$					
I^2 (inconsistency)	0.00%					
95% CI for I^2	0.00–69.98					

Bias indicators: Begg–Mazumdar: Kendall's Tau = –0.333333 $P=0.2389$ (low power); Egger: bias = 0.081309 (95% CI = –2.562044 to 2.724662) $P=0.94$; Harbord–Egger: bias = 0.057432 (92.5% CI = –2.538737 to 2.653601) $P=0.9624$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

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Table 6 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for *BsmI Bb* polymorphism, respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
Chang 2000	16/157	16/248	1.645	0.798–3.393		
Balazs Gyorffy 2002	53/107	44/103	1.316	0.764–2.268		
Vaselin Scrabic 2003	58/134	74/132	0.598	0.368–0.971		
J J San Pedro 2005	40/71	44/88	1.290	0.688–2.418		
Diego Garcia 2007	110/216	74/203	1.809	1.224–2.674		
C Panierakis 2009	43/100	23/96	2.394	1.296–4.422		
Chung Cheon 2015	13/81	4/113	5.210	1.632–16.633		
Total (fixed effects)	333/866	279/983	1.430	1.160–1.762	3.347	0.001
Total (random effects)	333/866	279/983	1.534	1.001–2.350	1.966	0.049
Q	21.6238					
DF	6					
Significance level	$P=0.0014$					
I^2 (inconsistency)	72.25%					
95% CI for I^2	40.02–87.16					

Bias indicators: Begg–Mazumdar: Kendall's Tau = –0.333333 $P=0.3813$ (low power); Egger: bias = 2.518064 (95% CI = –4.133965 to 9.170093) $P=0.3752$; Harbord–Egger: bias = 2.595692 (92.5% CI = –3.668787 to 8.860172) $P=0.3955$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

pooled odds ratio of 0.624 (95 percent confidence interval (CI): 0.418–0.933, $P=0.022$). There was indication of heterogeneity ($P=0.0075$).

Forest plots are shown in Fig. 2A, B and C for BsmI BB, Bb and bb alleles, respectively. Individual and pooled odds ratio estimates for the BsmI alleles are represented as squares and diamonds. In view of these estimates, there is evidence that BsmI-Bb or BsmI-bb alone is associated with type 1 diabetes.

For FokI-FF, the odds ratio ranged from 0.485 to 1.636 (Table 8). The fixed-effects model yielded a pooled odds ratio of 1.057 (95 percent confidence interval (CI): 0.817–1.367, $P=0.675$). There was indication of homogeneity ($P=0.1443$).

For FokI-Ff, the odds ratio ranged from 0.645 to 1.222 (Table 9). The fixed-effects model yielded a pooled odds ratio of 0.724 (95 percent confidence interval (CI): 0.564–0.929, $P=0.011$). There was indication of homogeneity ($P=0.4324$).

For FokI-ff, the odds ratio ranged from 0.128 to 2.558 (Table 10). The random-effects model yielded a pooled odds ratio of 1.159 (95 percent confidence interval (CI): 0.573–2.344, $P=0.681$). There was indication of heterogeneity ($P=0.0384$).

Table 7 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for *BsmI bb* polymorphism, respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
T J Chang 2000	137/157	231/248	0.504	0.255–0.995		
Balazs Gyorffy 2002	35/107	40/103	0.766	0.435–1.348		
Vaselin Scrabic 2003	52/134	41/132	1.407	0.848–2.336		
J J San Pedro 2005	16/71	27/88	0.657	0.321–1.347		
Diego Garcia 2007	77/216	115/203	0.424	0.286–0.628		
C Panierakis 2009	15/100	20/96	0.671	0.321–1.402		
Chung Cheon 2015	68/81	108/113	0.242	0.0826–0.710		
Total (fixed effects)	400/866	582/983	0.632	0.508–0.786	–4.114	<0.001
Total (random effects)	400/866	582/983	0.624	0.418–0.933	–2.298	0.022
Q	17.5208					
DF	6					
Significance level	$P=0.0075$					
I^2 (inconsistency)	65.76%					
95% CI for I^2	23.26–84.72					

Bias indicators: Begg–Mazumdar: Kendall's Tau = –0.142857 $P=0.5619$ (low power); Egger: bias = –0.656941 (95% CI = –7.053883 to 5.74) $P=0.8023$; Harbord–Egger: bias = 0.561504 (92.5% CI = –6.312289 to 5.189281) $P=0.8354$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

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Table 8 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for *FokI FF* polymorphism respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
Balazs Gyorffy 2002	36/107	29/103	1.294	0.719–2.328		
Tatijana Semunik 2005	42/132	73/232	1.016	0.642–1.609		
J J San Pedro 2005	31/71	41/88	0.888	0.474–1.666		
C Panierakis 2009	64/100	50/96	1.636	0.923–2.898		
Greear R M 2013	21/55	28/50	0.485	0.223–1.058		
Total (fixed effects)	194/465	221/569	1.057	0.817–1.367	0.420	0.675
Total (random effects)	194/465	221/569	1.036	0.733–1.465	0.202	0.840
Q	6.8448					
DF	4					
Significance level	$P=0.1443$					
I^2 (inconsistency)	41.56%					
95% CI for I^2	0.00–78.48					

Bias indicators: Begg–Mazumdar: Kendall's Tau=–0.6 $P=0.00833$ (low power); Egger: bias=–3.653382 (95% CI=–14.60785 to 7.301086) $P=0.3664$; Harbord–Egger: bias=–3.796013 (92.5% CI=–13.262673 to 5.670648) $P=0.3612$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

For TagI-TT, the odds ratio ranged from 0.203 to 1.181 (Table 11). The random-effects model yielded a pooled odds ratio of 0.644 (95 percent confidence interval (CI): 0.440–0.942, $P=0.023$). There was indication of heterogeneity ($P=0.0044$).

For TaqI-Tt, the odds ratio ranged from 0.580 to 2.983 (Table 12). The random-effects model yielded a pooled odds ratio of 1.062 (95 percent confidence interval (CI): 0.785–1.438, $P=0.697$). There was some indication of heterogeneity ($P=0.0536$).

For TaqI-tt, the odds ratio ranged from 0.524 to 3.586 (Table 13). The fixed-effects model yielded a pooled odds ratio of 1.655 (95 percent confidence interval (CI): 1.677–2.295, $P=0.001$). There was indication of heterogeneity ($P=0.3261$).

Forest plots are shown in Fig. 3 and B for TaqI-TT and tt alleles, respectively. Individual and pooled odds ratio estimates for the TaqI alleles are represented as squares and diamonds. In view of these estimates, there is evidence that TaqI-TT and TaqI-tt alone is associated with type 1 diabetes.

Discussion

There are a number of reports on *Fok*I, *Apa*I, *Taq*I and *Bsm*I polymorphisms of the VDR gene in diabetic patients, there have not been conclusive evidence that any of these polymorphisms has causative association with type 1 DM in children. In a 2006 meta-analysis that focused on

Table 9 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for *FokI Ff* polymorphism respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
Balazs Gyorffy 2002	49/107	56/103	0.709	0.412–1.221		
Tatijana Semunik 2005	63/132	136/232	0.645	0.419–0.991		
J J San Pedro 2005	35/71	39/88	1.222	0.652–2.287		
C Panierakis 2009	31/100	43/96	0.554	0.309–0.993		
Greear R M 2013	21/55	22/50	0.786	0.361–1.714		
Total (fixed effects)	199/465	296/569	0.724	0.564–0.929	–2.538	0.011
Total (random effects)	199/465	296/569	0.723	0.563–0.929	–2.535	0.011
Q	3.8098					
DF	4					
Significance level	$P=0.4324$					
I^2 (inconsistency)	0.00%					
95% CI for I^2	0.00–79.45					

Bias indicators: Begg–Mazumdar: Kendall's Tau=–0.4 $P=0.4833$ (low power); Egger: bias=1.95378 (95% CI=5.613844–9.521404) $P=0.4715$; Harbord–Egger: bias=2.01803 (92.5% CI=–4.313428 to 8.349488) $P=0.4557$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

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Table 10 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for *FokI ff* polymorphism respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
Balazs Gyorffy 2002	22/107	18/103	1.222	0.612–2.441		
Tatijana Semunik 2005	29/132	23/232	2.558	1.410–4.643		
J J San Pedro 2005	5/71	8/88	0.758	0.237–2.426		
C Panierakis 2009	1/100	7/96	0.128	0.0155–1.064		
Greear R M 2013	7/55	5/50	1.312	0.388–4.435		
Total (fixed effects)	64/465	61/569	1.374	0.943–2.003	1.656	0.098
Total (random effects)	64/465	61/569	1.159	0.573—2.344	0.411	0.681
Q	10.1246					
DF	4					
Significance level	$P=0.0384$					
I^2 (inconsistency)	60.49%					
95% CI for I^2	0.00–85.20					

Bias indicators: Begg–Mazumdar: Kendall's Tau = –0.6 $P=0.0833$ (low power); Egger: bias = –3.173487 (95% CI = –6.536026 to 0.189052) $P=0.575$; Harbord–Egger: bias = –4.109035 (92.5% CI = –8.5417147 to 0.323644) $P=0.0889$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

VDR polymorphisms, FokI, ApaI, TaqI, BsmI and type 1 DM association included mainly adult samples and did not reveal any specific association (25). However, out of 19 published papers included in this meta-analysis, authors of only five papers specifically looked for the presence of autoantibodies to distinguish type 1 diabetes from type 2. In other 14 studies included in this meta-analysis, investigators used only one criteria (e.g., ketosis, early requirement of insulin). This may be one of the main reasons for different statistical results other than ethnic diversities when compared to our results. DM1 is mainly a disease of pediatric age: considering the qualitative assessment of study inclusion criteria, choosing studies where diagnosis is at pediatric age with age matching control samples, and/or taking American Diabetes Association criteria would end up with more reliable meta-analysis results. In our study, mean age of control samples are in pediatric range. In another meta-analysis involving Chinese adult samples, authors concluded that BsmI polymorphisms in the VDR region would increase the risk of type 1 DM in East Asians (26). In the study of Zhang J, Asian samples with BsmI polymorphism was found to have a significant association with increased risk of type 1 DM (27). The study of Qin WH demonstrated a significant relationship among BsmI B allele and BB genotype and increased risk for type 1 DM in Asians, whereas this study included Latino and African adult samples and authors also found another

Table 11 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for TaqITT polymorphism respectively.

Study	Intervention	Controls	Odds ratio	95% CI	z	P
Chang 2000	142/157	233/248	0.609	0.289–1.284		
Balazs Gyorffy 2002	44/107	42/103	1.014	0.585–1.759		
Vaselin Scrabic 2003	54/134	48/132	1.181	0.720–1.938		
J J San Pedro 2005	24/71	31/88	0.939	0.486–1.813		
Diego Garcia 2007	115/216	121/203	0.772	0.524–1.137		
C Panierakis 2009	10/100	34/96	0.203	0.0933–0.440		
Greear R M 2013	18/55	26/50	0.449	0.204–0.990		
Chung Cheon 2015	66/81	105/113	0.335	0.135–0.834		
Total (fixed effects)	473/921	640/1033	0.713	0.580–0.876	–3.213	0.001
Total (random effects)	473/921	640/1033	0.644	0.440–0.942	–2.270	0.023
Q	20.6282					
DF	7					
Significance level	$P=0.0044$					
I^2 (inconsistency)	66.07%					
95% CI for I^2	28.03–84.00					

Bias indicators: Begg–Mazumdar: Kendall's Tau = –0.642857 $P=0.0141$ (low power); Egger: bias = –3.773452 (95% CI = –8.197852 to 0.650947) $P=0.0819$; Harbord–Egger: bias = –3.522136 (92.5% CI = –8.048273 to 1.004) $P=0.1452$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

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Table 12 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for TaqITt polymorphism respectively.

Study	Intervention	Controls	Odds ratio	95% CI	*z*	*P*
Chang 2000	15/157	14/248	1.766	0.828–3.766		
Balazs Gyorffy 2002	28/107	33/103	0.752	0.414–1.367		
Vaselin Scrabic 2003	55/134	72/132	0.580	0.357–0.943		
J J San Pedro 2005	36/71	43/88	1.076	0.576–2.012		
Diego Garcia 2007	79/216	69/203	1.120	0.750–1.673		
C Panierakis 2009	64/100	59/96	1.115	0.625–1.990		
Greear R M 2013	26/55	24/50	0.971	0.451–2.091		
Chung Cheon 2015	15/81	8/113	2.983	1.199–7.423		
Total (fixed effects)	318/921	322/1033	1.017	0.829–1.248	0.165	0.869
Total (random effects)	318/921	322/1033	1.062	0.785–1.438	0.390	0.697
Q	13.8658					
DF	7					
Significance level	$P=0.0536$					
I^2 (inconsistency)	49.52%					
95% CI for I^2	0.00–77.47					

Bias indicators: Begg–Mazumdar: Kendall's Tau = 0.047619 $P > 0.9999$ (low power); Egger: bias = 1.307065 (95% CI = –4.196619 to 6.810748) $P = 0.5682$; Harbord–Egger: bias = 1.410342 (92.5% CI = –3.284733 to 6.105417) $P = 0.5305$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

specific association with BsmIbb genotype and type 1 DM in overall populations (28). The novel finding in our study was the presence of an increased risk of type 1 DM in carriers of *Bsm*IBB, *Bsm*IBb and *Taq*Itt polymorphisms and decreased risk of type 1 DM in children with *Bsm*Ibb and *Taq*ITT polymorphisms. There are GWAS studies that widen our approach to vitamin D receptor polymorphisms and DM1.

Meta-analysis may be more reliable when evaluating genotype frequencies in certain diseases because in a way it may reduce the effect of biased sampling or nonrandom mating in individual study population. Results of studies so far, regarding VDR polymorphisms and DM1 susceptibility, are conflicting. In the study of Garcia and coworkers, an association was found between BsmI polymorphism and DM1 (15). The frequency of genotype bb was found to be significantly lower in the cases than that in controls. Among five prevalent haplotypes, BAT has been found to be statistically more frequent in study group in the same study. Among genotype combinations, AabbTT was found to be higher in controls. In our study population, genotype combination frequencies were not

Table 13 *P* values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for TaqItt polymorphism respectively.

Study	Intervention	Controls	Odds ratio	95% CI	*z*	*P*
T J Chang 2000	0/157	1/248	0.524	0.0212–12.939		
Balazs Gyorffy 2002	33/107	26/103	1.321	0.721–2.418		
Vaselin Scrabic 2003	25/134	11/132	2.523	1.186–5.367		
J J San Pedro 2005	11/71	14/88	0.969	0.410–2.290		
Diego Garcia 2007	22/216	13/203	1.657	0.811–3.386		
C Panierakis 2009	22/100	7/96	3.586	1.453–8.849		
Greear R M 2013	6/55	5/50	1.102	0.314–3.862		
Chung Cheon 2015	0/81	0/113	–			
Total (fixed effects)	119/921	77/1033	1.677	1.225–2.295	3.230	0.001
Total (random effects)	119/921	77/1033	1.655	1.163–2.356	2.798	0.005
Q	6.9433					
DF	6					
Significance level	$P=0.3261$					
I^2 (inconsistency)	13.59%					
95% CI for I^2	0.00–75.19					

Bias indicators: Begg–Mazumdar: Kendall's Tau = –0.047619 $P > 0.9999$ (low power); Egger: bias = –6.680722 (95% CI = –3.88097 to 2.519525) $P = 0.608$; Harbord–Egger: bias = –1.122847 (92.5% CI = –3.907446 to 1.661601) $P = 0.4074$.
DF, degree of freedom; Q, heterogeneity in meta analysis.

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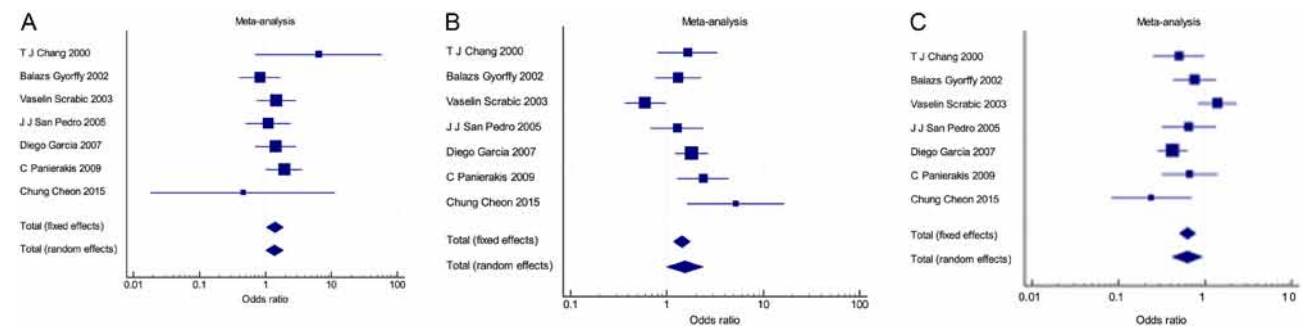

Figure 2
(A, B and C) Forest plots showing individual and pooled odds ratio estimates of *BsmI BB*, *BsmI Bb*, *BsmIbb* polymorphisms, respectively.

assessed because of unavailable data, and this may be one of the limitations of our study.

In the study of San-Pedro JI, an association of an haplotype 'fBAt' and risk of type 1 DM in Basque population has been identified (16). In the study of Skrabic V, BBAAtt genotype combination was found to be associated with type 1 DM in Dalmatian population of southern Croatia, with the 'tt' genotype preferentially presented in the affected individuals (17). This was also noticed in previous studies that focused on association of VDR gene polymorphisms with increased susceptibility to T1DM in Taiwanese, Japanese, South Asian (Indian) and German populations (29, 30, 31, 32). *Taq*I polymorphism among type 1 DM patients and control subjects differed significantly, with the VDR tt genotype occurring more frequently in T1DM patients. No difference was noticed in the genotype frequencies of BsmI and ApaI polymorphisms in cases and controls. We evaluated *Taq*Itt polymorphism frequency and demonstrated a significant increase in diabetic children in our study. In the study of Zemunik and coworkers, some evidence of association of Tru91–BsmI haplotype and type 1 DM in population of South Croatia was found (17). In our meta-analysis, we have included two studies from Croatia. One of the limitations of this study was that its sample size was small, it only included nine studies and the power of this study is not high. In the study of Panierakis and coworkers, homogeneous southern European population with low incidence of type 1 DM was included in the study group, and they found an association of T1DM and *Fok*I, *Bsm*I, *Apa*I and *Taq*I polymorphisms. In this study, *Fok*IFF genotype and F allele and *Bsm*IBB genotype and B allele were less frequent in individuals with T1DM (21). In the same study, *Apa*IAA genotype and A allele, as well as *Taq*ITT genotype and T allele were more frequent in individuals. Greear and coworkers also studied the association of *Taq*1, *Fok*1, *Apa*1 and type 1 DM and found no significant difference in distribution of VDR polymorphisms in diabetic patients, whereas diabetic patients had significantly decreased levels of vitamin D levels than healthy controls (22). In the study of Cheon CK and coworkers, the frequency of bb and TT genotype has been found to be significantly

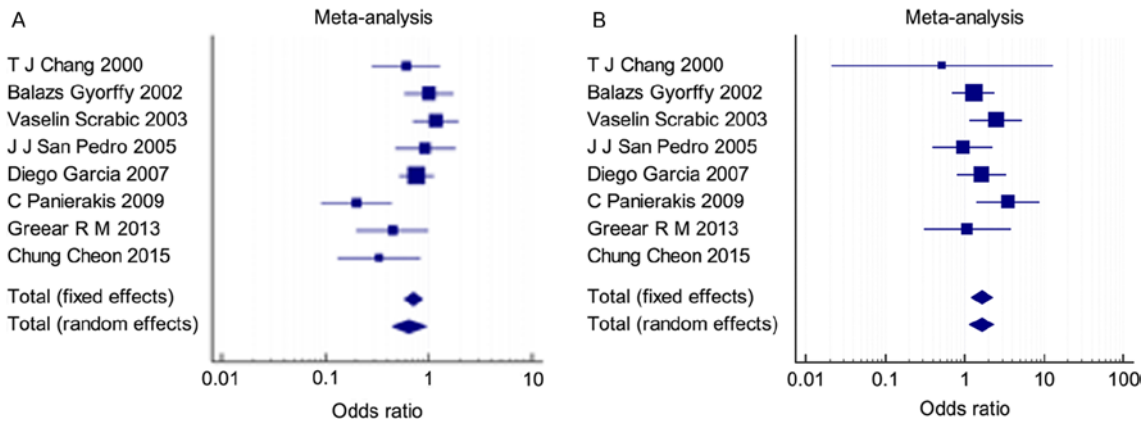

Figure 3
(A and B) Forest plots showing individual and pooled odds ratios of TaqITT and TaqItt polymorphisms, respectively.

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increased among carriers demonstrating a protective effect in Korean subjects (23). Gyorffy and coworkers suggested a strong linkage disequilibrium between the 'b' and 'a' alleles in his study. The close loci of these polymorphisms might be an explanation for the stability of linkage, but the background of these combinations need further investigation (19). In the same study, a strong association has been found between carrier state of the 'b'+'a'+'u' alleles and the presence of type 1 DM in females. There are other reports as well that point out to a gender-specific association and consequence of gene polymorphism (33). A number of studies have shown that patients with 1 DM have low levels of vitamin D although other studies have conflicting results (34, 35, 36). In 2010, GWAS study in approximately 30,000 individuals from European descent identifies variants at four loci that were associated with 25(OH)D levels: GC rs2282679, dhcr7 RS 12785878 and CYP2R1 (37). A second GWAS of 25(OH)D levels confirmed the findings with GC, DHCR7 and CYP2R1 (38). These variants are located within or near genes involved in vitamin D transport (GC), cholesterol synthesis (DHCR7) and hydroxylation (CYP2R1 and CTP24A1) (37). Cooper and coworkers recently tested genetic variants influencing 25(OH)D metabolism for an association with both circulating 25(OH)D metabolism for an association with both circulating 25(OH)D concentrations and T1D. They replicated the associations found in the GWAS of the four vitamin D metabolism genes (GC, DHCR7, CYP2R1 and CYP24A1) with 25(OH)D in control subjects and found that CYP27B1, DHCR7 and CYP2R1 were associated with type 1 diabetes (39). The Fok1 polymorphism of the VDR, which increases the transcriptional activity of VDR, has been suggested as an influencing factor for susceptibility to T1DM. It affects insulin secretion and sensitivity and has been found to be a susceptibility factor for the development of diabetic retinopathy (40, 41). In addition, vitamin D-binding protein gene polymorphisms were found to be associated with diabetes-associated antibody insulinoma antigen 2 and with T1DM (42). In the study of Greear and coworkers, low vitamin D levels in the diabetic children have been attributed to inflammatory or other pathologic processes, mainly as a consequence of the disease rather than being a risk factor, as previously stated in DAISY study (43). In the study of Chang and coworkers, the allele frequency of the BsmI differed between Taiwanese patients and controls significantly (20). There are some limitations in this meta-analysis. The power of this study should further be increased by additional studies, and this meta-analysis involves only nine studies. Some of the studies contained small number of cases, and background of the patients varied across included studies. However our meta-analysis employed a random-effects model designed to encounter these variations and found significant effect of polymorphisms on type 1 DM susceptibility.

As a conclusion, our meta-analysis of accessible published data has demonstrated statistically significant association between BsmIBB, BsmIBb, BsmIbb, *Taq*ITT and Taqtt polymorphisms and susceptibility to type 1 DM in children; however, influence of vitamin D receptor gene polymorphisms on susceptibility to type 1 diabetes deserves further investigations. Meta-analysis includes larger data sets and accordingly may demonstrate more reliable statistical results to rule out genotype–phenotype correlations of diseases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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