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Association study of type 2 diabetes genetic susceptibility variants and risk of pancreatic cancer: an analysis of PanScan-I data

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Abstract

Objective—To examine associations between recently identified common type 2 diabetes (T2D) susceptibility genetic variants and pancreatic cancer risk.

Methods—Using data on individuals of European ancestry from the Cancer Genetic Markers of Susceptibility PanScan-I study (1,763 pancreatic cancer cases and 1,802 controls), we tested associations for 37 T2D susceptibility variants with pancreatic cancer risk. Associations with pancreatic cancer were also tested for three composite T2D susceptibility measures, incorporating data on all 37 variants, and for ten additional variants related to T2D-related phenotypes, including fasting glucose and beta-cell function.

Results—Of the 37 T2D risk alleles, two showed nominally significant positive associations with pancreatic cancer risk (FTO rs8050136 per-allele OR = 1.12; CI: 1.02–1.23; MTNR1B rs1387153 OR = 1.11; CI: 1.00–1.23) and one showed an inverse association (BCL11A rs243021 OR =0.88; CI: 0.80–0.97). The composite T2D susceptibility measures were not associated with pancreatic cancer. The glucose-raising allele of MADD rs11039149 was associated with increased risk of pancreatic cancer (OR = 1.14; CI:1.03–1.27).

Conclusions—Overall, these results do not provide strong evidence that common variants underling T2D or related phenotypes also affect pancreatic cancer risk; however, associations for FTO, MTNR1B, BCL11A, and MADD variants warrant further investigation in larger studies. Hypothesis-driven analyses of existing genome-wide genetic data can be cost-efficient and promising approaches for investigating genetic susceptibility to complex diseases.

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Keywords

Pancreatic cancer; Type 2 diabetes; Risk score; Genome-wide association study

Introduction

A large body of epidemiological evidence suggests that type 2 diabetes (T2D) is associated with risk for pancreatic cancer (PanCa). For example, a recent meta-analysis has estimated an odds ratio (OR) of 1.82 for risk PanCa among diabetics compared with non-diabetics [1]. However, the underlying cause of this association is unclear. It is possible T2D or T2D-related biological phenotype(s), such as fasting insulin or glucose levels, cause an increase in PanCa risk [2–4]. This association may be partially attributable to the effect of PanCa on T2D risk (i.e., reverse causation), whereby by the presence of a tumor in the pancreas induces pancreas dysfunction, increasing T2D risk [5–10]. Although not considered in many epidemiologic studies, it is also possible that unmeasured factors influence risk for both diseases, such as genetic factors (i.e., pleiotropy), smoking, or obesity, inducing an association between the two conditions [11].

Examining the effects of T2D genetic susceptibility variants on PanCa risk may help us better understand the relationship between these two diseases. If T2D itself is a causal factor influencing PanCa risk, then we expect T2D genetic susceptibility measures to associate with increased PanCa risk due to the association of T2D susceptibility with the T2D phenotype. Alternatively, if latent, undetected PanCa causes an increase T2D risk, such associations would be absent, because T2D is not influencing PanCa risk. And finally, if T2D and PanCa share specific genetic susceptibility factors, a plausible scenario considering both conditions involve pancreas dysfunction, we would expect at least some T2D susceptibility alleles to associate with PanCa risk.

Recently, genome-wide association (GWA) studies have identified approximately 38 single nucleotide polymorphisms (SNPs) that associate with T2D risk [12–23]. Furthermore, GWA studies have identified approximately 19 SNPs that associated with T2D-related phenotypes, such as fasting plasma glucose, and insulin, glucose and insulin responses to an oral glucose challenge, and homeostasis model assessment surrogates for beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) [12–14, 21, 22, 24]. In light of this new knowledge regarding T2D-related genetic variants and the connection of T2D to PanCa risk, a comprehensive examination of these variants in relation to PanCa risk is warranted.

In this work, we have tested the association of 37 of the 38 known T2D genetic susceptibility variants with PanCa risk, using data on individuals of European ancestry participating in a large collaborative case–control GWA study that has recently been used to identify several PanCa susceptibility loci [25, 26]. In addition to assessing these T2D SNPs for potential pleiotropic effects on PanCa, we have assessed the combined effects of these variants on PanCa risk, to assess the possibility that their effects on PanCa are weak and mediated through the T2D phenotype. Finally, we evaluate associations for 18 of the 19 SNPs that have been shown in GWA studies to be associated with diabetes-related traits (i.e., fasting glucose and insulin, HOMA-B, HOMA-IR, and response to an oral glucose

challenge). By integrating prior evidence from epidemiological and genetic studies, this focused and hypothesis-driven analysis existing GWA data has the potential to generate new insights regarding PanCa susceptibility in a cost-efficient manner.

Materials and methods

The Cancer Genetic Markers of Susceptibility (CGEMS) PanScan-I GWA study has been previously described [25, 26]. Participants for this collaborative case–control study were drawn from 12 different cohort studies and one case–control study. Cases were diagnosed with primary adenocarcinoma of the exocrine pancreas. A control was matched to each case based on birth year, sex, and race/ethnicity. Controls were free of PanCa at the time of diagnosis of the matched case. Genotyping was conducted at the National Cancer Institute's Core Genotyping Facility using HumanHap550 and HumanHap550-Duo Illumina assays. CGEMS provided high-quality genotype data for 1,895 cases and 1,937 controls (unmatched) that were downloaded in October 2009 using the database of genotypes and phenotypes (dbGAP; http://www.ncbi.nlm.nih.gov/gap).

This analysis was focused on PanScan participants of European ancestry. We assessed population structure using ~12,000 single nucleotide polymorphisms (SNPs) with low pair-wise linkage disequilibrium ($r^2 < 0.05$ for any pair) and high-quality genotyping (<1% missing) in Pan-Scan-I and HapMap3 founder individuals (from CEU, YRI, and CHB + JPT datasets). Principal components analysis (PCA) [27] was used to identify PanScan-I participants who did not cluster tightly with the CEU HapMap population of European ancestry. Based on this analysis, 253 individuals who were not of predominantly European ancestry were excluded. Based on identity-by-descent estimates generated for all pairs of participants, fourteen individuals with suspected relatives in the study were removed. Based on X-chromosome genotype data, four individuals were determined to have incorrect sex assignment and were removed. The resulting sample size was 1,763 cases and 1,802 controls. PCA was then used to generate principal components of ancestry among individuals of European ancestry.

We identified 38 SNPs with established associations of T2D in individuals of European ancestry from the existing evidence from GWA studies of T2D [12–23]. Similarly, we identified 19 SNPs with previously established associations with T2D-related traits, including fasting glucose, fasting insulin, response to glucose challenge, homeostasis model assessment surrogates for beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) [12–14, 21, 22, 24]. The majority of these SNPs were present in the PanScan-I dataset. For the SNPs that were not present, appropriate tagSNPs ($r^2 > 0.8$) present in the PanScan data were identified using the Genome-wide Linkage Disequilibrium Repository and Search engine (GLIDERS) program [28]. No appropriate SNP or tagSNP for KCNQ1 SNP rs231362 or GIPR SNP rs10423928 was available, resulting in 37 available T2D SNPs (out of 38) and 18 available SNPs for T2D-related phenotypes (out of 19). There are 8 SNPs that are present in both of these sets, because they have shown associations with both T2D risk and T2D-related phenotypes in previous studies. Due to this overlap, a total of 47 SNPs were included in this analysis. Of these 47 SNPs, none had >1% missing data, and no individual

was missing data on more than 3 SNPs. Hardy–Weinberg equilibrium was tested in controls for these SNPS.

Next, using data on the 37 T2D SNPs, we constructed two T2D genetic susceptibility measures: "T2D risk allele count" and "T2D relative risk" (as described previously [29]). The allele count is the total number of T2D risk alleles carried by an individual study participant. For individuals missing data on one or more SNPs, the total allele count was computed after assigning the missing SNP the average allele count (in controls) for that SNP. The relative risk measure is similar to the allele count but assigns weights to alleles based on previously reported effect sizes [12–23]. This measure is the product of the previously reported relative risk estimates for each risk allele, with each relative risk raised to the power of the number of alleles carried by each individual. The product was divided by the average product in the population to obtain a mean "T2D relative risk" that is relative to the average risk in the population. This measure had a mean of one and was skewed to the right; log transformation generated an approximate normal distribution.

All T2D autosomal SNPs and susceptibility measures were tested for association with PanCa using logistic regression adjusted for sex, categorical age groups (<51, 51–60, 61–70, 71–80, and >80), and two principle components representing axes of European ancestry. Odds ratios (OR) and 95% confidence intervals (CI) were estimated. Genotypes were coded additively as 0, 1, or 2 risk alleles. X-chromosome SNP rs5945326 was tested for association with PanCa risk among men and women, separately. All analyses were repeated for men and women and within 10-year age groups. Regressions were performed using SAS, version 9.1 (SAS Institute Inc., Cary NC, USA). Data manipulation and quality control procedures were performed using PLINK (http://pngu.mgh.harvard.edu/purcell/plink/) [30].

Results

The 1,763 cases and 1,802 controls used in this analysis were closely matched on age and sex. Characteristics of these study participants have been described previously [25]. In controls, none of the 45 autosomal SNPs (one SNP was X-linked) deviated significantly from Hardy–Weinberg equilibrium ($p > 0.05$), and all had observed allele frequencies very similar to those reported in previous studies in populations of European ancestry.

Two T2D SNPs showed nominally significant associations consistent with a positive effect of T2D on PanCa risk: FTO SNP rs8050136 ($p = 0.02$) and MTNR1B SNP rs1387153 ($p = 0.01$) (Table 1). However, the T2D risk allele for BCL11A SNP rs243021 showed an inverse association with PanCa risk ($p = 0.01$). The glucose-raising allele of MADD SNP rs11039149 [21] showed a nominally significant association with increased PanCa risk (p = 0.01) (Table 2). For all SNPs, OR estimates were similar before and after adjustment for European ancestry, as measured using PCA.

Neither the allele count nor the relative risk T2D composite risk measure showed a clear association with PanCa risk (Table 3). Both showed an increasing trend for risk in quartiles 2 and 3, but risk in quartile 4 was only slightly higher than the risk for quartile 1, resulting in modest p values for the trend (allele count $p = 0.48$; relative risk $p = 0.32$). The association

between the risk allele count and PanCa risk was similar in women (per-allele OR = 1.01, CI: 0.98–1.04) and in men (OR = 1.01; CI:0.98–1.03). This association was negative in the <51 age group (per-allele OR = 0.88; CI: 0.78–0.99). It was null in the 51–60 (OR = 1.00; CI: 0.95–1.05), the 61–70 (OR = 1.00; CI: 0.98–1.03), and >80 (OR = 0.99; CI:0.92–1.06) age groups. The association was positive in the 71–80 (OR = 1.03; CI: 1.00–1.06) age group.

Discussion

In this large case–control analysis of T2D susceptibility variants and PanCa, none of 47 variants examined showed strong evidence of association with PanCa risk. The T2D risk alleles for two SNPs (FTO rs8050136 and MTNR1B rs1387153) showed nominally significant associations with increased PanCa risk, consistent with the hypothesis that T2D or obesity (which is influenced by the FTO locus [31]) increases PanCa risk [32]. In contrast, the T2D risk allele for BCL11A SNP rs243021 showed an inverse association with PanCa risk. MADD SNP rs11039149 showed a nominally significant association with PanCa risk ($p = 0.01$), consistent with the hypothesis that elevated glucose levels increase PanCa risk. However, the observed associations may be chance findings, considering that 47 SNPs were tested for association with PanCa risk. One prior study showed a borderline association between the C allele of PPARG rs6802898 and increased PanCa risk among smokers [33], although our results do not convincingly support this finding (per-allele OR = 1.03, CI = 0.90–1.19). Variation in the CAPN10 gene, a reported T2D susceptibility gene, has also been reported to be associated with PanCa risk in the same sample of smokers [34]. We did not evaluate CAPN10 variation in this analysis because no CAPN10 SNP has been shown to be associated with T2D in GWA studies, a criterion for inclusion in this analysis.

In an attempt to assess the causality of the widely reported association between the T2D phenotype and PanCa [1], we tested the association for two composite measures of T2D genetic susceptibility, generated using data on 37 T2D SNPs, with PanCa risk. We did not find strong evidence of an association. However, the present analysis did not have ideal power for detecting such a relationship, considering the magnitudes of the association between T2D susceptibility and T2D and the association between T2D and PanCa. More specifically, we evaluated power under following assumption: (a) T2D susceptibility explains 3% of the T2D phenotype, (b) T2D has a prevalence of 0.20 (considering both diagnosed and undiagnosed T2D [35]), (c) T2D increases PanCa risk by 1.82-fold [1], and (d) the T2D susceptibility effects PanCa risk only through T2D. Datasets simulated under these assumptions suggest that our analysis had ~55% power to detect an association between T2D susceptibility and PanCa risk, demonstrating the difficulty in attempting to draw inferences regarding the effects of the T2D phenotype using T2D susceptibility variants, even in large studies. If T2D phenotype data were obtained for PanScan-I participants, our findings suggest that Mendelian randomization analyses would not produce strong evidence for a causal effect of T2D on PanCa, due to the lack of a clear association between T2D susceptibility and PanCa in this dataset. However, our power to detect an association at $p < 0.05$ for any single variant with a per-allele OR of 1.2 was >80% for MAF >0.14 (CaTS power calculator [36]).

Recent research suggests that the association between T2D and PanCa may be partially due to the effect of undetected PanCa on T2D risk. For example, several studies have shown that T2D–PanCa association is strongest among individuals diagnosed with T2D within a year of their PanCa diagnosis, compared with T2D of longer duration [6, 7, 9]. Similarly, several studies have shown a reverse dose–response relationship, where increasing duration of T2D results in decreasing risk of PanCa, compared with short T2D duration [1, 5, 7, 9, 10]. These findings suggest that the true effect of T2D on PanCa risk may be somewhat smaller than the relative risk of 1.82 reported in a recent meta-analysis [1], further decreasing our power to detect an association between composite T2D susceptibility measures and PanCa risk.

We examined associations for SNP related to T2D biomarkers (fasting plasma glucose and insulin, response to an oral glucose challenge, HOMA-B, and HOMA-IR) because these specific phenotypes could be more closely related to PanCa risk than T2D itself. While we did not observe convincing associations for any of these SNPs, several T2D-related biomarkers have shown association with PanCa risk in prospective cohort studies, namely insulin, glucose, and insulin-like growth factor-1 (IGF-1). For example, among men smokers, prospective measures of insulin have been associated with PanCa risk [2]. Measures of fasting glucose have shown positive associations with PanCa in cohorts of American smokers [2] and Koreans [3, 37]. In a large screening cohort, association with PanCa risk has been observed for pre-diagnostic circulating free IGF-1 (IGF-1/IGFBP-3 molar ratio) [38], but not total IGF-1 [39, 40].

Our study has several limitations. For example, there are known parent-of-origin effects for H19/IFG2 SNP rs2334499 and KCNQ1 SNPs rs2237892 and rs231362 (no adequate tagSNP) [41], however, we did not account for these effects in this analysis, as we have no available data on maternal/paternal transmission. Instead, our “T2D relative risk” susceptibility measure relied on the marginal association estimates that have been previously reported [23]. In addition, there was no available data on type 2 diabetes status for this analysis. Future studies of PanCa should integrate T2D-related SNP and phenotype data into the same analysis, ideally, with a larger sample size. Because our analysis was restricted to individuals of European ancestry, these findings may not be generalizable to populations of non-European ancestry.

In summary, this study did not provide evidence for strong pleiotropic effects for known, common T2D-related genetic variants on PanCa risk in individuals of European descent. Furthermore, T2D risk scores generated by combining information on many T2D risk variants did not show strong associations with PanCa risk. Despite these overall null findings, we have observed a few SNPs underlying T2D or related phenotypes, which warrant further investigation for association with PanCa risk. More generally, this analysis is an example of a hypothesis-driven approach that utilizes available GWA data and leverages information on known biological and epidemiological relationships. Such research is a promising and cost-efficient strategy for generating new insights regarding susceptibility to complex diseases in general.

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Table 1

Associations of 37 of 38 known type 2 diabetes (T2D) risk alleles with pancreatic cancer risk

Gene region	SNP	Chrom	OR for T2D[a]	Risk/non-risk allele	Risk allele frequency in PanScan-I		OR	95% CI	*P*
					Cases (*n* = 1,763)	Controls (*n* = 1,802)			
NOTCH2	rs2641348	1	1.13	C/T	0.112	0.106	1.07	0.92–1.24	0.42
PROX1	rs340874	1	1.07	G/A	0.534	0.538	1.00	0.91–1.09	0.95
GCKR	rs780094	2	1.06	G/A	0.614	0.617	1.00	0.91–1.10	0.95
THADA	rs13414140	2	1.15	C/T	0.888	0.884	1.04	0.90–1.20	0.62
BCL11A	rs243021	2	1.08	T/C	0.449	0.479	0.88	0.80–0.97	0.008
IRS1	rs2943641	2	1.11	C/T	0.642	0.648	0.97	0.88–1.07	0.16
PPARG	rs6802898	3	1.14	C/T	0.871	0.868	1.03	0.90–1.19	0.65
ADAMTS9	rs4411878	3	1.08	C/T	0.757	0.750	1.06	0.95–1.18	0.30
ADCY5	rs2877716	3	1.12	C/T	0.771	0.768	1.00	0.90–1.12	0.93
IGF2BP2	rs4402960	3	1.14	T/G	0.312	0.298	1.06	0.96–1.18	0.26
WFS1	rs10012946	4	1.12	C/T	0.604	0.599	1.02	0.93–1.13	0.66
ZBED3	rs7708285	5	1.08	G/A	0.283	0.269	1.08	0.97–1.20	0.59
CDKAL1	rs7756992	6	1.14	G/A	0.275	0.280	0.97	0.87–1.07	0.52
DGKB-TMEM195	rs2191348	7	1.06	T/G	0.528	0.544	0.94	0.86–1.03	0.18
JAZF1	rs1635852	7	1.10	T/C	0.487	0.507	0.93	0.84–1.02	0.10
GCK	rs4607517	7	1.07	A/G	0.174	0.160	1.08	0.96–1.23	0.21
KLF14	rs13234407	7	1.07	G/A	0.525	0.520	1.00	0.91–1.10	0.95
TP53IMP1	rs896854	8	1.06	A/G	0.501	0.504	0.99	0.91–1.09	0.88
SLC30A8	rs13266634	8	1.15	C/T	0.693	0.680	1.07	0.96–1.18	0.22
CDKN2A/B	rs2383208	9	1.20	A/G	0.810	0.817	0.96	0.85–1.08	0.47
CHCHD9	rs10512085	9	1.11	A/G	0.931	0.919	1.17	0.98–1.39	0.08
CDC123	rs11257655	10	1.11	T/C	0.214	0.212	1.01	0.90–1.13	0.89
HHEX/IDE	rs1111875	10	1.15	G/A	0.570	0.573	0.99	0.90–1.08	0.77
TCF7L2	rs7903146	10	1.37	T/C	0.272	0.284	0.95	0.85–1.05	0.30
H19/IGF2	rs2334499	11	1.08	T/C	0.418	0.411	1.03	0.94–1.14	0.43
KCNQ1	rs2237892	11	1.29	C/T	0.934	0.926	1.14	0.94–1.36	0.17
KCNQ1	rs231362	11	1.11	G/A	-	No	tagSNP	Available	-

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Gene region	SNP	Chrom	OR for T2D[a]	Risk/non-risk allele	Risk allele frequency in PanScan-I		OR	95% CI	*P*
					Cases (*n* = 1,763)	Controls (*n* = 1,802)			
KCNJ11	rs5215	11	1.14	C/T	0.372	0.378	0.97	0.88–1.06	0.49
CENTD2	rs1552224	11	1.14	T/G	0.843	0.837	1.04	0.92–1.18	0.89
MTNR1B	rs1387153	11	1.15	T/C	0.311	0.289	1.11	1.00–1.23	0.05
HMGA2	rs2612067	12	1.10	C/A	0.106	0.102	1.03	0.89–1.20	0.18
TSPAN8	rs1353362	12	1.09	C/T	0.277	0.285	0.96	0.87–1.06	0.43
HNF1A	rs7965349	12	1.07	C/T	0.809	0.801	1.05	0.93–1.18	0.41
ZFAND6	rs4778582	15	1.06	A/G	0.664	0.667	0.99	0.89–1.09	0.78
PRC1	rs8042680	15	1.07	A/C	0.320	0.321	0.98	0.89–1.09	0.74
FTO	rs8050136	16	1.17	A/C	0.426	0.394	1.12	1.02–1.23	0.02
HNF1B	rs4430796	17	1.10	G/A	0.475	0.462	1.05	0.95–1.15	0.34
DUSP9	rs5945326	X	1.07	G/A					
females					0.239	0.246	0.97	0.82–1.13	0.66
males					0.255	0.235	1.06	0.96–1.19	0.26

[a]Previously reported odds ratio for the association between the T2D risk allele and T2D risk [12–23]

Table 2

Associations with pancreatic cancer risk for 18 of the 19 SNPs involved in T2D-related phenotypes (fasting glucose and insluin, HOMA-B, HOMA-IR, and/or response to an oral glucose challenge)

Gene region	SNP	Chrom	Risk/non-risk allele	Associated trait(s)	Risk allele frequency in PanScan-I		OR	95% CI	*P*
					Cases (*n* = 1,763)	Controls (*n* = 1,802)			
PROX1[a]	rs340874	1	G/A	FPG, HOMA-B	0.535	0.538	1.00	0.91–1.09	0.93
GCKR[a]	rs780094	2	G/A	FPG, HOMA-IR, FI, OGC	0.614	0.617	1.00	0.91–1.09	0.95
G6PC2	rs560887	2	GA	FPG, HOMA-B	0.693	0.703	0.95	0.85–1.05	0.27
ADCY5[a]	rs2877716	3	C/T	FPG, HOMA-B, OGC	0.771	0.768	1.00	0.90–1.12	0.93
SLC2A2	rs10513685	3	G/A	FPG, HOMA-B	0.855	0.856	0.99	0.87–1.14	0.93
DGKB, TMEM195[a]	rs2191348	7	T/G	FPG, HOMA-B	0.527	0.543	0.94	0.86–1.03	0.18
GCK[a]	rs4607517	7	A/G	FPG, HOMA-B	0.172	0.160	1.08	0.96–1.23	0.21
SLC30A8[a]	rs13266634	8	C/T	FPG	0.693	0.680	1.07	0.96–1.18	0.22
GLIS3	rs7041847	9	A/G	FPG, HOMA-B	0.508	0.507	1.00	0.91–1.10	0.97
ADRA2A	rs10787315	10	C/T	FPG, HOMA-B	0.898	0.900	0.99	0.85–1.16	0.90
TCF7L2[a]	rs7903146	10	T/C	FPG, OGC	0.272	0.284	0.95	0.85–1.05	0.31
CRY2	rs11607883	11	G/A	FPG	0.488	0.467	1.09	0.99–1.19	0.09
MADD	rs11039149	11	A/G	FPG	0.745	0.720	1.14	1.03–1.27	0.01
FADS1	rs174537	11	G/T	FPG, HOMA-B	0.650	0.658	0.96	0.87–1.06	0.42
MTNR1B[a]	rs1387153	11	T/C	FPG, HOMA-B	0.311	0.289	1.11	1.00–1.23	0.05
IGF1	rs2162679	12	A/G	HOMA-IR, IF	0.843	0.837	1.07	0.95–1.22	0.27
VPS13C	rs1436958	15	T/G	OGC	0.420	0.436	0.94	0.86–1.04	0.22
C2CD4B	rs12440695	15	T/C	FPG	0.638	0.618	1.09	0.98–1.20	0.10
GIPR	rs10423928	19	A/T	OGC	-	No	tagSNP	Available	-

FPG fasting plasma glucose, *FI* fasting insulin, *OGC* glucose and insulin responses to an oral glucose challenge, *HOMA-B* homeostasis model assessment surrogate for beta-cell function, *HOMA-IR* homeostasis model assessment surrogate for insulin resistance (HOMA-IR)

[a]Data also included in Table 1

Table 3

Associations between T2D genetic risk measures and pancreatic cancer risk

T2D genetic risk measure	Cases (*n* = 1,763)	Controls (*n* = 1,802)	OR	95% CI	*P*
Risk allele count (categories)					
<34	20.5	22.7	1.00	Ref	*P* trend = 0.48
34–36	29.1	28.4	1.14	0.94–1.37	
37–38	20.0	17.8	1.24	1.00–1.52	
>38	30.5	31.1	1.08	0.89–1.30	
Risk allele count (continuous)			1.01[a]	0.99–1.03	0.36
T2D relative risk (quartiles)					
0.24–0.71	23.6	26.3	1.00	Ref	*P* trend = 0.32
0.72–0.92	25.3	24.6	1.13	0.94–1.36	
0.93–1.19	26.4	23.7	1.23	1.02–1.29	
1.20–3.41	24.7	25.3	1.07	0.89–1.30	
T2D relative risk (continuous)			1.05[b]	0.92–1.19	0.46
T2D relative risk (log-transformed)			1.08[b]	0.94–1.25	0.27

[a]Per-allele odds ratio;

[b]Odds ratio for pancreatic cancer for a 1-unit change in the relative risk for T2D