Diabetes in the Old Order Amish

Characterization and heritability analysis of the Amish Family Diabetes Study

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OBJECTIVE — The Old Order Amish (OOA) are a genetically well-defined closed Caucasian founder population. The Amish Family Diabetes Study was initiated to identify susceptibility genes for type 2 diabetes. This article describes the genetic epidemiology of type 2 diabetes and related traits in this unique population.

RESEARCH DESIGN AND METHODS — The study cohort comprised Amish probands with diabetes who were diagnosed between 35 and 65 years of age and their extended adult family members. We recruited 953 adults who represented 45 multigenerational families. Phenotypic characterization included anthropometry, blood pressure, diabetes status, lipid profile, and leptin levels.

RESULTS — The mean age of study participants was 46 years, and the mean BMI was 26.9 kg/m^2. Subjects with type 2 diabetes were older, more obese, and had higher insulin levels. The prevalence of diabetes in the OOA was approximately half that of the Caucasian individuals who participated in the Third National Health and Nutrition Examination Survey (95% CI 0.23–0.84). The prevalence of diabetes in the siblings of the diabetic probands was 26.5% compared with a prevalence of 7.0% in spouses (λ_s = 3.28, 95% CI 1.58–6.80). The heritability of diabetes-related quantitative traits was substantial (13–70% for obesity-related traits, 10–42% for glucose levels, and 11–24% for insulin levels during the oral glucose tolerance test; P = 0.01 to <0.0001).

CONCLUSIONS — Type 2 diabetes in the Amish has similar phenotypic features to that of the overall Caucasian population, although the prevalence in the Amish community is lower than that of the Caucasian population. There is significant familial clustering of type 2 diabetes and related traits. This unique family collection will be an excellent resource for investigating the genetic underpinnings of type 2 diabetes.

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Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; dBP, diastolic blood pressure; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LADA, latent autoimmune diabetes of adults; NHANES III, Third National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; OOA, Old Order Amish; sBP, systolic blood pressure; STR, subscapular-to-triceps ratio; WHR, waist-to-hip ratio.

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

Diabetes is one of the most common chronic diseases in the U.S., having a prevalence of 7.5% among people aged ≥20 years (1). Diabetes prevalence rates vary widely in different regions of the world. In some traditional communities, such as those of the Mapuche Indians and Melanesians, diabetes is rare or absent, whereas high prevalence rates are observed in some Arab, Asian Indian, Chinese, and Hispanic American populations (2). In the U.S., diabetes is more common in African-Americans, Mexican Americans, Japanese Americans, and Native Americans than in non-Hispanic Caucasians (1).

Type 2 diabetes accounts for 95% of all diabetes. Although both insulin resistance and β-cell dysfunction are well documented, the molecular basis of type 2 diabetes is poorly understood (3,4). It has long been considered a disorder resulting from both genetic and nongenetic influences (5). The current understanding of the genetic basis of diabetes is largely restricted to a few distinct monogenic forms of the disease with clear Mendelian modes of inheritance (3,4); there has been limited progress in identifying specific genetic defects responsible for the most common form(s) of type 2 diabetes, which is likely to be heterogeneous and polygenic.

The Amish Family Diabetes Study was initiated in 1995 with the goal of identifying the genetic determinants of type 2 diabetes and related traits through positional cloning approaches. The Amish, named after their original leader Jacob Ammann, immigrated from western Europe (mainly Switzerland) to the U.S. to escape religious persecution over a 50-year period beginning in 1727 (6). The earliest immigrants settled in Pennsylvania. Later groups settled in Ohio, Indiana, and Illinois. There are no longer any Amish living in Europe. Approximately 200 of these families settled in Lancaster County, Pennsylvania, and can be considered the founders of today's Lancaster Amish community (7). Today's Amish population in the Lancaster area exceeds 30,000 (8).

All Amish are ruralites, and most earn their living by farming. They are resistant to

assimilation into the surrounding dominant culture and are widely known for their old-fashioned social and technological practices and characteristic dress. They do not proselytize and do not allow outsiders to marry into the sect. They represent both a religious and a genetic isolate (6). There is a high degree of consanguinity in the Old Order Amish (OOA). Although first-cousin marriages are not permitted, on average, OOA married couples are more closely related than second cousins once removed but less related than second cousins (9). Other features of this population include low relocation rates, a relatively high standard of living, large family sizes (average sibship size 6–7), and essentially complete genealogies dating back to the early 1700s (12–14 generations). All of these characteristics facilitate the collection of large families and extended pedigrees for genetic studies.

In this initial report, we describe the design of the Amish Family Diabetes Study, the genetic epidemiology of diabetes, and the heritability of diabetes-related traits in this unique founder population.

RESEARCH DESIGN AND METHODS

Study recruitment

Subject recruitment for the Amish Family Diabetes Study began in February 1995. The protocol was approved by the Institutional Review Board of the University of Maryland. Informed consent, including permission to contact relatives, was obtained before participation. Individuals with adult-onset diabetes were identified by door-to-door interviews and by word-of-mouth. Probands were defined as individuals with previously diagnosed diabetes with age at diagnosis between 35 and 65 years. The diabetic probands' first- and second-degree family members aged ≥18 years were recruited. If another diabetic individual was identified in the family (e.g., an aunt or uncle), then the family was expanded further to include that person's first- and second-degree relatives aged ≥18 years. The efficiency of this type of sequential sampling strategy for genetic linkage studies has been previously described (10).

Phenotypic characterization

Study subjects were examined either at the Amish Diabetes Research Clinic in Strasburg, Pennsylvania, or at their homes. Height and weight were measured using a stadiometer and calibrated scale with shoes removed and in light clothing. Waist circumference was measured at the level of the umbilicus, and hip circumference was measured at the widest protuberance across the pelvis. Skinfold thickness was measured with calipers in triplicate at 2 sites, the subscapular and triceps. The ratios of waist-to-hip circumference (WHR) and subscapular-to-triceps skinfold thickness (STR) were calculated as indexes of abdominal and central adipose distributions. Systolic (first phase) and diastolic (fifth phase) blood pressure were obtained in duplicate by use of a standard sphygmomanometer with the subject sitting for at least 5 min and was recorded to the nearest 1 mmHg.

After an overnight fast, an indwelling angiocatheter was placed in an antecubital vein. After acquisition of a fasting blood sample, a 75-g oral glucose tolerance test (OGTT) was administered. Blood samples were then drawn for determination of glucose and insulin values at 30-min intervals for 3 h during the OGTT. Glucose concentrations were assayed with a Beckman glucose analyzer (Beckman Coulter, Fullerton, CA) using the glucose oxidase method (interassay coefficient of variation = 1.52%) (11). Insulin and leptin levels were determined by radioimmunoassay (Linco, St. Louis, MO) (interassay coefficients of variation = 4.42 and 4.25%, respectively). The total glucose and insulin areas under the curve (AUCs) during the 3-h OGTT were determined with the trapezoid method.

HbA_{1c} levels were measured by high-pressure liquid chromatography (interassay coefficient of variation = 4.3% for low standard and 2.5% for high standard), and the fasting lipid profile (total cholesterol, HDL cholesterol, and triglyceride levels) was assayed by Quest Diagnostics (Baltimore, MD) (interassay coefficient of variation = 1.6% for total cholesterol, 5.0% for HDL cholesterol, and 1.6% for triglycerides). Levels of antibodies to GAD, a marker of immune destruction of pancreatic β-cells, were measured by radioligand-binding assay (12) in a subset of 455 subjects (48 subjects with diabetes).

Previously known diabetes was determined by a self-report of diabetes and any of the following: *1*) a single fasting venous plasma glucose level ≥7 mmol/l or a 2-h OGTT venous plasma glucose level ≥11.1 mmol/l; *2*) current treatment with insulin or oral hypoglycemic agents; or *3*) confirmed diagnosis by a physician. Newly defined diabetes was determined by the lack of diabetes history by self-report and positive OGTT results (either a fasting venous plasma glucose level ≥7 mmol/l or a 2-h OGTT venous plasma glucose level ≥11.1 mmol/l). Impaired glucose tolerance (IGT) was defined as a 2-h OGTT venous plasma glucose level ≥7.8 mmol/l but <11.1 mmol/l, and impaired fasting glucose (IFG) was defined as a fasting plasma glucose level ≥6.1 mmol/l but <7 mmol/l. The definitions of IGT and IFG excluded subjects with diabetes.

Statistical methods

To obtain descriptive details of the collection, clinical characteristics of study subjects were computed as unadjusted means ± SD. Means were compared using analysis of variance (ANOVA) (SYSTAT 8.0; SPSS, Chicago); *P* values were adjusted for age and sex, and, where appropriate, BMI. To obtain unbiased estimates of the prevalence of diabetes and IGT in the overall OOA population, we compared age-specific prevalence rates in spouses of OOA diabetic probands and their family members. We compared diabetes and IGT prevalence in the OOA with corresponding rates from the general U.S. Caucasian population, as estimated from the Third National Health and Nutrition Examination Survey (NHANES III) (1). Using the indirect method of age adjustment (13), we applied prevalence rates obtained from the NHANES III to determine the expected number of diabetes cases in the OOA. Direct comparisons of diabetes prevalence between OOA and the NHANES III were then obtained by comparing the number of cases observed in the OOA with the number expected if the OOA had the same age-specific prevalence rates as the NHANES III. The confidence interval for the ratio of observed-to-expected was also calculated (13). The λ_s was estimated by comparing the prevalence rates of type 2 diabetes between siblings of diabetic probands and spouses of OOA diabetic probands and their family members, adjusting for age with the Mantel-Haenszel procedure (14).

The heritabilities of diabetes- and obesity-related traits were computed using standard quantitative genetic methods (15). Heritability was defined in the narrow sense as the proportion of total phenotypic variance that could be attributed to the additive effects of genes. It was estimated as a function of the covariance among all possible relationship pairs in the pedigree. We simultaneously adjusted for the effects of age, age^2, and sex. Parameter estimates were

Table 1—*Number of pairwise relationships among examined subjects in the Amish Family Diabetes Study*

Pairwise relationship	*n*
Parent-offspring	658
Sib-sib	1,568
Grandparent-grandchild	139
Avuncular	2,346
Half-sib	8
Grand-avuncular	490
Great-grand–avuncular	22
First cousins	4,750
First cousins, once removed	5,560
First cousins, twice removed	1,124
First cousins, three times removed	25
Second cousins	4,169
Second cousins, once removed	3,231
Third cousins	2,064
Third cousins, once removed	518
Total	26,672

Data are *n* from 8 pedigrees consisting of 953 subjects.

obtained using maximal likelihood procedures, as implemented in the SOLAR software package (Southwest Foundation for Biomedical Research, San Antonio, TX) (16). Although it is possible to combine all of the study participants into a single 11-generation pedigree (17), it was not computationally feasible to perform heritability analysis with such a complex pedigree structure. Therefore, we combined families with overlapping individuals so that the original 45 families were reduced to 8 pedigrees ranging in size from 3 to 844 individuals. Subjects with unknown diabetes status due to missing data ($n = 25$) were excluded from all analyses, and subjects with diabetes ($n = 109$) were excluded from heritability analysis of insulin. Similarly, subjects currently taking antihypertensive medications were excluded from heritability analysis of blood pressure. Data on HbA_{1c}, insulin, leptin, and triglycerides were transformed by their natural logarithms to normalize the data distributions.

RESULTS — The Amish Family Diabetes Study was well received by the OOA community, and the participation rate was excellent (>80%). Of those who did not participate, the most common reasons given were *1*) lived over 60 miles from the clinic, *2*) personal reasons, and *3*) debilitating illnesses that precluded their participation. By the end of March 1998, 953 adults aged ≥18 years from 45 multigenerational families were studied. The mean sibship size was 4.5 (range 1–16). The 8 extended pedigrees formed by combining these 45 families provided a very large number of relationship pairs for our genetic analyses (Table 1).

Overall, 53% of the study subjects were women. The overall frequency of diabetes in this study population ascertained through a diabetic proband was 11.7%. Diabetes was significantly more common in women (13.5%) than men (9.7%) ($P = 0.02$), although after removing probands from the sample, the prevalence in men and women was approximately similar (10.5% in women, 7.3% in men, $P = 0.1$). Clinical characteristics of OOA subjects with diabetes and IGT and/or IFG were similar to those observed in other Caucasian populations (Table 2) (18,19). Compared with euglycemic subjects, those with diabetes or IGT and/or IFG were older, more obese, and had higher blood pressure and triglyceride levels. Amish individuals with diabetes and impaired glucose tolerance also had higher insulin levels than euglycemic individuals, suggesting insulin resistance.

Table 3 compares the age-specific prevalence rates of diabetes and IGT between spouses of OOA diabetic probands and their family members and Caucasians from NHANES III (1). For the sake of comparison, diabetes status was defined by World Health Organization criteria (20) for both the OOA and NHANES III. As in NHANES III Caucasians, the prevalence of diabetes increased with age in the OOA. Diabetes prevalence was lower in the OOA across all age groups than in the general U.S. Caucasian population. The overall prevalence of diabetes in the OOA was 5.0% (14 of 280 subjects). A total of 22.4 cases would be expected among subjects aged 40–74 years if the OOA experienced the same prevalence rates as the NHANES III. Thus, the diabetes prevalence in the OOA was only 0.54 times that of the national rate for U.S. Caucasians (95% CI 0.23–0.84). In contrast, the prevalence of IGT in the OOA was 1.38 times that of NHANES III Caucasians (95% CI 0.93–1.83). The mean BMI in all of the age groups was comparable with those of NHANES III (data not shown) (21).

Diabetes was diagnosed in a total of 109 OOA individuals. Characteristics of these diabetic subjects are summarized in Table 4. Of those individuals, 57% were newly diagnosed at our research clinic. Approximately 16% of the diabetic subjects

Table 2—*Clinical characteristics of study subjects by diabetes status*

Variable	Euglycemic	IGT and/or IFG*	Diabetes
n	659	160	109
Age	41.7 ± 14.4	51.1 ± 15.4†	60.8 ± 14.8†
Sex (M/F)	335/324	56/104	42/67
BMI (kg/m^2)	26.4 ± 4.4	28.3 ± 5.1‡	28.0 ± 5.7‡
Leptin (ng/ml)	9.0 ± 9.5	13.7 ± 12.6‡	13.5 ± 9.7†
Waist (cm)	90.1 ± 11.2	94.1 ± 11.4‡	95.9 ± 12.3†
WHR	0.86 ± 0.06	0.86 ± 0.06	0.88 ± 0.06‡
STR	0.38 ± 0.22	0.41 ± 0.20	0.46 ± 0.23‡
sBP (mmHg)	118.6 ± 13.8	127.3 ± 18.0†	136.1 ± 24.1†
dBP (mmHg)	77.2 ± 9.0	80.6 ± 9.7‡	81.0 ± 11.9‡
Total cholesterol (mmol/l)	5.38 ± 1.13	5.77 ± 1.33	5.83 ± 1.33‡
HDL cholesterol (mmol/l)	1.32 ± 0.35	1.31 ± 0.32	1.28 ± 0.35
Triglyceride (mmol/l)	0.85 ± 0.48	1.09 ± 0.63‡	1.15 ± 0.66†
Glucose (mmol/l)			
Fasting	5.0 ± 0.4	5.3 ± 0.6†	8.1 ± 3.8†
OGTT at 2 h	5.6 ± 1.2	8.7 ± 1.2†	14.6 ± 4.4†
Insulin (pmol/l)			
Fasting	65 ± 39	74 ± 39	86 ± 41†
OGTT at 2 h	206 ± 161	426 ± 296†	400 ± 287†

Data are *n* unadjusted means ± SD. *P* values for BMI, leptin, waist, WHR, and STR were adjusted for age and sex; *P* values for all other traits were adjusted for age, sex, and BMI. Of the study subjects, 25 with unknown diabetes status were excluded. *Of 160 subjects, 142 had IGT, 12 had IFG, and 6 had both IGT and IFG. †$P < 0.001$ between the euglycemic group and the IGT/IFG or diabetic groups; ‡$P < 0.05$ between the euglycemic group and the IGT/IFG or diabetic groups. dBP, Diastolic blood pressure; sBP, systolic blood pressure.

Table 3—*Age-specific prevalence rates of diabetes and IGT in the spouses of OOA diabetic probands, their family members, and the NHANES III Caucasian cohort, based on WHO criteria*

	Diabetes			IGT		
Age-group (years)	NHANES III Caucasians*	Observed in OOA	Expected in OOA†	NHANES III Caucasians*	Observed in OOA	Expected in OOA‡
20–39	NA†	1.1 (1/93)	NA	NA	6.5 (6/93)	NA
40–49	5.2	2.8 (2/72)	(3.7/72)	11.1	12.5 (9/72)	(8.0/72)
50–59	13.0	7.4 (4/54)	(7.0/54)	13.3	20.4 (11/54)	(7.2/54)
60–74	22.3	11.5 (6/52)	(11.6/52)	20.9	30.8 (16/52)	(10.9/52)
≥75	NA	11.1 (1/9)	NA	NA	33.3 (3/9)	NA
Overall§	14.3	6.7 (12/178)	12.6 (22.4/178)	15.3	20.2 (36/178)	14.6 (26.1/178)

Data are % (*n*). *Data are from reference 1; †ratio of observed-to-expected among those subjects aged 40–74 years was 0.54 (95% CI 0.23–0.84); ‡ratio of observed-to-expected among those subjects aged 40–74 years was 1.38 (0.93–1.83); §prevalence rate for subjects aged 40–74 years. NA, not available.

were diagnosed before the age of 35 years. More than half of all previously known cases were on insulin (53.2%), whereas only 6.4% of previously known cases did not take any medications for diabetes.

The prevalence of GAD antibody positivity in diabetic subjects whose age at diagnosis was ≥35 years was 10.0%. This rate did not differ significantly from that in subjects with either normal glucose tolerance (6.6%) or IGT (5.6%). In contrast, the prevalence of GAD antibody positivity was 50% in diabetic subjects with an age at diagnosis <35 years, which is significantly higher than that in nondiabetic subjects ($P < 0.001$). These results are in accordance with the hypothesis that a large proportion of diabetes cases with an age at diagnosis <35 years may have autoimmune type 1 diabetes or latent autoimmune diabetes of adults (LADA) (22), and, therefore, we excluded subjects with age of diagnosis <35 years ($n = 17$) from further analyses of type 2 diabetes–related traits.

To determine the magnitude of familial aggregation of type 2 diabetes in the OOA, we compared prevalence rates of diabetes (age at diagnosis ≥35 years) between siblings of diabetic probands and the spouses of probands and their family members. The prevalence of type 2 diabetes was significantly higher in the probands' siblings aged ≥35 years (9 of 34 [26.5%]) than in the spouse group (13 of 187 [7.0%]). The sibling relative risk (λ_s) adjusted for age by the Mantel-Haenszel procedure was 3.28 (95% CI 1.58–6.80). In contrast, the prevalence of IGT was similar between the 2 groups (23.5% among diabetic probands' siblings vs. 20.9% in the spouse group).

Heritability estimates for obesity, blood pressure, lipids, HbA_{1c}, glucose, and insulin in the Amish Family Diabetes Study are shown in Table 5. Heritability of both BMI and leptin was 42%. Heritability of the body composition measures were 37% for waist circumference, 13% for WHR, and 70% for STR ($P < 0.001$ for all). Concentrations of lipids were also highly heritable, with familiality accounting for 35, 50, and 54% of variation in triglycerides, HDL-cholesterol, and total cholesterol, respectively ($P < 0.0001$ for all). Familiality accounted for 18 and 24% of the variation in systolic and diastolic blood pressure ($P < 0.0001$), 31% of the variation in HbA_{1c} values ($P = 0.002$), 10–42% of the variation in glucose levels ($P < 0.0001$), and 11–24% of the variation in insulin levels during the OGTT ($P = 0.014$ for fasting insulin and $P < 0.0001$ for insulin at 120 min).

Among adult subjects, the majority of men made their living as farmers (40%) and laborers (33%), and the majority of women identified their occupations as housewives (64%), farmers' wives (10%), or shopkeepers, teachers, or craft makers (e.g., quilting) (21%). Of our respondents, 87% said they had no leisure physical activity, and for those who did, such activities were mostly walking and playing ball (baseball, volleyball, or table tennis). Approximately 42% of men reported they had ever smoked cigarettes, compared with only 1.4% of women. Among ever-smoking men, most started smoking cigarettes between ages 16 and 20 years, but then stopped smoking in their early 20s. Less than 3% of all OOA subjects reported that they currently smoked.

CONCLUSIONS

The Amish Family Diabetes Study was designed to elucidate the genetic epidemiology of type 2 diabetes in a genetically well-defined founder population. The study population included ~5% of the total adult OOA population in the Lancaster area. Participation rates for the study were high, resulting in the enrollment of large families. We were further able to reconstruct the complex pedigree struc-

Table 4—*Characteristics of 109 subjects with diabetes*

Diabetic characteristic	*n* (%)
Newly diagnosed diabetes	62/109 (56.9)
Age at diagnosis <35 years	17/109 (15.6)
Mean HbA_{1c} (%)	7.04 ± 2.26
Previously diagnosed diabetes	47/109 (43.1)
On insulin	25/47 (53.2)
On oral agents	19/47 (40.4)
On no medication	3/47 (6.4)
Diabetic cases with positive GAD antibody*	—
Age at diabetes diagnosis <35 years	4/8 (50.0)
Age at diabetesdiagnosis ≥35 years	4/40 (10.0)

Data are *n* (%) or means ± SD. *GAD antibody was measured in a subset of 455 subjects (48 with diabetes). The prevalence rates of GAD antibody positivity in euglycemic subjects and subjects with IGT were 6.6 and 5.6%, respectively.

Table 5—*Heritability estimates of diabetes-related traits in the OOA*

Phenotype	*n*	h^2	*P*	h^2 Reported by others	References
BMI	889	0.42 ± 0.07	<0.0001	0.21–0.79	31–33,35–37,39,40
Ln (leptin)	868	0.42 ± 0.07	<0.0001	0.39–0.73	35–37
Waist	887	0.37 ± 0.07	<0.0001	0.81	38
WHR	887	0.13 ± 0.05	0.0005	0.06–0.39	34,36,37
STR	887	0.70 ± 0.05	<0.0001	0.24–0.32	33,39
sBP (mmHg)	855	0.18 ± 0.06	<0.0001	0.15–0.42	32,33,40
dBP (mmHg)	855	0.24 ± 0.07	<0.0001	0.25–0.30	32,33,40
Total cholesterol	846	0.54 ± 0.08	<0.0001	0.37–0.51	31–33,40
HDL cholesterol	847	0.50 ± 0.07	<0.0001	0.45–0.66	31–33,40
Ln (triglycerides)	843	0.35 ± 0.07	<0.0001	0.13–0.53	31–33,40
Ln (HbA_{1c})	847	0.31 ± 0.06	0.0022	NA	NA
Fasting glucose	886	0.10 ± 0.04	<0.0001	0.18–0.64	33,35,40
Glucose 120	807	0.30 ± 0.06	<0.0001	0.16–0.51	33,35,40
Glucose AUC	761	0.42 ± 0.06	<0.0001	NA	NA
Ln (fasting insulin)	790	0.11 ± 0.06	0.0143	0.19–0.65	33,35,38,40
Ln (insulin 120)	742	0.24 ± 0.08	<0.0001	0.13–0.48	33,40
Insulin AUC	691	0.15 ± 0.08	0.0092	NA	NA

Data are *n* from 8 pedigrees consisting of 953 subjects. dBP, Diastolic blood pressure; h^2, heritability estimates; Ln, natural log transformed; NA, not available; sBP, systolic blood pressure.

ture of the study population through extensive interviews with participating subjects and by record linkage with the extensive genealogical database previously compiled for the Lancaster County OOA population (17). The mean kinship coefficient in this population is ~0.037, indicating that the average degree of relatedness between any two random individuals was less than that of first-cousins but greater than that of second-cousins (23).

The phenotypic characteristics of adult-onset diabetes in the OOA are similar to typical type 2 diabetes and, thus, atypical and/or monogenic forms of diabetes (e.g., maturity onset diabetes of the young, maternally-inherited diabetes and deafness, and type A syndrome of extreme insulin resistance) are uncommon in the Amish. Based on the association between age of diabetes diagnosis and GAD antibody prevalence, it is likely that both types 1 and 2 diabetes exist in this population. To minimize the possibility that probands for our study had type 1 diabetes, we required that age of diabetes onset in the proband be at least 35 years.

An unexpected result obtained from this study was the lower prevalence of diabetes observed among the OOA compared with the general U.S. Caucasian population. The observed prevalence of diabetes among spouses of probands and their family members was only 0.54 as high as that expected if these individuals had experienced the same diabetes risk as in the general U.S. Caucasian population. Interestingly, the prevalence of IGT in the OOA was similar to or slightly higher in spouse control subjects, as compared with the general U.S. Caucasian population. This raises the interesting hypothesis that the OOA may not be protected against glucose intolerance, but fewer individuals with impaired glucose tolerance eventually develop overt diabetes. By virtue of their predominantly agrarian lifestyle, the OOA may be more physically active than the general U.S. Caucasian population. One speculation is that this relatively active lifestyle provides partial protection against conversion from IGT to type 2 diabetes. Several studies have reported beneficial effects of physical activity on insulin sensitivity and glucose tolerance (24,25).

Diabetes aggregates in families in the OOA as it does in other populations (26,27). In this study, the prevalence of diabetes was 3.28 times as high in the siblings of diabetic probands than in the spouse control group, a finding similar to that observed in other Caucasian populations (28–30). By contrast, there was no familial aggregation of IGT in the OOA. These findings suggest that genes may be important determinants of progression of IGT to diabetes in the Amish.

To define type 2 diabetes genes, there may be value in dissecting the type 2 diabetes phenotype into genetically less complex traits that may be more proximal to the underlying pathophysiology. We observed moderate heritabilities for many of these quantitatively distributed traits, including glucose, insulin, obesity, blood pressure, and lipid levels. The heritability estimates we obtained from the Amish are in the range of those reported for other populations (Table 5).

The OOA (41,42) and other founder populations (43,44) have been used successfully to map genes for simple Mendelian diseases, especially those characterized by recessive transmission. More recently, founder populations have been used to map genes for complex diseases (45,46), including diabetes and related quantitative traits (47,48). To understand further the genetic contribution to type 2 diabetes, we have initiated additional studies of the OOA, including a genome scan. Because of their unique ancestral history, there may be advantages to trying to identify diabetes susceptibility genes in this population. First, because of the relatively small number of founders, it is possible that a complex genetic disease like type 2 diabetes will have equally strong genetic determinants in this population, as compared with the general Caucasian population, but will be attributed to a smaller number of genes, which should facilitate their identification and characterization. Second, diabetes susceptibility genes present in the Amish are likely to be a subset of those that are relevant to the general Caucasian population. Third, the large family structure characteristic of the OOA and the large number of individuals for which quantitative trait information has been obtained lead to greater power because of the very large number of relative pairs that are present. Fourth, uniformity of lifestyle may minimize potential confounding effects of variable phenotypic expression of susceptibility genes, which would further enhance our ability to identify these genes. However, the use of founder populations to map genes for complex disease poses special challenges. For example, the complex pedigree structures can greatly complicate the estimation of allele-sharing among pedigree members. In addition, once linkage is observed, fine mapping may be difficult if linkage disequilibrium extends over large regions of the chromosome. Furthermore, the genetic defects identified in these populations will need to be verified in other populations to evaluate their implication in public health.

In summary, the OOA are a genetically and socioculturally well-defined founder population. Type 2 diabetes in the OOA is

phenotypically similar to that of the general Caucasian population, although its prevalence is lower. There is substantial familial aggregation of the disease, and diabetes-related quantitative traits are heritable. These results provide the rationale for a genome-wide search, which is currently in progress, for type 2 diabetes susceptibility genes in this unique population.

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