# Extended Family History of Diabetes and Autoimmune Diseases in Children With and Without Type 1 Diabetes

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**OBJECTIVE** — To determine the extended family history of diabetes or autoimmune diseases in families with and without children having type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — Three hundred case families and 381 control families were interviewed using structured questionnaires.

**RESULTS** — The proportion of case children having at least one relative with type 1 diabetes outside the nuclear family was higher than that of control children (50.3 vs. 31.8%, $P < 0.001$). The proportions of case and control children having relatives with type 2 diabetes or gestational diabetes were similar. Other autoimmune diseases occurred more frequently among the case children (9.7 vs. 1.1%, $P < 0.001$), in the case nuclear families (22.0 vs. 12.9%, $P = 0.002$) and in relatives outside the case nuclear family (72.0 vs. 62.2%, $P = 0.007$).

**CONCLUSIONS** — Type 1 diabetes and autoimmune diseases not only cluster in the nuclear families of children with type 1 diabetes but are also overrepresented in their extended families.

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First degree relatives of patients with type 1 diabetes clearly have an increased disease risk (1–5), but little information is available about the occurrence of type 1 diabetes outside the nuclear family (6). It is also unclear whether type 2 diabetes and gestational diabetes are more frequently present in the families of children with type 1 diabetes (7–9). Type 1 diabetes is known to be associated with other autoimmune diseases, but there is a scarcity of data on the frequency of autoimmune diseases among other family members (10).

## RESEARCH DESIGN AND METHODS

— All families having a child with type 1 diabetes being treated at the Department of Pediatrics, Oulu University Hospital in September 2003 were invited to participate in this study ($n$ = 306). Six families refused. The parents were interviewed, and a structured questionnaire was completed by a trained nurse (LM). Control children matched for year of birth, sex, and geographical region of residence were picked at random from the Central Population Register. The data for each family were included only once.

The families were asked about the presence of any type of diabetes in siblings, parents, and other relatives. The type of diabetes (type 1, type 2, and gestational), the age at diagnosis, and the mode of treatment (diet, medication, and insulin) were enquired. The parents were also asked about the occurrence of other autoimmune diseases in the family (celiac disease, rheumatoid arthritis, systemic lupus erythematosus, Still's disease, Sjögren's syndrome, thyroid dysfunction, hypothyroidism, hyperthyroidism, goitre, psoriasis, scleroderma, ulcerative colitis, Crohn's disease, Addison's disease, multiple sclerosis, and myasthenia gravis).

We analyzed the relatives in three groups: nuclear family (the case child, siblings, and parents), extended family (nuclear family together with grandparents, siblings of parents and their children, and siblings of grandparents and their children), and extended family excluding the nuclear family.

Data analysis was performed with the SPSS for Windows statistical software (version 16.0; SPSS, Chicago, IL). The study was approved by the local ethics committee.

## RESULTS

— Data were obtained from 300 families with at least one child having type 1 diabetes and from 381 control families without diabetic children. The mean age of the case children at the time of data collection was 11.9 years (4.29 SD, range 1.3–19.0), and that of the control children was 12.4 years (4.33 SD, range 1.1–19.9, $P = 0.102$). The mean age of the case children at diagnosis was 6.7 years (3.87 SD, range 0.56–15.98).

The proportion of children having relatives with type 1 diabetes was higher among the case children (Table 1). No differences were found between the case and control children in the proportion having relatives with type 2 diabetes (Table 1) or in the history of gestational diabetes between the case and control mothers (8.0 vs. 8.9%, $P = 0.668$) or grandmothers (1.7 vs. 0.8%, $P = 0.290$).

Celiac disease, rheumatoid arthritis, or thyroid dysfunction had been diagnosed more often in the case children than in the control children (4.7 vs. 0.5%, $P < 0.001$; 1.3 vs. 0.0%, $P = 0.024$; 2.7 vs. 0.3%, $P = 0.006$, respectively). In addition, two case children had psoriasis and one had purpura, and one control child was diagnosed with Crohn's disease. Altogether, 9.7% of case and 1.1% of control children had an autoimmune disease other than type 1 diabetes ($P < 0.001$).

A total of 22.0% of the nuclear families of the case children had at least one family member with another autoim-

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**Table 1—*Proportions of children having a relative with type 1 or type 2 diabetes in their father's or mother's family***

| | Type 1 diabetes in given family members | | | Type 2 diabetes in given family members | | |
|---|---|---|---|---|---|---|
| | Case children | Control children | *P* | Case children | Control children | *P* |
| *n* | 300 | 381 | | 300 | 381 | |
| Father | 5.0 | 1.3 | 0.005 | 0.3 | 1.6 | 0.111 |
| Father's sibling(s) | 5.7 | 2.6 | 0.043 | 3.3 | 5.0 | 0.289 |
| Paternal cousin(s) | 6.3 | 3.9 | 0.154 | 0.0 | 0.3 | Not tested |
| Paternal grandparents | 2.0 | 1.3 | 0.480 | 24.3 | 25.5 | 0.736 |
| Any relative in the father's family* | 31.0 | 16.8 | <0.001 | 43.3 | 41.2 | 0.577 |
| Any relative in the father's family** | 28.3 | 16.3 | <0.001 | 43.3 | 40.9 | 0.531 |
| Mother | 2.0 | 0.5 | 0.076 | 0.3 | 0.0 | Not tested |
| Mother's sibling(s) | 7.3 | 2.9 | 0.007 | 8.3 | 5.2 | 0.108 |
| Maternal cousin(s) | 8.7 | 3.9 | 0.016 | 0.0 | 0.0 | Not tested |
| Maternal grandparents | 1.3 | 1.3 | 0.981 | 28.7 | 33.1 | 0.218 |
| Any relative in the mother's family* | 30.0 | 19.4 | 0.001 | 51.0 | 52.5 | 0.699 |
| Any relative in the mother's family** | 28.7 | 19.2 | 0.004 | 51.0 | 52.5 | 0.699 |
| Any relative in either the father's or mother's family | 54.0 | 32.5 | <0.001 | 70.3 | 69.8 | 0.884 |
| Any relative in either the father's or mother's family** | 50.3 | 31.8 | <0.001 | 70.3 | 69.8 | 0.884 |

Data are percent. Siblings were not included in the analysis because the control children were selected to represent families without children having type 1 diabetes. None of the siblings of the case or control children had type 2 diabetes. *Extended family (parents, grandparents, siblings of parents and their children, siblings of grandparents and their children). **Extended family with the nuclear family excluded.

mune disease compared with 12.9% of the control nuclear families ($P = 0.002$). Celiac disease in particular was more common in the case nuclear families (8.0 vs. 2.9%, $P = 0.003$).

When considering extended family outside the nuclear family, a larger proportion of the case children had a positive family history of another autoimmune disease in at least one relative (72.0 vs. 62.2%, $P = 0.007$), the difference being statistically significant for rheumatoid arthritis but not for celiac disease or thyroid dysfunction (45.7 vs. 30.4%, $P < 0.001$; 31.7 vs. 28.6%, $P = 0.387$; 25.2 vs. 28.0%, $P = 0.410$, respectively).

**CONCLUSIONS** — This analysis of a population-based series of families of children with type 1 diabetes and control families demonstrates that type 1 diabetes or other autoimmune diseases not only cluster among the parents and siblings of the case children but also occur more often among relatives outside the nuclear family.

The strength of this study lies in the systematically collected data from case and control families in a country that has the highest incidence of type 1 diabetes in the world (11). To our knowledge, this is the first report to describe type 1 diabetes and other autoimmune diseases among relatives other than parents, siblings, or grandparents. However, the major limitation of the study was that family history data were based on interviews only and may therefore be inaccurate.

Analysis of the maternal and paternal relatives separately yielded similar differences between the case and control children (Table 1). We confirmed that case children more often have a father than a mother with type 1 diabetes (5.0 vs. 2.0%). However, there was no such difference in the proportion of case children having at least one father's or mother's sibling with type 1 diabetes (5.7 vs. 7.3%). These observations suggest that intrauterine factors may contribute to relative protection of children of mothers with type 1 diabetes.

In children with type 1 diabetes, another autoimmune disease was observed more often than in the control children, confirming earlier reports that have showed an association between type 1 diabetes and other autoimmune diseases such as autoimmune thyroiditis and celiac disease (12–13). Juvenile rheumatoid arthritis diagnosed by a pediatrician was also more common among the case children, which is a novel finding but needs to be confirmed in a larger dataset. Interestingly, type 1 diabetes has been reported to be more frequent in children with juvenile idiopathic arthritis than could be expected on the basis of its general U.S. prevalence (14).

No differences in the occurrence of type 2 diabetes or gestational diabetes were observed between the case and control families, which is in line with recent data showing that different genes predispose to type 1 and type 2 diabetes (15).

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