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Association between parental history of diabetes and type 2 diabetes genetic risk scores in the PPP-Botnia and Framingham Offspring Studies

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Abstract

Objective—Parental history of diabetes and specific gene variants are risk factors for type 2 diabetes, but the extent to which these factors are associated is unknown.

Methods—We examined the association between parental history of diabetes and a type 2 diabetes genetic risk score (GRS) in two cohort studies from Finland (population-based PPP-Botnia Study) and the US (family-based Framingham Offspring Study).

Results—Mean (95% CI) GRS increased from 16.8 (16.8–16.9) to 16.9 (16.8–17.1) to 17.1 (16.8–17.4) among PPP-Botnia participants with 0, 1, and 2 parents with diabetes, respectively (p_{trend}=0.03). The trend was similar among Framingham Offspring but was not statistically significant (p=0.07). The meta-analyzed p value for trend from the two studies was 0.005.

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Conflict of Interest

The authors have a competing interest to declare. J.B.M. has a consulting agreement with Interleukin Genetics, Inc. No other potential conflicts of interest relevant to this article were reported.

J.L.V. researched data and wrote the manuscript. P.S. researched data and contributed to discussion. A.J. genotyped the PPP Botnia samples and contributed to discussion. C.S.F., V.L., and B.I. researched data and reviewed the manuscript. L.G., J.B.M., & P.W.F. researched the data, contributed to discussion, and edited the manuscript.

Conclusions—The very modest associations reported above suggest that the increased risk of diabetes in offspring of parents with diabetes is largely the result of shared environmental/lifestyle factors and/or hitherto unknown genetic factors.

Keywords

Type 2 diabetes mellitus; genetic risk score; family history

Introduction

Type 2 diabetes is a heritable disease. Having a parent with diabetes increases the risk of diabetes in the proband two-fold, with up to a six-fold risk when both parents are affected[1, 2]. Estimates of the additive genetic heritability of type 2 diabetes range from 25% to 40%[3, 4]. Recent genetic association studies are beginning to explain some of this heritability, having identified at least 40 independent, common single-nucleotide polymorphisms (SNPs) associated with an increased risk of type 2 diabetes[5]. Genetic risk scores (GRS), consisting of the weighted sums of SNP risk alleles, can predict the risk of type 2 diabetes even after adjustment for parental diabetes[5–7]. Nonetheless, adjustment for GRS does not attenuate the relationship between parental diabetes and type 2 diabetes risk[5], and the known diabetes risk SNPs still only account for about 10% of the heritability of type 2 diabetes[8]. While these findings suggest that genetic susceptibility to diabetes, as currently assessed, explains little of the association between parental history and diabetes risk, no study has yet reported effect estimates for the relationship of diabetes parental history and the known genetic risk factors for the disease. Here we used one family-based and one population-based cohort study to test the hypothesis that the degree of parental diabetes (0, 1, or 2 affected parents) is positively associated with type 2 diabetes genetic risk as characterized by an increasing weighted GRS.

Methods

The population-based PPP-Botnia Study and the family-based Framingham Offspring Study (FOS) have been described previously[9, 10]. All participants gave written informed consent and the studies were approved by the respective research ethics committees.

PPP-Botnia Study

We identified 4,219 unrelated participants in the population-based PPP-Botnia study in whom information on reliable parental history of diabetes and 33 type 2 diabetes variants were available at baseline[10]. Each of these loci has a confirmed association with type 2 diabetes in large genome-wide association studies and consortia[11–13]. For each participant, we calculated an additive 33-SNP weighted GRS using the same approach previously reported in the FOS[5]. Diabetes in the proband's parents was identified from validated self-reported questionnaire data[10].

Framingham Offspring Study

For the present analyses, we identified the 1,836 FOS participants for whom genotype data and parental diabetes status were available. For each participant, we calculated a GRS consisting of the same 33 SNPs except one (see Table caption) as those used in the PPP-Botnia Study. Because many parents of the FOS participants were themselves in the Framingham Heart Study[14], their diabetes status was systematically assessed, defined as random plasma glucose level >11.0 mmol/L (>200 mg/dL) at any study examination, plasma glucose >11.0 mmol/L (>200 mg/dL) one hour after a 50-g oral glucose tolerance test (examination cycle 10 only), or use of diabetes therapy.

Statistical Analyses

In PPP-Botnia, which is comprised of unrelated individuals, a generalized linear model was fitted. To account for relatedness among participants in FOS, we used mixed-effects linear models. Both models were adjusted for the age and sex of the proband, from which adjusted mean (95% CI) GRS values were output. P-values were calculated from the test for trend between the GRS and the number of parents with diabetes (0,1,2). A two-tailed p value <0.05 represented statistical significance. We meta-analyzed the tests of trends from the two cohorts using METAL software (http://www.sph.umich.edu/csg/abecasis/Metal/). All other statistical analyses were performed with SAS v9.2 software (SAS, Carey, NC).

Results

PPP-Botnia participants had a mean age of 47.9 (SD 15.3), and 1,077 (26%) had at least one parent with diabetes. The mean baseline age of the Framingham Offspring in this analysis was 33.6 (SD 9.5) years, and 398 (22%) had at least one parent with diabetes. Mean GRS increased modestly but significantly with increasing number of diabetic parents in the PPP-Botnia Study (p=0.03) but not among the FOS (p=0.07) (Table 1). The meta-analyzed p value for trend was 0.005.

Conclusions

Using data from a large population-based cohort, we have demonstrated a weak but statistically significant association between the number of parents with diabetes and an individual's type 2 diabetes GRS in PPP-Botnia. The same trend was apparent in the smaller, younger FOS. Differences in the mean values of GRS between the two cohorts likely result from differences in the methods by which parental diabetes was ascertained and in the distribution of risk alleles between these two ancestrally distinct populations. Although not previously demonstrated, an association between GRS and parental history of diabetes is consistent with prior studies showing each to be predictive of type 2 diabetes,[1, 5, 7]. It is somewhat surprising that GRS and parental diabetes history are only weakly associated when one considers the strong relationship between the latter and the risk of type 2 diabetes. This finding suggests that the heritability of type 2 diabetes may be mediated to a much greater extent by factors other than the genetic information carried in the common SNP variants identified to date. In part, this is because the majority of these SNPs are not themselves the true causal variants but, rather, imperfect tags of them. It is likely that large-scale sequencing efforts will discover these causal variants and new rare risk variants for type 2 diabetes that may increase our ability to predict the disease and elucidate its pathophysiology. Nevertheless, families share more than genetic variation and it is possible that shared environmental factors, including dietary patterns, physical activity habits, and intrauterine exposure to diabetes, may account for some of the excess risk of type 2 diabetes conferred by parental diabetes. Indeed, the findings presented here suggest that shared environmental factors may play a much more important role in the transmission of type 2 diabetes from parents to their children than common genetic risk factors. Importantly, many shared environmental risk factors known to have a major impact on type 2 diabetes risk are also potentially modifiable, and thus amenable to preventive interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table

Mean age- and sex-adjusted weighted genetic risk score (GRS) (95% confidence interval) by parental history of diabetes in the PPP-Botnia and Framingham Offspring Studies (FOS)

	PPP-Botnia		Framingham Offspring	
Number of parents with diabetes	**n**	**Mean GRS**	**n**	**Mean GRS**
0	3142	16.8 (16.8–16.9)	1438	16.6 (16.5–16.8)
1	965	16.9 (16.8–17.1)	363	16.8 (16.6–17.0)
2	112	17.1 (16.8–17.4)	35	17.3 (16.6–18.1)
p_{trend}		**0.032**		**0.072**

P_{trend} corresponds to the regression coefficients for number of parents with diabetes as a predictor of GRS in generalized (PPP-Botnia) and mixed-effects (FOS) linear models. GRS consists of the same 33 single-nucleotide polymorphisms (SNPs) in both cohorts except rs2237895 in PPP-Botnia and rs2237892 in FOS.