Brief Genetics Report

DPB1 Alleles Are Associated With Type 1 Diabetes Susceptibility in Multiple Ethnic Groups

Thomas D. Cruz, Ana M. Valdes, Alma Santiago, Teresa Frazer de Llado, Leslie J. Raffel, Adina Zeidler, Jerome I. Rotter, Henry A. Erlich, Marian Rewers, Teodorica Bugawan, and Janelle A. Noble

Genetic associations between type 1 diabetes and alleles at the HLA class II locus DPB1 have been previously reported. Observed associations could be due to variation in the DPB1 locus itself or to linkage disequilibrium (LD) between DPB1 alleles and other susceptibility loci. One measure of whether the association of an allele with a disease reflects a true effect of the locus or is simply due to LD is the observation of that association in multiple ethnic groups. Previous type 1 diabetes associations have been reported for DPB1*0301 and DPB1*0202 (predisposing) and for DPB1*0402 (protective). In this study, results are reported from testing these associations in three different sample sets: 1) Puerto Rican case and control subjects, 2) Mexican-American simplex families, and 3) high-risk (DR3/DR4) individuals with and without an affected relative. DPB1*0301 was associated in all three groups, even after accounting for LD with DRB1-DQB1. DPB1*0202 and DPB1*0402 were positively and negatively associated, respectively, in two of the three populations. These results suggest that the observed DPB1 associations, especially that of the DPB1*0301 allele, with type 1 diabetes are likely to be true associations. This supports the concept that multiple genes in the HLA region can affect type 1 diabetes susceptibility. Diabetes 53: 2158–2163, 2004

Type 1 diabetes is a multifactorial autoimmune disease with both environmental and genetic susceptibility (1–3). The HLA region of chromosome 6p21 is estimated to contribute >50% of the total genetic risk (4,5). Association studies have demonstrated that multiple loci within the HLA region appear to contribute to disease risk (1,6–8).

The genes encoding DR and DQ are well established to have the greatest genetic effect on type 1 diabetes susceptibility. The DPB1 gene encodes the β-chain of the DP molecule, which has similar structure and function to DR and DQ. Genetic associations of DPB1 alleles with type 1 diabetes susceptibility have been reported (5,7–12), with one report showing no detectable association (13). Type 1 diabetes associations of DPB1 alleles could either be due to changes in the encoded polypeptide chain or to linkage disequilibrium (LD) between DPB1 alleles and other susceptibility loci.

Positive type 1 diabetes association of DPB1*0301 has been reported in several studies in which the LD of DPB1 with DR-DQ genes has been taken into account (7,10,11). An increased risk due to allele DPB1*0202 and a decreased risk due to allele DPB1*0402 have also been reported (10,11).

This study examines DPB1 association with type 1 diabetes in three different settings: 1) a case-control study from Puerto Rico, 2) transmission disequilibrium test analysis of Mexican-American type 1 diabetic simplex families, and 3) comparison of HLA high-risk (DR3/DR4-DQB1*0302; DR4≠DRB1*0403) individuals with and without an affected first-degree relative, collected as part of the Diabetes AutoImmunity Study of the Young (DAISY). The hypothesis underlying the DAISY data in this study is that DPB1 allele frequency differences may at least partially account for the higher rate of autoimmunity and type 1 diabetes observed in high-risk, first-degree relatives compared with high-risk individuals without a first-degree relative (see below). These data demonstrate reproducibility of associations among ethnic groups and support a role for the DPB1 locus as a risk factor for type 1 diabetes.

Previously observed disease associations for DPB1*0301 and DPB1*0202 (positive) and DPB1*0402 (negative) with type 1 diabetes (5,7,9–12) were tested in three
distinct sample sets with three different study designs (described in Research Design and Methods).

**Mexican and Puerto Rican sample sets.** Table 1 shows the results of allele frequency determination for the DPB1 locus in 91 patients and 82 control subjects from Puerto Rico and in 84 Mexican-American simplex families. In the Puerto Rican data, significant association was seen for DPB1*0301 ($P = 0.024$). The data were suggestive, although not statistically significant, of a positive disease association with the allele DPB1*0202 ($P = 0.058$). DPB1*1701 also appeared positively associated with type 1 diabetes in these data ($P = 0.009$); however, negative type 1 diabetes association for DPB1*1701 was previously reported (10) for Caucasian families. This difference may be attributable to differences in LD patterns between populations. For Mexican-American families, expected associations were observed: positive association for DPB1*0202 ($P = 0.027$) and DPB1*0301 ($P = 0.002$) and negative association for DPB1*0402 ($P = 0.017$).

Because of the strong LD within the HLA region, some apparent associations may simply be “bystander” effects caused by LD with highly predisposing or protective DR- and DQ-encoding loci. DRB1 and DQB1 genotypes were determined for all individuals in both datasets. Values were calculated for LD between DRB1-DQB1 haplotypes and DPB1 alleles (Table 2).

In both the Mexican-American and the Puerto Rican populations, DPB1*0401 was in positive LD with DRB1*0101-DQB1*0501. Other LD patterns differed between the two populations. DPB1*0402 was in positive LD with DRB1*0701 in the Puerto Rican data but in negative LD with DRB1*0701 in the Mexican-American data. DPB1*0402 had a clear protective effect among Mexican Americans, but the reduced frequency in patients was not significant in Puerto Ricans. The very high positive LD with DRB1*0701 (type 1 diabetes protective) may reduce the power to detect any additional protective effect of DPB1*0402 in Puerto Ricans. No significant LD was observed for DPB1*0202 in either population, although this may be attributable to a lack of power resulting from small sample size rather than the absence of LD. DPB1*0202 is found primarily on DR3 haplotypes in Caucasians (10); it is not attributable solely to LD of DPB1 alleles with DRB1-DQB1 haplotypes. Revised expected values for all DPB1 alleles were calculated based on the LD results. Deviation from the null hypothesis was tested (Table 3). For both populations, results for DPB1*0301 and DPB1*0202 still suggest a positive type 1 diabetes association after correction for LD. The novel negative association of DPB1*1701 with

### Table 1

<table>
<thead>
<tr>
<th>DPB1</th>
<th>Control subjects (%)</th>
<th>Type 1 diabetic patients (%)</th>
<th>$\chi^2$</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0101</td>
<td>15.24</td>
<td>10.44</td>
<td>1.57</td>
<td>NS</td>
</tr>
<tr>
<td>0202</td>
<td>7.93</td>
<td>16.48</td>
<td>5.08</td>
<td>0.024</td>
</tr>
<tr>
<td>0401</td>
<td>26.22</td>
<td>20.33</td>
<td>1.29</td>
<td>NS</td>
</tr>
<tr>
<td>0501</td>
<td>3.66</td>
<td>1.00</td>
<td>0.24</td>
<td>NS</td>
</tr>
<tr>
<td>0901</td>
<td>0.00</td>
<td>1.65</td>
<td>2.7</td>
<td>0.1</td>
</tr>
<tr>
<td>1101</td>
<td>0.00</td>
<td>1.10</td>
<td>0.24</td>
<td>NS</td>
</tr>
<tr>
<td>1301</td>
<td>3.66</td>
<td>1.10</td>
<td>2.44</td>
<td>NS</td>
</tr>
<tr>
<td>1401</td>
<td>3.66</td>
<td>1.65</td>
<td>1.34</td>
<td>NS</td>
</tr>
<tr>
<td>1501</td>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1701</td>
<td>1.83</td>
<td>8.24</td>
<td>6.82</td>
<td>0.009</td>
</tr>
<tr>
<td>1801</td>
<td>0.61</td>
<td>1.10</td>
<td>0.24</td>
<td>NS</td>
</tr>
<tr>
<td>1901</td>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2301</td>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3301</td>
<td>0.61</td>
<td>1.65</td>
<td>0.8</td>
<td>NS</td>
</tr>
<tr>
<td>5001</td>
<td>1.83</td>
<td>0.00</td>
<td>3.33</td>
<td>0.068</td>
</tr>
<tr>
<td>5101</td>
<td>0.61</td>
<td>1.10</td>
<td>0.24</td>
<td>NS</td>
</tr>
<tr>
<td>5901</td>
<td>0.61</td>
<td>1.10</td>
<td>0.24</td>
<td>NS</td>
</tr>
<tr>
<td>6001</td>
<td>1.22</td>
<td>0.55</td>
<td>0.45</td>
<td>NS</td>
</tr>
<tr>
<td>7501</td>
<td>1.83</td>
<td>2.20</td>
<td>0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>6.10</td>
<td>8.24</td>
<td>0.55</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>164</td>
<td>182</td>
<td>33.1</td>
<td>0.023</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AFBACs (control) (%)</th>
<th>Transmitted to type 1 diabetes (%)</th>
<th>$\chi^2$</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.94</td>
<td>4.76</td>
<td>0.63</td>
<td>NS</td>
</tr>
<tr>
<td>13.97</td>
<td>11.90</td>
<td>0.25</td>
<td>NS</td>
</tr>
<tr>
<td>0.74</td>
<td>5.36</td>
<td>4.88</td>
<td>0.027</td>
</tr>
<tr>
<td>6.62</td>
<td>20.24</td>
<td>9.86</td>
<td>0.002</td>
</tr>
<tr>
<td>22.06</td>
<td>18.45</td>
<td>0.49</td>
<td>NS</td>
</tr>
<tr>
<td>37.50</td>
<td>22.62</td>
<td>5.68</td>
<td>0.017</td>
</tr>
<tr>
<td>4.41</td>
<td>4.76</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>0.00</td>
<td>1.19</td>
<td>1.62</td>
<td>NS</td>
</tr>
<tr>
<td>0.00</td>
<td>0.60</td>
<td>0.81</td>
<td>NS</td>
</tr>
<tr>
<td>2.21</td>
<td>1.79</td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>0.00</td>
<td>1.19</td>
<td>1.62</td>
<td>NS</td>
</tr>
<tr>
<td>0.00</td>
<td>1.19</td>
<td>1.62</td>
<td>NS</td>
</tr>
<tr>
<td>4.41</td>
<td>3.57</td>
<td>0.13</td>
<td>NS</td>
</tr>
<tr>
<td>0.74</td>
<td>0.00</td>
<td>1.24</td>
<td>NS</td>
</tr>
<tr>
<td>0.00</td>
<td>0.60</td>
<td>0.81</td>
<td>NS</td>
</tr>
<tr>
<td>0.74</td>
<td>0.00</td>
<td>1.24</td>
<td>NS</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

$^*$Statistically significant $P$ values (≤0.05) are shown in roman text. $P$ values that may be suggestive of a weak association ($P > 0.05$ but ≤0.10) are shown in italics.
type 1 diabetes in the Puerto Rican data also remains significant \((P = 0.011)\) but may be spurious or unique to this population. The protective effect of DPB1*0402 in the Mexican-American data remains \((P = 0.012)\) after LD correction.

**DAISY samples.** Table 4 shows a comparison of DPB1 allele frequencies for the two groups of DAISY samples. High type 1 diabetes risk individuals (DR3/4-DQB1*0302; DR4≠DRB1*0403) were selected from both the General Population Cohort (GPC) and the Sibling-Offspring Cohort (SOC) (see Research Design and Methods). This study design differs from the others in that the comparison is not between patients and control subjects but between HLA-matched individuals with or without a type 1 diabetic relative. The observed higher type 1 diabetes risk for high-risk SOC subjects than for high-risk GPC subjects leads to the testable hypothesis that the SOC subjects are enriched in non–DR-DQ susceptibility alleles.

The data show that DPB1*0301 is significantly overrepresented in the SOC \((P = 0.04)\) compared with the GPC, whereas DPB1*0402 is underrepresented in the SOC \((P = 0.002)\) compared with the GPC, consistent with previous observations for these alleles. DPB1*0202 was rare and did not differ significantly between the two populations. To address issues of ethnic differences between the GPC and SOC, the Caucasian subset of these samples was analyzed separately. In the Caucasian-only sample, DPB1*0301 remained overrepresented in the SOC, although not significantly \((P = 0.087)\), suggestive of a positive type 1 diabetes association. The underrepresentation of DPB1*0402 in the SOC remained significant \((P = 0.01)\) in the Caucasian set, supporting a protective effect on type 1 diabetes susceptibility.

The HLA class II DR- and DQ-encoding loci are strongly associated with type 1 diabetes susceptibility, but even the highest-risk DR-DQ genotype (DR3/DR4-DQB1*0302) only predicts an \(\sim 7\%\) risk of disease in the general population. Increasing the predictive value of genetics for type 1 diabetes susceptibility requires identification of other risk factors. Because effects of other genetic susceptibility loci are expected to be modest, associations of such loci are difficult to identify and replicate and can be confounded by DR-DQ heterogeneity. The frequency of the DR3/DR4 heterozygous genotype is too low in the Mexican-American and Puerto Rican control groups to make any risk estimates based on DPB1 subgroup; the frequency of DR4/DRX genotypes was sufficient. The data suggest that for DR4/DRX individuals \((X ≠ DR3 or DR4)\), the added risk of carrying at least one copy of either DPB1*0202 or DPB1*0301 increases the probability of developing type 1 diabetes by \(60\%\) in the Puerto Ricans and \(104\%\) in the Mexican Americans. In addition, not carrying DPB1*0402 increases the probability of developing type 1 diabetes by \(16\%\) in the Puerto Ricans and \(83\%\) in the Mexican Americans (data not shown).

Whether the DP molecules themselves directly affect type 1 diabetes susceptibility remains in question. A recent study \((12)\) showed DPB1 associations consistent with those seen in the present study, but the authors attributed the associations to LD of DPB1 with other genetic loci in the HLA region, citing LD of DPB1 with a microsatellite marker, located beyond the HLA region and not in proximity to any candidate functional gene. The protein encoded by the DPB1 locus has a similar function to that of DR and DQ, and DPB1 associations have been replicated in multiple studies, supporting the notion that polymorphism in the DPB1 locus itself may affect type 1 diabetes susceptibility.

The results reported here support previous reports of effects for three DPB1 alleles, DPB1*0202, DPB1*0301, and DPB1*0402, on type 1 diabetes susceptibility \((5,7,9–12)\). The relative consistency among studies suggests that these alleles represent a useful addition to genetic models of determining type 1 diabetes risk. Whether the DPB1 locus is causally involved in or merely a marker for type 1 diabetes susceptibility, the consistent associations of spe-
cific DPB1 alleles with type 1 diabetes susceptibility observed in this and other studies suggest that DPB1 genotyping can be a useful tool to increase the predictive power of genetics for type 1 diabetes susceptibility.

RESEARCH DESIGN AND METHODS

Mexican-American families. A total of 84 Mexican-American families (proband plus one or both parents) are included. Control frequencies were determined from AFIPACs (affected family-based control subjects) (14). Families were ascertained by the investigators at the Los Angeles County Hospital/University of Southern California Medical School (LAC/USC) and Children’s Hospital of Los Angeles between 1989 and 1993 (7,15,16). Type 1 diabetes was defined according to the National Diabetes Data Group. To be considered of Mexican ancestry, probands had to have a minimum of three of four grandparents born in Mexico. The study was approved by the institutional review board at LAC/USC. Written informed consent was obtained from all subjects and/or their parents before their participation. DPB1 data were previously reported for 42 of these families (7).

Puerto Rican type 1 diabetic patients and control subjects. The Puerto Rican registry of children with diabetes was established as part of the World Health Organization’s DiaMonD project (17). In 1990, an island-wide registry of new cases of childhood type 1 diabetes was established in Puerto Rico (18). Healthy control subjects (n = 82) from the same area were recruited. Informed consent for sample collection was approved by the institutional review board of the Ponce School of Medicine.

DAISY. The DAISY (19) is a prospective study of the natural history of type 1 diabetes, including limited genetic screening and extensive epidemiological data collection. DAISY has two main cohorts, the GPC, ascertained as cases, indicating either type 1 diabetes or presence of autoantibodies. The null hypothesis (H0) is that DPB1 allele frequencies will differ between patients and control subjects due to 1) LD between DPB1 and DRB1-DQB1 and 2) chance (sampling), consistent with a neutral role for DPB1 polymorphism relative to disease predisposition.

TABLE 3
Observed and expected DPB1 allele frequencies under the hypothesis that differences between case and control subjects are due exclusively to LD with DRB1-DQB1 in Puerto Rican and Mexican-American samples

<table>
<thead>
<tr>
<th></th>
<th>Puerto Rican case-control data</th>
<th>Mexican-American family data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 1 diabetes</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td></td>
<td>Frequency: observed (%)</td>
<td>Frequency: observed (%)</td>
</tr>
<tr>
<td></td>
<td>Frequency: expected (%)</td>
<td>Frequency: expected (%)</td>
</tr>
<tr>
<td></td>
<td>Observed counts</td>
<td>Observed counts</td>
</tr>
<tr>
<td></td>
<td>$\chi^2$</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td></td>
<td>$P^*$</td>
<td>$P^*$</td>
</tr>
<tr>
<td>DPB1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0101</td>
<td>10.44</td>
<td>4.76</td>
</tr>
<tr>
<td></td>
<td>16.17</td>
<td>2.90</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.663</td>
</tr>
<tr>
<td></td>
<td>2.15</td>
<td>NS</td>
</tr>
<tr>
<td>0201</td>
<td>6.04</td>
<td>11.90</td>
</tr>
<tr>
<td></td>
<td>8.84</td>
<td>13.65</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>0.91</td>
<td>0.181</td>
</tr>
<tr>
<td>0202</td>
<td>2.20</td>
<td>5.36</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>3.6</td>
<td>4.88</td>
</tr>
<tr>
<td></td>
<td>0.058</td>
<td>0.027</td>
</tr>
<tr>
<td>0301</td>
<td>16.48</td>
<td>20.24</td>
</tr>
<tr>
<td></td>
<td>8.46</td>
<td>6.76</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>4.38</td>
<td>9.611</td>
</tr>
<tr>
<td></td>
<td>0.036</td>
<td>0.002</td>
</tr>
<tr>
<td>0401</td>
<td>20.33</td>
<td>18.45</td>
</tr>
<tr>
<td></td>
<td>27.78</td>
<td>21.58</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>2.01</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>0402</td>
<td>13.74</td>
<td>22.62</td>
</tr>
<tr>
<td></td>
<td>19.77</td>
<td>38.34</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>1.89</td>
<td>6.263</td>
</tr>
<tr>
<td>0501</td>
<td>1.10</td>
<td>4.76</td>
</tr>
<tr>
<td></td>
<td>0.65</td>
<td>4.34</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.03</td>
</tr>
<tr>
<td>0601</td>
<td>0.00</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0.53</td>
<td>1.619</td>
</tr>
<tr>
<td>0801</td>
<td>1.10</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>2.19</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.063</td>
</tr>
<tr>
<td>0901</td>
<td>1.10</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>1.619</td>
</tr>
<tr>
<td>1001</td>
<td>1.10</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>2.22</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.476</td>
</tr>
<tr>
<td>1101</td>
<td>1.10</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>2.19</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.063</td>
</tr>
<tr>
<td>1301</td>
<td>1.10</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>3.86</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
<td>1.619</td>
</tr>
<tr>
<td>1401</td>
<td>1.65</td>
<td>3.57</td>
</tr>
<tr>
<td></td>
<td>3.79</td>
<td>4.37</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>1.49</td>
<td>0.122</td>
</tr>
<tr>
<td>1501</td>
<td>0.00</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1.19</td>
<td>1.619</td>
</tr>
<tr>
<td>1701</td>
<td>8.24</td>
<td>3.57</td>
</tr>
<tr>
<td></td>
<td>1.93</td>
<td>4.37</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6.54</td>
<td>0.111</td>
</tr>
<tr>
<td>1801</td>
<td>1.10</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>1.236</td>
</tr>
<tr>
<td>1901</td>
<td>0.00</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0.81</td>
<td>1.236</td>
</tr>
<tr>
<td>2301</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1.236</td>
<td>NS</td>
</tr>
<tr>
<td>3301</td>
<td>1.65</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.74</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>0</td>
</tr>
<tr>
<td>5001</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>1.93</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3.51</td>
<td>0.061</td>
</tr>
<tr>
<td>5101</td>
<td>1.10</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.00</td>
</tr>
<tr>
<td>5901</td>
<td>1.10</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.00</td>
</tr>
<tr>
<td>6601</td>
<td>0.55</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>1.30</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.53</td>
<td>0.00</td>
</tr>
<tr>
<td>7501</td>
<td>2.35</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>1.54</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Statistically significant P values (≤0.05) are shown in roman text. P values that may be suggestive of a weak association (P > 0.05 but ≤0.10) are shown in italics.
TABLE 4  
DPB1 allele frequency distribution among DR3/DR4-DQB1*0302 (DR4 ≠ DRB1*0403) samples from DAISY in the GPC and among individuals who have a first-degree relative with type 1 diabetes (SOC)

<table>
<thead>
<tr>
<th>DPB1</th>
<th>GPC frequency (%)</th>
<th>SOC frequency (%)</th>
<th>$\chi^2$</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0101</td>
<td>15.40</td>
<td>15.00</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>0201</td>
<td>9.60</td>
<td>12.00</td>
<td>0.48</td>
<td>NS</td>
</tr>
<tr>
<td>0202</td>
<td>2.00</td>
<td>1.00</td>
<td>0.45</td>
<td>NS</td>
</tr>
<tr>
<td>0301</td>
<td>9.60</td>
<td>17.00</td>
<td>4.21</td>
<td>0.040</td>
</tr>
<tr>
<td>0401</td>
<td>36.20</td>
<td>39.00</td>
<td>0.18</td>
<td>NS</td>
</tr>
<tr>
<td>0402</td>
<td>13.60</td>
<td>2.00</td>
<td>9.61</td>
<td>0.002</td>
</tr>
<tr>
<td>0501</td>
<td>0.80</td>
<td>1.00</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>0601</td>
<td>4.20</td>
<td>5.00</td>
<td>0.12</td>
<td>NS</td>
</tr>
<tr>
<td>0701</td>
<td>0.40</td>
<td>1.00</td>
<td>0.60</td>
<td>NS</td>
</tr>
<tr>
<td>1101</td>
<td>0.80</td>
<td>0.00</td>
<td>0.80</td>
<td>NS</td>
</tr>
<tr>
<td>1301</td>
<td>0.80</td>
<td>1.00</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>1401</td>
<td>2.60</td>
<td>0.00</td>
<td>2.60</td>
<td>NS</td>
</tr>
<tr>
<td>1401</td>
<td>0.60</td>
<td>1.00</td>
<td>0.20</td>
<td>NS</td>
</tr>
<tr>
<td>1501</td>
<td>0.80</td>
<td>2.00</td>
<td>1.20</td>
<td>NS</td>
</tr>
<tr>
<td>1701</td>
<td>1.00</td>
<td>0.00</td>
<td>1.00</td>
<td>NS</td>
</tr>
<tr>
<td>Other †</td>
<td>1.60</td>
<td>3.00</td>
<td>0.89</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>500</td>
<td>100</td>
<td>22.44</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Data are shown for the complete sample set and for the Caucasian subset. *Statistically significant $P$ values ($≤0.05$) are shown in roman text. $P$ values that may be suggestive of weak association ($P > 0.05$ but $≤0.10$) are shown in italics. †Other describes a group of nine alleles, each of which appears fewer than two times in the GPC and SOC combined.

Under H0, the expected allele frequencies at DPB1 can be computed using the equation derived by Thomson (14).

\[ q_{DPB1} = \frac{N_p}{N} \]

\[ D_{ij} = \sum_{i,j} P_{ij} \frac{N_{ij}}{N} \]

\[ \chi^2 = \frac{(o - e)^2}{e} \]

\[ o = q_{DPB1} N_p; \quad e = q_{DPB1} N; \]

\[ x = o + e \]

\[ o' = \frac{x N_p}{N_p + N_e}; \quad e' = \frac{x N}{N_p + N_e} \]

For any individual DPB1, N_p is patient sample size, N is control sample size, q_{DPB1} is observed frequency of the 1th allele in patients, and q'_{DPB1} is derived from Eq. 1.

ACKNOWLEDGMENTS

This work was supported by an American Diabetes Association Career Development Award (to J.A.N.), National Institutes of Health (NIH) Grant AI29049 (to H.A.E.), a minority supplement to AI29049 (to T.D.C.), NIH Grant DK16722 (to J.A.N.), summer internship support from NIH Grant T35 HL07807 (to T.D.C.), the Cedars-Sinai Board of Governors Chair in Medical Genetics, and the NIH Sponsored Research Program Extramural Associates Development Award 5-G11-HD33674-05 (to A.S.).

The authors thank Catherine Nicklas for excellent technical assistance.

REFERENCES