Human Genome Epidemiology (HuGE) Review

Meta-Analysis of Vitamin D Receptor Polymorphisms and Type 1 Diabetes: A HuGE Review of Genetic Association Studies

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Several polymorphisms in the vitamin D receptor (VDR) gene have been reported to be associated with the risk of developing type 1 diabetes, yet published findings have been conflicting. In this study, the authors attempted to evaluate the evidence regarding the association. They searched all relevant reports from original papers published from 1997 to December 2005. Predefined criteria were used to identify 1) case-control association studies examining the FokI (11 studies), BsmI (13 studies), ApaI (9 studies), and TaqI (7 studies) polymorphisms and 2) a few family-transmission studies with analysis of these four polymorphisms. In random-effects modeling, the 95% confidence intervals of the summary odds ratios for all four polymorphisms included 1, indicating no effect. Except for FokI, no heterogeneity was found. The 95% confidence intervals of the transmission proportions all included 0.5, indicating no effect. Thus, the authors found no evidence for an association between VDR gene polymorphisms and type 1 diabetes risk in either case-control studies or family-transmission studies. In fact, a reanalysis of previously published data (McDermott et al., Diabetologia 1997;40:971–5) indicated no evidence of an association as reported.

association; diabetes mellitus, type 1; epidemiology; genetics; meta-analysis; polymorphism, genetic; receptors, calcitriol; VDR

Abbreviations: CI, confidence interval; SNP, single nucleotide polymorphism; VDR, vitamin D receptor.

Editor’s note: This article is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/).

That type 1 diabetes has a strong genetic component is now indisputable. Human leukocyte antigen class II genes have been identified as the most important genetic factor in determining the risk of developing type 1 diabetes. The VNTR (variable number of tandem repeats) polymorphism located in the promoter region of the insulin gene and the cytotoxic T-cell-associated antigen-4 gene also have been identified (1, 2). However, these genes are neither sufficient nor necessary to cause type 1 diabetes. Hence, the search for other genes and environmental triggers has been ongoing.

Investigators from several epidemiologic studies have reported that dietary vitamin D supplementation during infancy and childhood reduces the risk of type 1 diabetes (3–5). Recently, in the Diabetes Autoimmunity Study in the Young, Fronczak et al. (6) reported that the presence of islet autoantibodies in offspring was inversely correlated with maternal dietary vitamin D intake during pregnancy. Vitamin D receptor (VDR) polymorphisms are reported to
be associated with insulin secretory capacity in humans (7). In experimental studies, oral administration of 1α,25-
dihydroxyvitamin D₃, the activated form of vitamin D, com-
pletely protects NOD mice from type 1 diabetes (8, 9). In
addition, it has been reported that a vitamin D analog can
down-regulate proinflammatory chemokine production by
pancreatic islets, thereby inhibiting T-cell recruitment and
development of type 1 diabetes (10). These epidemiologic
and experimental data appear to indicate that vitamin D
deficiency may be involved in the pathogenesis of type 1
diabetes, possibly because vitamin D is a potent modulator
of the immune system and is involved in regulating cell
proliferation and differentiation (11, 12).

Vitamin D and its analogs exert their actions through
VDR, which is a member of the steroid hormone recep-
tor superfamily. The VDR gene, located on chromosome
12q12–q14, has at least five promoter regions (13), eight
protein-coding exons, and six untranslated exons, which
are alternatively spliced (14). FokI (in exon 2), BsmI and
ApaI (both in intron 8), and TaqI (in exon 9) are the
four common single nucleotide polymorphisms (SNPs)
(rs10735810, rs1544410, rs7975232, and rs731236, respec-
tively) in the VDR gene that have been most often investi-
gated (12, 15).

The first report of a type 1 diabetes-VDR association was
made by McDermott et al. (16) in 1997. They reported that
the “h” allele of the BsmI polymorphism in the VDR gene
was preferentially transmitted to offspring afflicted with
type 1 diabetes. As with other genetic association studies,
however, reports on the type 1 diabetes-VDR association
have been conflicting. A recent study involving over 3,000
families with type 1 diabetes found no evidence for an
association of type 1 diabetes with any of the four SNPs men-
tioned above or with any of numerous other polymorphisms
across the VDR gene (17).

Since an individual study may not have enough statistical
power to detect any association between type 1 diabetes and
VDR polymorphisms, a meta-analysis that combines data
from all published studies may provide a more accurate
estimate of effect sizes, leading to a reduced probability
of false-negative results (18). Thus, we conducted a com-
prehensive and quantitative assessment of the association
between type 1 diabetes and the four aforementioned poly-
morphisms. We sought to estimate effect sizes and to de-
termine the extent of heterogeneity in the strength of
associations between studies.

MATERIALS AND METHODS

Search strategy and inclusion/exclusion criteria

We searched the US National Library of Medicine’s
fcg) in a systematic and diligent manner for all genetic
association studies on VDR and type 1 diabetes published
from 1997, when the VDR-type 1 diabetes association was
first reported (16), through December 2005. We focused on
the four most-studied polymorphisms: ApaI, BsmI, FokI,
and TaqI. The search used the keywords “association
studies,” “insulin-dependent diabetes,” “type 1 diabetes,”
“vitamin D receptor,” “ApaI,” “BsmI,” “FokI,” “TaqI,”
and “polymorphisms,” as well as combinations thereof. The
references of all computer-identified publications were
searched for additional studies, and the PubMed option
“Related Articles” was used to search for potentially rele-
vant papers. Papers published in any language were selected
if they met the following criteria: 1) the publication was an
association study, either of the case-control type or a family-
transmission study, and 2) the publication reported geno-
typic frequencies of VDR polymorphisms in unrelated type 1
diabetes patients and unrelated individual controls, or re-
ported proportions of transmission of specific alleles at a
locus in the VDR gene. In the case of sequential or multiple
publications of analyses of the same data or overlapping
data sets, the publication that reported data from the largest
or most recent study was included, as recommended by
Little et al. (19).

Data extraction

Following the MOOSE (Meta-analysis Of Observational
Studies in Epidemiology) guidelines for reporting on meta-
analyses of observational studies (20), the following data
were extracted from the eligible studies: authors’ names;
region/country where the study was conducted; year of
publication; numbers of cases/patients and controls or
number of families studied; mean age (or range) at onset
of type 1 diabetes in cases/patients or probands; diagnostic
criteria; mean age (and standard deviation) or age range in
the control group; manner in which the controls were se-
lected; and number of subjects with the VDR genotype in
both cases and controls. Information on whether the inves-
tigators had made any attempt to test for Hardy-Weinberg
proportion in the controls, to check for and correct geno-
typing errors, and to control for confounding risk factors
was also noted.

The search produced 21 published papers on the genetic
association between the VDR gene and type 1 diabetes, 20 in
English (7, 16, 17, 21–38) and one in Spanish (39). Data
used in the article by Marti et al. (39) appeared to be iden-
tical to the data reported by Audi et al. (32), so the paper
by Marti et al. was excluded. Eerligh et al. (31) did not
report the transmission probability of any VDR polymor-
phism, and thus this paper was also excluded. The more
detailed genotypic data not presented in the paper by Yokota
et al. (28) were kindly provided by Dr. Yokota and were
included. Turpeinen et al. (35) reported data on populations
from three different geographic regions; these data were
counted as three different studies in this analysis. For simi-
lar reasons, data from two different areas (Barcelona and
Navarre) in the paper by Audi et al. (32) were counted as
two separate studies. Therefore, of the 21 papers identified,
two were excluded. Of the 19 remaining papers, six were
family studies reporting numbers of transmitted alleles
or haplotypes at ApaI, BsmI, FokI, and/or TaqI in type 1
diabetes patients (16, 17, 24, 25, 34, 37), and the rest re-
ported genotype/haplotype frequencies at FokI, BsmI, ApaI,
and/or TaqI in cases and controls. In all cases, genotypes
TABLE 1. Characteristics of case-control studies included in a meta-analysis of the relation between the FokI polymorphism in the vitamin D receptor gene and type 1 diabetes

<table>
<thead>
<tr>
<th>First author (reference no.)</th>
<th>Year</th>
<th>Region and country where the study was conducted</th>
<th>Mean age of onset in cases and/or age range (years)</th>
<th>Sex composition in cases (% male)</th>
<th>Source of controls</th>
<th>Mean age of controls (years)</th>
<th>Genotype distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ban (23)</td>
<td>2001</td>
<td>Tokyo, Japan</td>
<td>26.0 (3.7)‡</td>
<td>45.5</td>
<td>People without a family history of diabetes/autoimmune diseases</td>
<td>NR†</td>
<td>6 52 52 0.18 30 138 82 0.02</td>
</tr>
<tr>
<td>Gyorffy (27)</td>
<td>2002</td>
<td>Budapest, Hungary</td>
<td>5.8 (3.2); 1–14</td>
<td>53.3</td>
<td>Blood donors</td>
<td>NR</td>
<td>18 59 30 0.29 21 48 34 0.70</td>
</tr>
<tr>
<td>Fassbender (26)</td>
<td>2002</td>
<td>Frankfurt, Germany</td>
<td>23.25 (11.79)</td>
<td>56</td>
<td>Convenience samples</td>
<td>33.5 (10.9)</td>
<td>10 30 35 0.50 8 30 19 0.62</td>
</tr>
<tr>
<td>Yokota (28)</td>
<td>2002</td>
<td>Tokushima, Japan</td>
<td>0.4–18; median, 8.9</td>
<td>38.0</td>
<td>Unrelated nondiabetic persons</td>
<td>NR</td>
<td>12 46 50 0.90 20 59 41 0.96</td>
</tr>
<tr>
<td>Turpeinen (35)</td>
<td>2003</td>
<td>Turku, Finland</td>
<td>&lt;15</td>
<td>50</td>
<td>Healthy infants enrolled in the DIPP† Study</td>
<td>NR</td>
<td>50 150 74 0.11 102 414 292 0.02</td>
</tr>
<tr>
<td>Turpeinen (35)</td>
<td>2003</td>
<td>Tampere, Finland</td>
<td>&lt;15</td>
<td>50</td>
<td>Healthy infants enrolled in the DIPP Study</td>
<td>NR</td>
<td>7 28 20 0.71 61 226 170 0.33</td>
</tr>
<tr>
<td>Turpeinen (35)</td>
<td>2003</td>
<td>Oulu, Finland</td>
<td>&lt;15</td>
<td>50</td>
<td>Healthy infants enrolled in the DIPP Study</td>
<td>NR</td>
<td>37 114 98 0.76 93 360 342 0.95</td>
</tr>
<tr>
<td>Audi (32)</td>
<td>2004</td>
<td>Barcelona, Spain</td>
<td>NR</td>
<td>NR</td>
<td>Regional match</td>
<td>NR</td>
<td>18 68 69 0.94 28 142 105 0.06</td>
</tr>
<tr>
<td>Audi (32)</td>
<td>2004</td>
<td>Navarre, Spain</td>
<td>NR</td>
<td>NR</td>
<td>Regional match</td>
<td>NR</td>
<td>6 45 35 0.14 22 53 41 0.61</td>
</tr>
<tr>
<td>Zemunik (36)</td>
<td>2005</td>
<td>Split, Croatia</td>
<td>8.6 (4.3)</td>
<td>53.7</td>
<td>Children undergoing check-ups</td>
<td>8.2 (4.9)</td>
<td>29 63 42 0.65 23 136 73 &lt;0.01</td>
</tr>
<tr>
<td>San-Pedro (38)</td>
<td>2005</td>
<td>Basque Country, Spain</td>
<td>14.5 (9.9)</td>
<td>NR</td>
<td>Blood donors</td>
<td>NR</td>
<td>5 35 31 0.34 8 39 41 0.91</td>
</tr>
</tbody>
</table>

* Based on the χ² test.
† HWP, Hardy-Weinberg proportion; NR, not reported; DIPP, Diabetes Prediction and Prevention.
‡ Numbers in parentheses, standard deviation.
<table>
<thead>
<tr>
<th>First author (reference no.)</th>
<th>Year</th>
<th>Region and country where the study was conducted</th>
<th>Mean age of onset in cases and/or age range (years)</th>
<th>Sex composition in cases (% male)</th>
<th>Source of controls</th>
<th>Mean age of controls and/or age range (years)</th>
<th>Genotype distribution</th>
<th>Cases p value* for HWP</th>
<th>Controls p value* for HWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hauache (21)</td>
<td>1998</td>
<td>San Paulo, Brazil</td>
<td>12 (3.9); 0–17</td>
<td>57.7</td>
<td>Adult volunteers</td>
<td>Range, 18–49; median, 32.5</td>
<td>bb Bb BB p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang (22)</td>
<td>2000</td>
<td>Taiwan</td>
<td>8.8 (5.6)</td>
<td>NR</td>
<td>Regional match</td>
<td>NR</td>
<td>&lt;0.01 231 16 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gyorffy (27)</td>
<td>2002</td>
<td>Budapest, Hungary</td>
<td>5.8 (3.2); 1–14</td>
<td>53.2</td>
<td>Blood donors</td>
<td>NR</td>
<td>0.39 34 52 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fassbender (26)</td>
<td>2002</td>
<td>Frankfurt, Germany</td>
<td>23.25 (11.79)</td>
<td>56</td>
<td>Convenience samples</td>
<td>33.5 (10.9)</td>
<td>0.85 14 25 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motohashi (30)</td>
<td>2003</td>
<td>Tokyo, Japan</td>
<td>34.6 (16.9)</td>
<td>47</td>
<td>Unrelated healthy volunteers</td>
<td>44.4 (13.7)</td>
<td>0.40 127 64 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpeinen (35)</td>
<td>2003</td>
<td>Turku, Finland</td>
<td>&lt;15</td>
<td>−50</td>
<td>Healthy infants enrolled in the DIPP Study</td>
<td>NR</td>
<td>356 389 99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpeinen (35)</td>
<td>2003</td>
<td>Tampere, Finland</td>
<td>&lt;15</td>
<td>−50</td>
<td>Healthy infants enrolled in the DIPP Study</td>
<td>NR</td>
<td>533 488 154</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpeinen (35)</td>
<td>2003</td>
<td>Oulu, Finland</td>
<td>&lt;15</td>
<td>−50</td>
<td>Healthy infants enrolled in the DIPP Study</td>
<td>NR</td>
<td>403 305 110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skrabic (29)</td>
<td>2003</td>
<td>Split, Croatia</td>
<td>8.6 (4.3)</td>
<td>53.7</td>
<td>Children undergoing check-ups</td>
<td>8.24 (4.9)</td>
<td>0.34 52 58 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audi (32)</td>
<td>2004</td>
<td>Barcelona, Spain</td>
<td>NR</td>
<td>NR</td>
<td>Regional match</td>
<td>NR</td>
<td>0.93 59 73 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audi (32)</td>
<td>2004</td>
<td>Navarre, Spain</td>
<td>NR</td>
<td>NR</td>
<td>Regional match</td>
<td>NR</td>
<td>0.90 26 40 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bianco (33)</td>
<td>2004</td>
<td>Genoa, Italy</td>
<td>2–22.5</td>
<td>67.7</td>
<td>Blood donors</td>
<td>20–39.8</td>
<td>0.92 5 14 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>San Pedro (38)</td>
<td>2005</td>
<td>Basque Country, Spain</td>
<td>14.5 (9.9)</td>
<td>NR</td>
<td>Blood donors</td>
<td>NR</td>
<td>0.37 16 40 15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Based on the x² test.
† HWP, Hardy-Weinberg proportion; NR, not reported; DIPP, Diabetes Prediction and Prevention.
‡ Numbers in parentheses, standard deviation.
### TABLE 3. Characteristics of case-control studies included in a meta-analysis of the ApaI polymorphism in the vitamin D receptor gene and type 1 diabetes

<table>
<thead>
<tr>
<th>First author (reference no.)</th>
<th>Year</th>
<th>Region and country where the study was conducted</th>
<th>Mean age of onset in cases and/or age range (years)</th>
<th>Sex composition in cases (% male)</th>
<th>Source of controls</th>
<th>Mean age of controls and/or age range (years)</th>
<th>Genotype distribution (Cases)</th>
<th>Genotype distribution (Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang (22)</td>
<td>2000</td>
<td>Taiwan</td>
<td>8.8 (5.6)†</td>
<td>NR†</td>
<td>Regional match</td>
<td>NR</td>
<td>65</td>
<td>130 105 13 0.95</td>
</tr>
<tr>
<td>Gyorffy (27)</td>
<td>2002</td>
<td>Budapest, Hungary</td>
<td>5.8 (3.2); 1–14</td>
<td>53.3</td>
<td>Blood donors</td>
<td>NR</td>
<td>27</td>
<td>26 43 32 0.19</td>
</tr>
<tr>
<td>Yokota (28)</td>
<td>2002</td>
<td>Tokushima, Japan</td>
<td>0.4–18; median, 8.9</td>
<td>38.0</td>
<td>Unrelated nondiabetic persons</td>
<td>NR</td>
<td>46</td>
<td>62 44 14 0.22</td>
</tr>
<tr>
<td>Turpeinen (35)</td>
<td>2003</td>
<td>Turku, Finland</td>
<td>&lt;15</td>
<td>–50</td>
<td>Healthy infants enrolled in the DIPP† Study</td>
<td>NR</td>
<td>35</td>
<td>152 441 204 &lt;0.01</td>
</tr>
<tr>
<td>Turpeinen (35)</td>
<td>2003</td>
<td>Tampere, Finland</td>
<td>&lt;15</td>
<td>–50</td>
<td>Healthy infants enrolled in the DIPP Study</td>
<td>NR</td>
<td>13</td>
<td>69 229 152 0.29</td>
</tr>
<tr>
<td>Turpeinen (35)</td>
<td>2003</td>
<td>Oulu, Finland</td>
<td>&lt;15</td>
<td>–50</td>
<td>Healthy infants enrolled in the DIPP Study</td>
<td>NR</td>
<td>43</td>
<td>165 389 289 0.11</td>
</tr>
<tr>
<td>Skrabic (29)</td>
<td>2003</td>
<td>Split, Croatia</td>
<td>8.6 (4.3)†</td>
<td>53.7</td>
<td>Children undergoing check-ups</td>
<td>8.24 (4.9)</td>
<td>16</td>
<td>15 66 51 0.44</td>
</tr>
<tr>
<td>Bianco (33)</td>
<td>2004</td>
<td>Genoa, Italy</td>
<td>2–22.5</td>
<td>67.7</td>
<td>Blood donors</td>
<td>20–39.8</td>
<td>2</td>
<td>5 20 11 0.55</td>
</tr>
<tr>
<td>San-Pedro (38)</td>
<td>2005</td>
<td>Basque Country, Spain</td>
<td>14.5 (9.9)</td>
<td>NR</td>
<td>Blood donors</td>
<td>NR</td>
<td>19</td>
<td>17 43 28 0.91</td>
</tr>
</tbody>
</table>

* Based on the χ² test.
† HWP, Hardy-Weinberg proportion; NR, not reported; DIPP, Diabetes Prediction and Prevention.
‡ Numbers in parentheses, standard deviation.

### TABLE 4. Characteristics of case-control studies included in a meta-analysis of the TaqI polymorphism in the vitamin D receptor gene and type 1 diabetes

<table>
<thead>
<tr>
<th>First author (reference no.)</th>
<th>Year</th>
<th>Region and country where the study was conducted</th>
<th>Mean age of onset in cases and/or age range (years)</th>
<th>Sex composition in cases (% male)</th>
<th>Source of controls</th>
<th>Mean age of controls and/or age range (years)</th>
<th>Genotype distribution (Cases)</th>
<th>Genotype distribution (Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang (22)</td>
<td>2000</td>
<td>Taiwan</td>
<td>8.8 (5.6)†</td>
<td>NR†</td>
<td>Regional match</td>
<td>NR</td>
<td>0 15 142 0.81</td>
<td>1 14 233 0.59</td>
</tr>
<tr>
<td>Gyorffy (27)</td>
<td>2002</td>
<td>Budapest, Hungary</td>
<td>5.8 (3.2); 1–14</td>
<td>53.3</td>
<td>Blood donors</td>
<td>NR</td>
<td>27</td>
<td>32 42 &lt;0.01</td>
</tr>
<tr>
<td>Fassbender (26)</td>
<td>2002</td>
<td>Frankfurt, Germany</td>
<td>23.25 (11.79)</td>
<td>56</td>
<td>Convenience samples</td>
<td>33.5 (10.9)</td>
<td>10</td>
<td>18 20 19 0.04</td>
</tr>
<tr>
<td>Yokota (28)</td>
<td>2002</td>
<td>Tokushima, Japan</td>
<td>0.4–18; median, 8.9</td>
<td>38.0</td>
<td>Unrelated nondiabetic persons</td>
<td>NR</td>
<td>5</td>
<td>18 101 0.71</td>
</tr>
<tr>
<td>Skrabic (29)</td>
<td>2003</td>
<td>Split, Croatia</td>
<td>8.6 (4.3)†</td>
<td>53.7</td>
<td>Children undergoing check-ups</td>
<td>8.24 (4.9)</td>
<td>25</td>
<td>11 72 48 0.04</td>
</tr>
<tr>
<td>Bianco (33)</td>
<td>2004</td>
<td>Genoa, Italy</td>
<td>2–22.5</td>
<td>67.7</td>
<td>Blood donors</td>
<td>20–39.8</td>
<td>6</td>
<td>5 21 10 0.38</td>
</tr>
<tr>
<td>San-Pedro (38)</td>
<td>2005</td>
<td>Basque Country, Spain</td>
<td>14.5 (9.9)</td>
<td>NR</td>
<td>Blood donors</td>
<td>NR</td>
<td>11</td>
<td>14 43 31 0.95</td>
</tr>
</tbody>
</table>

* Based on the χ² test.
† HWP, Hardy-Weinberg proportion; NR, not reported.
‡ Numbers in parentheses, standard deviation.
<table>
<thead>
<tr>
<th>First author (reference no.) and haplotype</th>
<th>Region and country where the study was conducted</th>
<th>Year</th>
<th>No. of families</th>
<th>Mean age of onset in cases and/or age range (years)</th>
<th>Sex composition in cases (% male)</th>
<th>Haplotype transmitted</th>
<th>Haplotype not transmitted</th>
<th>No. of alleles transmitted to affected offspring/ no. of possible transmissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDermott (16)</td>
<td>Madras, India</td>
<td>1997</td>
<td>93</td>
<td>11.1 (6.6)*; 1–29</td>
<td>31</td>
<td>BAT</td>
<td>a: 64/127</td>
<td>b: 75/132 (or 53/84 as reported by McDermott et al. (16))</td>
</tr>
<tr>
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<td></td>
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<td></td>
</tr>
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<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>baT</td>
<td>34</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pani (24)</td>
<td>Bonn, Germany</td>
<td>2000</td>
<td>152</td>
<td>11.2; 1–35</td>
<td>50</td>
<td>BAT</td>
<td>a: 57/113</td>
<td>b: 77/166</td>
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<td>2002</td>
<td>204</td>
<td>12.1 (6.7); 0.75–43</td>
<td>49.1</td>
<td>NR</td>
<td>NR</td>
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</tr>
<tr>
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</tr>
<tr>
<td>t: 75/171</td>
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</tr>
<tr>
<td>Kooleman (37)</td>
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<td>206</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>t: 102/171</td>
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<td>2004</td>
<td>59</td>
<td>8.5 (3.2); 1–14</td>
<td>40.7</td>
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<td>NR</td>
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<td>t: 23/48</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nejentsev (17)</td>
<td>Mixed: United Kingdom, Finland, Norway, Romania, and United States</td>
<td>2004</td>
<td>2,594–3,763</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>a: 2,097/4,229</td>
</tr>
<tr>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>t: 1,558/3,195</td>
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<td></td>
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</tr>
<tr>
<td>t: 1,385/2,791</td>
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<td>t: 1,688/3,294</td>
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</tr>
</tbody>
</table>

* Numbers in parentheses, standard deviation. 
† NR, not reported.
Statistical analysis

The goals of this analysis were to pool crude odds ratio estimates from included case-control studies, to identify any heterogeneity, and, if heterogeneity was present, to attempt to identify its sources. For each included study, we computed the odds ratio for having type 1 diabetes in people with the restriction site (lowercase letter) as compared with people without the site (uppercase letter) and its 95 percent confidence interval, as well as the standard error of the log odds ratio. We chose the log odds ratio simply because, unlike the odds ratio, its standard error is unaffected by its magnitude. For family studies, we calculated a summary of transmission proportions, weighted by the inverse of the estimated variance of the transmission proportion of each study.

Since all four of the studied SNPs (FokI, BsmI, ApaI, and TaqI) are diallelic, we calculated summary odds ratios incorporating both within- and between-study variation, using a random-effects model proposed by DerSimonian and Laird (40). This model provides a means of testing for heterogeneity in odds ratio estimates across studies. The random-effects model stipulates that, in addition to sampling errors, the studies may have genuine variations in their results attributable to some unknown variables not accounted for by all studies.

For gene transmission data, we calculated the pooled estimate of the transmission proportion by using the inverse of the variance of the individual estimates as weights. The test for heterogeneity was carried out using the method of Pothoff and Whittinghill (41).
Funnel plots were used to examine asymmetry, in which the odds ratios were plotted on a logarithmic scale against the inverse of their corresponding standard errors, a measure of precision (42). The funnel plots were also used to plot the transmission proportions from each study against the inverse of their standard errors. If bias is absent, small studies will have odds ratios or transmission proportions that are widely scattered but symmetric about the odds ratio or the transmission proportion estimates provided by larger, more precise studies. In this case, the plot would resemble a funnel with the tip pointing approximately towards the true log odds ratio or the transmission proportion. If publication bias is present, the plot will be asymmetric, since some studies with negative findings are not published.

To examine whether the association between a particular allele at a given locus and type 1 diabetes was genuine rather than an artifact of multiple comparisons, we used funnel plots to search for frequency differences in specific alleles between cases and controls. Specifically, we plotted the difference in allele/genotype frequency, \( p_i - q_i \), versus its standard error. When the odds ratio was of interest, the log odds ratio versus its standard error was plotted. When no allele is associated with type 1 diabetes, the plot should resemble a funnel, with the tip of the funnel pointing to 0. When a particular allele/genotype is associated with type 1 diabetes, the frequency difference of that particular allele/genotype should conspicuously stand out. To control for multiple comparisons when testing for differences in \( k \) genotypes of a gene between cases and controls, we used the resampling procedure described by Westfall and Young (43) for computing adjusted \( p \) values.

We also employed funnel plots to examine whether a particular haplotype was genuinely preferentially transmitted to offspring with type 1 diabetes rather than an artifact of multiple comparisons, where the precision was defined as the standard error of the transmission proportion. The \( p \) value for excessive transmission was calculated under the null hypothesis that the transmission proportion was 50 percent. Since different haplotypes are transmitted independently, we used the method of Benjamini and Hochberg (44) to control for multiple comparisons with a 5 percent false-discovery rate.

### Table 6. Numbers of vitamin D receptor gene BsmI-ApaI-TaqI haplotypes transmitted and not transmitted to offspring with type 1 diabetes as reported in studies by McDermott et al. (16) and Pani et al. (24), along with unadjusted \( p \) values for transmission and their significance after adjustment for multiple comparisons (false-discovery rate = 0.05)*

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>McDermott et al. (16)</th>
<th>Pani et al. (24)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>Transmitted</td>
<td>Not transmitted</td>
</tr>
<tr>
<td>BAT</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>BaT</td>
<td>—†</td>
<td>—</td>
</tr>
<tr>
<td>Bat</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>bAT</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>bAt</td>
<td>35</td>
<td>19</td>
</tr>
<tr>
<td>baT</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>bat</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

* Data were extracted from table 2 of the paper by McDermott et al. (16) and table 2 of the paper by Pani et al. (24).
† Unadjusted \( p \) values for transmission were calculated under the null hypothesis of equal transmission proportions based on a binomial distribution.
‡ No data.

FIGURE 2. Funnel plot of transmission proportions for the \( b \) allele at BsmI in four studies of vitamin D receptor gene polymorphisms (16, 17, 24, 34). Each word represents a different study (see third column of table 5). The vertical dashed line represents a null effect.
on the 1,101 cases/patients and 2,805 controls, while 13 studies et al. (38).

RESULTS

Characteristics of included studies

In the 19 published papers included in the meta-analysis, the BsmI, ApaI, and TaqI polymorphisms had been investigated in both case-control studies and family studies. Nine studies on the ApaI-type 1 diabetes association recruited 1,101 cases/patients and 2,805 controls, while 13 studies on the BsmI polymorphism recruited 1,601 cases/patients and 4,207 controls. For the FokI polymorphism, 11 studies included 1,424 cases and 3,301 controls, while seven studies on the TaqI polymorphism included 681 cases/patients and 781 controls. Detailed characteristics of each study, along with p values for testing Hardy-Weinberg proportion, are listed in tables 1–4 for FokI, BsmI, ApaI, and TaqI, respectively. The characteristics of all of the family studies are listed in table 5.

The frequency of the “f” allele at FokI among controls ranged from 56.3 percent in Hungarians to 68.8 percent in the Basque population of Spain. The frequency of the “a” allele at ApaI among controls ranged from 26.4 percent in Chinese in Taiwan to 63.6 percent in Croatians, while the frequency of the “b” allele ranged from 36 percent in Taiwan Chinese to 53.5 percent in Germans. The frequency of the “r” allele at TaqI ranged from 50.9 percent (Germans) to 96.8 percent (Taiwan Chinese).

For family studies, the number of families studied ranged from 59 in the paper by Angel et al. (34) to over 3,000 in the paper by Nejentsev et al. (17).

Diagnosis of type 1 diabetes

Type 1 diabetes is often diagnosed mainly on the basis of clinical symptoms alone, which include malaise, weight loss, thirst, and polyuria. Insulin is required soon after diagnosis, and ketosis is common. The presence of autoantibodies (to glutamic acid decarboxylase 65, islet antigen 2, and insulin) adds to confidence in the diagnosis, while elevated C-peptide levels are not normally required for diagnosis. Of the articles surveyed here, only eight (22–24, 26, 29, 34–36) used the World Health Organization criteria for type 1 diabetes, which in essence are captured by our description above. Investigators in five papers (16, 23, 27, 30, 35) specifically looked for the presence of autoantibodies to distinguish type 1 diabetes from type 2 diabetes. In the rest of the papers, investigators used only one criterion (e.g., ketosis, early requirement for insulin) to diagnose type 1 diabetes.

Qualitative assessment of included studies

Most studies focused on juvenile type 1 diabetes, as seen by the age ranges of the cases/probands selected (tables 1–5). For case-control-type association studies, the selection of cases or patients varied: Some investigators selected prevalent cases, while others selected incident cases. In the earlier studies, researchers tended to pay less attention to methodological details, such as the criteria used for case/patient selection and age.

The selection of controls varied substantially. Some groups of controls were population-based while others were hospital-based, and both appeared to be selected on the basis of convenience. For population-based controls, for example, terms such as “donors” or “racially matched controls” were used. For hospital-based studies, controls ranged from healthy children undergoing check-ups to healthy infants without type 1 diabetes enrolled in an intervention trial.

Despite such heterogeneity, there were several features shared by all case-control studies. First, no information was provided in any surveyed study regarding the assessment of Hardy-Weinberg proportion in controls. Since assessment of Hardy-Weinberg proportion is regarded as an important criterion in the evaluation of genetic association studies (19), caution should be exercised in interpreting these studies. Second, in no study was an attempt made to match controls with the cases on factors that may have confounded the results. For example, human leukocyte antigen is by far the only genetic factor consistently reported to be associated with type 1 diabetes, yet no study attempted to match control human leukocyte antigen haplotypes with those of cases. In some studies, the controls as a group were apparently younger than the cases, leaving open the possibility that some of them may have developed type 1 diabetes later in life. Lastly, none of the studies made much of an attempt to control for known risk factors for type 1 diabetes,

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Transmitted</th>
<th>Not transmitted</th>
<th>Unadjusted p value†</th>
<th>Significant after adjustment?</th>
</tr>
</thead>
<tbody>
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<tr>
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<td>3</td>
<td>1.0000</td>
<td>No</td>
</tr>
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</table>

* Data were extracted from table III of the paper by San-Pedro et al. (38).
† Unadjusted p values for transmission were calculated under the null hypothesis of equal transmission proportions based on a binomial distribution.
such as dietary intake of vitamin D during infancy and/or childhood.

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

Case-control studies. The odds ratio for type 1 diabetes for the “f” allele at FokI ranged from 0.71 to 1.58 (figure 1, upper left panel). The random-effects model yielded a pooled odds ratio of 1.05 (95 percent confidence interval (CI): 0.89, 1.25). There was some indication of mild heterogeneity ($\chi^2 = 18.65, p = 0.045$; estimated variance of random effect: $\tau^2 = 0.04$).

For BsmI, the odds ratio ranged from 0.55 to 13.49 (figure 1, upper right panel). The random-effects model yielded a pooled odds ratio of 1.09 (95 percent CI: 0.88, 1.36). Again, there was no sign of heterogeneity ($\chi^2 = 15.13, p = 0.23$, $\tau^2 = 0.03$). For ApaI, the odds ratio ranged from 0.62 to 2.27 (figure 1, lower left panel). The pooled summary odds ratio based on a random-effects model was 1.11 (95 percent CI: 0.90, 1.37). There was no indication of heterogeneity among studies ($\chi^2 = 12.83, p = 0.12$, $\tau^2 = 0.04$).

For TaqI, the odds ratio ranged from 0.93 to 1.47 (figure 1, lower right panel). The random-effects model yielded a pooled odds ratio of 1.02 (95 percent CI: 0.86, 1.20).

There was no sign of heterogeneity ($\chi^2 = 2.08, p = 0.91$, $\tau^2 = 0.00$).

In view of these summary estimates, there is no evidence that any of the four SNPs alone is associated with type 1 diabetes.

Family transmission studies. For the “f” allele at FokI, the pooled estimate of the transmission proportion was 0.490 (95 percent CI: 0.474, 0.507), with a strong indication of heterogeneity ($\chi^2 = 9.64, p = 0.008$).

The pooled estimate of the transmission proportion of the “a” allele at ApaI locus from six studies (table 5) was 0.498 (95 percent CI: 0.484, 0.512). There was no indication of heterogeneity ($\chi^2 = 4.68, p = 0.32$). For the “t” allele at TaqI, the pooled estimate of the transmission proportion was 0.496 (95 percent CI: 0.479, 0.514). Heterogeneity did not appear to be present ($\chi^2 = 2.44, p = 0.65$). For the BsmI polymorphism, we used the numbers reported by McDermott et al. (16); that is, the “b” allele was considered to have been transmitted 53 out of 84 times, although table 2 in the published article (16) gave the number as 75/132. The pooled estimate of the transmission proportion was 0.490 (95 percent CI: 0.473, 0.506). There was no indication of heterogeneity ($\chi^2 = 7.26, p = 0.06$).

The funnel plot of the transmission proportions of the “b” allele from four studies is depicted in figure 2. The plot...
shows that as the sample size increases, the transmission proportion gravitates towards the equal transmission proportion of 0.5. Funnel plots for FokI, ApaI, and TaqI produced similar patterns (data not shown). Therefore, there was little indication that any of the four polymorphisms showed preferential transmission to affected offspring.

Combined haplotypes and the risk of type 1 diabetes

For transmission of haplotypes, data were available from McDermott et al. (16), Pani et al. (24), and San-Pedro et al. (38) (tables 6 and 7). McDermott et al. reported that the “b” allele was preferentially transmitted to affected offspring (53 of 84 times; \( p = 0.016 \)) and that the bAT haplotype was transmitted as well (35 of 54 times; \( p = 0.0295 \)) (16). Interestingly, an entirely different transmission proportion for the “b” allele could be deduced from McDermott et al.’s table 2 (reproduced in table 7 here): 0.568 (75/132 = 0.568; \( p = 0.069 \)) in an exact test based on the binomial distribution), which was not significant at the 5 percent level. Using the procedure of Benjamini and Hochberg (44) with a 5 percent false-discovery rate, we did not find any evidence that the haplotype bAT was preferentially transmitted to affected offspring (table 6). The funnel plot appeared to indicate that the extent to which the transmission proportion for the BAt haplotype deviated from the null was no more pronounced than that for BAT (figure 3, left panel).

Pani et al. (24) reported that the haplotype BAt conferred the highest risk of type 1 diabetes. The funnel plot did not appear to dispute this claim (figure 3, right panel). However, with a family-wise false-discovery rate of 5 percent, the evidence for preferential transmission of the BAt haplotype disappeared (table 6).

San-Pedro et al. (38) did not find a transmission distortion of the three-locus haplotype examined by McDermott et al. (16) and Pani et al. (24) (table II in the published article (38)). They did report, however, that one four-locus haplotype, fBAT, was transmitted more frequently to offspring with type 1 diabetes (table 7). Although this distortion was still significant after adjustment for multiple testing, the result appeared to be incongruent with other studies. The funnel plot indicated that it did not deviate much from the funnel shape (figure 4).

Revisiting the evidence presented in the first report

Some inconsistencies in the first report on the VDR-type 1 diabetes association (16), as mentioned above, prompted us to reexamine the data presented by McDermott et al. According to table 1 in the paper by McDermott et al. (16), the proportions of transmitted BsmI-TaqI haplotypes were as follows: BT, 11/38; bT, 41/59; Bt, 21/50; and bT, 2/3. This led to the conclusion that the bT haplotype was preferentially transmitted to affected offspring (16). However, the three-locus haplotype data in McDermott et al.’s table 2 (16) were more informative than the two-locus data, and the proportions of transmitted BsmI-TaqI haplotypes could be deduced to be the following: BT, 15/46; bT, 69/116; Bt, 23/48; and bt, 6/16 (these are the minimum numbers, since in some cases the three-locus haplotype or its transmission cannot be determined but that of the two-locus haplotype can). Transmissions increased 51 percent, from 150 for the BsmI-TaqI system to 226 for the BsmI-ApaI-TaqI system, with the same family data. The two-locus haplotype data deduced from the three-locus data yielded a transmission proportion for the bT haplotype of 0.595 (69/116 = 0.595), which had a \( p \) value of 0.025 using a binomial distribution under the null hypothesis. Since four tests have been performed for the four haplotypes, the result was not significant with a 5 percent false-discovery rate. Taken together, it appears that claims made in the first report (16) that the “b” allele, the bT haplotype, and the bAT haplotype were preferentially transmitted to affected offspring are not supported by the data if the more informative data set is used and adjustment for multiple comparisons is made.

DISCUSSION

In this meta-analysis of data from 19 reports on a possible genetic association between type 1 diabetes and four well-characterized VDR polymorphisms, we found little, if any, evidence for such an association in either case-control-type studies or family-transmission-type studies. The 95 percent confidence intervals for the pooled estimates of odds ratios or transmission proportions were fairly narrow, suggesting that large genetic effects due to these polymorphisms are unlikely. With the exception of FokI, the evidence of no association appears to be fairly consistent, as seen by the small amount of heterogeneity among pooled studies. For FokI, two out of five studies with positive findings were
from the Japanese population (figure 1), indicating that ethnicity might be a possible source of heterogeneity. Unfortunately, the small sample size and our having only two Asian population studies among 11 precluded us from conducting a meaningful investigation of possible ethnic effects. Findings from several reports that a particular polymorphism or haplotype was associated with the risk of developing type 1 diabetes, when examined more closely, turned out to be artifacts due to failure to control for multiple comparisons.

Aside from the small amount of evidence for an association after more appropriate data analysis, perhaps a more disquieting observation is the enormous inconsistency among different studies, not just between positive and negative studies but also among the positive studies. For example, while the first report by McDermott et al. (16) stated that the $bAT$ haplotype is the high-risk haplotype, Pani et al. (24) reported that $BAr$ is the high-risk haplotype. Again, ethnicity may be involved. However, two studies conducted in Caucasians also reported different results: One found that the combined genotype $BBAAtt$ confers increased risk (29), and the other reported that $BbAATT$ and $BbAATt$ are the high-risk genotypes and that $BbAATt$ is protective (33).

After pooling data from all of the published studies on the VDR-type 1 diabetes association, the fact that we found no evidence for such an association is not entirely surprising. Inconsistency aside, it seemed that the data presented in the first report (16), when analyzed more appropriately, did not support the claim of such an association. The funnel plots appeared to buttress this view: As more and more studies were conducted, the odds ratio estimate gravitated toward the null value. That having been said, we admit that we reanalyzed data on only the four most-studied SNPs in the VDR gene, and there are over 200 other SNPs in the same gene which might be associated with type 1 diabetes. Even if none of these SNPs is associated with type 1 diabetes, it is possible that VDR, as a gene mediating the action of vitamin D, may still be involved in the pathogenesis of type 1 diabetes.

The biochemical evidence for a putative relation between VDR polymorphisms and type 1 diabetes risk is very scanty. Granted, the action of vitamin D is mediated through VDR, and certain polymorphisms in the VDR gene, especially promoter or 3′-UTR (untranslated region) polymorphisms, may influence receptor transduction efficiency, transcription, or mRNA stability (13). However, it is well known that vitamin D status varies worldwide with season and not solely with diet. Without measuring an individual’s vitamin D biosynthesis, it is perhaps not adequate to examine the relation between the VDR polymorphism and type 1 diabetes. This view appears to be supported by a surprising finding in VDR knockout (45) mice: They were protected from low-dose streptozotocin-induced diabetes, since immune defects observed in VDR knockout mice can be restored by calcium homeostasis normalization (46). The intriguing correlation, reported in several epidemiologic studies, between geographic latitude and the incidence of type 1 diabetes—showing an inverse correlation between monthly hours of sunshine and diabetes incidence (5)—does not always hold true: In Finland and Sardinia, which have the highest incidence of type 1 diabetes in the world, no such correlation was found (47).

The findings of this analysis appear to be consistent with a well-recognized problem in genetic association studies of complex diseases (48, 49): lack of replication. In an extensive review of 166 gene-disease associations, Hirschhorn et al. (50) found that only six (<4 percent) of the associations had been consistently replicated. Ioannidis et al. (51) reported a slightly better percentage of 16. In fact, quantitative analyses of published association studies have revealed that significant heterogeneity or lack of consistency is common, and that a small sample size in the first publication and a large number of studies are two independent predictors of discrepancies (52). In addition, the magnitude of the genetic effect differs significantly between large studies and small studies (51), as was also evidenced in this analysis. With these well-documented problems, it is perhaps prudent to exercise caution when reviewing association studies.

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REFERENCES


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