Expression of GAD65 and Islet Cell Antibody (ICA512) Autoantibodies Among Cytoplasmic ICA+ Relatives Is Associated With Eligibility for the Diabetes Prevention Trial—Type 1

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More than 71,000 relatives of type 1 diabetic patients have been screened for cytoplasmic islet cell antibodies (ICAs), GAD65 autoantibodies (GAAs), and ICA512 autoantibodies (ICA512AAs). Among those 71,148 relatives, 2,448 were cytoplasmic ICA+, and the remainder were ICA-. Of the ICA+ group, 1,229 (50.2%) were positive for GAAs and/or ICA512AAs. Among ICA− relatives, 1,897 (2.76%) were positive for GAAs and/or ICA512AAs. Given the large number of relatives positive for cytoplasmic ICA and negative for “biochemically” determined autoantibodies, and the converse, we analyzed the proportion of ICA+ relatives found eligible to participate in the intervention phase of Diabetes Prevention Trial—Type 1 (DPT-1). To be eligible for the parenteral insulin DPT-1 trial, a relative had to have first-phase insulin secretion below the 1st percentile of cut-points (for parents) or below the 10th percentile (for siblings and offspring). To be eligible for the oral insulin trial, a relative had to have first-phase insulin secretion above cut-points (>1st percentile for parents, >10th percentile for siblings/offspring) and be positive for anti-insulin autoantibodies. For both trials, DQB1*0602 was an exclusion criteria, cytoplasmic ICA positivity had to be confirmed, and an oral glucose tolerance test had to result in nondiabetic levels. Of 572 relatives found to be eligible for trial entry, 442 (77.3%) were positive for GAAs and/or ICA512AAs, although overall only 50.2% of ICA+ relatives were positive for GAAs and/or ICA512AAs. The positive predictive value for trial eligibility for ICA+ relatives with GAAs or ICA512AAs who completed staging was 51.0%. In contrast, only 11.9% of ICA+ but GAA− and ICA512AA− relatives were found to be eligible by DPT criteria for trial entry. Positivity for biochemically determined autoantibodies among cytoplasmic antibody-positive relatives is associated with eligibility for the DPT-1 study. Diabetes 50:1735–1740, 2001

Type 1A diabetes is strongly associated with the presence of islet cell–related autoantibodies, autoantibodies that usually precede by years the development of overt diabetes (1,2). The detection of cytoplasmic islet cell antibodies (ICAs), as measured by indirect immunofluorescence on sections of normal human pancreas, has been associated with increased risk of type 1A diabetes in first-degree relatives (3,4) and school children (5–7). Within the last 8 years, investigators have cloned a series of islet-related autoantigens and developed radioassays for autoantibodies reacting with these “biochemically” defined autoantigens (7–15). International workshops (16–18) have compared assays for anti-insulin autoantibodies (IAAs), anti-GAD65 autoantibodies (GAA), and anti-ICA512 autoantibodies (ICA512AA); such assays are now performed in laboratories throughout the world. These assays can be set up with cutoffs, allowing high sensitivity, with specificities >99th percentile of healthy control values. The most important risk factor for the development of type 1A diabetes is the expression of multiple anti-islet autoantibodies (2,19), especially in the presence of loss of first-phase insulin release (FPIR) on intravenous glucose tolerance tests (IVGTTs) (5,20–23). In particular, expression of two or more of GAA, ICA512AA, or IAA is associated with a high risk of progression to type 1A diabetes (2,16,23). These assays can be performed in 96-well filtration plates with counting on a 96-well beta counter. Thus the assays are semiautomated and relatively inexpensive. In the present study (an ancillary study of Diabetes Prevention Trial—Type 1 [DPT-1]), we screened >71,000 relatives of type 1 diabetic patients for cytoplasmic ICAs, GAAs, and ICA512AAs. We analyzed the association between cytoplasmic ICA positivity and GAA and/or ICA512AA positivity. In addition, we studied the prognostic value of
TABLE 1
Demographic characteristics of DPT-1 relatives screened for ICAs, GAAs, and ICA512AAs

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>Subjects tested for ICAs, GAAs, and ICA512AAs (n = 71,148)</th>
<th>Total DPT-1 subjects tested for ICA (n = 79,119)</th>
<th>ICA+</th>
<th>GAA+</th>
<th>ICA512AA+</th>
<th>GAA+ and ICA512AA+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31,264 (43.9)</td>
<td>34,743 (43.9)</td>
<td>3.98</td>
<td>4.22</td>
<td>1.66</td>
<td>1.21</td>
</tr>
<tr>
<td>Female</td>
<td>39,867 (56.0)</td>
<td>44,359 (56.1)</td>
<td>3.06†</td>
<td>3.82‡</td>
<td>1.22§</td>
<td>0.85*</td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (0.0)</td>
<td>17 (0.0)</td>
<td>0.88</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56,641 (79.6)</td>
<td>63,177 (79.9)</td>
<td>3.62</td>
<td>4.16</td>
<td>1.50</td>
<td>1.08</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7,773 (10.9)</td>
<td>8,552 (10.8)</td>
<td>2.74†</td>
<td>3.35‡</td>
<td>1.14§</td>
<td>0.71§</td>
</tr>
<tr>
<td>Black</td>
<td>1,916 (2.7)</td>
<td>2,174 (2.7)</td>
<td>2.38</td>
<td>3.88</td>
<td>0.75§</td>
<td>0.54§</td>
</tr>
<tr>
<td>American Indian</td>
<td>222 (0.3)</td>
<td>234 (0.3)</td>
<td>3.70</td>
<td>2.31</td>
<td>0.46</td>
<td>0.46</td>
</tr>
<tr>
<td>Asian/Pacific Island</td>
<td>686 (1.0)</td>
<td>779 (1.0)</td>
<td>3.29</td>
<td>4.34</td>
<td>1.50</td>
<td>1.05</td>
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<tr>
<td>Other</td>
<td>1,161 (1.6)</td>
<td>1,288 (1.6)</td>
<td>2.46</td>
<td>2.90</td>
<td>1.32</td>
<td>0.88</td>
</tr>
<tr>
<td>Unknown</td>
<td>2,749 (3.9)</td>
<td>2,915 (3.7)</td>
<td>2.83</td>
<td>2.87</td>
<td>0.99</td>
<td>0.81</td>
</tr>
<tr>
<td>Age (years)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0–5</td>
<td>8,443 (11.9)</td>
<td>9,448 (11.9)</td>
<td>3.00</td>
<td>3.45</td>
<td>1.58</td>
<td>1.07</td>
</tr>
<tr>
<td>6–11</td>
<td>18,497 (26.0)</td>
<td>20,504 (25.9)</td>
<td>3.72‡</td>
<td>4.02§</td>
<td>1.67</td>
<td>1.33</td>
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<tr>
<td>12–17</td>
<td>13,974 (19.6)</td>
<td>15,453 (19.5)</td>
<td>4.07*</td>
<td>4.61*</td>
<td>1.93</td>
<td>1.50§</td>
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<tr>
<td>18–29</td>
<td>8,395 (11.8)</td>
<td>9,379 (11.9)</td>
<td>3.64§</td>
<td>3.77</td>
<td>1.53</td>
<td>1.20</td>
</tr>
<tr>
<td>30–45</td>
<td>21,839 (30.7)</td>
<td>24,335 (30.8)</td>
<td>3.01</td>
<td>3.90</td>
<td>0.70*</td>
<td>0.42*</td>
</tr>
<tr>
<td>Relationship to proband</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>27,585 (38.8)</td>
<td>30,507 (38.6)</td>
<td>4.36</td>
<td>4.95</td>
<td>2.04</td>
<td>1.53</td>
</tr>
<tr>
<td>Offspring</td>
<td>17,321 (24.3)</td>
<td>19,274 (24.4)</td>
<td>3.16*</td>
<td>3.61*</td>
<td>1.22§</td>
<td>0.80*</td>
</tr>
<tr>
<td>Parent</td>
<td>15,776 (22.2)</td>
<td>17,229 (22.4)</td>
<td>2.72*</td>
<td>3.61*</td>
<td>0.60§</td>
<td>0.41*</td>
</tr>
<tr>
<td>Non–first-degree relatives</td>
<td>10,073 (14.2)</td>
<td>11,214 (14.2)</td>
<td>2.48*</td>
<td>2.90*</td>
<td>0.90*</td>
<td>0.60*</td>
</tr>
<tr>
<td>Unspecified relation</td>
<td>395 (0.6)</td>
<td>395 (0.5)</td>
<td>8.38</td>
<td>12.04</td>
<td>8.12</td>
<td>6.02</td>
</tr>
</tbody>
</table>

Data are n (%) or %. *P < 0.0001; †P < 0.001; ‡P < 0.01; §P < 0.05. All P values were calculated in comparison to the first subgroup (male, white, age 0–5 years, sibling) with corresponding group of each column.

biochemically determined autoantibodies relative to eligibility for DPT-1 among ICA+ relatives.

RESEARCH DESIGN AND METHODS

Subjects. With nine coordinating clinical centers and >370 affiliate and satellite centers, the DPT-1 has screened relatives throughout the U.S. and Canada for cytoplasmic ICAs. To have been eligible for screening, an individual must have been a first-degree relative of a type 1 diabetic patient and between ages 2.5 and 45 years or have been a second-degree relative and between ages 2.5 and 20 years. Individuals were eligible for participation in the trial between ages 3 and 45 years. If a relative was found to be ICA+ or was ICA+ based on initial screening samples; 500 of these were staged and found to be eligible for a DPT-1 intervention (Fig. 1). An additional 72, whose initial ICA sample was negative, were then found to be ICA+ on follow-up and were determined to be trial-eligible. Thus, 572 relatives were trial-eligible at the time of our analysis.

The results of the determination of IAAs, DQ typing, and IVGTT are based on initial screening samples; 500 of these were staged and found to be eligible for a DPT-1 intervention (Fig. 1). An additional 72, whose initial ICA sample was negative, were then found to be ICA+ on follow-up and were determined to be trial-eligible. Thus, 572 relatives were trial-eligible at the time of our analysis.

ICA assay. Cytoplasmic ICAs were determined on frozen sections of human pancreas by the DPT-1 ICA Core Laboratory (in Gainesville, FL, from February 1994 to September 1997; in New Orleans, LA, from September 1997 to December 1998) (7) Samples were considered positive at ≥10 JDFU. In the recent Immunology of Diabetes Society (IDS) Combinatorial Autoantibody Workshop (Orvieto, Italy, November 1995), this ICA assay had a specificity of 100%, with a sensitivity of 74.4% for new-onset patients aged <30 years.

GAA and ICA512AA assay. GAA and ICA512AA levels were measured simultaneously by combined GAA and ICA512AA radioassay, as previously described, in the DPT-1 GAA and ICA512AA Core Laboratory (Denver, CO; full-length GAD65 and ICA512bdc cDNA clones) (24). The assay was performed in 96-well filtration plates with autoantibody bound [3H]GAD65 and [35S]ICA512 precipitated with protein A Sepharose. The cut-points were set at indexes of 0.032 (mean ± 2 SD for GAAs) and 0.071 (mean ± 6 SD for ICA512AAs), the 99th and 100th percentile, respectively, of 198 normal controls. The interassay coefficients of variation were 6.5 and 9.6%, respectively, for GAA and ICA512AA assays, with the samples of index values <1. In the IDS Combinatorial Workshop, for patients younger than age 30 years, assay specificity was 99 and 100% and sensitivity was 83.7 and 74.4% for GAA and ICA512AAs, respectively. ICA512bdc and ICA512ic autoantibody assays. A subset of 2,151 samples from these DPT-1 samples was randomly selected, and two different con-
FIG. 2. A: Of 71,148 relatives of type 1 diabetic patients originally screened, 2,448 (3.44%) were ICA+. Of these ICA+ relatives, 1,229 (50.2%; 1.73% of total population screened) were GAA+ and/or ICA512AA+. Of the 68,700 ICA− relatives, 1,897 (2.76%; 2.67% of total population screened) were GAA+ and/or ICA512AA+. B: ICA positivity among relatives with indicated biochemical (Bioch) autoantibody positivity.

RESULTS

Of 71,148 initial screening samples measured for GAA, ICA512AAs, and cytoplasmic ICAs, 2,448 (3.44%) were ICA+ and 68,700 (96.56%) were ICA−. Among the 2,448 ICA+ relatives, 1,229 (50.2%, 1.73% of total relatives screened) were positive for GAA and/or ICA512AAs (554 [22.6%] GAA only, 104 [4.3%] ICA512AAs only, and 571 [23.3%] GAs and ICA512AAs). Among ICA− relatives, 1,897 (2.8% of ICA−, 2.67% of total relatives screened) were positive for GAs and/or ICA512AAs (1,582 GAAs only, 180 ICA512AAs only, and 135 GAs and ICA512AAs). The prevalence of GAs and ICA512AAs among ICA+ and ICA− relatives is summarized in Fig. 2A. Figure 2B displays ICA positivity among individuals with GAs and/or ICA512AAs. In total, 39.3% (1,229 of 3,126) of the individuals positive for GAs and/or ICA512AAs were ICA+, 25.9% (554 of 2,136) of individuals with GAs alone were ICA+, 36.6% (104 of 284) of individuals with ICA512AAs alone were ICA+, and 80.9% (571 of 706) of individuals with both GAs and ICA512AAs were ICA+. Table 1 summarizes positivity for each autoantibody relative to sex, ethnicity, age, and relationship to proband.

Two different constructs are often used for the determination of ICA512 (IA-2) autoantibodies in international workshops: ICA512bdc (amino acids 256–556:630–979) and ICA512ic (amino acids 605–979). The cut-points for positivity were set at indexes of 0.048 and 0.010, representing the 99th percentile for ICA512bdc and ICA512ic, respectively, of 198 normal controls. The intra-assay coefficient of variation was 12% (n = 6) at medium-low positive levels, and the inter-assay coefficient of variation was 12% (n = 10).

ICA512AA assay. ICA512AAs were determined with a fluid phase radioassay using polyethylene glycol precipitation in the DPT-1 IAA Core Laboratory (Boston, MA) (26). The cut-point was 39 nU/ml (mean ± 2 SD), which was the 99th percentile of 151 normal controls. The intra-assay coefficient of variation was 10.3% at low positive values. In the IDS Combinatorial Workshop, the assay had a specificity of 91% and sensitivity of 49%.

IVGTT. The IVGTT was performed according to the ICARUS (Insulin Carotid US Scandinavica) protocol (27). The 1 + 3 min insulin was used as the index of FPIR. Insulin levels were determined in the DPT-1 β-Cell Function Core Laboratory (Seattle, WA) (6). Eligibility for the parental insulin trial of DPT-1 required an FPIR <50 μU/ml for ages <8 years, <100 μU/ml for ages ≥8 years, and <60 μU/ml for parents of diabetic patients.

HLA-DQ typing. HLA-DQ typing was determined as part of the DPT-1 study using sequence-specific oligonucleotide probes in the DPT-1 HLA Core Laboratory (Denver, CO) (28). Individuals with HLA-DQA1*0102, DQB1*0602 were included (noneligible) from the DPT-1 trial.

Statistical analysis. Categorical variables were analyzed using χ² tests or Fisher’s exact tests, depending on cell size. Continuous variables were compared using Student’s t test or Wilcoxon’s rank-sum test, depending on the distribution of the variable of interest. An analysis of variance was used for comparisons of a continuous variable across more than two levels. Statistical analyses were performed using SAS, True Epistat, and Prism Software.
To further analyze the association between cytoplasmic ICAs and GAAs or ICA512AAas, the levels of these autoantibodies were compared within different subgroups of relatives. The levels of GAAs of ICA+ relatives ($n = 1,125$, median 0.548, range 0.033–1.978) were significantly higher than the levels of ICA− relatives ($n = 1,171$, median 0.135, range 0.033–1.983; median-test, $P < 0.001$). The levels of ICA512AAs of ICA+ relatives ($n = 675$, median 0.685, range 0.072–1.867) were also significantly higher than the levels of ICA− relatives ($n = 315$, median 0.170, range 0.072–1.388; median-test, $P < 0.001$). The ICA titers of ICA+ relatives with GAA and/or ICA512AA positive ($n = 1,229$) and negative ($n = 1,219$) subgroups were compared. The median titers of ICA were 160 and 20 for the GAA- and/or ICA512AA-positive versus the GAA- and ICA512AA-negative group, respectively ($P < 0.001$, Wilcoxon’s rank-sum test).

The mIAA assay is a methodology that has recently become available and allows more rapid analysis of IAAs. With ~6,400 screening samples analyzed for mIAAs, 1.6% of the samples with no autoantibodies (including those negative for ICAs, GAAs, and ICA512AAs) were mIAA+. There were 160 ICA+ sera negative for GAAs and ICA512AAs and only 3 of 160 (1.9%) mIAA+. In contrast, 23% (28 of 122) of the ICA+ sera with GAAs and/or ICA512AAs were mIAA+ ($P < 0.0001$).

Given the large number of relatives positive for cytoplasmic ICAs and negative for biochemically determined autoantibodies (1,219 of 2,448), we compared the results of IVGTTs among the relatives who had cytoplasmic ICAs only ($n = 862$), ICAs with GAAs only ($n = 386$), ICAs with ICA512AAs only ($n = 67$), and ICAs with both GAAs and ICA512AAs ($n = 384$) (Fig. 4). The mean of FPIR (mean ± SE) was 190.0 ± 5.4 for relatives with ICAs alone, 141.0 ± 6.4 for relatives with ICAs plus GAAs only, 117.4 ± 12.8 for relatives with ICAs plus ICA512AAs only, and 108.4 ± 4.0 for relatives with ICAs plus both GAAs and ICA512AAs ($P < 0.001$, $F$ test). Using Tukey’s method with an overall $\alpha$ of 0.05, examination of the multiple comparisons indicated that relatives with ICAs alone had significantly higher FPIRs than relatives with ICAs plus GAAs or ICA512AAs or relatives with ICAs plus both GAAs and ICA512AAs.

To be eligible for the parenteral insulin DPT-1 trial, a relative had to have FPIR $<1$st percentile of cut-points (for parents) or $<10$th percentile (for siblings and offspring). To be eligible for the oral insulin trial, a relative had to have FPIR above cut-points ($>1$st percentile for parents, $>10$th percentile for siblings/offspring) and be positive for anti-IAAs. For both trials, DQB1*0602 was an exclusion criteria and cytoplasmic ICAs had to be confirmed. Overall, 164 ICA+ relatives were found to have diabetes during staging and were thus considered not to be trial-eligible (131 of 164 were GAA+ and/or ICA512AA+). Among the relatives with GAAs and/or ICA512AAs on their initial screening samples who completed staging, 51.0% (442 of 866) have been found to date to be eligible for trial entry. In contrast, 11.9% (130 of 1,088) of ICA+ relatives negative for GAAs and ICA512AAs were found to be eligible for trial entry ($P < 0.001$). Of 572 relatives in Table 2 who were found to be eligible for trial entry (318 for parental trial and 254 for oral trial), a total of 77.3% (442 of 572) were GAA+ and/or ICA512AA+, 70.8% (405 of 572) were GAA+, 43.5% (249 of 572) were ICA512AA+, and 37.0% (212 of 572) were both GAA+ and ICA512AA+. Of 1,382 relatives who completed staging and were found to not be eligible for trial entry, 286 were confirmed ICA− from later tests and only 8.7% (25 of 286) of them were GAA+ and/or ICA512AA+ compared with 50.2% (1,229 of 2,448) of the total ICA+ group. In the ICA+ group, 163 had HLA-DQB1*0602 and were thus not trial eligible. Of this group, 32 of 163 (19.6%) were GAA+ and/or ICA512AA+ positive.

**DISCUSSION**

Large-scale trials for the prevention of type 1A diabetes, such as the DPT-1 trial, were designed before the development and detailed characterization of quantitative assays for autoantibodies reacting with ICA512 (IA-2) and GAD65. Thus, the entry criteria for the DPT-1 trial are based on the positivities of cytoplasmic ICAs and IAAs, FPIR, and HLA typing, but are not related to the presence...
or absence of GAD65 and ICA512 autoantibodies. It is thus possible to analyze the correlation between the presence of the latter two autoantibodies among ICA+ relatives and eligibility for entry into the DPT-1 trial.

In our study, 50% (1,229 of 2,448) of cytoplasmic ICA+ relatives were positive for autoantibodies reacting with either GAD65 or ICA512 (IA-2) in comparison to 2.8% (1,897 of 68,700) of ICA− relatives. Thus, as expected, cytoplasmic ICA+ relatives were enriched for relatives with positive GAD65 or ICA512 autoantibodies. Nevertheless, only 39.3% (1,229 of 3,126) of individuals who were positive for GAAs or ICA512AAs were cytoplasmic ICA+. Individuals with ICA512AAs were more often ICA+ (68.2%, 675 of 990) compared with individuals with GAAs (39.6%, 1,125 of 2,842), and approximately half of ICA+ relatives were negative for both GAAs and ICA512AAs. With 6,420 screening samples analyzed for mIAAs, only 1.9% (3 of 160) of ICA+ individuals negative for GAAs and ICA512AAs were mIAA− versus 23.0% (28 of 122) of ICA+ individuals positive for GAAs and/or ICA512AAs.

A number of studies have indicated that the presence of cytoplasmic ICAs in the absence of both GAAs and ICA512AAs is associated with a very small risk of progression to diabetes (2,19). Both a high titer of ICAs and low FPIR are associated with a high risk of developing type 1 diabetes among first-degree relatives (2,3,29). The present data also indicate that the levels of cytoplasmic ICAs in sera positive for GAAs and ICA512AAs are significantly higher (P < 0.001) than when GAAs and ICA512AAs are not present. FPIR was significantly different among the ICA+ groups, according to GAA and ICA512AA positivity. The mean level of FPIR of relatives with ICA+ who were also negative for GAAs and ICA512AAs was ∼200 μU/ml, significantly greater than the level for ICA+ relatives also positive for GAAs and/or ICA512AAs.

Staging for DPT-1 was designed to identify ICA+ relatives with a relatively high risk of progression to diabetes. Thus, if GAA and ICA512AA positivity on the initial screening sample identifies higher-risk relatives and the staging criteria identify a high-risk population, GAA and ICA512AA positivity should correlate with trial eligibility. Among the relatives who were found to be eligible for the trial, 442 of 572 (77.3%) relatives (76.4% for parenteral trial and 78.3% for oral trial, respectively) were positive for GAAs and/or ICA512AAs on their first screening sample. In contrast, only 50.2% of all ICA+ relatives were positive for GAAs and/or ICA512AAs, and 51.0% (442 of 866) of ICA+ relatives with GAA+ or ICA512AA+ relatives were eligible. Only 11.9% (130 of 1,088) of cytoplasmic ICA+ relatives negative for GAAs and ICA512AAs were found to be eligible for trial entry. The positive predictive value for trial eligibility for ICA+ relatives with GAAs or ICA512AAs was 51.0%. The negative predictive value for relatives not being eligible for trial participation when they were ICA+ but GAA- and ICA512AA-negative was 88.1%. These data suggest that the biochemical antibodies expressed by ICA+ relatives in the initial screening sample can be used to a large extent to predict the results of the staging process. It is likely that if future trials for the prevention of type 1A diabetes use ICA testing, it may be more efficient to stage for trial entry only those relatives positive for GAA and/or ICA512AA with eligibility. It should also be realized that the staging criteria includes one cutoff for variables set at the 10th percentile of control populations (e.g., IVGTT response of children), thus a proportion of individuals would be found eligible with this criterion.

In all, 60.7% (1,897 of 3,126) of relatives with GAAs and/or ICA512AAs were cytoplasmic ICA−. In this group, the levels of both GAAs and ICA512AAs were significantly lower than the levels of the ICA+ group. Inasmuch as the presence of cytoplasmic ICAs initiates the staging process for DPT-1, the percentage of such relatives having low FPIR, anti-IAAs, or the HL-A allele DQB1*0602 is currently unknown. If one were to consider designing trials for the prevention of type 1A diabetes in the absence of determination of cytoplasmic ICAs (i.e., by GAA and ICA512AA screening), the prognosis of ICA− GAA+ and/or ICA512AA− relatives would be an important consideration. Studies of this group (as an ancillary study of the DPT-1) are underway.

With our current information, we believe that the design of future trials identifying relatives with a risk of diabetes similar to the oral or parenteral DPT trials might consider determination of GAAs and ICA512AAs followed by staging that might include determination of cytoplasmic ICAs. Further follow-up and analysis of the DPT-1 cohort should aid in the design of such trials; in particular, the analysis of ICA− relatives expressing biochemical autoantibodies will be required to determine whether the trials are sufficient to identify high-risk individuals without cytoplasmic ICA analysis.

ACKNOWLEDGMENTS

This research was supported by grants from the National Institutes of Health (NIH) (5R37-DK-32083-16 and R01-A1-39213) and by Grant M01-RR-00069 from the General
Clinical Research Program, National Centers for Research Resources, NIH. We thank Bayer for GAD/ICA512 grant funding for supplies. The DPT-1 was supported through cooperative agreements by NIH institutes (Division of Diabetes, Endocrinology, and Metabolic Diseases [National Institute of Diabetes and Digestive and Kidney Diseases]; the National Institute of Allergy and Infectious Diseases; the National Institute of Child Health and Human Development; and the National Center for Research Resources), the American Diabetes Association, the Juvenile Diabetes Foundation International, and various corporate sponsors.

REFERENCES