# Consequences of a Family History of Type 1 and Type 2 Diabetes on the Phenotype of Patients With Type 2 Diabetes

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OBJECTIVE — To investigate the impact of a family history of type 1 and type 2 diabetes on the phenotype of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — In a population-based study, we compared the phenotype in 3 groups of patients with type 2 diabetes. The first group had no family history of diabetes ($FH^-$, $n$ = 148); the second group had a family history of type 2 diabetes only ($FH^+_{TYPE2}$, $n$ = 1,211); and the third group had a family history of both type 1 and type 2 diabetes ($FH^+_{MIXED}$, $n$ = 240). Furthermore, we studied the frequency of GAD antibodies (GADabs), HLA-DQB1 risk genotypes, and the presence of coronary heart disease (CHD) according to family history in unrelated patients with type 2 diabetes from 787 families (148 $FH^-$, 546 $FH^+_{TYPE2}$, and 93 $FH^+_{MIXED}$).

RESULTS — Patients with no family history of diabetes were older at the onset of the disease, had a better β-cell function ($P$ = 0.004), and had higher HDL cholesterol concentrations ($P$ = 0.006) than patients with a family history of diabetes. Patients with a family history of only type 2 diabetes had higher BMI and fasting C-peptide concentrations ($P$ = 0.031) but lower frequency of GADab (11 vs. 23%, $P$ = 0.001) and DQB1 risk genotypes (37 vs. 54%, $P$ = 0.003) compared with patients with a family history of both type 1 and type 2 diabetes. In addition, hypertension ($P$ = 0.05) and CHD ($P$ = 0.031) were more common in $FH^+_{TYPE2}$ than in $FH^+_{MIXED}$ patients. In patients <60 years old, a family history of type 1 diabetes was associated with a reduced risk of CHD independent of age, hypertension, and HDL cholesterol concentrations. The results were similar when the $GADab^+$ patients were excluded from the analysis.

CONCLUSIONS — A family history of both type 1 and type 2 diabetes had a profound influence on the phenotype of patients with type 2 diabetes, which suggests a genetic interaction between type 1 and type 2 diabetes.

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Both type 1 and type 2 diabetes have a strong genetic component, and both types of diabetes cluster in the same families (1–12). Type 2 diabetes is a heterogeneous disease characterized by insulin resistance and impaired β-cell function. Studies in nondiabetic offspring of patients with type 2 diabetes have shown that defects in both insulin action and insulin secretion seem to be inherited (13,14). However, in these studies, only a family history of type 2 diabetes has been considered without taking into account the possible effect of a family history of type 1 diabetes. Furthermore, it is not known whether familial patients with type 2 diabetes are phenotypically similar to sporadic patients with type 2 diabetes without a family history of diabetes.

To address these questions, we compared the clinical phenotype in patients with type 2 diabetes who were divided into the following 3 groups: *1*) those without a family history of diabetes ($FH^-$), *2*) those with a family history of type 2 diabetes only ($FH^+_{TYPE2}$), and *3*) those with a family history of both type 1 and type 2 diabetes ($FH^+_{MIXED}$). In addition, we compared the type 1 diabetes–associated HLA-DQB1 genotype frequency in the 3 groups of patients with type 2 diabetes.

The data emphasize the importance of considering the genetic background of diabetes when studying the phenotype of patients with type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Study subjects

The Botnia Study is a population-based study aiming at the identification of genes that increase susceptibility to type 2 diabetes (13). Since 1990, patients with type 2 diabetes and their available family members have been recruited from a total of 1,377 families. The average number of family members was 8, and the average number of diabetic family members was 2.6. Families with maturity-onset diabetes of the young (MODY) were excluded after DNA analysis (15). All available family members were subjected to an oral glucose tolerance test (OGTT). Type 2 diabetes was diagnosed according to the revised World Health Organization criteria (16). Diagnosis of type 1 diabetes was based on initiation of insulin treatment within 6 months after diagnosis and/or a fasting C-peptide concentration <0.2 nmol/l. Patients who did not fulfill these criteria and did not have MODY mutations were considered to

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Abbreviations: AER, albumin excretion rate; apoB, apolipoprotein B; CHD, coronary heart disease; CV, coefficient of variation; dBP, diastolic blood pressure; $FH^+$, family history of diabetes; $FH^-$, no family history of diabetes; $FH^+_{MIXED}$, family history of both type 1 and type 2 diabetes; $FH^+_{TYPE2}$, family history of type 2 diabetes only; FS, fasting serum; GADab, GAD antibody; MODY, maturity-onset diabetes of the young; OGTT, oral glucose tolerance test; OHA, oral hypoglycemic agents; RR, relative risk; sBP, systolic blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

have type 2 diabetes. The protocols were approved by the local ethics committees.

The study included the first consecutive 1,599 patients with type 2 diabetes from 787 families, most of them originating from the western coast of Finland (Botnia). The families comprised 5,670 subjects altogether. The presence of diabetes in the relative was either confirmed with measurements of fasting blood glucose or an OGTT (>90% of subjects) or based on the use of oral hypoglycemic agents (OHA) or insulin. The OGTT was performed for 91% of the nondiabetic subjects. Patients were divided into the following 2 groups according to family history of type 2 diabetes in their first- or second-degree relatives: *1*) patients without a family history of diabetes ($FH^-$, $n$ = 148) and 2) patients with a family history of type 2 diabetes ($FH^+$). The $FH^+$ group was further subdivided into those with a family history of type 2 diabetes only ($FH^+_{TYPE2}$, $n$ = 1,211) and those with a family history of both type 1 and type 2 diabetes ($FH^+_{MIXED}$, $n$ = 240). Patients with a third-degree family history of type 1 diabetes (e.g., cousins) were included in the $FH^+_{MIXED}$ group, but 76% of the patients in that group had either first- or second-degree relatives with type 1 diabetes. The frequency of HLA-DQB1 genotypes (02/0302,0302/X, 02/X, and 0602[3]/X) associated with an increased or decreased risk of type 1 diabetes, GAD antibodies (GADabs), insulin treatment, hypertension, or coronary heart disease (CHD) were compared between the unrelated patients with $FH^-$ ($n$ = 148), $FH^+_{TYPE2}$ ($n$ = 546), and $FH^+_{MIXED}$ ($n$ = 93) diabetes randomly selected from the 787 families (1 patient per family).

A standardized health questionnaire covering the subjects' medical history, including current and previous medication, was completed by specially trained nurses; the information included hypertension, cardiovascular diseases, myocardial infarction, stroke, smoking habits, alcohol consumption, and physical activity, in addition to a family history of diabetes. Combined with the local hospital records, myocardial infarction and stroke (including both ischemic and hemorrhagic) were defined as events requiring hospitalization; CHD was defined as the use of oral nitroglycerine or typical chest pain or a history of previous myocardial infarction. This information on the CHD was validated against electrocardiogram changes compatible with ischemic heart disease (17). Hypertension was defined as systolic blood pressure (sBP) of ≥160 mmHg and/or a diastolic blood pressure (dBP) of ≥90 mmHg or the use of antihypertensive drugs.

Microalbuminuria was defined as urinary albumin excretion rate (AER) of 30–300 mg/24 h or 20–200 µg/min in overnight urine collections and macroalbuminuria as AER >300 mg/24 h or >200 µg/min in 2 of 3 urine collections. This information was available for 63% of the subjects.

The subjects were classified as smokers if they were currently smoking or were known to have smoked within 1 year before the interview, or as nonsmokers if they had never smoked at any time or had not smoked for >1 year before the interview. This information was available for 54% of the subjects.

### Metabolic measurements

An OGTT was performed for all subjects aged >15 years with fasting blood glucose <10 mmol/l and not treated with insulin. After a 12-h overnight fast, the subjects ingested 75 g of glucose in a volume of 300 ml. Samples for measurements of blood glucose and serum insulin were drawn at −10, 0, 30, 60, and 120 min, and incremental glucose and insulin areas under the curve were calculated. The 30-min incremental insulin area was used to evaluate the early insulin response. Blood glucose was measured with a hexokinase method (Boehringer Mannheim, Mannheim, Germany). Serum insulin concentrations were measured by radioimmunoassay (Pharmacia, Uppsala, Sweden) with an interassay coefficient of variation (CV) of 5%. Fasting serum (FS)-C-peptide concentrations were measured by a radioimmunoassay with an interassay CV of 9% (Human C-peptide RIA Kit; Linco, St. Charles, MO). $HbA_{1c}$ concentration was measured by a high-performance liquid chromatography with a reference value of 5–7%.

The plasma concentrations of cholesterol and triglycerides and separate lipoprotein fractions were determined by enzymatic methods using commercial kits (Boehringer Mannheim). The ratio of total cholesterol to apolipoprotein B (apoB) concentrations was calculated (after converting apoB to mmol/l) and used as a measure of LDL particle size. Urinary AER was measured by immunoturbidimetry from 3 overnight urine collections. GADab were measured by a radio-immunoprecipitation method using $^{35}S$-labeled recombinant human $GAD_{65}$ produced by in vitro transcription/translation (18).

### HLA DQB1 genotypes

HLA DQB1 genotyping was performed by polymerase chain reaction for the second exon followed by dot-blot hybridization with sequence-specific oligonucleotide probes labeled with digoxigenin (DIG Oligonucleotide 3′-End Labelling Kit; Boehringer Mannheim) (18). Three DQB1 probes were used to distinguish DQB1 alleles 0201 or 0202 (02), 0302, and 0602 or 0603 [0602/(3)] alleles. The genotypes were presented as 02/0302, 0302/X, 02/X, 0602(3)/X, 0302/0602(3), 02/0602(3), and X/X, whereby X could mean either a homozygous allele or any allele other than 02, 0302, or 0602(3). The 02/0302, 0302/X, or 02/X genotypes were considered DQB1-risk genotypes (19).

### Statistical analysis

Data are presented as means ± SD or medians (interquartile ranges). The statistical analysis was performed with either Biomedical Data Processing (BMDP, Los Angeles, CA) or Number Cruncher Statistical Systems (NCSS, Kaysville, UT) statistical software. The group frequencies were compared using the $\chi^2$ or Fisher's exact tests. Differences between group means were tested with analysis of variance or covariance with age, BMI, and waist-to-hip ratio as covariates, or using Mann-Whitney or the Kruskal-Wallis tests where appropriate. Logarithmic transformation was performed to variables with skewed distribution. A multiple logistic regression analysis was carried out with CHD as the dependent variable and age, FS-C-peptide, HDL cholesterol concentrations, and presence of hypertension, DQB1 risk genotype, family history of type 1 diabetes, or family history of type 2 diabetes as independent variables. Serum cholesterol concentration, micro- or macroalbuminuria, or smoking history did not differ between patients with and without CHD and were not included in the regression analysis. Hypertension, DQB1 risk genotypes, and family history of type 1 or type 2 diabetes were treated as binary variables in the analysis (presence = 1, absence = 0).

RESULTS — The $FH^-$ patients presented with diabetes at a later age than the $FH^+_{TYPE2}$ patients ($P < 0.0001$, Table 1). Also, the $FH^-$ patients had a lower BMI than the $FH^+_{TYPE2}$ patients (27.4 ± 4.1 vs. 29.1 ± 4.9 kg/m$^2$, $P <$ 0.0001). β-Cell function, as judged from FS-C-peptide concentration (0.64 ± 0.38 vs. 0.67 ± 0.35 nmol/l, $P$ = 0.020) and incremental early insulin secretion during OGTT

Table 1—*Clinical characteristics of patients with type 2 diabetes without family history of diabetes (FH$^-$), with family history of type 2 diabetes only (FH$^+_{TYPE2}$), or with family history of both type 1 and type 2 diabetes (FH$^+_{MIXED}$)*

| | FH$^-$ | *P* | FH$^+_{TYPE2}$ | *P* | FH$^+_{MIXED}$ |
|---|---|---|---|---|---|
| *n* (M/F) | 148 (62/86) | | 1,211 (539/672) | | 240 (140/136) |
| Age (years) | 71.3 ± 11.6 | <0.0001 | 64.8 ± 11.1 | | 64.4 ± 12.8 |
| Age at onset (years) | 62.9 ± 12.1 | <0.0001 | 55.7 ± 12.2 | | 54.2 ± 13.7 |
| Duration (years) | 7.2 (7.0) | | 8.5 (11.2) | | 9.1 (11.3) |
| BMI (kg/m$^2$) | 27.4 ± 4.1 | <0.0001 | 29.1 ± 4.9 | 0.005 | 28.1 ± 4.5 |
| Waist-to-hip ratio | 0.91 ± 0.08 | <0.0001 | 0.94 ± 0.08 | | 0.93 ± 0.08 |
| Fasting blood glucose (mmol/l) | 8.7 ± 3.1 | | 8.7 ± 2.8 | | 8.5 ± 3.1 |
| $HbA_{1c}$ (%) | 7.9 ± 1.8 | | 7.6 ± 1.7 | | 7.7 ± 1.8 |
| Fasting insulin (mU/l) | 16.6 ± 14.2 | | 18.1 ± 20.4 | | 18.6 ± 23.1 |
| FS-C-peptide (nmol/l) | 0.67 ± 0.35 | 0.020* | 0.64 ± 0.38 | 0.031* | 0.54 ± 0.35 |
| 30-Min incremental insulin area (mU/l) | 412 (485) | 0.024* | 289 (402) | | 283 (355) |
| dBP (mmHg) | 81.5 ± 10.0 | | 81.8 ± 10.8 | | 82.2 ± 10.3 |
| sBP (mmHg) | 148.7 ± 19.7 | | 144.6 ± 20.7 | | 144.5 ± 18.7 |
| Cholesterol (mmol/l) | 5.8 ± 1.2 | | 5.8 ± 1.2 | | 5.8 ± 1.2 |
| Triglycerides (mmol/l) | 1.9 ± 1.4 | | 2.0 ± 1.4 | | 1.9 ± 1.5 |
| HDL cholesterol (mmol/l) | 1.25 ± 0.30 | 0.0003 | 1.16 ± 0.32 | | 1.18 ± 0.32 |
| ApoA1 (mg/dl) | 133.1 ± 23.5 | | 133.1 ± 22.1 | | 133.4 ± 23.5 |
| ApoA2 (mg/dl) | 34.1± 6.3 | | 35.3 ± 6.2 | | 34.3 ± 5.8 |
| ApoB (mg/dl) | 97.2 ± 21.3 | 0.007 | 103.3 ± 25.2 | | 101.1 ± 24.4 |
| Micro-/macroalbuminuria† (%) | 15/1 | | 15/3 | | 12/5 |
| Smoking history (%) | 26 | 0.020 | 36 | | 28 |
| Treatment: insulin/OHA/diet (%) | 17/34/49 | <0.001 (df2) | 25/41/35 | <0.001 (df2) | 36/33/30 |

Data are *n*, means ± SD, medians (interquartile ranges), or %. *Adjusted for age, BMI, and waist-to-hip ratio. †Microalbuminuria or macroalbuminuria was defined as AER >20 µg/min or >200 µg/min, respectively.

(median [interquartile range]: 289 [402] vs. 412 [485] mU/l, $P = 0.024$) was reduced in FH$^+_{TYPE2}$ patients compared with FH$^-$ patients; the lowest concentrations were seen in patients with a family history of both type 1 and type 2 diabetes (FH$^+_{MIXED}$: 283 [355] mU/l; $P = 0.002$ vs. FH$^-$ patients) (Table 1). HDL cholesterol concentrations were lower in FH$^+_{TYPE2}$ patients than in FH$^-$ patients (1.16 ± 0.32 vs. 1.25 ± 0.30 mmol/l, $P = 0.0003$) and no difference was seen between FH$^+_{TYPE2}$ and FH$^+_{MIXED}$. ApoB concentrations were higher (Table 1) and the total cholesterol/apoB ratio (used as a measure of LDL particle size) was lower in FH$^+_{TYPE2}$ patients than in FH$^-$ patients (2,044 ± 444 vs. 2,146 ± 442, $P = 0.001$).

GADabs were more common in patients with a family history of both type 1 and type 2 diabetes (23%) than in those with a family history of only type 2 diabetes (11%) or without a family history of diabetes (9%) ($P < 0.001$). Also, the frequency of DQB1 risk genotypes was higher in FH$^+_{MIXED}$ patients (54%) than in FH$^+_{TYPE2}$ patients (37%, $P = 0.003$) or FH$^-$ patients (36%, $P < 0.008$) (Table 2). To exclude the possibility that the phenotypic differences were a result of patients with a latent autoimmune form of type 1 diabetes, we repeated the analysis after exclusion of the GADab$^+$ patients; this analysis yielded virtually identical results (Table 3).

The frequency of hypertension (47 vs. 58%, $P = 0.05$) and CHD (19 vs. 30%, $P = 0.031$) was lower in FH$^+_{MIXED}$ patients than in FH$^+_{TYPE2}$ patients. There was no difference in frequency of micro- or macroalbuminuria or smoking history between the FH$^+_{MIXED}$ and the FH$^+_{TYPE2}$ patients (Table 1). Compared with the risk in FH$^-$ patients, the relative risk (RR) of CHD was decreased in FH$^+_{MIXED}$ patients (RR = 0.57, $P = 0.053$) and increased in FH$^+_{TYPE2}$ patients (RR = 1.53, $P = 0.052$). In a mul-

Table 2—*Frequency of HLA-DQB1 genotypes, GADab, mode of treatment, albuminuria, smoking, hypertension, and CHD in 787 unrelated patients with type 2 diabetes randomly selected from the families (1 per family)*

| | Family history of diabetes | | | | |
|---|---|---|---|---|---|
| | FH$^-$(%) | *P* | FH$^+_{TYPE2}$ (%) | *P* | FH$^+_{MIXED}$ (%) |
| HLA DQB1 genotype | | | | | |
| Risk | 36 | NS | 37 | 0.003 | 54 |
| Protective | 35 | 0.064 | 26 | 0.068 | 16 |
| GADab$^+$ | 9 | NS | 11 | 0.001 | 23 |
| Insulin/OHA/diet | 17/34/49 | — | 23/42/35 | <0.0001 | 44/31/24 |
| Albuminuria (micro-/macro-) | 16 (15/1) | NS | 17 (15/2) | NS | 18 (9/9) |
| Smoking | 26 | NS | 33 | NS | 32 |
| Hypertension | 59 | NS | 58 | 0.050 | 47 |
| CHD | 29 | NS | 30 | 0.031 | 19 |

Data are %. The risk genotypes include 02/0302 or 0302/X or 02/X, and the protective genotypes 0602(3)/X (X denotes either a homozygous allele or any allele other than 02, 0302, or 0602[3]). *n* = 462 (129 FH$^-$, 241 FH$^+_{TYPE2}$, and 92 FH$^+_{MIXED}$ patients).

Table 3—*GADab⁻ patients with type 2 diabetes divided into those without family history of diabetes ($FH^-$), with family history of type 2 diabetes only ($FH^+_{TYPE2}$), or with family history of both type 1 and type 2 diabetes ($FH^+_{MIXED}$)*

| | $FH^-$ | *P* | $FH^+_{TYPE2}$ | *P* | $FH^+_{MIXED}$ |
|---|---|---|---|---|---|
| *n* (M/F) | 134 (53/81) | | 1,114 (505/609) | | 198 (85/113) |
| Age (years) | 71.0 ± 11.3 | <0.0001 | 64.9 ± 11.0 | | 65.5 ± 12.6 |
| Age at onset (years) | 62.7 ± 11.8 | <0.0001 | 55.9 ± 12.0 | | 55.3 ± 13.6 |
| Duration (years) | 7.3 (6.2) | | 8.4 (11.0) | | 9.1 (12.1) |
| BMI (kg/m$^2$) | 24.4 ± 4.0 | 0.0001 | 29.2 ± 4.9 | 0.038 | 28.4 ± 4.2 |
| Waist-to-hip ratio | 0.90 ± 0.08 | <0.0001 | 0.93 ± 0.08 | | 0.93 ± 0.08 |
| Fasting blood glucose (mmol/l) | 8.6 ± 2.9 | | 8.6 ± 2.7 | | 8.3 ± 2.8 |
| $HbA_{1c}$ (%) | 7.8 ± 1.8 | | 7.5 ± 1.6 | | 7.6 ± 1.8 |
| Fasting insulin (mU/l) | 15.6 ± 12.2 | | 17.7 ± 18.1 | | 17.9 ± 19.9 |
| FS-C-peptide (nmol/l) | 0.66 ± 0.35 | | 0.66 ± 0.38 | | 0.61 ± 0.35 |
| 30-Min incremental insulin area (mU/l) | 460 (484) | 0.009* | 288 (395) | | 324 (341) |
| dBP (mmHg) | 82.2 ± 10.2 | | 81.9 ± 10.7 | | 82.5 ± 10.3 |
| sBP (mmHg) | 149.4 ± 19.8 | | 146.8 ± 20.6 | | 145.5 ± 18.9 |
| Cholesterol (mmol/l) | 5.8 ± 1.2 | | 5.8 ± 1.1 | | 5.9 ± 1.2 |
| Triglyceride (mmol/l) | 1.9 ± 1.4 | | 2.1 ± 1.6 | | 2.0 ± 1.3 |
| HDL cholesterol (mmol/l) | 1.24 ± 0.28 | 0.0003 | 1.15 ± 0.30 | | 1.15 ± 0.29 |
| ApoB (mg/dl) | 97.9 ± 21.3 | 0.018 | 103.9 ± 25.3 | | 103.4 ± 24.8 |
| Micro-/macroalbuminuria† (%) | 14/1 | | 15/3 | | 13/6 |
| Smoking (*n* [%]) | 33 (26) | 0.019 | 197 (36) | 0.041 | 25 (26) |
| Insulin/OHA/diet (%) | 16/38/48 | 0.02 (df 2) | 22/41/36 | 0.02 (df 2) | 32/34/34 |
| Hypertension (*n* [%]) | 83 (62) | | 632 (57) | | 105 (53) |
| CHD (*n* [%]) | 40 (30) | | 349 (32) | 0.027 | 47 (24) |

Data are *n*, *n* (%), means ± SD, or medians (interquartile ranges). *Adjusted for age, BMI, and waist-to-hip ratio. †Microalbuminuria or macroalbuminuria was defined as AER >20 μg/min or >200 μg/min, respectively.

tiple logistic regression analysis, we tested whether age, FS-C-peptide and HDL cholesterol concentrations, hypertension, DQB1 risk genotype, and family history of type 1 and/or type 2 diabetes were associated with CHD (Table 4). Age, hypertension, and HDL cholesterol concentrations were independent risk factors for CHD in patients with type 2 diabetes. In addition, in patients <60 years of age, a family history of type 1 diabetes was associated with a reduced risk of CHD ($P$ = 0.033). The inclusion of cholesterol, microalbuminuria, or smoking history in the regression analysis did not change the results (data not shown).

Table 4—*Multiple regression analysis of factors associated with coronary heart disease in patients with type 2 diabetes*

| Variables | Regression coefficient | SE | *P* |
|---|---|---|---|
| All patients (*n* = 301 ) | | | |
| Age (years) | 0.0466 | 0.0135 | 0.0005 |
| Hypertension | 0.9594 | 0.2955 | 0.0011 |
| HDL cholesterol | −1.6199 | 0.4987 | 0.0011 |
| Age <60 years (*n* = 82) | | | |
| Hypertension | 1.8418 | 0.8422 | 0.0287 |
| HDL cholesterol | −5.7977 | 2.1783 | 0.0077 |
| Family history of type 1 diabetes | −2.5522 | 1.2034 | 0.0339 |
| Age >60 years (*n* = 219) | | | |
| Age (years) | 0.0338 | 0.0204 | 0.0969 |
| Hypertension | 0.8562 | 0.3246 | 0.0083 |
| HDL cholesterol | −1.2366 | 0.5200 | 0.0174 |

The following variables were included in the analysis: age, FS-C-peptide concentration, HDL cholesterol concentrations, presence of hypertension, DQB1 risk genotype, family history of type 1 diabetes, and family history of type 2 diabetes.

## CONCLUSIONS

The study emphasizes the importance of not only a family history of diabetes but also the type of diabetes as determinants of the phenotype of patients with type 2 diabetes. Without knowledge about the underlying genetic defects, familial type 2 diabetes cannot be distinguished as a different disease entity from sporadic type 2 diabetes. However, the data clearly demonstrate that familial type 2 diabetes is associated with a more severe phenotype (i.e., earlier age at onset, more severe β-cell dysfunction, and more features of the metabolic syndrome) compared with sporadic patients with type 2 diabetes. Furthermore, among the patients with a family history of type 2 diabetes, the introduction of type 1 diabetes in the family history markedly "changed the picture." Type 2 patients from the mixed type 1/type 2 diabetes families had an increased frequency of type 1 diabetes-associated HLA-DQB1 genotypes and GADabs but lower frequency of hypertension and cardiovas-

cular disease. They also required insulin therapy more often than patients with a family history of type 2 diabetes only.

The difference in age at onset between familial and sporadic patients with type 2 diabetes suggests that if the genetic load for type 2 diabetes is low, the manifestation of type 2 diabetes is delayed. Only a few studies have reported on the influence of a family history of type 2 diabetes on the phenotype of patients with type 2 diabetes (20–22). However, either the studies have included a relatively small number of patients with type 2 diabetes or the patients have had a mild form of diabetes (22). On the other hand, several studies have examined the effect of a family history of diabetes on nondiabetic first-degree relatives (13,14,22,23). These individuals have in general displayed early features of the metabolic syndrome, such as abdominal obesity, elevated blood pressure, and dyslipidemia consistent with the findings in the diabetic probands in the present study (13). The study also demonstrates that family history of type 1 diabetes changes the phenotype of type 2 diabetic patients toward a more type 1–like phenotype. However, this phenotype with late onset and high BMI differs from that in classical type 1 diabetes. Although the patients with type 2 diabetes from the mixed type 1/type 2 families had an increased frequency of type 1 diabetes–associated allele, HLA-DQB1*0302, the genotype conferring the highest risk for classical type 1 diabetes, 0201/0302, was rare among them (data not shown). This is compatible with data in type 1 diabetes that 0201/0302 genotype would predispose toward a more severe autoimmune destruction of the β-cells than the 0302/X genotype (24,25). We do not know whether the patients with type 2 diabetes show signs of insulitis, but the increased frequency of GADabs, observed also in other populations (26), points at the coexistence of pancreatic autoimmunity. Of note, the present study demonstrates that although the frequency of GADab is higher in the mixed families than in the other type 2 families, the phenotypic differences associated with the type 1 diabetes family history are not restricted to the $GADab^+$ patients. The 0302 allele is in linkage disequilibrium with the serologically determined HLA-antigen DR4. An increased frequency of DR4 or DQB1*0302 has been shown in type 2 diabetic patients (27–29), particularly in type 2 patients with impaired β-cell function and increased need for insulin therapy (18,27). A higher than expected transmission of DR4 from patients with type 2 diabetes to offspring with type 1 diabetes has also been shown (6).

The patients with type 2 diabetes from the mixed type 1/type 2 families had less cardiovascular disease than the common type 2 diabetic patients. There is other information to support this finding. An increased prevalence of type 1 diabetes–associated HLA haplotypes and HLA-DR4 has been reported in elderly Finnish men with type 2 diabetes (29), suggesting that the HLA-DR4 antigen may be associated with a longer survival in patients with type 2 diabetes. In support of this, HLA-DR4 was increased in patients with type 2 diabetes who survived during a 10-year follow-up period (30).

In conclusion, the study demonstrates a profound influence of a family history of type 1 and type 2 diabetes on the phenotype and the outcome of patients with type 2 diabetes. The finding also points at a genetic interaction between type 1 and type 2 diabetes and the importance of a shared genetic background.

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