

Heritability of Proliferative Diabetic Retinopathy

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OBJECTIVE—Diabetic nephropathy clusters in families, suggesting that genetic factors play a role in its pathogenesis. We investigated whether similar clustering exists for proliferative retinopathy in families with two or more siblings with type 1 diabetes.

RESEARCH DESIGN AND METHODS—The FinnDiane Study has characterized 20% (4,800 patients) of adults with type 1 diabetes in Finland. In 188 families, there were at least two siblings with type 1 diabetes. Ophthalmic records were obtained for 369 of 396 (93%) and fundus photographs for 251 of 369 (68%) patients. Retinopathy was graded based on photographs and/or repeated ophthalmic examinations using the Early Treatment of Diabetic Retinopathy grading scale.

RESULTS—Mean age at onset of diabetes was 14.3 ± 10.2 years, and mean duration was 25.9 ± 11.8 years. Proliferative retinopathy was found in 115 of 369 patients (31%). The familial risk of proliferative retinopathy was estimated in 168 of 188 sibships, adjusted for A1C, duration, and mean blood pressure. Proliferative retinopathy in the probands (48 of 168) was associated with an increased risk (odds ratio 2.76 [95% CI 1.25–6.11], $P = 0.01$) of proliferative retinopathy in the siblings of probands (61 of 182). The heritability of proliferative retinopathy was $h^2 = 0.52 \pm 0.31$ ($P < 0.05$).

CONCLUSIONS—We found a familial clustering of proliferative retinopathy in patients with type 1 diabetes. The observation cannot be accounted for by conventional risk factors, suggesting a genetic component in the pathogenesis of proliferative retinopathy in type 1 diabetes. *Diabetes* 57:2176–2180, 2008

Diabetic nephropathy and proliferative retinopathy are severe microvascular complications of diabetes. Diabetic nephropathy clusters in families, suggesting that genetic factors play a role in the pathogenesis of this complication (1). However, there is not yet evidence for a similar clustering of proliferative retinopathy in families with type 1 diabetes.

After 20 years of diabetes, almost all patients with type 1 diabetes and 58% of patients with type 2 diabetes show signs of retinopathy. When retinopathy worsens, severe visual loss eventually threatens 5–10% of patients (2). The most severe form of retinopathy is proliferative retinopa-

thy, and most of the patients with this complication will become blind after 5–10 years without treatment (3). The prevalence of proliferative retinopathy varies between 13 and 50% after 15–20 years of diabetes duration in patients needing insulin (2,4).

The prevalence of any retinopathy is strongly related to duration and glucose exposure (2,4). Furthermore, poor glycemic control increases the incidence and progression of retinopathy (5,6). Nevertheless, glycemic exposure seems to explain only a part of the risk of proliferative retinopathy (7). In patients with type 2 diabetes, high blood pressure increases the incidence of retinopathy (8). It is noteworthy that proliferative retinopathy is associated with diabetic nephropathy, a complication that is at least in part genetically determined (2). Such an association suggests that familial factors may also contribute to the development of proliferative retinopathy.

Therefore, the aim of this study was to elucidate whether there is a familial clustering of proliferative retinopathy in patients with longstanding type 1 diabetes and to estimate the degree of familiarity by calculating the heritability of proliferative retinopathy.

RESEARCH DESIGN AND METHODS

The present study was undertaken as part of the ongoing FinnDiane Study (Finnish Diabetic Nephropathy Study), a nationwide multicenter project with the aim of identifying genetic and environmental risk factors for diabetic complications in type 1 diabetes. The protocol is in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Helsinki University Central Hospital.

The FinnDiane Study has, to date, recruited 4,800 patients with type 1 diabetes. All patients who visit any of the participating 92 hospitals and health care centers are given an opportunity to take part in the FinnDiane Study. The response rate has been 78% (9). Although FinnDiane is not a population-based study in the strict sense, the distribution of the patients closely follows the distribution of the general population in Finland. As a part of the baseline visit, patients answered the question of whether any of their close relatives had type 1 diabetes, as defined by having an age at onset of 40 years or less and insulin treatment initiated within 1 year of the diagnosis. With these criteria, 188 families with at least two siblings with type 1 diabetes were found (Table 1). All of the siblings were contacted, and those siblings who agreed to take part signed a consent form and were characterized at a FinnDiane center. Data on medication, cardiovascular status, diabetic complications, hypertension, and cardiovascular disease were obtained using a standardized questionnaire, which was completed by the patient's attending physician. Blood pressure was measured twice in the sitting position using a mercury sphygmomanometer after a rest of at least 10 min. Anthropometric data, such as height and weight, were recorded, and blood was drawn for the laboratory measurements, including A1C.

We were able to obtain ophthalmic records for 369 of 396 (93%) patients. Photographs were available for 251 of 369 (68%) of these patients, and records of repeated fundus examinations performed by a specialist in ophthalmology for 332 of 369 (90%) patients. Both were available for 217 of 369 (59%) patients. Those patients with images available (68%) had been photographed on a median of three separate occasions (interquartile range [IQR] 1–5). For 34 of 369 (9%) patients, the only source of information was the screening photographs taken at the local health centers. A diabetologist's evaluation of the fundi was the only source of information for only 3 of 369 (1%) of the patients, all of whom had mild diabetic retinopathy. All available patient data were used to score the severity and progression of retinopathy, a procedure handled by an ophthalmologist unaware of the demographic data and the presence or

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TABLE 1
Structure of sibships

Siblings with type 1 diabetes in the same family	Families	Patients with type 1 diabetes	Ophthalmic data available	Patients with proliferative retinopathy
2 siblings	171	342	323	101
3 siblings	14	42	38	13
4 siblings	3	12	8	1
Total	188	396	369	115

absence of other complications. The Early Treatment of Diabetic Retinopathy (ETDRS) grading scale was used, where 10 represents no retinopathy; 61 and upward, proliferative retinopathy; and 80, advanced retinopathy (10). Patients without photographs were assigned a most probable estimate of ETDRS score based on the descriptions of repeated fundus examinations. The eye with the more severe retinopathy was used to define the severity of retinopathy of the patient.

Patient's nephropathy status was classified according to their urinary albumin excretion rate (AER) in at least two of three overnight or 24-h urine collections. Normal AER was defined as an AER <20 $\mu\text{g}/\text{min}$ or AER <30 mg/24 h, microalbuminuria as an AER ≥ 20 and <200 $\mu\text{g}/\text{min}$ or ≥ 30 and <300 mg/24 h, macroalbuminuria as an AER ≥ 200 $\mu\text{g}/\text{min}$ or ≥ 300 mg/24 h, and end-stage renal disease as when the patient required dialysis or renal transplantation.

Statistical analysis. The siblings were ranked by age, and the oldest sibling was designated as the proband of each sibship. There were four twin pairs from four different families, and the sibling with the longest duration of diabetes was chosen as the proband in these particular sibships. Two twin pairs were monozygotic as determined by microsatellite markers (ABI MD-10 V2.5; Applied Biosystems, Foster City, CA).

Data are presented as means \pm SD for continuous, normally distributed variables and median and IQR for non-normally distributed variables. Means \pm SE are given for heritability estimates. Unadjusted intrafamilial associations were estimated by calculating intraclass correlations (ICCs) for sibpairs. The FCOR program of the SAGE software package (Case Western Reserve University, Cleveland, OH) was used with a uniform weighting scheme, giving equal weights for each sibship regardless of the number of

sibpairs within the sibships (11). The correlations between ordinal ETDRS scores and nephropathy status were also calculated with the FCOR program using the same weighting scheme. Mean differences in current age and duration of diabetes between probands and siblings were calculated using a linear mixed model (Table 2).

To study familial aggregation of proliferative retinopathy or any retinopathy, three complementary analyses were used. First, the presence or absence of proliferative retinopathy or any retinopathy in the proband was estimated as a risk factor for the corresponding condition in the other siblings. The familial risks were estimated with logistic regression models, adjusted for conventional risk factors, and fitted with generalized estimating equations using exchangeable correlation structure to account for correlations within sibships (12). Second, to measure the degree of concordance within sibships, the ICC of durations of diabetes to the diagnosis of proliferative retinopathy was calculated in the 29 sibships in which two siblings had proliferative retinopathy (Fig. 1). Third, the heritability (h^2) of proliferative retinopathy was estimated by a liability threshold model as implemented in the SOLAR software (SOLAR, version 4.0.7; Southwest Foundation for Biomedical Research, San Antonio, TX) with A1C, mean arterial pressure, sex, and duration of diabetes as covariates. The liability threshold model is an extension of the variance components model to dichotomous traits, such as proliferative retinopathy (13). In the variance components model, the overall phenotypic variation is partitioned into individual variance components due to polygenic effects (multiple unmeasured genes under an additive variance), covariates (e.g., duration, sex, A1C, and blood pressure), and random environmental effects. The estimated h^2 is defined as the ratio of the genetic variance component to the residual phenotypic variance and is an estimate of the

TABLE 2
Clinical characteristics and concordance within sibships (intraclass correlations) for the siblings with type 1 diabetes

Variable	n (396)	Mean \pm SD	Range	ICC (95% CI)
Age at onset (years)	387	14.3 \pm 10.2	0.2–40.0	0.15 (0.02–0.21)
Duration of diabetes at the latest ophthalmic examination (years)	369	25.9 \pm 11.8	1.0–55.4	0.39 (0.26–0.45)
Difference of duration between probands and siblings (years)		2.4 \pm 1.3*		
Current age (years)	387	40.2 \pm 11.5	14.5–69.3	0.69 (0.61–0.73)
Age difference between proband and siblings (years)		4.9 \pm 1.2*		
A1C (%)	380	8.5 \pm 1.5	5.0–13.8	0.22 (0.09–0.29)
Systolic pressure (mmHg)	378	135 \pm 18	95–215	0.20 (0.07–0.27)
Diastolic pressure (mmHg)	378	80 \pm 9	50–113	0.10 (–0.04 to 0.16)
MAP (mmHg)	378	100 \pm 12	72–140	0.18 (0.04–0.25)
BMI (kg/m^2)	354	25.3 \pm 3.9	16.2–43.0	0.21 (0.07–0.28)
Total cholesterol (mmol/l)	341	4.9 \pm 1.0	1.9–12.0	0.21 (0.06–0.30)
HDL cholesterol (mmol/l)	341	1.6 \pm 0.52	0.2–4.3	0.33 (0.18–0.40)
Current smoking	369	Yes 86 (23%) No 83 (77%)		0.15 (0.01–0.22)
ETDRS score	169	40 (IQR 20–62) [†]	10–80	0.37 (0.24–0.43)
PDR		Yes 115 (31%) No 254 (69%)		0.28 (0.14–0.35)
Nephropathy status	328	Normoalbuminuria 202 (54%) Microalbuminuria 51 (14%) Macroalbuminuria 50 (14%) End-stage renal disease 25 (7%)		0.26 (0.06–0.36)

Data are *SE or [†]median value (188 sibships, men/women 202/167) unless otherwise indicated. MAP, mean arterial pressure; PDR, proliferative retinopathy.

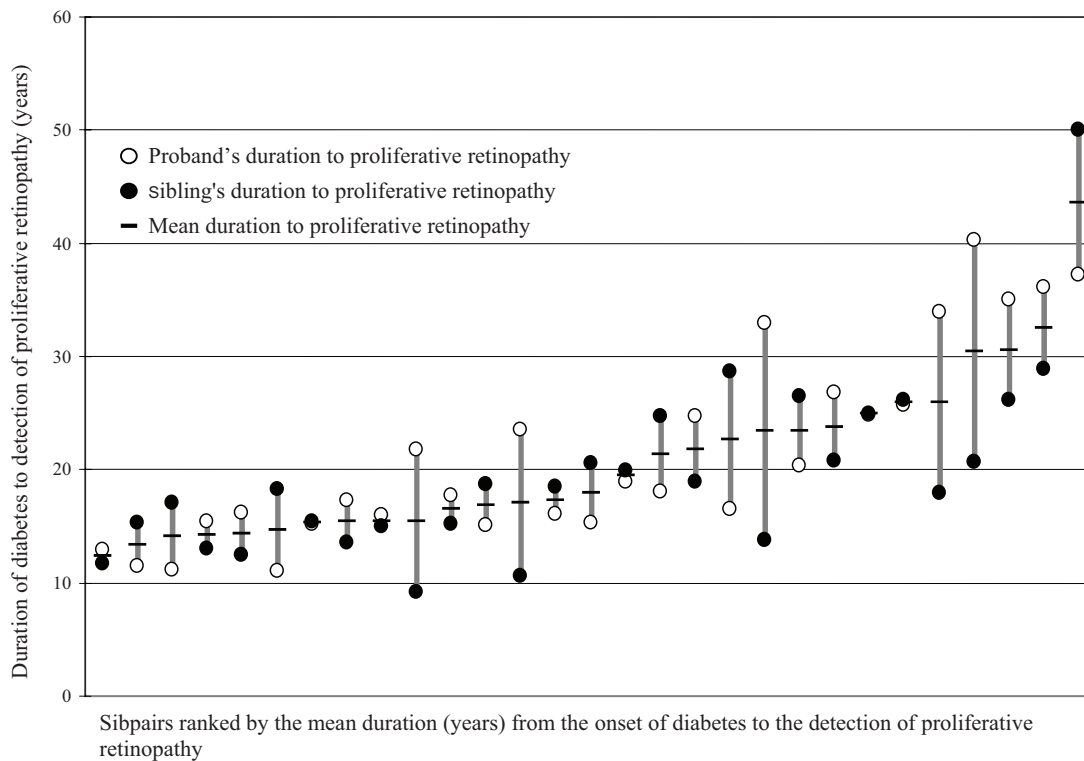


FIG. 1. Concordance within sibship (ICC) of survival time without proliferative retinopathy in the 29 sibpairs in which both members had proliferative retinopathy (ICC 0.47 [95% CI 0.14–0.71], $P = 0.004$).

familiality of the trait. The significance of the genetic component was determined by a likelihood ratio test. All other statistical calculations except the ICCs and the variance component models were performed with SPSS 15.0 (SPSS, Chicago, IL).

RESULTS

Table 1 depicts the structure of the sibships and the availability of ophthalmic data. Table 2 shows the clinical characteristics of the studied patients and unadjusted ICCs within sibships. Mean age at onset of diabetes was 14.3 ± 10.2 years. The ratio of men to women was 202:167, and mean duration of diabetes was 25.9 ± 11.8 years. The patients' highest ETDRS scores were achieved at a median of 2.1 (IQR -10.4 to 1.0) years before the FinnDiane baseline visit. A strong positive association was found between the ETDRS score and the nephropathy status ($r = 0.63$, $P < 0.001$), which was available for 328 patients.

Proliferative retinopathy was found in 115 of 369 patients (31.1% [95% CI 26.4–35.9]). In 8 of 115 (7.0%) patients, proliferative retinopathy was discovered at their first examination by an ophthalmologist. Thus, there were no available reference points for these patients without proliferative retinopathy. The other patients ($n = 107$) had

all had at least one ophthalmic examination at a median of 1.0 (IQR -2.2 to -0.4) years before the diagnosis. Detailed records of treatment and follow-up were available for each patient with proliferative retinopathy. Mean duration from onset of diabetes to proliferative retinopathy was 20.9 ± 7.5 years.

The familial risk of proliferative retinopathy was estimated in 182 siblings of 168 probands. Siblings of probands with proliferative retinopathy had higher unadjusted risk of proliferative retinopathy (odds ratio [OR] 4.07 [95% CI 2.06–8.07], $P < 0.001$) when compared with siblings of probands without proliferative retinopathy. When adjusted for duration of diabetes, A1C, and mean arterial pressure, proliferative retinopathy in the probands (48 of 168) remained a significant risk factor (2.76 [1.25–6.11], $P = 0.01$) for the corresponding condition in the siblings (61 of 182) (Table 3). In contrast, the absence of any retinopathy in the probands (37 of 168) was not associated with absence of any retinopathy in the siblings (39 of 182) of the probands (2.0 [0.82–5.10], $P = 0.13$). The absence of any retinopathy was associated with lower A1C (0.77 [0.59–0.99], $P = 0.04$) and shorter dura-

TABLE 3
Familial risk of proliferative retinopathy

Variable	OR (95% CI)	B (SE)	P value
PDR status of proband (yes/no)	2.76 (1.25–6.11)	1.02 (0.40)	0.01
MAP (mmHg)	1.03 (0.99–1.06)	0.02 (0.17)	0.15
A1C (%)	1.33 (1.03–1.73)	0.29 (0.14)	0.03
Duration of diabetes (years)	1.13 (1.08–1.17)	0.12 (0.02)	<0.001
Men	1.12 (0.51–2.45)	0.12 (0.40)	0.8

The presence of proliferative retinopathy in the proband was used as risk factor for proliferative retinopathy in 182 siblings of 168 probands in a logistic regression analysis. MAP, mean arterial blood pressure; PDR, proliferative diabetic retinopathy.

tion of diabetes (0.85 [0.78–0.92], $P < 0.001$) but not with blood pressure (1.1 [0.98–1.06], $P = 0.30$) or sex (0.96 [0.36–2.53], $P = 0.93$).

The 29 proband-sibling pairs in which both members had proliferative retinopathy were concordant for the survival time without proliferative retinopathy (ICC 0.47 [0.14–0.71], $P = 0.004$) (Fig. 1). Despite a slightly shorter duration of diabetes (25.0 ± 11.8 vs. 26.8 ± 11.9 years, $P = 0.15$), the younger siblings had a higher prevalence of proliferative retinopathy (34.4% [66 of 192] vs. 27.7% [49 of 177], $P = 0.17$) and often had a shorter duration between developing diabetes and developing proliferative retinopathy (20.2 ± 7.0 vs. 21.7 ± 8.0 years, $P = 0.17$) (Fig. 1). To make sure these trends did not bias the estimates of familial risk, we further calculated the risk of proliferative retinopathy by either designating the probands randomly (2.88 [1.32–6.27], $P = 0.01$) or designating the siblings with the longest duration as probands (2.48 [1.02–6.04], $P = 0.04$). Thus, the selection of the oldest sibling as proband does not seem to produce a significant bias to the estimate of familial risk.

The heritability of proliferative retinopathy was $h^2 = 0.52 \pm 0.31$ ($P < 0.05$) in a sample of 362 of 396 patients. The sex of the patient was left out from the variance component model as being nonsignificant ($P > 0.1$). The proportion of variance attributable to all covariates (A1C, duration, and blood pressure) was 0.23 (Kullback-Leibler R^2).

DISCUSSION

This study shows an increased risk (OR 2.76 [95% CI 1.25–6.11], $P = 0.01$) of proliferative retinopathy in siblings of probands with proliferative retinopathy in type 1 diabetes. Such a familial clustering was supported by the estimated heritability of proliferative retinopathy $h^2 = 0.52 \pm 0.31$ ($P < 0.05$). Notably, this degree of familiarity is similar to the previously reported clustering for diabetic nephropathy in type 1 patients and suggests that genes may play a major role also for the development of severe retinopathy. In previous studies regarding diabetic nephropathy, ~50% of the risk could not be attributed to the familial clustering of conventional risk factors (14). Similarly, genetic risk factors may explain 50% of the risk of proliferative retinopathy.

Diabetic retinopathy continues to progress even after improvement of glycemic control (5,15). The more severe the retinopathy is, the longer the delay before a beneficial effect of improved glycemic control is observed (5). Thus, retinopathy appears to have an inherent momentum of progression that by time leads to an almost linear increase in the incidence of proliferative retinopathy (2). Further proof of familiarity is the conspicuous concordance of the survival times within sibships (Fig. 1). Taken together, these findings may be consistent with an altered expression of one or more critical genes induced by hyperglycemia.

Previous studies have been able to show familial clustering of severe nonproliferative retinopathy in families with type 2 diabetes (16,17) and in families with a mixture of both type 1 and type 2 patients (18). However, no studies thus far have given estimates for the familial risk of proliferative retinopathy. Despite the familiarity of nonproliferative retinopathy, attempts to find evidence for an involvement of any major loci in diabetic retinopathy have turned out inconclusive. Three genome-wide scans have offered suggestive evidence of linkage, though on a num-

ber of different chromosomes in patients with type 2 diabetes (19–21). The associations to various biologically relevant candidate genes have been extraordinarily difficult to replicate (22). Such results are typical for multifactorial diseases with only a moderate familiarity. The genetic component of diabetic retinopathy is likely to be polygenic and does not exclude the importance of interacting environmental risk factors in the determination of the ultimate risk. Some environmental risk factors such as blood pressure and A1C also appear to be determined at least in part by genetic factors. In this study, a single A1C measurement was a significant risk factor in both the logistic regression analysis and the heritability calculation despite the patients' highest ETDRS scores occurring at a median of 2.1 (IQR –10.4 to 1.0) years before the date of the A1C measurement in the FinnDiane Study. This could be a reflection of the predictive value of biological, between-individual variations in A1C, distinct from the mean blood glucose (23). In fact, it has been noted that a single A1C measurement offers a fair estimate of the glycemic control during the previous 10 years (24). Another significant risk factor in this study was blood pressure. Increased blood pressure is considered to be a multifactorial trait with an estimated genetic contribution in the range of 30–50% (25). The present study may be limited by the fact that the longitudinal changes in these risk factors could not be recorded, leaving possible residual intrafamilial correlations unaccounted for. However, it has been shown in a simulation study that familial clustering of two additive environmental risk factors only leads to a slight excess in the clustering of a disease among the siblings (26). Therefore, it is unlikely that the degree of familiarity observed here is the result of familial clustering of glycemic control and blood pressure alone.

Microalbuminuria is a known predictor for the development of proliferative retinopathy in patients with type 1 diabetes (27). There is controversy as to whether this association is due to hyperglycemia or whether nephropathy is truly an independent risk factor for proliferative retinopathy. It has been observed that after renal transplantation or initiation of dialysis, visual function stabilizes (28). The stabilization could also be due to other factors, such as lower blood pressure during renal replacement therapy (29). A strong positive association between the severity of retinopathy and the severity of nephropathy was noted in this study ($r = 0.63$, $P < 0.001$), which supports the hypothesis that there are common predisposing factors behind these two microvascular complications.

Retinal photography has been reported to be the most sensitive screening method for diabetic retinopathy. The sensitivity is in excess of 80% in detecting proliferative retinopathy (30). Ophthalmoscopy has less sensitivity but, conversely, higher specificity. It provides good results in the hands of trained professionals such as ophthalmologists and diabetologists (30). A high percentage of patients with diabetes in Finland are undergoing regular fundus photography. The national guidelines for the screening of diabetic retinopathy were already published in 1992 and updated in 2006 (31) emphasizing fundus photography as the preferable screening method (32). The majority of the patients in this study had attended several screening examinations. Many were examined and treated by ophthalmologists, and eventually 68% had fundus photographs available. Even with these repeated examinations, the absence or presence of any retinopathy was not found to cluster within families. This could reflect the fact that

almost all patients with long enough duration of type 1 diabetes will eventually develop some degree of retinopathy, thus making the detection of familial clustering more difficult.

The FinnDiane Study is not by definition a population-based study, which may limit the generalizability of the results. However, selection bias is unlikely because the geographic distribution of FinnDiane patients closely follows the distribution of the genetically homogeneous general population and also because we could obtain as much as 93% of the ophthalmic data in the sibships. Furthermore, the treatment of diabetes and its complications is fairly uniform across Finland. The prevalence of proliferative retinopathy in this study (31.1% [95% CI 26.4–35.9]) corresponds to the prevalence (32.1% [29.2–35.0]) in an independent sample of 1,001 patients with a 24.2 ± 11.7 duration of diabetes in the FinnDiane Study and to the prevalence (37.5% [34.6–40.4]) in a previous population-based study of type 1 diabetes patients with similar duration of diabetes in Finland (33).

In conclusion, this study found a familial clustering of proliferative retinopathy in patients with type 1 diabetes that cannot be accounted for by conventional risk factors. This suggests a significant genetic component in the pathogenesis of proliferative retinopathy.

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