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Accessibility
Inherited Variation in Vitamin D Genes Is Associated With Predisposition to Autoimmune Disease: Type 1 Diabetes

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OBJECTIVE—Vitamin D deficiency (25-hydroxyvitamin D [25(OH)D] < 50 nmol/L) is commonly reported in both children and adults worldwide, and growing evidence indicates that vitamin D deficiency is associated with many extraskelatal chronic disorders, including the autoimmune diseases type 1 diabetes and multiple sclerosis.

RESULTS—Type 1 diabetic patients have lower circulating levels of 25(OH)D than similarly aged subjects from the British population. Only 4.3 and 18.6% of type 1 diabetic patients reached optimal levels (≥ 75 nmol/L) of 25(OH)D for bone health in the winter and summer, respectively. We replicated the associations of four vitamin D metabolism genes (GC, DHCR7, CYP2R1, and CYP24A1) with 25(OH)D in control subjects. In addition to the previously reported association between type 1 diabetes and CYP27B1 (P = 1.4 × 10⁻³), we obtained consistent evidence of type 1 diabetes being associated with DHCR7 (P = 1.2 × 10⁻³) and CYP2R1 (P = 3.0 × 10⁻³).

CONCLUSIONS—Circulating levels of 25(OH)D in children and adolescents with type 1 diabetes vary seasonally and are under the same genetic control as in the general population but are much lower. Three key 25(OH)D metabolism genes show consistent evidence of association with type 1 diabetes risk, indicating a genetic etiological role for vitamin D deficiency in type 1 diabetes. Diabetes 60:1624–1631, 2011

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Vitamin D deficiency is commonly reported in both children and adults (1), and the well-established musculoskeletal consequences include osteomalacia, a softening of bones caused by defective bone mineralization (known as rickets in children), and osteoporosis, a reduced bone mineral density and deterioration in structural bone strength. Other more recently reported consequences are the extraskelatal conditions, which include common cancers (2,3) and coronary artery (4) and autoimmune diseases. The autoimmune or immune-mediated diseases include type 1 diabetes, multiple sclerosis, Crohn’s disease, and rheumatoid arthritis (5–8). In type 1 diabetes, vitamin D supplementation has been shown to be protective against this chronic disorder (5), caused by T-cell–mediated destruction of insulin-producing β-cells in the pancreas.

The main source of vitamin D is through the action of sunlight (ultraviolet B irradiance) on the skin, which results in the endogenous production of vitamin D₃ (cholecalciferol). The only other source is exogenous, through diet as either vitamin D₂ (ergocalciferol) or D₃. Vitamin D enters the circulation bound to vitamin D–binding proteins (DBPs) and lipoproteins and is released to the liver and hydroxylated to form 25-hydroxyvitamin D [25(OH)D]. A subject’s vitamin D status is routinely determined by their levels of 25(OH)D, the inactive circulating form of vitamin D and an established marker of vitamin D availability (7), which has a half-life of 2 weeks (9). 25(OH)D is hydroxylated in the kidneys or in cells of the immune system by the CYP27B1 enzyme (CYP1α) to form 1,25-dihydroxyvitamin D [1,25(OH)₂D, calcitriol], the biologically active form responsible for maintaining calcium and phosphorus homeostasis (9).

A substantial proportion of 25(OH)D variation has been attributed to genetic factors, with heritability estimates of 28.8% (10) and 43% (11) reported. A recent genome-wide association (GWA) meta-analysis of circulating levels of 25(OH)D in 33,996 samples of European descent from 14 cohorts reported convincing evidence for four loci, namely GC/4p12 (rs2282679 P = 1.9 × 10⁻¹⁰), DHCR7/11q12 (rs12785878 P = 2.1 × 10⁻²⁵), CYP2R1/11p15 (rs10741657 P = 3.3 × 10⁻²⁰), and CYP24A1/20q13 (rs6013897 P = 6.0 × 10⁻¹⁰) (12). These single nucleotide polymorphisms (SNPs) are within or near genes involved in vitamin D transport (GC), cholesterol synthesis (DHCR7), and hydroxylation (CYP2R1 and CYP24A1). No loci linked to skin pigmentation were detected, despite being a major
factor in determining 25(OH)D concentrations. More recently, vitamin D receptor (VDR)-binding sites were reported to be overrepresented near genes associated with type 1 diabetes, Crohn’s disease, and rheumatoid arthritis (13).

Recent evidence indicates that the production and degradation of 1,25(OH)₂D is a major signaling component in both the innate (14) and adaptive (15) immune systems. Vitamin D signaling plays an essential role in the activation of monocytes/macrophages in response to infection (14) and possibly in naïve T-cell activation (15,16). These cell populations are central to the development of the autoimmune disease type 1 diabetes (17). However, the relationship between circulating levels of 25(OH)D and immune responsiveness is largely undefined (14).

Type 1 diabetes is a strongly inherited autoimmune disease that affects ~0.4% of European ancestry populations, and incidence has been increasing at 3% per year, with a decreasing trend in age at diagnosis since the 1950s (18). A large number of potential environmental exposures correlate with type 1 diabetes incidence, including viral infection, sanitation and improvements in health care, and dietary intake. The effect of the vitamin D hormone [1,25(OH)₂D] in type 1 diabetes was first proposed based upon the observation that incidence rates of type 1 diabetes were negatively correlated with sunlight exposure, resulting in higher incidence at higher latitudes (1), and the distinctive seasonal pattern in type 1 diabetes incidence, with the largest proportion of cases diagnosed during the winter and the lowest during the summer (19). Subsequent evidence includes that type 1 diabetic patients have lower levels of 25(OH)D than age- and sex-matched control subjects (20,21). Type 1 diabetic patients have decreased bone mineral density and a greater risk of fracture compared with control subjects (20,21), type 1 diabetic patients have median of 45 years (age range 17–65 years), between September 2005 and February 2006, and from the type 1 diabetic patients, who had a median age of 13 years (age range 3–72; median 12 years, range 4–18) between March 2001 and November 2004. We used the mean of two 25(OH)D concentrations, duplicates on the same plate, and read against the same standard curves for type 1 diabetic patients. In addition, 25(OH)D concentrations were determined using DiaSorin radioimmunoassay (31). Blood samples were taken from the UKBS-CC control subjects, who had a median age of 45 years (age range 17–65 years), between September 2005 and February 2006, and from the type 1 diabetic patients, who had a median age of 13 years (age range 3–72; median 12 years, range 4–18) between March 2001 and November 2004. We analyzed 1,902 NDNS young people of white European ancestry and a median age of 12 years. NDNS 25(OH)D concentrations were also determined by DiaSorin radioimmunoassay.

25(OH)D concentrations were converted from ng/mL to nmol/L, for consistency between studies, by multiplying by 2.496. We defined circulating levels of 25(OH)D as being severely deficient (<25 nmol/L) (15), deficient (25 nmol/L ≤ 25(OH)D <50 nmol/L), insufficient [50 nmol/L ≤ 25(OH)D < 75 nmol/L], or optimal (>75 nmol/L) for bone health (33). We defined U.K. seasons as winter (December to February), spring (March to May), summer (June to August), and autumn (September to November).

Statistical analyses. All statistical analyses were performed in either Stata (www.stata.com) or R (www.r-project.org). The type 1 diabetic case subjects with 25(OH)D concentrations were analyzed using linear regression models. The 25(OH)D concentrations were natural log transformed to better approximate a normal distribution, and covariates were selected using forward regression. We tested for an association between type 1 diabetes and an SNP, we added to the model ($\text{df} = 9.5; r^2 = 0.35$ with rs2282679 from this gene). We analyzed 1,902 NDNS young people of white European ancestry and a median age of 12 years.

25(OH)D concentrations were converted from ng/mL to nmol/L, for consistency between studies, by multiplying by 2.496. We defined circulating levels of 25(OH)D as being severely deficient (<25 nmol/L) (15), deficient (25 nmol/L ≤ 25(OH)D <50 nmol/L), insufficient [50 nmol/L ≤ 25(OH)D < 75 nmol/L], or optimal (>75 nmol/L) for bone health (33). We defined U.K. seasons as winter (December to February), spring (March to May), summer (June to August), and autumn (September to November).
RESULTS

Seasonality of type 1 diabetes diagnosis. We confirmed in 4,127 British type 1 diabetic patients with known month of diagnosis, the previously reported (19) distinct seasonal variation in the incidence of type 1 diabetes (Fig. 1), with the largest proportion (14.0%) of patients diagnosed in January and the lowest (6.4%) in May.

Vitamin D status in type 1 diabetic case subjects compared with the general population. As an indication of vitamin D status within type 1 diabetic patients compared with the general population, we compared 618 type 1 diabetic patients aged 4–18 years with 1,002 NDNS young people aged 4–18 years (32). Figure 2 shows that there was seasonal variation in 25(OH)D concentrations in both NDNS young people and type 1 diabetic patients ($P = 3.9 \times 10^{-33}$ and $1.2 \times 10^{-25}$, respectively), with higher levels in summer and autumn compared with winter and spring.

The majority of NDNS young people surveyed from the general population had suboptimal levels of 25(OH)D (<75 nmol/L) even in the summer months, when only 46.4% had optimal levels of 25(OH)D for bone health ($\geq 75$ nmol/L; Table 1). The suboptimal vitamin D status of the type 1 diabetic patients was even more pronounced with only 18.6% of patients having optimal levels of 25(OH)D in the summer. The lowest proportion of subjects with optimal levels of 25(OH)D was in winter (6.9% of NDNS young people and 16.5% type 1 diabetic patients), and the lowest proportion in the summer (0.4% of NDNS young people and 1.1% of type 1 diabetic patients) (Table 1).

We fit a logistic regression model to test for an association between vitamin D status and type 1 diabetes risk. We adjusted for season, and the vitamin D status reference group consisted of subjects with optimal levels of 25(OH)D concentrations. The odds ratio (OR) for insufficient subjects was 3.31 (95% CI 2.40–4.56), for deficient subjects was 5.50 (3.89–7.77), and for severely deficient was 8.40 (4.74–14.90) (3-df $P = 1.1 \times 10^{-33}$).

Vitamin D metabolism genes and 25(OH)D concentrations. We replicated the associations of the four 25(OH)D concentration loci (12) ($GC$ $rs2282679$, $P = 8.9 \times 10^{-13}$), $DHCR7$ $rs12785878$, $P = 9.9 \times 10^{-4}$), $CYP2R1$ $rs10741657$, $P = 4.4 \times 10^{-3}$ and $CYP24A1$ $rs6013897$, $P = 0.016$), validating both our measurement of vitamin D concentrations and SNP imputation ($rs10741657$) in 2,610 UKBS-CC control samples (Table 2). In the smaller sample of 720 type 1 diabetic patients, we did not conduct SNP imputation and, consequently, analyzed a proxy SNP for $rs2282679$ ($rs4588$, see RESEARCH DESIGN AND METHODS) in $GC$. We replicated the association of $GC$ ($rs4588$ $P = 5.2 \times 10^{-13}$) and found some evidence for $DHCR7$ ($rs12785878$ $P = 0.036$) and $CYP24A1$ ($rs6013897$ $P = 0.054$), thereby validating our measurement of vitamin D concentrations. The SNP effects on 25(OH)D concentrations were consistent between UKBS-CC control and type 1 diabetic patient samples. No evidence was found for $CYP2R1$ ($rs10741657$ $P = 0.14$) in the type 1 diabetic patients and for the remaining three vitamin D metabolism genes in UKBS-CC control or type 1 diabetic patient samples (Table 2).

Vitamin D metabolism genes and type 1 diabetes. We tested the four 25(OH)D concentration loci (12) for an association with type 1 diabetes and found evidence of an association with $DHCR7$ ($rs12785878$ $T>G$; OR for minor allele 1.07 [95% CI 1.02–1.13]; $P = 6.8 \times 10^{-3}$) in case/control collections and some evidence (relative risk [RR] 1.10 [95% CI 0.99–1.21]; $P = 0.067$) in family collections (combined $P = 1.2 \times 10^{-5}$). There was consistent evidence in the case/control and family collections for an association.
with type 1 diabetes at both SNPs in CYP2R1 (combined
P = 3.6 × 10^{-4}; Table 3). We also found some evidence for
one of the GC SNPs (rs4588 C>A, OR 0.95 [95% CI 0.91–
1.00]; P = 0.050) in the case/control collection but not in
the family collection (P = 0.71). No evidence of an asso-
ciation was found in the case/control collection for
CYP24A1 (rs6013897 T>C; combined
P = 1.4 × 10^{-4}).

DISCUSSION
We observed, as have others, the concordance between
seasonality of both type 1 diabetes diagnosis (Fig. 1) and
25(OH)D concentrations (Fig. 2), with the highest disease
incidence and lowest 25(OH)D concentrations in the
winter. We found that type 1 diabetic patients have lower
circulating levels of 25(OH)D than similarly aged subjects
from the British population (Table 1; Fig. 2), which is
consistent with the findings of two previous studies in Italy
(21) and Sweden (20). Importantly, the two previous studies compared 25(OH)D concentrations of type 1 di-
abetic patients measured soon after diagnosis with age-
and sex-matched control subjects and, here, 25(OH)D
centrations were measured at a median time of 5 years
(lower and upper quartiles 2 and 8 years, respectively)
after diagnosis. This indicates that the circulating levels of
25(OH)D are lower than in the general population soon
after diagnosis and remain lower several years after di-
agnosis, suggesting that the lower levels are not a conse-
quence of the proinflammatory immune system that exists
before and shortly after diagnosis (38). In addition, be-
cause the two previous studies (20,21) measured 25(OH)D
soon after diagnosis, the lower levels are unlikely to be a
consequence of treatment with insulin or dietary changes
following type 1 diabetes diagnosis.

TABLE 1
Vitamin D status in 618 type 1 diabetic patients aged 4–18 years compared with 1,002 NDNS young people aged 4–18 years

<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>Winter (December to February)</th>
<th>Spring (March to May)</th>
<th>Summer (June to August)</th>
<th>Autumn (September to November)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>23 (16.5)</td>
<td>9 (5.9)</td>
<td>2 (1.1)</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td>NDNS</td>
<td>18 (6.9)</td>
<td>8 (4.1)</td>
<td>1 (0.4)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Deficient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>79 (56.8)</td>
<td>72 (47.4)</td>
<td>45 (25.4)</td>
<td>57 (38.0)</td>
</tr>
<tr>
<td>NDNS</td>
<td>108 (41.5)</td>
<td>87 (45.1)</td>
<td>27 (14.4)</td>
<td>47 (27.4)</td>
</tr>
<tr>
<td>Insufficient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>31 (22.3)</td>
<td>65 (42.8)</td>
<td>97 (54.8)</td>
<td>70 (46.7)</td>
</tr>
<tr>
<td>NDNS</td>
<td>91 (35.0)</td>
<td>78 (40.4)</td>
<td>99 (41.8)</td>
<td>137 (43.9)</td>
</tr>
<tr>
<td>Optimal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>6 (4.3)</td>
<td>6 (3.9)</td>
<td>33 (18.6)</td>
<td>18 (12.0)</td>
</tr>
<tr>
<td>NDNS</td>
<td>43 (16.5)</td>
<td>20 (10.4)</td>
<td>110 (46.4)</td>
<td>124 (39.7)</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>139</td>
<td>152</td>
<td>177</td>
<td>150</td>
</tr>
<tr>
<td>NDNS</td>
<td>260</td>
<td>193</td>
<td>237</td>
<td>312</td>
</tr>
</tbody>
</table>

We defined circulating levels of 25(OH)D as being severely deficient (<25 nmol/L) (15), deficient [25 nmol/L ≤ 25(OH)D < 50 nmol/L], insufficient [50 nmol/L ≤ 25(OH)D < 75 nmol/L], or optimal [≥75 nmol/L] for bone health (33).

As the musculoskeletal consequences of vitamin D de-
fi ciency are well established, the proportion of young peo-
ple with severely deficient circulating levels of 25(OH)D is
of major concern. Based on the 1997 NDNS of young peo-
ples aged 4–18 years, >5% (26 of 453; Table 1) of young
people in winter and spring are severely deficient.

The comparison of 25(OH)D levels do not take into ac-
count covariates such as BMI. Bryden et al. (39) reported,
based on 76 type 1 diabetic patients aged 11–18 years (43
male and 33 female), that the BMI of female type 1 diabetic
patients was significantly greater than that of the general
population, which could be associated with a reduction in
25(OH)D concentrations (40). However, the observed dif-
fferences between 25(OH)D concentrations in type 1 di-
abetic patients and the general population are unlikely to
be explained by BMI differences alone because we found
no difference between 25(OH)D concentrations and type 1
diabetic patient sex (P = 0.42), and both male and female
type 1 diabetic patients have lower 25(OH)D concen-
trations than the general population (Table 1).

We replicated the associations of the four 25(OH)D
concentration loci in the UKBS-CC control subjects (P =
0.016 to 8.9 × 10^{-10}; Table 2), and three of four showed
evidence of disease association in the type 1 diabetic
patients (P = 0.054 to 5.2 × 10^{-10}, Table 2), despite the
small sample size (720 type 1 diabetic patients). The con-
sistency of the 25(OH)D concentration loci effects in type
1 diabetic patients and the UKBS-CC control subjects in-
dicate that type 1 diabetes itself is unlikely to confound or
mask these genetic associations, a valid concern given that
theoretically its treatment and renal complications (41)
could effect 25(OH)D concentrations. We note, however,
that inconsistent evidence of an association between gly-
cosylated hemoglobin and 25(OH)D levels has been re-
ported (20,40,42).

The four 25(OH)D concentration loci provide an un-
biased instrument to test the hypothesis that circulating
levels of 25(OH)D are linked to type 1 diabetes or, indeed, to any other disease or trait in which a relationship with vitamin D has been proposed. Consequently, we tested the four 25(OH)D concentration loci along with the three remaining vitamin D metabolism genes for an association with type 1 diabetes. In addition to the previously reported association between type 1 diabetes and CYP2B1 (24), we found consistent statistical evidence of type 1 diabetes being associated with DHCR7 (P = 1.2 × 10^{-3}) and CYP2R1 (P = 3.0 × 10^{-3}) in both case/control and family collections (Table 3). Importantly, the coefficients of both of these 25(OH)D concentration loci show that the alleles associated with lower levels of 25(OH)D have an increased type 1 diabetes risk (Tables 2 and 3). There was some evidence for GC (rs4588 P = 0.050) in the case/control collection but not in the family population (P = 0.71). A study from Germany has also reported an association with rs17041657/CYP2R1 in 203 type 1 diabetic families (RR 0.64 [95% CI 0.48–0.87]; P = 4 × 10^{-3}) and in 284 case and control samples (OR 0.78 [95% CI 0.61–1.00]; P = 0.05) (42). We note that the analysis of CYP27B1 included the case/control samples analyzed previously with an additional 196 case and 1,680 control samples and 1,933 of 2,774 families analyzed previously (24). Bailey et al. (24), in the 2,774 families, obtained more evidence of an association between type 1 diabetes and CYP2B1 (2,774 family P = 3.9 × 10^{-3}, 1,933 family P = 0.011, Table 3).

The most associated 25(OH)D concentration locus, GC, only showed some evidence of an effect on type 1 diabetes in the case/control collection, despite the fact that type 1 diabetic patients have lower levels of 25(OH)D than the general population and two other 25(OH)D concentration loci, DHCR7 and CYP2R1, were associated with type 1 diabetes. One possible explanation is that the GC locus may only affect the levels of 25(OH)D bound to the DBP, without altering the amount of free and unbound 25(OH)D. Most circulating 25(OH)D is bound to DBP (80–90%) and to albumin (10–20%), with <1% unbound (43). An additional

### Table 3

<table>
<thead>
<tr>
<th>Gene, SNP, allele</th>
<th>8,517 Case and 10,438 control subjects</th>
<th>1,933 Families</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR for minor allele (95% CI)</td>
<td>RR for minor allele (95% CI)</td>
</tr>
<tr>
<td>CYP27A1, rs17407271, A&gt;T</td>
<td>0.98 (0.93–1.02)</td>
<td>0.97 (0.89–1.05)</td>
</tr>
<tr>
<td>GC, rs4588, C&gt;A</td>
<td>0.95 (0.91–1.00)</td>
<td>0.98 (0.89–1.08)</td>
</tr>
<tr>
<td>GC, rs7041, G&gt;T</td>
<td>0.98 (0.93–1.03)</td>
<td>0.98 (0.89–1.07)</td>
</tr>
<tr>
<td>DHCR7, rs12785878, T&gt;G</td>
<td>1.07 (1.02–1.13)</td>
<td>1.10 (1.08–1.21)</td>
</tr>
<tr>
<td>CYP2B1, rs10741657, G&gt;A</td>
<td>0.96 (0.92–1.00)</td>
<td>0.87 (0.78–0.95)</td>
</tr>
<tr>
<td>CYP2B1, rs1794714, G&gt;A</td>
<td>1.04 (1.00–1.08)</td>
<td>1.13 (1.04–1.24)</td>
</tr>
<tr>
<td>VDR (FokI), rs2228570, C&gt;T</td>
<td>0.99 (0.95–1.04)</td>
<td>0.92 (0.85–1.00)</td>
</tr>
<tr>
<td>VDR (BsmI), rs1544410, G&gt;A</td>
<td>1.00 (0.95–1.05)</td>
<td>0.93 (0.85–1.01)</td>
</tr>
<tr>
<td>VDR (Cdx2), rs11568820, G&gt;A</td>
<td>1.00 (0.94–1.07)</td>
<td>1.12 (0.91–1.22)</td>
</tr>
<tr>
<td>CYP2B1, rs10877012, G&gt;T</td>
<td>0.93 (0.89–0.98)</td>
<td>0.89 (0.82–0.97)</td>
</tr>
<tr>
<td>CYP24A1, rs2296241, G&gt;A</td>
<td>1.00 (0.95–1.05)</td>
<td>0.92 (0.85–1.01)</td>
</tr>
</tbody>
</table>

We assumed a model of multiple allelic effects because this model was not significantly different from the full genotype model for any of the SNPs tested. We report the maximum number of case, control, and family samples genotyped.
consideration is the difference in affinities of 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub> to DBP and VDR, which makes D<sub>3</sub> more bioavailable than D<sub>2</sub> (43). Standard immunoassays detect the bound and unbound forms. Because the relationship between 25(OH)D levels and immune responsiveness remains largely undefined (14,15) and the biological relationship between circulating 25(OH)D and type 1 diabetes risk remains to be determined, we can only assume that 25(OH)D concentrations may be an indirect surrogate for vitamin D signaling within immune cells.

Recent studies suggest that the vitamin D metabolism gene CYP27B1, associated with both type 1 diabetes (24,25) and multiple sclerosis (26), has a role in vitamin D signaling within immune cells (15). Inducible CYP27B1 and VDR expression has been identified within monocytes, macrophages, and T-cells as being critical in responses to mycobacterial infection and possibly in naïve T-cell activation and proliferation (14–16,23). Consequently, the inducibility of CYP27B1 or VDR expression and/or 1,25(OH)<sub>2</sub>D concentrations within the immune cells such as monocytes, macrophages, and T-cells could be a relevant quantitative phenotype in additional analyses of the relationship between vitamin D metabolism and the development of autoimmune disease. In such future studies, children with type 1 diabetes–affected siblings and mothers with a family history of type 1 diabetes and their newborns should provide additional insight into the association of vitamin D metabolism and susceptibility to type 1 diabetes and perhaps to other autoimmune diseases, such as multiple sclerosis (7).

Since the advent of GWA studies, great progress has been made in identifying susceptibility loci for autoimmune diseases such as type 1 diabetes (44) and in understanding how susceptibility alleles affect immune systems. The susceptibility alleles of three type 1 diabetes loci collectively provide a relevant example for the current study and for its interpretation: PTPN22 (45) has been associated with lower T-cell signaling and reduced T-cell activation (46), PTPN2 (47) has been associated with lower T-cell interleukin (IL)-2 cytokine signaling (48), and IL2RA (49) has been associated with reduced IL-2 production in memory T-cells (50). These results indicate that inherited impairment or lowering of T-cell signaling and activation is a predisposing phenotype for type 1 diabetes. Recently, von Essen et al. (15) have suggested that severely low circulating levels of 25(OH)D are associated with reduced T-cell activation and proliferation, although there are other considerations to be taken into account in the interpretation of these studies (16). Taken together, these studies indicate a common mechanism in type 1 diabetes predisposition, T-cell hypersensitivity, which may be restored to normal levels by vitamin D supplementation to achieve optimal levels of 25(OH)D, a hypothesis that can be tested in future studies.

In conclusion, we have linked the genetic determinants of circulating levels of 25(OH)D (DHCGR and CYP2R1) and vitamin D signaling in T-cells (CYP27B1) with type 1 diabetes risk. This provides the evidence that vitamin D deficiency of type 1 diabetic patients probably plays a primary, causal role in the pathogenesis of type 1 diabetes and is not secondary to hyperglycemia, diet, or to treatment with insulin (20). However, we cannot yet fully rule out that treatment with insulin may be responsible for the lowering of circulating levels of 25(OH)D or of CYP2B1 expression within monocytes, macrophages, and T-cells. Consequently, this study supports the potential of vitamin D supplementation as part of a prevention strategy for autoimmune disease and for vitamin D deficiency–related comorbidities in type 1 diabetic patients in later life. Randomized controlled trials of vitamin D supplementation will be required to establish both causality (5) and health benefits for existing type 1 diabetic patients. A first step will be to establish if optimal 25(OH)D concentrations can be achieved in the circulation of patients with type 1 diabetes by oral supplementation and if improved 25(OH)D status alters any of the emerging immunophenotypes being associated with this autoimmune disease (50).

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