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

Ozlem Atan Sahin1, Damla Goksen2, Aysel Ozpınar3, Muhittin Serdar3 and Huseyin Onay4

1Department of Pediatrics, Acıbadem University School of Medicine, Atasehir, Istanbul, Turkey
2Department of Pediatric Endocrinology, Faculty of Medicine, Ege University, Bornova, Izmir, Turkey
3Department of Biochemistry, Acıbadem University, School of Medicine, Atasehir, Istanbul, Turkey
4Department of Medical Genetics, Faculty of Medicine, Ege University, Bornova, Izmir, Turkey

Abstract

Background: There have been studies focused on FokI, BsmI, Apal and TaqI 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, Apal, 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 FokI, Apal, TaqI and BsmI 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 FokI, Apal, TaqI and BsmI 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, BsmIBB (P < 0.05), BsmIBb (P < 0.05), BsmIbb (P < 0.05), TaqITT (P < 0.05) and TaqItt (P < 0.05) in children.

Conclusion: The results indicated that BsmIBB, BsmIBb and TaqItt polymorphisms were associated with an increased risk of type 1 DM, whereas BsmIbb and TaqITT had protective effect for type 1 DM in children.

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 FokI F>f (rs10735810), BsmI B>b (rs1544410), Apal A>a...
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Methods

Search strategy criteria

For meta-analysis, all published studies evaluating the associations between type 1 DM and FokI, Apal, TaqI and BsmI 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, Apal, 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 FokI, Apal, TaqI or BsmI polymorphism at pediatric age. For the primary analysis and to allow appropriate comparison of all studies, cases and controls were classified based on FokI, Apal, TaqI and BsmI 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, Apal, TaqI or BsmI polymorphisms. MedCalc Software Accaliaan 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, Apal, 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,
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, ApaI, BsmI, FokI and TaqI 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 TaqI 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 ApaI, BsmI, FokI and TaqI 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             | 8.2±4.9                     | 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      |
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.

| 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|       |     |
| Greer 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                          | 16.347       |          |            |            |       |     |
| DF                         | 7            |          |            |            |       |     |
| Significance level         | P=0.0221     |          |            |            |       |     |
| I² (inconsistency)         | 57.18%       |          |            |            |       |     |
| 95% CI for I²              | 5.93–80.51   |          |            |            |       |     |

Table 3 | P values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for Apal 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         | 115/216      | 125/203  | 1.139      | 0.609–2.129|       |     |
| Diego Garcia 2007          | 58/100       | 57/96    | 0.945      | 0.535–1.669|       |     |
| C Panierakis 2009          | 24/55        | 32/50    | 0.435      | 0.198–0.956|       |     |
| Greer R M 2013             | 32/81        | 34/113   | 1.517      | 0.833–2.765|       |     |
| Chung Cheon 2015           | 439/921      | 516/1033 | 0.873      | 0.729–1.046| −1.473| 0.141|
| Total (fixed effects)      | 439/921      | 516/1033 | 0.866      | 0.664–1.131| −1.054| 0.292|
| Total (random effects)     | 14.2512      |          |            |            |       |     |
| Q                          | 7            |          |            |            |       |     |
| Significance level         | P=0.0469     |          |            |            |       |     |
| I² (inconsistency)         | 50.88%       |          |            |            |       |     |
| 95% CI for I²              | 5.00–78.02   |          |            |            |       |     |

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

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

For Apal-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 heterogeneity (P=0.0221).
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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 pooled odds ratio of 1.397 (95 percent confidence interval (CI): 1.034–1.888, $P = 0.030$). There was indication of homogeneity ($P = 0.0014$).

### Table 4

| 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 |

### Table 5

| 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 |

### Table 6

| 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 |

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.
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 |          |            |              |       |        |
| I² (inconsistency) | 72.25%   |          |            |              |       |        |
| 95% CI for I²  | 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.

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  | −4.114| <0.001 |
| 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 |          |            |              |       |        |
| I² (inconsistency) | 65.76%    |          |            |              |       |        |
| 95% CI for I²  | 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.
For TaqI-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 \( FokI \), \( ApaI \), \( TaqI \) and \( BsmI \) 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 8

| Study               | Intervention | Controls | Odds ratio | 95% CI        | \( z \) | \( P \) |
|---------------------|--------------|----------|------------|---------------|--------|-------|
| Balazs Gyorffy 2002 | 36/107       | 29/103   | 1.294      | 0.719–2.328   |        |       |
| Tatjana 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) \( P = 0.3664 \);

DF, degree of freedom; Q, heterogeneity in meta analysis.

### Table 9

| Study               | Intervention | Controls | Odds ratio | 95% CI        | \( z \) | \( P \) |
|---------------------|--------------|----------|------------|---------------|--------|-------|
| Balazs Gyorffy 2002 | 49/107       | 56/103   | 0.709      | 0.412–1.221   |        |       |
| Tatjana 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: \( P = 0.04324 \)
\( I^2 \) (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) \( P = 0.4715 \);

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 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  | 1.656 | 0.098 |
| Tatjana Semunik 2005   | 29/132       | 23/232   | 2.558      | 1.410–4.643  | 2.37  | 0.020 |
| J J San Pedro 2005     | 5/71         | 8/88     | 0.758      | 0.237–2.426  | 0.87  | 0.385 |
| C Panierakis 2009      | 1/100        | 7/96     | 0.128      | 0.0155–1.064 | 1.312 | 0.188 |
| Greear R M 2013        | 7/55         | 5/50     | 1.312      | 0.388–4.435  | 0.411 | 0.681 |
| 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) \( P = 0.0899 \). DF, degree of freedom; Q, heterogeneity in meta analysis.

Table 11  \( P \) values testing Hardy–Weinberg proportion and test for heterogeneity of studies included in the meta-analysis for TaqI TT polymorphism respectively.

| Study                  | Intervention | Controls | Odds ratio | 95% CI       | z   | P     |
|------------------------|--------------|----------|------------|--------------|-----|-------|
| Chang 2000             | 142/157      | 233/248  | 0.609      | 0.289–1.284  | 1.014 | 0.313 |
| Balazs Gyorffy 2002    | 44/107       | 42/103   | 1.014      | 0.585–1.759  | 1.181 | 0.229 |
| Vasilin Scabaric 2003  | 54/134       | 48/132   | 1.181      | 0.720–1.938  | 0.939 | 0.353 |
| J J San Pedro 2005     | 24/71        | 31/88    | 0.939      | 0.486–1.813  | 0.939 | 0.345 |
| Diego Garcia 2007      | 115/216      | 121/203  | 0.772      | 0.524–1.137  | 0.722 | 0.467 |
| C Panierakis 2009      | 10/100       | 34/96    | 0.203      | 0.0933–0.440 | 0.713 | 0.458 |
| Greear R M 2013        | 18/55        | 26/50    | 0.449      | 0.204–0.990  | 0.449 | 0.549 |
| Chung Cheon 2015       | 66/81        | 105/113  | 0.335      | 0.135–0.834  | 0.335 | 0.738 |
| 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.
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 BsmIBB, BsmIBb and TaqITT polymorphisms and decreased risk of type 1 DM in children with BsmIbb and TaqITT 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 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    | 3.230| 0.001 |
| Balazs Gyorffy 2002 | 28/107       | 33/103   | 0.752      | 0.414–1.367    | 0.673| 0.500 |
| Vaselin Scarbic 2003 | 55/134       | 72/132   | 0.580      | 0.357–0.943    | 2.230| 0.025 |
| J J San Pedro 2005 | 36/71        | 43/88    | 1.076      | 0.576–2.012    | 3.445| 0.001 |
| Diego Garcia 2007 | 79/216       | 69/203   | 1.120      | 0.750–1.673    | 1.991| 0.046 |
| C Panierakis 2009 | 64/100       | 59/96    | 1.115      | 0.625–1.990    | 1.642| 0.100 |
| Greear R M 2013 | 26/55        | 24/50    | 0.971      | 0.451–2.091    | 1.473| 0.141 |
| Chung Cheon 2015 | 25/81        | 9/113    | 2.983      | 1.199–7.423    | 3.336| 0.001 |
| 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 |

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.

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     |
|----------------|--------------|----------|------------|----------------|------|-------|
| Chang 2000     | 15/157       | 14/248   | 1.766      | 0.828–3.766    | 3.230| 0.001 |
| Balazs Gyorffy 2002 | 28/107       | 33/103   | 0.752      | 0.414–1.367    | 0.673| 0.500 |
| Vaselin Scarbic 2003 | 55/134       | 72/132   | 0.580      | 0.357–0.943    | 2.230| 0.025 |
| J J San Pedro 2005 | 36/71        | 43/88    | 1.076      | 0.576–2.012    | 3.445| 0.001 |
| Diego Garcia 2007 | 79/216       | 69/203   | 1.120      | 0.750–1.673    | 1.991| 0.046 |
| C Panierakis 2009 | 64/100       | 59/96    | 1.115      | 0.625–1.990    | 1.642| 0.100 |
| Greear R M 2013 | 26/55        | 24/50    | 0.971      | 0.451–2.091    | 1.473| 0.141 |
| Chung Cheon 2015 | 25/81        | 9/113    | 2.983      | 1.199–7.423    | 3.336| 0.001 |
| 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 |

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 = -4.196619 (95% CI = -3.284733 to 6.105417) $P = 0.5305$. DF, degree of freedom; Q, heterogeneity in meta analysis.
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). TaqI 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 TaqItt 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 FokI, BsmI, ApaI and TaqI polymorphisms. In this study, FokIIF genotype and F allele and BsmIBB genotype and B allele were less frequent in individuals with T1DM (21). In the same study, ApaIAA genotype and A allele, as well as TaqITT genotype and T allele were more frequent in individuals. Greear and coworkers also studied the association of TaqI, FokI, ApaI 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 2
(A, B and C) Forest plots showing individual and pooled odds ratio estimates of BsmI BB, BsmI Bb, BsmIbb polymorphisms, respectively.

Figure 3
(A and B) Forest plots showing individual and pooled odds ratios of TaqITT and TaqItt polymorphisms, respectively.
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 combination needs further investigation (19). In the same study, a strong association has been found between carrier state of the ‘b+’ 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 CYP24A1) (37). Cooper and coworkers recently tested genetic variants influencing 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 Greer 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 BsmIIB, BsmIIB, BsmIbb, TaqIT and TaqIT 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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