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Genetic Risk Score in Diabetes Associated With Chronic Pancreatitis Versus Type 2 Diabetes Mellitus

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INTRODUCTION: **Diabetes mellitus (DM) is a complication of chronic pancreatitis (CP). Whether pancreatogenic diabetes associated with CP-DM represents a discrete pathophysiologic entity from type 2 DM (T2DM) remains uncertain. Addressing this question is needed for development of specific measures to manage CP-DM. We approached this question from a unique standpoint, hypothesizing that if CP-DM and T2DM are separate disorders, they should be genetically distinct. To test this hypothesis, we sought to determine whether a genetic risk score (GRS) based on validated single nucleotide polymorphisms for T2DM could distinguish between groups with CP-DM and T2DM.**

METHODS: **We used 60 T2DM single nucleotide polymorphisms to construct a weighted GRS in 1,613 subjects from the North American Pancreatitis Study 2 and 2,685 subjects from the Multi-Ethnic Study of Atherosclerosis, all of European origin.**

RESULTS: **The mean GRS was identical between 321 subjects with CP-DM and 423 subjects with T2DM (66.53 vs 66.42, $P = 0.95$), and the GRS of both diabetic groups was significantly higher than that of nondiabetic controls (n = 3,554, $P < 0.0001$). Exploratory analyses attempting to enrich the CP-DM group for pancreatogenic diabetes, such as eliminating diabetes diagnosed before CP, requiring pancreas-specific comorbidities, or removing those with a family history of diabetes, did not improve the ability of the GRS to distinguish between CP-DM and T2DM.**

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DISCUSSION: **Recognizing that we lacked a gold standard to define CP-DM, our study suggests that CP-DM may be a subtype of T2DM, a notion that should be tested in future, large prospective studies.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A59

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INTRODUCTION

While diabetes mellitus (DM) arising as a result of diseases of the exocrine pancreas has come to be known as type 3c DM, we recently proposed that it be classified based on the underlying disorder, as mechanisms of hyperglycemia likely differ between pancreatic disorders (1). Of the pancreatic diseases associated with pancreatogenic DM, pancreatitis is the most common, accounting for up to 80% of cases, of which ~80% are acute pancreatitis and ~20% are chronic pancreatitis (CP), with smaller percentages caused by pancreatic ductal adenocarcinoma (~18%) and cystic fibrosis (~2%) (2). CP is a progressive fibroinflammatory syndrome with multiple etiologies and variable characteristics of atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, and pancreatic exocrine dysfunction (3). The prevalence of diabetes in patients with CP (herein, designated CP-DM) is approximately 30%–40% and is increased in patients with concurrent alcohol use, longer duration of CP, and after pancreatic surgery (4–8). Some patients with CP never develop CP-DM, however, suggesting that other modifying genetic and environmental factors are important (9–11). Indeed, patients with CP with obesity, a family history of diabetes, or African ancestry are at a higher risk of CP-DM than patients with CP without these risk factors for type 2 DM (T2DM) (4). However, this does not account for the high prevalence of diabetes in CP, nor provides insight into the underlying mechanisms of beta-cell dysfunction.

Pancreatogenic DM is often unrecognized and misdiagnosed as type 1 DM (T1DM) or T2DM (12,13). Among 31,789 new cases of adult-onset diabetes, 1.8% occurred after a diagnosis of acute or CP (and were therefore likely to be pancreatogenic DM), which exceeded the proportion of new cases of T1DM (1.1%) (13). Furthermore, those with pancreatogenic DM had higher hemoglobin A1c levels and required insulin earlier than those with typical T2DM. This illustrates the clinical importance of distinguishing pancreatogenic DM from T2DM, as the former may require more intensive care (11,14).

Disease subclassification is important to facilitate targeted treatment in diabetes, with the best-known example being T1DM vs T2DM. Differentiating the various types of maturity-onset diabetes of the young (MODY) is another example. MODY caused by heterozygous mutations in the glucokinase gene (MODY2) has a mild phenotype and usually does not require treatment (15). Other types of MODY usually progress to severe, often insulin-requiring diabetes. Of the latter, identification of those with mutations in *HNF1A* (MODY3) or *HNF4A* (MODY1) is crucial because these patients have excellent glycemic responses to sulfonylurea therapy (16).

MODY illustrates the role genetics can play in classifying different subtypes of diabetes. Genome-wide association studies (GWAS) have provided numerous robust loci that can be aggregated into genetic risk scores (GRSs) that can be used to effectively distinguish between common types of diabetes. Despite the modest proportion of heritability explained by GWAS single nucleotide polymorphisms (SNPs), GRSs based on SNPs for T1DM or T2DM have been found to separate groups of individuals with these 2 disorders (17). GRSs based on T1DM variants were able to discern MODY from T1DM in infants with neonatal diabetes (18). Furthermore, GRS analysis concluded that latent autoimmune diabetes of adults (LADA) is a form of T1DM, rather than a distinct disorder (19).

Given successes in the use of GWAS-derived variants in GRSs to clarify diabetes subtypes, either confirming that 2 conditions are distinct (T1DM and T2DM) or are manifestations of the same underlying pathophysiology (T1DM and LADA), we used a similar strategy in the current study, examining whether a GRS based on T2DM variants could differentiate CP-DM from T2DM.

METHODS

Subjects

The current study is based on 2 established and previously genotyped cohorts. The first is the North American Pancreatitis Study 2 (NAPS2), a cross-sectional case-control cohort study in 3 phases (NAPS2 original, NAPS2 Continuation and Validation [NAPS2-CV], and NAPS2 Ancillary Study [NAPS2-AS]) with samples collected between 2000 and 2014 that were used to conduct the first GWAS for CP (20) and other studies (4). Methodology and data collection procedures for the NAPS2 have been previously described (21). Herein, diabetes was defined in the NAPS2 based on the physician questionnaire response or patient self-report. Subjects (n = 1,613) who had undergone genome-wide genotyping were selected for the current study. Subjects with diabetes and CP or recurrent acute pancreatitis (RAP) were considered to have CP-DM. The NAPS2 provided 734 cases of CP, of which 246 had diabetes, and 438 cases of RAP, of which 75 had diabetes. In addition, 441 subjects without pancreatic disease (53 with diabetes) were also studied. Figure 1 illustrates the categorization of the study participants. All subjects are of European ancestry (previously confirmed using genetic data (20)). Regarding a subset of NAPS2 participants with diabetes and pancreatitis (n = 168), the physician questionnaire also classified diabetes as preexisting if diagnosed over 2 years before CP or RAP, as concurrent if diagnosed within 2 years before CP or RAP diagnosis, and as after CP or RAP when diagnosed after the CP or RAP diagnosis. For the subjects with CP, duration of disease was defined as the difference between the age of enrollment and the age at the first attack of acute pancreatitis, age at the first onset of symptoms, or age at diagnosis of CP, whichever came first. Duration of RAP was taken as the age at enrollment minus the age at the first attack of acute pancreatitis. These variables were combined as duration of pancreatic disease.

The second cohort was the Multi-Ethnic Study of Atherosclerosis (MESA). The MESA is a population-based longitudinal investigation of subclinical cardiovascular disease and its progression, wherein a total of 6,814 individuals, aged 45–84 years at baseline, were recruited from 6 US communities between 2000 and 2002 and followed at 5 subsequent examinations, with the last follow-up visit occurring from 2016 to 2018 (22). Thirty-eight

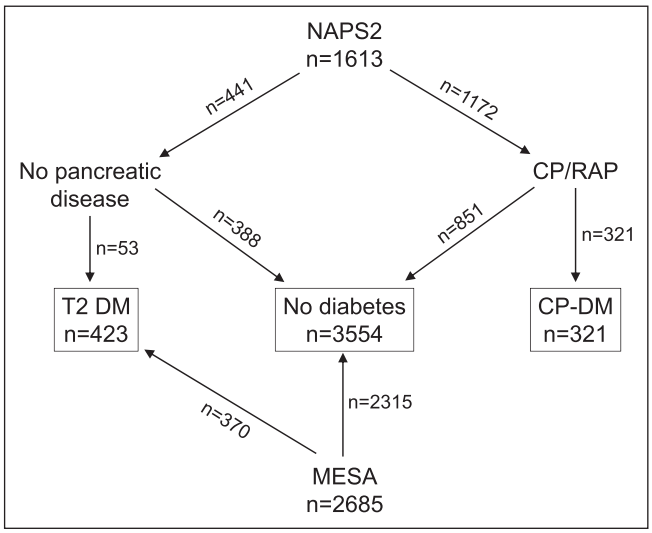

Figure 1. Flowchart of subject distribution. The chart outlines the numbers of subjects from the 2 cohorts who were categorized as nondiabetic, T2DM, or CP-DM. CP-DM, chronic pancreatitis–diabetes mellitus; MESA, Multi-Ethnic Study of Atherosclerosis; NAPS2, North American Pancreatitis Study 2; RAP, recurrent acute pancreatitis; T2DM, type 2 diabetes mellitus.

percent of the participants were white, 28% African American, 22% Hispanic, and 12% Asian. The MESA sample size was increased to over 7,000 by the MESA Air study initiated in 2004 (23). For the current effort, only subjects of non-Hispanic European origin from the MESA and MESA Air (n = 2,685, of whom 370 had diabetes) were selected to match the demographics of the NAPS2 (Figure 1). Diabetes was defined as the use of glucose-lowering medication or having a fasting blood glucose ≥7.0 mmol/L (126 mg/dL). In the current study, we included in the diabetic group those with prevalent and incident diabetes. The MESA subjects with diabetes and the NAPS2 subjects with diabetes but without pancreatic disease were considered to have typical T2DM.

For both cohorts, all participants gave written informed consent before their inclusion in research studies, and all studies were overseen by the relevant institutional review boards.

Genotyping and SNP selection

Subjects from the NAPS2 were genotyped on the Illumina OmniExpress beadchip, as previously described (20). The MESA was genotyped using the Affymetrix SNP 6.0 SNP Array, with imputation using the 1000 Genomes Project reference panel (phase 1, version 3) as reference, as previously described (24). At this time, imputation has not yet been completed in the NAPS2. Therefore, selection of T2DM SNPs initially focused on finding SNPs that were represented on the OmniExpress chip, comprising either the index SNPs or SNPs in linkage disequilibrium ($r^2 \geq 0.8$) with the index SNPs. The list of SNPs available in the NAPS2 was then cross-referenced to the MESA.

The primary source of data for SNP selection was a 2014 GWAS meta-analysis involving several diabetes genetics consortia (not including the MESA or NAPS2), which represented the most extensive analysis at the time the current study was conceived (25). As that GWAS included multiple ancestry groups, we focused on 73 independent ($r^2 > 0.1$) SNPs associated with T2DM from that study for which European-specific odds ratios (ORs) were reported (based on 12,171 T2DM cases and 74,124 controls). Of those, 67 were represented on the OmniExpress chip and were successfully genotyped in the NAPS2. We retained 60 of the original 67 SNPs that were associated with T2DM at genome-wide significance ($P < 5 \times 10^{-8}$) in GWAS data from a very large European GWAS for T2DM (56,862 T2DM cases and 824,006 controls) (26) that became available during the course of our study. Supplemental Table 1 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A59) lists the 60 SNPs ultimately studied herein.

Statistical analysis

GRSs were constructed based on the 60 SNPs described above, focusing on the alleles of each SNP that were associated with an increased risk of T2DM. Allele counts (0, 1, and 2) were used for directly genotyped SNPs, and dosage was used for imputed SNPs. We computed a weighted GRS as follows: $GRS = n \times [(SNP_1 \times \text{effect size}_1) + (SNP_2 \times \text{effect size}_2) + \ldots + (SNP_n \times \text{effect size}_n)]$/the sum of the effect sizes, where n is the number of SNPs, SNP_i is the number or dosage of T2DM-increasing alleles, and effect sizes were the natural log of the ORs. As recommended by best practices (27), we updated the ORs using results from the largest available T2DM GWAS (26). Using the same methods, a subset of 32 and 14 of the T2DM SNPs were used to construct a beta-cell function GRS and an insulin resistance GRS, respectively, based on functional assignments of these T2D SNPs from the literature (28,29) (see Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A59).

Demographics (age and body mass index [BMI]) and GRS between groups were compared using Student *t* tests (when comparing 2 groups, e.g., NAPS2 vs MESA) and one-way ANOVA with the Tukey honestly significant difference (HSD) *post hoc* test (when comparing more than 2 groups, e.g., no diabetes vs T2DM vs CP-DM). Chi square tests were used to compare sex and obesity between groups. Because it was not normally distributed, BMI was log transformed for all analyses; however, untransformed values are presented in tables to facilitate interpretation. Logistic regression models were used to adjust for age, sex, and BMI by including them as independent variables along with the GRS in models where the dependent variable compared the nondiabetic group with the T2DM group, the nondiabetic group with the CP-DM group, or the T2DM group with the CP-DM group.

Our sample size had 80% power (2 tailed, alpha 0.05) to detect a difference in mean 60 SNP-based GRS of 0.76 between the nondiabetic group and the T2DM group, mean difference of 0.85 between the nondiabetic group and the CP-DM group, and mean difference of 1.09 between the T2DM and CP-DM groups.

RESULTS

Demographic characteristics of the 2 cohorts are presented in Table 1. The sex distribution was identical between the cohorts, whereas mean BMI was higher in the MESA than in the NAPS2. Mean age was greater in the MESA, a result of the recruitment scheme of this cohort. Similar patterns between cohorts for age, sex, and BMI were seen when stratified by presence or absence of diabetes (Table 1). Table 2 compares groups without diabetes, with T2DM, and with CP-DM. The higher age of the T2DM group was partly a consequence of the large proportion of subjects from the MESA in this group. The proportion of men was higher

Table 1. Demographics and GRSs by cohort

All subjects	MESA (n = 2,685)	NAPS2 (n = 1,613)	*P* value
Age (yr)	62.7 ± 10.2	49.9 ± 15.8	<0.0001
Female, n (%)	1,400 (52.1)	844 (52.3)	0.91
BMI (kg/m^2)	27.8 ± 5.1	26.2 ± 5.9	<0.0001
Obese, n (%)	750 (28)	349 (22)	<0.0001
GRS	65.52 ± 5.24	65.31 ± 5.40	0.20
Diabetes	**MESA (n = 370)**	**NAPS2 (n = 374)**	***P* value**
Age (yr)	63.2 ± 9.6	54.5 ± 14.7	<0.0001
Female, n (%)	159 (43.0)	163 (43.6)	0.87
BMI (kg/m^2)	31.4 ± 5.8	27.9 ± 6.8	<0.0001
Obese, n (%)	190 (51)	163 (44)	<0.0001
GRS	66.69 ± 5.27	66.25 ± 5.51	0.26
No diabetes	**MESA (n = 2,315)**	**NAPS2 (n = 1,239)**	***P* value**
Age (yr)	62.7 ± 10.2	48.5 ± 15.9	<0.0001
Female, n (%)	1,241 (53.6)	681 (55.0)	0.91
BMI (kg/m^2)	27.2 ± 4.8	25.8 ± 5.5	<0.0001
Obese, n (%)	560 (24)	231 (19)	0.0005
GRS	65.33 ± 5.21	65.02 ± 5.34	0.093

Data are presented as mean ± SD for quantitative traits and number of subjects (percent) for female sex and obesity (defined as BMI ≥30 kg/m^2). *P* values are derived from Student *t* tests for quantitative traits and χ^2 for female sex and obesity.
BMI, body mass index; GRS, genetic risk score; MESA, Multi-Ethnic Study of Atherosclerosis; NAPS2, North American Pancreatitis Study 2.

in both diabetes groups compared with the nondiabetic group. While BMI was higher only in the T2DM group, the proportion of obese subjects differed between all groups.

The mean GRS was identical between the 2 cohorts (Table 1). The mean GRS was similar between 2,315 nondiabetic individuals from the MESA and 1,239 nondiabetic individuals from the NAPS2 (65.33 vs 65.02, $P = 0.093$), serving as a negative control and supporting the validity of the use of the GRS in joint analyses of the 2 cohorts. As a positive control, the mean GRS was found to be significantly greater in those with T2DM than those without diabetes (66.42 vs 65.23, $P < 0.0001$) (Table 2). The OR for T2DM vs no diabetes for each unit increment in the GRS was 1.043 (95% confidence interval [CI] 1.024–1.064, $P < 0.0001$), which was similar after adjustment for age, sex, and BMI (OR 1.049, 95% CI 1.029–1.071, $P < 0.0001$). In a further positive control analysis, we randomly removed nondiabetic subjects such that their number was the same as that of those with CP-DM (n = 321). The 423 subjects with T2D still had greater mean GRS than this reduced number of controls (66.42 vs 65.00, $P = 0.0004$), demonstrating that the discriminative power of the GRS was not driven by the large number of nondiabetic controls.

The mean GRS of those with CP-DM did not differ from that of those with T2DM, whereas it was significantly greater than those without diabetes (Figure 2 and Table 2). Quantitatively similar results were seen in analyses stratifying the cohort into weight categories (lean, overweight, and obese) (Table 3). These differences were also evident in logistic regression models that adjusted for age, sex, and BMI, wherein the OR for each unit increment in the GRS for T2DM vs CP-DM was 0.996 (95% CI 0.966–1.027, $P = 0.80$), whereas for CP-DM vs no diabetes, it was 1.051 (95% CI 1.028–1.074, $P < 0.0001$). CP-DM and T2DM also did not differ in terms of the beta-cell GRS or the insulin resistance GRS, which displayed similar patterns to the overall GRS (Table 4).

Recognizing that some subjects labeled as having CP-DM based on having CP or RAP and diabetes may actually have T2DM, we conducted a series of exploratory analyses wherein we attempted to enrich the CP-DM group for pancreatogenic DM. First, we examined the timing of the diabetes diagnosis relative to the diagnosis of CP or RAP. A subgroup was formed by excluding those with preexisting diabetes (diagnosed >2 years before CP or RAP). The GRS between this subset, presumably enriched for pancreatogenic DM, did not differ from the GRS of those with T2DM (Table 5), whereas their GRS remained higher than the GRS of subjects without diabetes (Table 5).

In another effort to enrich the CP-DM group for pancreatogenic DM, we defined a CP-DM group by requiring the presence of at least one pancreas-related comorbidity or complication that we previously found to be associated with diabetes in the NAPS2, including pancreatic calcification, pancreatic atrophy, exocrine insufficiency, or pancreatic surgery (4). We also examined CP-DM groups based on having each of these factors individually. In no case did the CP-DM group characterized by any pancreas-related comorbidity have a significantly different GRS than the

Table 2. Demographics and GRSs by diabetes status

	No diabetes (n = 3,554)	T2DM (n = 423)	CP-DM (n = 321)	*P* value (no diabetes vs T2DM)	*P* value (no diabetes vs CP-DM)	*P* value (T2DM vs CP-DM)
Age (yr)	57.7 ± 14.2	62.7 ± 10.7	53.8 ± 14.5	<0.0001	<0.0001	<0.0001
Female, n (%)	1922 (54)	188 (44)	134 (42)	0.0002	<0.0001	0.46
BMI (kg/m^2)	26.7 ± 5.1	31.2 ± 5.9	27.5 ± 6.8	<0.0001	0.26	<0.0001
Obese, n (%)	791 (22)	214 (51)	94 (29)	<0.0001	0.0055	<0.0001
GRS	65.23 ± 5.26	66.42 ± 5.38	66.53 ± 5.42	<0.0001	<0.0001	0.95

Data are presented as mean ± SD for quantitative traits and number of subjects (percent) for female sex and obesity (defined as BMI ≥30 kg/m^2). For the quantitative traits, all one-way ANOVA *P* values were <0.0001; *post hoc* Tukey HSD *P* values are reported in the table for pairwise comparisons. Chi-square *P* values are reported for female sex and obesity.
BMI, body mass index; CP-DM, chronic pancreatitis–diabetes mellitus; GRS, genetic risk score; T2DM, type 2 diabetes mellitus; NAPS2, North American Pancreatitis Study 2.

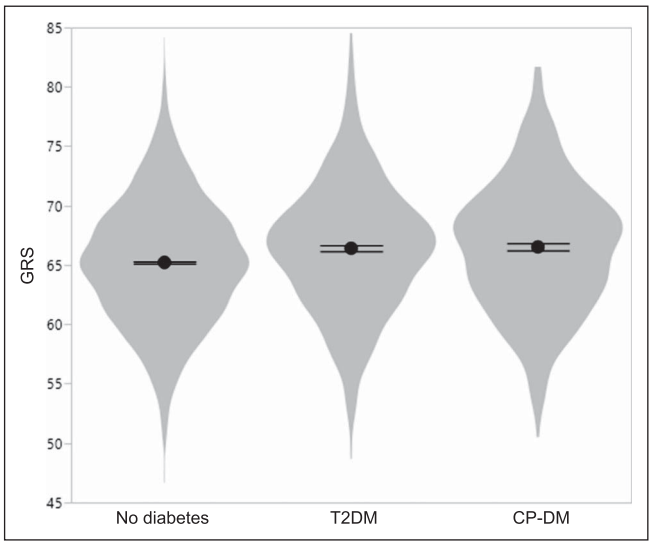

Figure 2. GRS by diabetes status. The contour plots depict the data density, with horizontal width representing frequency. The mean GRS (indicated by black dots) was similar in those with T2DM and CP-DM, whereas the mean GRS of both diabetes groups was higher than the GRS of the nondiabetic group. Error bars reflect SE. CP-DM, chronic pancreatitis–diabetes mellitus; GRS, genetic risk score; T2DM, type 2 diabetes mellitus.

T2DM group (Table 5). In most cases, the CP-DM subgroups demonstrated significantly higher mean GRSs than those without diabetes (Table 5).

Our previous study also found that canonical risk factors for T2DM, namely being overweight or obese or having a family history of diabetes, were strong predictors of diabetes in the NAPS2 (4). Therefore, to deplete the CP-DM group of subjects with T2DM, we constructed subgroups of CP-DM that were lean (BMI < 25 kg/m^2) or who had no family history of diabetes. As shown in Table 5, these measures also did not differentiate the GRS of those with CP-DM from the GRS of those with T2DM.

Finally, we stratified the CP-DM group by the median duration (4 years) of pancreatic disease at the time of enrollment in the NAPS2. Both the CP-DM subgroup with shorter duration of disease (less than 4 years) and the CP-DM subgroup with longer duration of disease (4 years or more) had similar mean GRS as the T2DM group (Table 5).

DISCUSSION

The premise of our study is that GRSs based on robust GWAS SNPs can differentiate between different types of diabetes. This has been observed for T1DM vs T2DM. A GRS based on 30 variants for T1DM was able to discriminate between T1DM and T2DM in 223 young adults aged 20–40 years (17). Among 3,887 individuals, risk scores for T1DM (30 SNPs) or T2DM (69 SNPs) were able to discriminate between the 2 types of diabetes (17). A GRS based on T1DM variants was used to estimate the prevalence of T1DM in a sample of 13,250 individuals who had developed diabetes in the first 6 decades of life; those identified by the T1DM GRS had lower BMI, earlier insulin requirement, and higher rates of diabetic ketoacidosis than those with T2DM (30). In a cohort of infants with neonatal diabetes, the T1DM GRS was able to distinguish MODY from T1DM (18). Another study determined GRSs for T1DM and T2DM in young adults with clinically defined T1DM, LADA, or T2DM (19). Genetically, those with T1DM and LADA were indistinguishable, suggesting that LADA is a particular presentation of T1DM, rather than a distinct condition or an intermediate trait between T1DM and T2DM. Thus, not only can the GRS separate different types of diabetes, it may also reveal whether certain types arise from similar etiologies.

Our results suggest that from the standpoint of T2DM genetic variants, CP-DM and T2DM are similar. This suggests that CP-DM may be a particular presentation of T2DM, similar to LADA being a type of T1DM. Indeed, we previously found that individuals with CP-DM were more likely to be overweight or obese and have a family history of diabetes compared with those with CP and no diabetes (4). We also found that pancreas-specific factors including exocrine insufficiency, atrophy, calcifications, and pancreas surgery were more likely in CP with diabetes than in CP without diabetes.

How may CP-DM be conceptualized in the framework of the pathophysiology of T2DM? Two key features lie at the heart of T2DM: insulin resistance and insufficient compensatory hyperinsulinemia. Insulin resistance arises largely because of lifestyle and environmental factors. Several studies also have suggested that insulin resistance (both whole body (31–34) and hepatic (34,35)) may also be a feature of pancreatogenic DM (11). Most individuals with insulin resistance respond with compensatory increases in beta-cell insulin production, raising circulating insulin levels to overcome tissue insulin resistance and maintain normoglycemia. Those individuals who cannot sustain this hyperinsulinemic compensation go on to develop impaired glucose tolerance and ultimately T2DM (36). The mechanisms underlying beta-cell failure in typical T2DM are multifactorial and remain to be fully determined (37). In setting of CP-DM, the additional insult of beta-cell dysfunction and ultimately loss resulting from chronic inflammation and pancreatic fibrosis likely contribute to beta-cell failure and an inability to compensate for insulin resistance, as supported by our finding that pancreas-specific factors increase the

Table 3. GRSs stratified by weight category

Stratum	Percent of cohort	No diabetes GRS	T2DM, GRS	CP-DM, GRS	*P* value (no diabetes vs T2DM)	*P* value (no diabetes vs CP-DM)	*P* value (T2DM vs CP-DM)	Overall *P* value
Lean	37.3%	65.32 ± 5.18	65.53 ± 5.44	66.38 ± 5.27	0.95	0.067	0.56	0.083
Overweight	25.6%	65.25 ± 5.32	67.03 ± 5.03	67.03 ± 4.75	0.0002	0.0038	0.99	<0.0001
Obese	36.4%	65.02 ± 5.28	66.22 ± 5.58	66.34 ± 6.16	0.012	0.066	0.98	0.0032

Data are presented as mean ± SD for the GRS. Overall *P* values are from one-way ANOVA; *post hoc* Tukey HSD *P* values are reported in the table for pairwise comparisons. Lean is defined as BMI <25 kg/m^2, overweight as BMI ≥25 and <30 kg/m^2, and obese as BMI ≥30 kg/m^2. BMI was not available in 32 subjects from the NAPS2.
BMI, body mass index; CP-DM, chronic pancreatitis–diabetes mellitus; GRS, genetic risk score; T2DM, type 2 diabetes mellitus.

Table 4. Beta-cell and insulin resistance GRSs by diabetes status

	No diabetes (n = 3,554)	T2DM (n = 423)	CP-DM (n = 321)	*P* value (no diabetes vs T2DM)	*P* value (no diabetes vs CP-DM)	*P* value (T2DM vs CP-DM)	Overall *P* value
Beta-cell GRS	33.98 ± 4.00	34.85 ± 4.29	34.84 ± 4.20	<0.0001	0.0007	0.99	<0.0001
Insulin resistance GRS	16.55 ± 2.42	16.80 ± 2.32	16.95 ± 2.50	0.11	0.012	0.67	0.0037

Data are presented as mean ± SD for the GRS. Overall *P* values are from one-way ANOVA; *post hoc* Tukey HSD *P* values are reported in the table for pairwise comparisons. The beta-cell GRS was constructed as the weighted sum of T2DM risk alleles at 32 SNPs implicated in beta-cell function; the insulin resistance GRS is based on 14 T2DM SNPs implicated in insulin resistance.
CP-DM, chronic pancreatitis–diabetes mellitus; GRS, genetic risk score; SNP, single nucleotide polymorphism; T2DM, type 2 diabetes mellitus.

odds for diabetes in CP (4). The model shown in Figure 3 depicts CP-DM in the context of T2DM.

A common assumption is that CP-DM arises simply from islet destruction and therefore represents primarily a disorder of absolute insulin deficiency accompanied by glucagon and pancreatic polypeptide deficiency. Although this is true in advanced cases of CP, evidence suggests that beta-cell dysfunction may arise early in the course of CP, well before islet destruction (38,39). A potential mechanism is that products of activated stellate cells or toxic factors produced in the diseased exocrine pancreas enter the islets and disturb beta-cell function, with inflammatory cytokines being likely candidates (40). Reduction in beta-cell mass on histology and reduced glucose-stimulated insulin release were documented in nondiabetic patients with advanced CP (41). A mechanism of beta-cell failure that does not involve massive destruction, but rather progressive dysfunction, fits well with the model in Figure 3. On the other hand, fulminant advanced CP may bypass the typical T2DM pathophysiology and lead directly to insulin-deficient diabetes.

We have not ruled out the possibility that CP-DM is a separate condition from T2DM because the definition of T2DM is broad. In CP, the stress on the islets may cause early beta-cell dysfunction and unmask T2DM, as suggested by our results using the GRS of T2DM SNPs. However, other genes may exist that are more specific for CP-DM that were not included in the current GRS. Because the prevalence of diabetes is much higher in patients with CP than age-matched controls, the group of patients with CP and diabetes likely represents a heterogeneous mixture of etiologies, including T2DM, CP-DM, loss of islet mass from surgery, pancreatic necrosis or destruction, and potentially patients with a combination of conditions. Such heterogeneity could have reduced the ability of the GRS to separate this group from the group of individuals with typical T2DM. Physiologic tests directed at discriminating pancreatogenic DM from T2DM, such as reduced pancreatic polypeptide response to mixed-nutrient ingestion (11), were not performed in the NAPS2. We conducted several exploratory analyses wherein we attempted to enrich the CP-DM group for pancreatogenic DM or deplete the

Table 5. GRSs in various CP-DM subgroups compared with the GRS in T2DM and in those without diabetes

Group	No. of subjects	Mean GRS	GRS difference vs T2DM	*P* value (vs T2DM)	GRS difference vs no diabetes	*P* value (vs no diabetes)
No diabetes	3,554	65.23	**−1.19**	**<0.0001**	0	NA
T2DM	423	66.42	0	NA	**1.19**	**<0.0001**
CP-DM	321	66.53	0.11	0.95	**1.30**	**<0.0001**
CP-DM with diabetes after CP or RAP	127	67.00	0.58	0.51	**1.77**	**0.0005**
CP-DM with any pancreatic comorbidity	252	66.29	−0.13	0.95	**1.06**	**0.0056**
CP-DM with pancreatic calcifications	152	66.30	−0.12	0.97	**1.07**	**0.036**
CP-DM with pancreatic atrophy	104	66.47	0.05	0.99	**1.24**	**0.047**
CP-DM with exocrine insufficiency	136	65.84	−0.58	0.50	0.61	0.38
CP-DM with pancreatic surgery	81	65.53	−0.89	0.35	0.30	0.86
CP-DM with BMI <25 kg/m^2	129	66.38	−0.04	0.99	**1.15**	**0.039**
CP-DM with no family history of diabetes	132	66.03	−0.39	0.74	0.80	0.19
CP-DM with shorter duration of pancreatic disease	146	66.96	0.54	0.53	**1.74**	**0.0003**
CP-DM with longer duration of pancreatic disease	163	66.14	0.28	0.84	0.92	0.078

For duration of pancreatic disease, shorter duration is less than 4 years and longer duration is 4 years or more. Statistically significant differences are highlighted in bold. All one-way ANOVA *P* values were <0.0001; *post hoc* Tukey HSD *P* values are reported in the table for pairwise comparisons.
BMI, body mass index; CP-DM, chronic pancreatitis–diabetes mellitus; GRS, genetic risk score; NA, not applicable; RAP, recurrent acute pancreatitis; T2DM, type 2 diabetes mellitus.

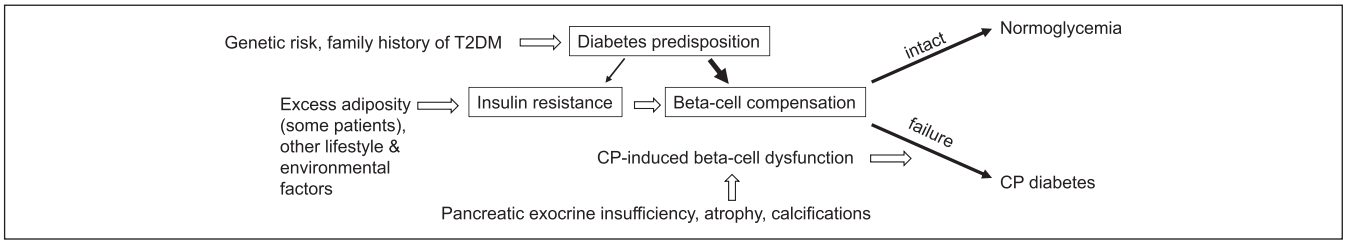

Figure 3. Pathophysiology of CP-DM in the context of T2DM. Early in the pathogenesis of T2DM, insulin resistance arises as a result of lifestyle and environmental factors and genetics, with excess adiposity contributing in many cases. Failure of beta-cell function to compensate for insulin resistance is the key event leading to diabetes. Beta-cell failure in typical T2DM is multifactorial and has a strong genetic component. The figure presents a model of CP-DM within this pathophysiologic framework, where several features (genetic risk, family history, and obesity) are shared with typical T2DM. Although excess adiposity contributes to insulin resistance in some cases, the proportion of obesity is expected to be lower in CP-DM than T2DM (Table 2). The pancreas-specific factors are proposed to contribute to the beta-cell failure that leads to CP-DM. CP-DM, chronic pancreatitis–diabetes mellitus; T2DM, type 2 diabetes mellitus.

CP-DM group of T2DM. Although none of these subgroup analyses could differentiate the CP-DM GRS from the T2DM GRS, the subgroups were generally small in sample size, limiting discriminative power. Results from the current study involving CP may not apply to pancreatogenic DM with other underlying conditions such as pancreatic adenocarcinoma or cystic fibrosis.

The prevalence of DM associated with CP increases with the duration of disease, from 8% to 10% at the time of CP diagnosis to over 80% 20–25 years later (6,7). In NAPS2 subjects with CP-DM, the duration of CP or RAP covered a wide range, from the diagnosis being made at enrollment to 40 years before enrollment (median 4 years). We conducted subgroup analyses to determine whether CP-DM exhibited a different genetic profile in those with shorter- or longer-term pancreatic disease. In neither case did the mean GRS differ from those with T2DM, suggesting that the genetic similarity between CP-DM and T2DM applies irrespective of the duration of underlying pancreatic disease.

GRSs stratified by weight category (Table 3) exhibited differences by diabetes status that were generally similar to those in the entire cohort. An exception was the lack of difference in the GRS between lean patients with T2DM and those without diabetes. Given the relatively high median BMI (27 kg/m^2) of participating cohorts in the GWAS that provided the SNPs for our GRS (25), it is tempting to propose that the SNPs are relevant to T2DM only in overweight or obese individuals. However, we believe that the lack of difference was a chance finding due to the low number (n = 57) of individuals with T2DM in the lean stratum.

Regardless of whether the underlying pathophysiology of CP-DM differs from that of T2DM, our study has potential clinical implications. Although our goal was not to assess the ability of a T2D GRS to predict CP-DM, our results suggest that among patients with CP of variable underlying etiologies, those with heightened genetic risk for T2DM are at a higher risk of CP-DM. Thus, in a personalized medicine approach, GRSs composed of T2DM variants may be used to risk stratify patients with CP, prompting closer surveillance or measures to prevent diabetes. Given the numerically small differences in mean GRSs between those with and without diabetes, consistent with observations in several other adult-onset polygenic conditions, focusing on those with extreme GRS values (e.g., top quintile) and integrating genetics with clinical risk factors may prove most useful for personalized risk stratification (42). Until further research is conducted on diabetes prevention in CP, lifestyle modification or metformin, which have been proven to prevent T2DM in people with prediabetes (43,44), could be offered to patients with CP at high genetic risk of diabetes. Metformin is a particularly attractive agent, given that observational studies suggest that it may prevent pancreatic cancer (45), which is a potential complication of CP. These potential uses of metformin would be investigational (not US Food and Drug Administration-approved indications). Other modalities to prevent diabetes in CP may arise from future genetic or physiologic research, either in typical T2DM or specific to CP-DM.

This study is the first to genetically compare CP-DM and T2DM. The GRS, composed solely of T2DM SNPs from GWAS, does not represent the overall role of genetics that would be expected from whole genome sequencing and comprehensive analysis of all known genetic variants linked to the complex pathobiology of pancreatic disease and/or diabetes. The most recent GWAS analysis for T2DM identified over 400 SNPs (26); however, given that most (>80%) of these are not present on the OmniExpress chip, we will not be able to examine them until imputation has been performed in the NAPS2 data set. The sample sizes may be considered modest by GWAS standards; however, given the greater power of the GRS over single SNPs, the GRS herein was able to distinguish between patients with and without diabetes, with similar effect sizes to other studies examining GRS association with T2DM (28). A possible limitation is that a much larger sample size may be needed to detect a subtle genetic difference between T2DM and CP-DM, especially if the latter group consists of a heterogeneous mix of both conditions. Such heterogeneity is likely, given that 24% (41 of 168) of those in the CP-DM group had diabetes that preceded pancreatitis, and that in 48% (153 of 321), the timing of these diagnoses was unknown. Another limitation is the lack of a gold standard method to diagnose CP-DM, which led to classification of all patients with CP herein with diabetes as having CP-DM. The fact that diabetes diagnosis was made in the NAPS2 by physician questionnaire response or patient self-report, rather than by objective laboratory measures, is another weakness. We also acknowledge that a small proportion of subjects from the MESA who have diabetes (assumed herein to have typical T2DM) may have pancreatic disease and CP-DM. The effects of this on the current results are expected to be negligible, given that the proportion of occult CP-DM within MESA subjects with diabetes is likely much smaller than the proportion of CP-DM within NAPS2 subjects with diabetes.

In conclusion, genetic risk based on robust T2DM variants does not separate patients with T2DM from CP-DM, suggesting that diabetes in CP/RAP may represent a subtype of T2DM,

where dysfunction, destruction, or removal of the exocrine pancreas is responsible for the beta-cell failure that precipitates diabetes in patients who are at an increased risk of beta-cell decompensation. Additional genetic risk factors that are mechanistically linked to CP cannot be ruled out in this study. Our consortium is conducting a prospective study of the natural history of CP (46), which will allow us to validate the current results and evaluate the predictive value of the T2DM GRS in incident CP-DM. Future studies will focus on genetic and physiologic definitions of pancreatogenic DM (47) toward the needed goal of better prevention and management of this previously under-recognized form of diabetes.

CONFLICTS OF INTEREST

Guarantor of the article: Mark O. Goodarzi, MD, PhD.

Specific author contributions: Study conception and design: M.O.G. and D.C.W. Acquisition and assembly of data: M.O.G., T.N., P.G., J.C., Y.-D.I.C., X.G., J.S.P., J.I.R., S.A., S.T.A., J.B., P.A.B., R.E.B., D.L.C., G.A.C., C.E.F., T.B.G., A.G., N.G., J.L., M.D.L., M.E.M., T.M., G.I.P., J.R., B.S.S., S.S., V.K.S., C.M.W., M.D.B., D.Y., and D.C.W. Statistical analysis: M.O.G., T.N., P.G., and J.C. Drafting of the manuscript: M.O.G. and D.C.W. Critical revision of the manuscript: P.G., Y.-D.I.C., J.S.P., T.M., S.J.P., W.G.P., D.K.A., and P.A.H. All authors approved the final manuscript.

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Study Highlights

WHAT IS KNOWN

- ✓ GRSs have demonstrated utility in differentiating different types of diabetes (type 1 vs type 2).
- ✓ Whether GRSs can distinguish pancreatogenic diabetes from T2DM has not been investigated.

WHAT IS NEW HERE

- ✓ Diabetes associated with CP resembles T2DM from the standpoint of a GRS composed of robust variants for T2DM.
- ✓ The mean GRS in patients with diabetes and CP was higher than that in nondiabetic controls.

TRANSLATIONAL IMPACT

- ✓ GRSs may in the future be included in clinical models to predict diabetes in patients with CP.
- ✓ Measures to prevent diabetes (such as lifestyle modification or metformin) may be offered to patients with CP at high genetic risk of diabetes.

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