

Extended Family History of Type 1 Diabetes and Phenotype and Genotype of Newly Diagnosed Children

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OBJECTIVE—To determine the frequency of newly diagnosed diabetic children with first- and second-degree relatives affected by type 1 diabetes and to characterize the effects of this positive family history on clinical markers, signs of β -cell autoimmunity, and HLA genotype in the index case.

RESEARCH DESIGN AND METHODS—Children ($n = 1,488$) with type 1 diabetes diagnosed under 15 years of age were included in a cross-sectional study from the Finnish Pediatric Diabetes Register. Data on family history of diabetes and metabolic decompensation at diagnosis were collected using a questionnaire. Antibodies to β -cell autoantigens (islet cell antibodies, insulin autoantibodies, GAD antibodies, and antibodies to the islet antigen 2 molecule) and HLA genotypes were analyzed.

RESULTS—A total of 12.2% of the subjects had a first-degree relative with type 1 diabetes (father 6.2%, mother 3.2%, and sibling 4.8%) and 11.9% had an affected second-degree relative. Children without affected relatives had lower pH ($P < 0.001$), higher plasma glucose ($P < 0.001$) and β -hydroxybutyrate concentrations ($P < 0.001$), a higher rate of impaired consciousness ($P = 0.02$), and greater weight loss ($P < 0.001$). There were no differences in signs of β -cell autoimmunity. The familial cases carried the HLA DR4-DQ8 haplotype more frequently than sporadic cases (74.0 vs. 67.0%, $P = 0.02$).

CONCLUSIONS—When the extended family history of type 1 diabetes is considered, the proportion of sporadic diabetes cases may be reduced to $<80\%$. A positive family history for type 1 diabetes associates with a less severe metabolic decompensation at diagnosis, even when only second-degree relatives are affected. Autoantibody profiles are similar in familial and sporadic type 1 diabetes, suggesting similar pathogenetic mechanisms.

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Familial clustering of type 1 diabetes is a conspicuous feature; the risk of developing type 1 diabetes is 8–15-fold higher in first-degree relatives (1–6) and twofold in second-degree relatives (1,7). Despite this, the vast majority of children are diagnosed with the sporadic form of diabetes. The proportion of children with an affected first-degree relative at the time of diagnosis is ~ 10 –12% (7–13), and

after decades of follow-up, this frequency increases to $>20\%$ (8,14,15). Fathers transmit the disease to their offspring more often than mothers (3,16). Accordingly, at diagnosis, 4–7% of children have a father with type 1 diabetes whereas only 1.5–3% have an affected mother (7–12,17). Fewer reports exist on type 1 diabetes in the extended family. Depending on the definition of second-degree relatives

and length of time from the diagnosis of the index case, 5–16% of children with type 1 diabetes have an affected second-degree relative (1,5,11,17–19).

Familial and sporadic type 1 diabetes have been suggested to differ in terms of pathogenetic mechanisms (20,21). The risk-associated HLA genotypes have been observed more often in familial type 1 diabetes (8,20,22,23), although not all studies have found significant differences (24). Two studies have noticed no differences in diabetes-associated autoantibodies, e.g., insulin autoantibodies (IAAs) (8), GAD antibodies (GADAs) (8), or islet cell antibodies (ICAs) (8,20). A recent study from Israel reported, however, higher frequencies of IAAs and a higher number of positive antibody responses among familial cases (13). In families with prior experience of type 1 diabetes in a first-degree relative, the clinical status of the child at diagnosis is less severe (8,13,21).

Data on the possible pathogenetic differences between familial and sporadic type 1 diabetes are still inconsistent and based on a positive family history in first-degree relatives only. To further our understanding of familial clustering of type 1 diabetes, we used data from the large, nationwide Finnish Pediatric Diabetes Register for a cross-sectional observational study. Since the knowledge of the effects of an extended family history on the diabetes of the index case is lacking, we included information on second-degree relatives (grandparents and siblings of parents). β -Cell autoimmunity, metabolic decompensation at diagnosis, and HLA genetics were compared in children with familial or sporadic type 1 diabetes. We postulated to see a stronger genetic susceptibility to type 1 diabetes and a milder metabolic decompensation in children with a positive family history for type 1 diabetes, whereas no differences were expected in the autoantibody profile.

RESEARCH DESIGN AND METHODS

Subjects

Since June 2002, the Finnish Pediatric Diabetes Register and Biobank has invited

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*A complete list of the investigators of the Finnish Pediatric Diabetes Register can be found in the APPENDIX.

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all pediatric patients diagnosed with diabetes in Finland to participate in the register and the Biobank. Compared with the information provided by all the pediatric units in Finland, the coverage of the Register is ~92% (25). Around 70% of the families participating in the register also provide blood samples for the Biobank from the index case and/or the first-degree relatives as soon as possible after the diagnosis of the index case. The samples are analyzed for diabetes-related autoantibodies (ICA, IAA, GADA, and antibodies to the islet antigen 2 molecule [IA-2A]) and HLA-DR-DQA1-DQB1 haplotypes (26).

Families participating in the register receive a structured questionnaire (Supplementary Data) at the time of diagnosis of the index child. A diabetes nurse or doctor answers the questions regarding clinical status and degree of metabolic decompensation at diagnosis and assists the family with questions on the family history of diabetes. The total number of first-degree relatives (parents and siblings) is asked, but the number of second-degree relatives other than grandparents (i.e., siblings of parents) is unknown. For parents, siblings, and grandparents, the diabetes status (no, yes, or unknown) and the diabetes type (type 1, type 2, gestational, or other diabetes) are asked separately, and families are asked to list any other relatives with type 1 diabetes. If the family is unsure of the diabetes type of a relative, the diabetes doctor or nurse classifies the disease according to the information provided by the family. For our analysis, however, parents with type 2 diabetes marked in the questionnaire were considered to have type 1 diabetes if autoantibodies other than IAA were detectable in their serum (8 of 2,916, 0.3%). The legal guardians of the children and their siblings 18 years of age or older give informed written consent. Participants 10–17 years of age give informed assent. The protocol has been approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa.

By October 2006, the Finnish Pediatric Diabetes Register comprised 2,663 children with type 1 diabetes. The median age was 8.23 years (range 0–16.98), and 56.2% were male. We excluded children with age at diagnosis >15 years, no information on their relatives in the register, or incomplete diabetes-associated autoantibody analyses by April 2007. One child with an affected father and two affected brothers was excluded because a novel insulin gene mutation was recognized. We planned to exclude any autoantibody-negative children with

diabetes occurring in three successive generations as suspected MODY (maturity-onset diabetes of the young) cases. Such children were not identified in the dataset, however. Only the first child from any family to be diagnosed with diabetes and registered was included as an index case. Consequently, 1,488 children were included in the study. The demographic characteristics of the children included in or excluded from the study did not differ.

The serum samples were taken a median of 5 days after diagnosis. For most of the children (92.2%), the sample was drawn within 14 days. Those with the serum sample taken >30 days after the diagnosis (103 of 1,488, 6.9%) were excluded from the autoantibody analysis. We have shown that insulin antibody

levels 1 month after the diagnosis correlate more strongly with the IAA titers at diagnosis than with insulin antibody levels 3 months later (unpublished data), indicating that even insulin antibodies detected 30 days after the diagnosis reflect an autoimmune response rather than a response to exogenous insulin.

The flowchart in Fig. 1 displays the grouping of the case subjects. For the analyses, the following categories were used. First, sporadic cases were compared with familial cases. These familial cases had first- and/or second-degree relatives with type 1 diabetes. Second, we used a classification into familial cases with affected first-degree relatives, familial with affected second-degree relatives, and familial with type 1 diabetes in both first- and

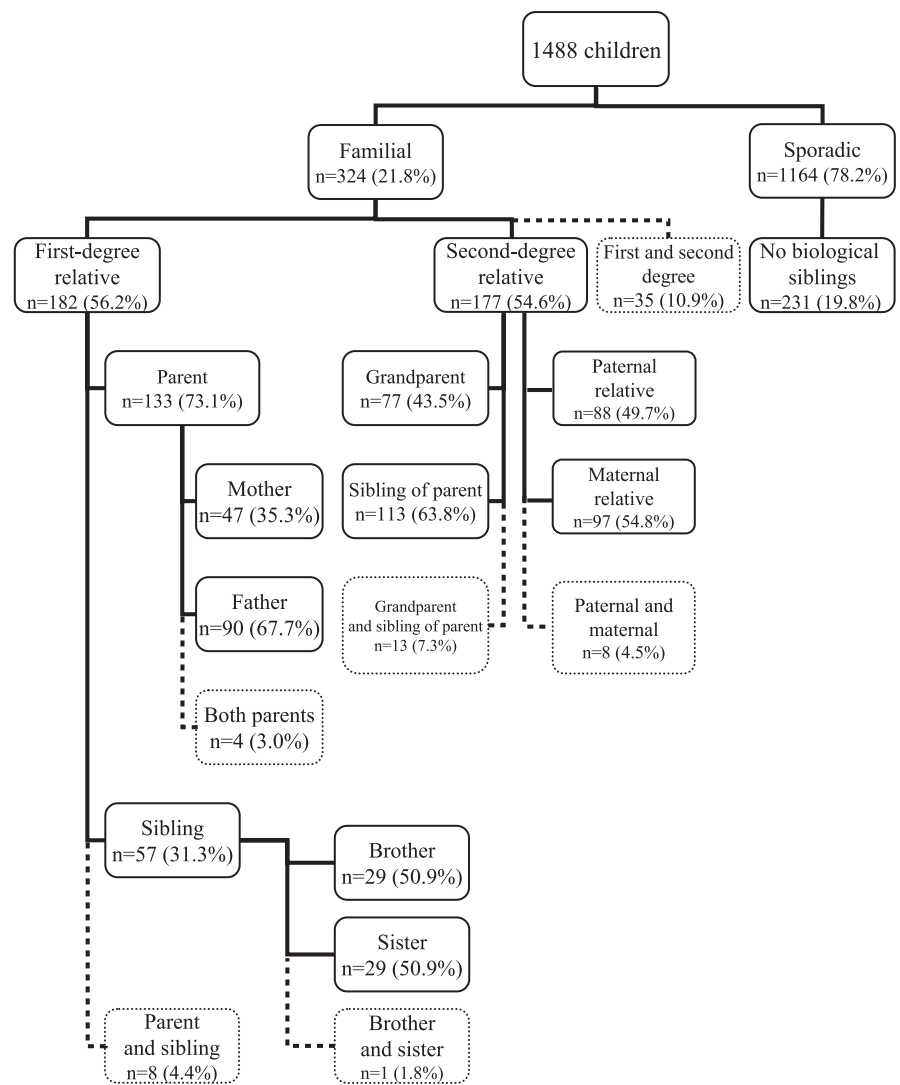


Figure 1—Grouping of the index case subjects according to who in the extended family was affected by type 1 diabetes. The dashed lines refer to the case subjects with affected relatives from more than one category of relatives. These case subjects are also included in the total number of each category of relatives.

second-degree relatives, as well as sporadic cases. Third, a closer analysis of familial cases was performed according to who in the immediate family (parent or sibling) or extended family (paternal or maternal second-degree relative) had diabetes.

Autoantibodies

ICAs were analyzed with indirect immunofluorescence on human group 0 donor pancreas with 2.5 JDFU as the detection limit (27). IAAs, GADAs, and IA-2As were quantified with specific radiobinding assays (28–30). The cutoff limits for antibody positivity were determined as the 99th percentiles in 354 Finnish, nondiabetic children and adolescents, and were 2.80 relative units (RU) for IAA, 5.36 RU for GADA, and 0.77 RU for IA-2A. According to the 2005 Diabetes Autoantibody Standardization Program, the disease sensitivities of these assays were 44, 82, and 72% and specificities were 98, 97, and 100%, respectively. When calculating the median antibody titers, we included only samples at or above the cutoff for antibody positivity.

HLA typing

HLA typing of major DR-DQ haplotypes was performed with a PCR-based, lanthanide-labeled hybridization method using time-resolved fluorometry for detection (26). HLA typing results were available for 97.7% of the index cases.

Markers of metabolic decompensation at diagnosis

Blood pH, plasma glucose, and β -hydroxybutyrate levels of the index children were analyzed in local laboratories at the time of diagnosis. Hemoglobin A_{1c} was not recorded because the methods used locally were not standardized and, accordingly, varied considerably between laboratories, hampering any nationwide comparison.

Data handling and statistical analysis

SPSS 17.0 and 19.0 statistical software packages (SPSS, Inc., Chicago, IL) were used for statistical analyses. Cross tabulation, χ^2 statistics, and Fisher exact test were applied for comparing frequencies of different variables. Differences in levels of variables were analyzed with Student *t* test or one-way ANOVA for parametric and Mann-Whitney *U* test/Wilcoxon rank sum test or Kruskal-Wallis test with Dunn post hoc test for nonparametric variables. A two-tailed *P* value of 0.05 or less was considered statistically significant, and Bonferroni correction for

multiple comparisons was not applied due to its overly conservative nature.

RESULTS—At diagnosis, the index cases were between 0.28 and 14.99 years of age (median 8.23). A majority of the subjects were male (846 of 1,488, 56.9%), and 80.6% (1,200 of 1,488) had at least one biological sibling. The proportion of children with a first-degree relative affected by type 1 diabetes was 12.2% (Fig. 1). Twelve children had two first-degree relatives with type 1 diabetes (0.8%) and one had four (0.1%). Ninety children (6.2%) had a father with type 1 diabetes, and 47 (3.2%) had an affected mother. Fifty seven subjects (3.9% out of a total of 1,488 children or 4.8% out of 1,200 children with at least one sibling) had a sibling with type 1 diabetes. Out of a total of 2,087 siblings, 2.9% had type 1 diabetes.

Of the 1,488 children, 177 (11.9%) had a second-degree relative affected by type 1 diabetes (Fig. 1). The number of these relatives per child varied between one and five. The total number of second-degree relatives of the subjects is unknown. Thirty eight (2.8%) had a paternal grandparent and 40 (2.8%) a maternal grandparent affected by type 1 diabetes, whereas 54 (3.7%) had an affected paternal sibling and 63 (4.2%) an affected maternal sibling. Taken together, 88 (6.0%) index children had an affected second-degree relative from the paternal side and 97 (6.5%) from the maternal side of the family. The proportions of children with affected grandfathers and grandmothers were similar, with 41 (2.9%) children having an affected grandfather and 37 (2.6%) an affected grandmother. Among the 5,580 grandparents with information on their diabetes status, 79 (1.4%) had type 1 diabetes.

In summary, 324 children (21.8%) had a first- and/or second-degree relative with type 1 diabetes, and 35 (2.4%) had both an affected first- and second-degree relative. The age of the index cases at diagnosis did not differ between any categories of comparisons.

Both sexes equally often had a first-degree (12.2% of the boys and 12.3% of the girls, *P* = 1.00) or second-degree relative (12.4% of boys and 11.2% of girls, *P* = 0.53) with type 1 diabetes. Similarly, both sexes equally often had a father with type 1 diabetes (6.4% of the boys and 6.0% of the girls, *P* = 0.82), a mother with type 1 diabetes (3.3% of boys and 3.0% of the girls, *P* = 0.83), or a sibling with type 1 diabetes (3.7% of boys and 4.1% of girls, *P* = 0.79). However, the proportion of

children with an affected paternal second-degree relative was 4.9% among boys and 7.5% among girls (*P* = 0.06). The respective proportion for affected maternal second-degree relatives was 7.8% for boys and 4.8% for girls (*P* = 0.03). A conspicuous majority of children with an affected maternal second-degree relative were boys (71.9%), when compared with those with an affected paternal relative (46.6%) or sporadic cases (56.6%, *P* = 0.002).

Metabolic decompensation at diagnosis

At the time of diagnosis, the clinical condition was significantly poorer in sporadic than familial cases (Table 1). Accordingly, the sporadic cases had ketoacidosis (*P* < 0.001) and impaired level of consciousness (*P* = 0.02) more often than the familial cases. Moreover, their weight loss was greater (*P* < 0.001), β -hydroxybutyrate (*P* < 0.001) and plasma glucose concentrations (*P* < 0.001) were higher, and blood pH was lower (*P* < 0.001) (Table 1). When comparing four groups (Table 2), it became evident that the less severe clinical condition at diagnosis was also true for children with an affected second-degree relative. No major differences were apparent between children with affected parents or siblings.

Autoantibodies

No significant differences in the frequencies or titers of various autoantibodies were observed when familial children were compared with sporadic cases (Table 1), or when comparing four groups (Table 2). However, the children with both affected first- and second-degree relatives tended to have a lower number of positive antibody responses (Table 2). There were no major differences in the levels or frequencies of autoantibodies between the index children with affected parents or siblings.

HLA genetics

The children with familial type 1 diabetes carried the *DRB1**0401/2/4/5-*DQA1**0301-*DQB1**0302 (DR4-DQ8) haplotype more often than sporadic children (74.0 vs. 67.0%, *P* = 0.02) (Table 1). Comparison between the four groups (presented in Table 2) revealed that the only significant difference was in the frequency of the DR4-DQ8 haplotype between sporadic cases and those with an affected second-degree relative (67.0 vs. 78.4%, *P* < 0.04). When comparing the sporadic cases with those with an affected maternal or paternal second-degree relative,

Table 1—Demographic, metabolic, immunological, and genetic markers in index children with familial type 1 diabetes and sporadic cases

	Familial (n = 324)	Sporadic (n = 1,164)	P value
Demographics			
Sex, male, %	57.7	56.6	0.77
Age at diagnosis, years, median (range)	8.20 (0.28–14.95)	8.23 (0.69–14.99)	0.99
Metabolic decompensation at diagnosis			
Plasma glucose, mmol/L, median (range)	22.2 (3.6–97.6)	24.9 (3.2–92.7)	<0.001
Ketoacidosis, %	9.8	21.4	<0.001
pH, median (range)	7.39 (6.80–7.54)	7.37 (6.87–7.52)	<0.001
β -Hydroxybutyrate, mmol/L, median (range)	0.7 (0–20.1)	2.2 (0–15.1)	<0.001
Impaired consciousness, %	2.3	5.8	0.02
Duration of symptoms, days, median (range)	8 (0–332)	10 (0–377)	0.10
Weight loss, kg, median (range)	0.70 (0–12.0)	1.5 (0–20.0)	<0.001
Autoantibodies			
ICA, %	90.8	93.8	0.09
ICA, JDFU, median (range)	40 (4–640)	40 (2.5–39,935)	0.51
IAA, %	43.9	44.3	0.96
IAA, RU, median (range)	9.9 (3.0–282.1)	10.1 (2.9–309.3)	0.82
IA-2A, %	73.8	76.3	0.42
IA-2A, RU, median (range)	100.4 (1.2–256.4)	102.0 (0.86–553.3)	0.46
GADA, %	65.6	67.1	0.68
GADA, RU, median (range)	37.4 (5.4–419.6)	41.0 (5.5–812.4)	0.47
Number of positive antibodies, median (mean)	3 (2.7)	3 (2.8)	0.19
Genetics			
DR3-DQ2/DR4-DQ8, %	23.6	21.4	0.45
DR3-DQ2/x ^a , %	14.2	17.0	0.26
DR4-DQ8/y ^b , %	50.3	45.6	0.15
x ^a /y ^b , %	11.7	15.7	0.09
DR3-DQ2 positive, %	37.7	38.3	0.92
DR4-DQ8 positive, %	74.0	67.0	0.02

RU, relative units. ^ax \neq DR4-DQ8. ^by \neq DR3-DQ2.

the index cases with affected maternal relatives more often carried the DR4-DQ8 haplotype than the sporadic cases (80.7 vs. 67.0%, $P = 0.01$). This finding differed significantly between the sexes, in that boys with affected maternal relatives more often carried the DR4-DQ8 haplotype compared with boys with affected paternal relatives (81.0 vs. 58.5%, $P = 0.03$) or sporadic cases (81.0 vs. 66.5%, $P = 0.03$) (Supplementary Table 1). In contrast, girls with affected paternal relatives had DR4-DQ8 (84.1 vs. 67.7%, $P = 0.04$) and girls with affected maternal relatives had the DR4/non-DR3 genotype (68.0 vs. 45.1%, $P = 0.04$) more frequently when compared with the sporadic group (Supplementary Table 1). There were no differences in the HLA genetics of the index children with affected parents or siblings.

CONCLUSIONS—This study had an optimal setting to characterize familial and sporadic type 1 diabetes in that the study subjects were derived from a nationwide register with a high level of ascertainment in the country with the highest incidence of type 1 diabetes globally. In keeping with earlier findings, we observed that 12.2% of the children with newly diagnosed type 1 diabetes had at least one affected first-degree relative (8–11). In previous studies, the proportion of type 1 diabetes patients with affected second-degree relatives has varied from 4.8 to 16.7% (1,5,11,17–19), with a proportion of 16% reported for newly diagnosed pediatric patients (5,11). In some studies, third-degree relatives (5,17,19) or only grandparents (18) have been included in the analyses, which hampers any subsequent comparison. In

addition, misclassification of type 1 diabetes as type 2 diabetes in older individuals might affect the results, as type 1 diabetes in such individuals might be milder at diagnosis and not requiring immediate insulin treatment (18,31). In our study, 11.9% of the children had type 1 diabetes in their second-degree relatives, a proportion similar to that of children with affected first-degree relatives. Taken together, 21.8% had an affected relative among first- and/or second-degree relatives, making the true proportion of children with newly diagnosed sporadic type 1 diabetes <80%.

In accordance with earlier reports (8–12,15,17), a higher proportion of fathers with type 1 diabetes than affected mothers was observed. Reports on reduced risk of type 1 diabetes in the same-sex offspring of an affected parent, i.e., fathers transmitting preferentially to daughters and mothers to sons, are controversial (3,4,9,12,16). Based on the data at hand, we cannot confirm such preferential transmission. Our results suggest, however, a similar phenomenon at the level of second-degree relatives; affected boys more often had maternal than paternal second-degree relatives with type 1 diabetes. Although the statistical power of the analysis is limited, HLA genetics support this finding; boys with affected maternal relatives and girls with affected paternal relatives had higher frequencies of the high-risk HLA haplotype DR4-DQ8. In general, the case subjects having affected grandfathers (2.9%) and grandmothers (2.6%) were equally distributed, and the proportions of type 1 diabetes from maternal (6.5%) and paternal (6.0%) second-degree relatives were equal. As our case subjects were ascertained through offspring rather than affected parents, differential transmission from fathers and mothers as well as reduced risk in the same-sex offspring could theoretically result from the male preponderance among type 1 diabetes cases (32). Sex differences in fecundity of affected fathers and mothers might cause a similar bias, but this could be excluded because affected fathers had an average of 2.18 children, compared with 2.02 among diabetic mothers ($P = 0.53$).

As expected, those with prior experiences of type 1 diabetes in the immediate family had a milder metabolic decompensation at diagnosis than sporadic cases (8,13,21). This can be readily explained by the better awareness of the parents in terms of early symptoms of type 1 diabetes facilitating a swift diagnosis and initiation of treatment. Recognition of hyperglycemia with blood glucose self-measurement equipment readily available

Extended family history of type 1 diabetes

Table 2—Demographic, metabolic, immunological, and genetic markers in index children with affected first-degree (group I), second-degree (group II), or both first- and second-degree relatives (group III) and sporadic cases (group IV)

	Familial cases				P value
	I. First degree (n = 147)	II. Second degree (n = 142)	III. First and second degree (n = 35)	IV. Sporadic (n = 1,164)	
Demographics					
Sex, male, %	55.8	59.2	60.0	56.6	0.91
Age at diagnosis, years, median (range)	8.41 (0.28–14.95)	7.68 (1.5–14.95)	8.69 (2.27–14.44)	8.23 (0.69–14.99)	0.98
Metabolic decompensation at diagnosis					
Plasma glucose, mmol/L, median (range)	22.7 (3.6–63.7)	22.8 (6.0–97.6)	18.5 (6.5–39.9)	24.9 (3.2–92.7)	<0.001 I vs. IV: 0.03 II vs. IV: 0.05 III vs. IV: <0.001
Ketoacidosis, %	11.3	10.0	3.0	21.4	<0.001 I vs. IV: 0.007 II vs. IV: 0.002 III vs. IV: 0.02
pH, median (range)	7.38 (6.80–7.54)	7.39 (6.90–7.48)	7.40 (7.27–7.48)	7.37 (6.87–7.52)	<0.001 I vs. IV: 0.02 II vs. IV: 0.02 III vs. IV: <0.001
β-Hydroxybutyrate, mmol/L, median (range)	0.5 (0–20.1)	1.07 (0–11.0)	0.25 (0–9.8)	2.2 (0–15.1)	<0.001 I vs. IV: <0.001 II vs. IV: <0.001 III vs. IV: <0.001
Impaired consciousness, %	2.2	3.0	0.0	5.8	0.08
Duration of symptoms, days, median (range)	7 (0–332)	9 (0–143)	8 (0–132)	10 (0–377)	0.04 I vs. IV: <0.04
Weight loss, kg, median (range)	0.5 (0–10.0)	1.0 (0–12.0)	0.0 (0–5.7)	1.5 (0–20.0)	<0.001 I vs. IV: <0.001 III vs. IV: <0.001
Autoantibodies					
ICA, %	91.2	92.1	83.3	93.8	0.10
ICA, JDFU, median (range)	40 (4–640)	40 (4–640)	23 (4–335)	40 (2.5–39,935)	0.55
IAA, %	47.4	42.5	33.3	44.3	0.54
IAA, RU, median (range)	9.9 (3.3–145.2)	10.7 (3.0–282.1)	10.9 (3.6–61.6)	10.1 (2.9–309.3)	0.96
IA-2A, %	78.1	73.2	56.7	76.3	0.07
IA-2A, RU, median (range)	101.2 (1.2–202.5)	99.2 (1.3–256.4)	96.6 (13.4–157.0)	102.0 (0.86–553.3)	0.48
GADA, %	67.2	66.9	53.3	67.1	0.47
GADA, RU, median (range)	42.9 (5.4–394.9)	31.0 (5.4–419.6)	53.2 (8.9–267.1)	41.0 (5.5–812.4)	0.77
Number of positive antibodies, median (mean)	3 (2.8)	3 (2.8)	2 (2.3)	3 (2.8)	0.05
Genetics					
DR3-DQ2/DR4-DQ8, %	25.5	23.0	17.6	21.4	0.63
DR3-DQ2/x ^a , %	15.2	12.9	14.7	17.0	0.63
DR4-DQ8/y ^b , %	45.5	55.4	50.0	45.6	0.17
x ^a /y ^b	13.6	8.5	17.1	15.7	0.13
DR3-DQ2 positive, %	40.7	36.0	32.4	38.3	0.76
DR4-DQ8 positive, %	71.2	78.4	67.6	67.0	0.05 II. vs. IV: <0.05

Comparisons between two groups with Dunn post-test or cross-tabulation and χ^2 statistics have been performed when the overall P value is significant. RU, relative units. ^ax ≠ DR4-DQ8. ^by ≠ DR3-DQ2.

in these families could be part of the explanation. Importantly, our results indicate that the metabolic status at diagnosis is ameliorated also if the relative with type 1 diabetes is a grandparent or parental sibling. In these families, blood glucose self-measurement equipment would not be similarly available. The small group of children with type 1 diabetes in both first- and second-degree relatives demonstrated a tendency to have even less metabolic decompensation at diagnosis than those with only one affected patient in the family, emphasizing the accumulated knowledge of the disease in such families.

As reported previously from Finland (8), the frequencies or levels of disease-associated autoantibodies in sporadic and familial cases of type 1 diabetes were alike. This suggests similar pathogenetic disease mechanisms in sporadic and familial diabetes. We were unable to reproduce the recent findings from Israel where higher frequencies of IAA as well as a higher number of positive antibody responses were observed among familial cases (13).

As hypothesized, the index cases with affected relatives in the extended family, especially among second-degree relatives, carried the DR4-DQ8 haplotype more often than the sporadic cases. Veijola et al. (8) have reported in familial type 1 diabetes a higher frequency of DR3/DR4 heterozygosity and lower frequency of protective alleles (DQB1*0602, 0603, or 0301). Similar differences have been observed in other studies (20,22,23), but not in all (24). Our observations suggest that the diabetes status of second-degree relatives affects the frequency of the DR4-DQ8 haplotype in the index case more than that of the first-degree relatives. This finding is difficult to explain, although affected grandparents have been shown to transmit their HLA haplotypes to affected grandchildren more often than expected (18). Our findings of genetic differences between familial and sporadic cases implicate a weak contributing effect of differential HLA DR-DQ haplotype frequencies to the familial clustering of type 1 diabetes. The data should be interpreted with caution, however, since these haplotypes are relatively frequent in the general population, and the differences are of borderline statistical significance and only seen in terms of one haplotype.

A limitation of our study is the lack of knowledge of the total number of second-degree relatives except grandparents, which prevents us from reporting the actual prevalence of diabetes in parental

siblings. In addition, a questionnaire-based study design is prone to recall bias either by over- or underreporting family members with type 1 diabetes. In this survey, information on second-degree relatives was insufficient for completion of all the fields in the questionnaire in 122 families (8.2%). Given that these cases were counted as nonfamilial cases in the analysis, our results are likely to be conservative and somewhat underestimate the prevalence of familial diabetes.

Our study setting lacked a control group of nondiabetic Finnish children, and we are thus not able to directly compare the prevalence of type 1 diabetes in families of diabetic and nondiabetic children. However, the prevalence of 2.9% of type 1 diabetes in siblings observed here can be compared with 0.5% in the general population <20 years of age in Finland in 2006. According to these estimates, the siblings of affected children have, compared with the general population, a sixfold risk of type 1 diabetes. Our register-based data on the time of diagnosis is a point estimation, and thus the life-time risk of type 1 diabetes in relatives, especially among siblings, is underestimated.

Our study shows that, considering the extended family history, the proportion of true sporadic cases of type 1 diabetes at diagnosis may be <80%. The proportion of case subjects with type 1 diabetes in first- and second-degree relatives was similar. The case subjects had equally affected paternal and maternal relatives, but an interesting difference in the distribution of sexes was observed between these groups. A novel observation is that the metabolic status at diagnosis is ameliorated in familial type 1 diabetes also when the affected person is a second-degree relative. Children with familial type 1 diabetes had an autoantibody profile very similar to that of sporadic cases, implying similar pathogenetic disease mechanisms. Familial cases carried the DR4-DQ8 haplotype more often than sporadic cases, implying that the enrichment of HLA class II-associated genetic risk might play a role in familial clustering of the disease.

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A.P. analyzed the data, wrote the first version of the manuscript, and edited the manuscript. T.H. was in charge of the autoantibody laboratory, reviewed the manuscript, and contributed to the discussion. S.J.R. reviewed the manuscript and contributed to the discussion. J.I. was responsible for the HLA genotyping, reviewed the manuscript, and contributed to the discussion. M.K. planned the study, contributed to the discussion, and reviewed the manuscript. Participants of the Finnish Pediatric Diabetes Register were involved in the planning of the study design and collection of data. M.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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