Do Variants Associated with Susceptibility to Pancreatic Cancer and Type 2 Diabetes Reciprocally Affect Risk?

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Abstract

Objectives

Although type 2 diabetes mellitus is a known risk factor for pancreatic cancer, the existence of shared genetic susceptibility is largely unknown. We evaluated whether any reported genetic risk variants of either disease found by genome-wide association studies reciprocally confer susceptibility.

Methods

Data that were generated in previous genome-wide association studies (GENEVA Type 2 Diabetes; PanScan) were obtained through the National Institutes of Health database of Genotypes and Phenotypes (dbGaP). Using the PanScan datasets, we tested for association of 38 variants within 37 genomic regions known to be susceptibility factors for type 2 diabetes. We further examined whether type 2 diabetes variants predispose to pancreatic cancer risk stratified by diabetes status. Correspondingly, we examined the association of fourteen pancreatic cancer susceptibility variants within eight genomic regions in the GENEVA Type 2 Diabetes dataset.

Results

Four plausible associations of diabetes variants and pancreatic cancer risk were detected at a significance threshold of \( p = 0.05 \), and one pancreatic cancer susceptibility variant was associated with diabetes risk at threshold of \( p = 0.05 \), but none remained significant after correction for multiple comparisons.

Conclusion

Currently identified GWAS susceptibility variants are unlikely to explain the potential shared genetic etiology between Type 2 diabetes and pancreatic cancer.
Introduction

It has been long recognized that Type 2 diabetes mellitus (T2DM) is a risk factor for development of pancreatic cancer (PaC). A meta-analysis of 17 case-control and 19 cohort or nested case-control studies found that the combined odds ratio (OR) was 1.82 for PaC risk among diabetic subjects compared to nondiabetic subjects [1]. Another meta-analysis supported a conclusion that long-standing diabetes of at least 5 years duration has a RR of 2.0 (95% CI, 1.2 to 3.2) for development of PaC [2]. Recently, a study analyzing 15 case-control studies from the Pancreatic Cancer Case-Control Consortium (PanC4) found that the OR for a diagnosis of diabetes two or more years before the diagnosis of PaC (long-standing diabetes) is 1.90 (95% CI:1.72 to 2.09), and such an association even persists for 20 or more years after diabetes was diagnosed (OR = 1.30, 95% CI 1.17 to 2.03) [3]. Thus, longstanding diabetes can increase risk of developing PaC. Interestingly, a population-based case-control study found that first-degree relative history of T2DM is associated with increased risk of PaC (OR 1.95, 95% CI 1.23–3.09) [4]. Any underlying link to explain these observations is unknown. Given the observations regarding family history, one potential explanation is that there is a shared genetic etiology for risk of both T2DM and PaC. With the significant research investment in genetic analysis of both diseases, particularly in genome-wide association studies (GWAS), it is now possible to test whether reported genetic susceptibility variants might be reciprocally associated with risk of developing either condition.

GWAS is a design that aims to agnostically identify genetic susceptibility to complex diseases [5]. This study design has been extensively employed in T2DM and PaC, and many genetic susceptibility variants have been identified [6,7]. For example, the GENEVA Genes and Environment Initiatives in Type 2 Diabetes study, which includes the Nurses’ Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) subsets, contributed to understanding the genetic predisposition to T2DM [8]. PanScan studies, comprised of PanScan 1, PanScan 2, and PanScan 3, have reported eight susceptibility loci for PaC [9,10,11].

We hypothesized that the susceptibility variants identified though these published GWAS contribute to a shared etiology. A study examining the association between T2DM susceptibility variants and PaC risk using the PanScan 1 dataset reported three variants that were associated with PaC risk [12]. However, this study did not validate their findings using an independent dataset. Associations between PaC susceptibility variants and T2DM risk were not estimated, thus limiting the knowledge on the potential role of these GWAS-derived variants in any shared etiology. To systematically evaluate this question, we analyzed the combined PanScan 1 and 2 data to evaluate whether T2DM susceptibility variants can predispose to PaC risk. Additionally, since around 15% of pancreatic cancer patients have a diagnosis of diabetes two or more years before the cancer diagnosis [3], it was of interest to assess whether the association between T2DM susceptibility variants and PaC risk can be differentiated by diabetes status of the studied individuals. We thus conducted a stratified analysis based on diabetes status (contrasting long-standing diabetes and no history of diabetes). We then used the GENEVA Type 2 Diabetes datasets to evaluate whether reported PaC susceptibility variants are associated with risk of T2DM. The overall study design is illustrated in Fig. 1.

Materials and Methods

Genotype data

Two publicly available GWAS datasets of GENEVA Type 2 Diabetes and PanScan were obtained through dbGaP [13] to investigate our hypothesis.

PanScan included genotypes generated in two phases: PanScan 1 and PanScan 2 (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id = phs000206.v3.p2). Briefly, PanScan
Thirty-eight GWAS derived Type 2 diabetes susceptibility variants

Test association with risk of Pancreatic cancer

PanScan (including PanScan1 and PanScan2 datasets)

Stratified analysis based on diabetes status

Mayo Clinic subset of PanScan (containing additional covariate data including diabetes status)

Fourteen GWAS derived Pancreatic Cancer susceptibility variants

Test association with risk of Type 2 diabetes

GENEVA Diabetes GWAS (including NHS and HPFS) datasets

1 consisted of 12 prospective cohort studies and a Mayo Clinic case-control study. The Illumina HumanHap550v3.0 genotyping platform genotyped 558,542 SNPs. Genotyping in PanScan 2 augmented PanScan 1 with 8 case-control studies from the PanC4. The Illumina Human610_Quadv1_B genotyping platform genotyped 581,188 SNPs. Age, sex, study site, and race comprised available covariate data. The Mayo Clinic subset drawn from PanScan 1 and 2 comprised 654 cases and 618 controls, with additional covariate information available: smoking status, first degree family history of cancer, body mass index (BMI), and diabetes status [14].

The GENEVA Genes and Environment Initiatives in Type 2 Diabetes study consisted of GWAS data generated using the NHS and HPFS cohorts. This dataset (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id = phs000091.v2.p1) included two subsets: NHS (1581 cases and 1810 controls), and HPFS (1164 T2DM cases and 1338 controls, and 68 cases of uncertain diabetes type). Both studies used the Affymetrix Affy_6.0 genotyping platform and 934,940 SNPs were genotyped. Available covariates included family history of diabetes, high blood pressure, high blood cholesterol, smoking status, physical activity, age, BMI, alcohol intake, fat intake measures, magnesium intake, cereal fiber intake, heme iron intake, glycemic load, and gender.

Quality Control filters

PanScan genotype data had been filtered previously for call rate, relatedness, controls that became cases, and sex chromosome abnormalities. If duplicates were genotyped, the individual with the higher call rate was used. The final analysis included 3360 cases and 3468 controls in the combined PanScan data. The Mayo Clinic subset analysis consisted of 63 cases and 23 controls in the long-standing diabetes group (a diabetes diagnosis of 2 or more years earlier than diagnosis of pancreatic cancer for cases, or 2 or more years earlier than date of enrollment for controls), and 448 cases and 557 controls without diabetes.
The GENEVA datasets had been pre-filtered for sex chromosome abnormalities, sample identity, and call rate. We further filtered for relatedness of the sample and Hardy–Weinberg equilibrium (HWE) for variants studied in both NHS and HPFS sets. For the HPFS, we additionally filtered out subjects with uncertain diabetes status. The final sample for our analysis consisted of 1579 cases and 1801 controls from the NHS set (all females), 1162 cases and 1336 controls from the HPFS set (all males), for a total of 2741 cases and 3137 controls.

**Genetic Variant Selection**

Thirty-eight T2DM susceptibility SNPs [8,15,16,17,18,19,20,21,22,23,24,25] and 14 PaC susceptibility SNPs [9,10,11] from published GWAS were included in our analyses. Thirty-seven of the 38 T2DM predisposition variants and five of the 14 PaC predisposition variants had been genotyped and were available in the PanScan datasets and GENEVA T2DM datasets, respectively. To represent variants which were not captured in the GWAS data, we captured the genotype by identifying SNPs in high LD ($r^2 > 0.5$) as determined by Haploview [26]. If multiple variants were identified for a variant of interest not in the GWAS, the SNP with the smallest p-value was chosen as representative for the association.

**Statistical Analysis**

Unconditional multivariable logistic regression assuming an additive model was employed in the association analyses. Available covariates were adjusted in the analyses. For associations reaching $p = 0.05$ threshold, a Bonferroni correction was conducted to adjust for multiple comparisons. Specifically, for the PaC dataset analysis, a threshold of $0.05/37 = 0.0014$ was used since all 38 variants from 37 genomic regions were tested; for the T2DM dataset analysis, a threshold of $0.05/6 = 0.008$ was used since 11 variants from 6 genomic loci were tested. Additionally, a correction of false discovery rate (FDR) was conducted to evaluate the significance [27].

For the PanScan data, covariates in the model included age, sex, study site, genotypic race (Eigenstrat principal components 1 and 2), and other significant principal components. We further conducted a stratified analysis in the Mayo Clinic subset according to diabetes status to investigate whether the T2DM susceptibility variants have a specific effect on either (1) long-standing diabetic PaC patients (cases who had long-standing diabetes 2 or more years before the diagnosis of pancreatic cancer) versus long-standing diabetic PaC controls, or (2) PaC cases and controls without diabetes.

In the GENEVA Type 2 Diabetes datasets, we conducted similar adjusted analysis. Covariates in the model included age, principal components (the first two components were used for NHS and 20 components were used for HPFS), family history of diabetes, high blood pressure, high blood cholesterol, smoking status, physical activity, BMI, alcohol intake, fat intake measures, magnesium intake, cereal fiber intake, heme iron intake, and glycemic load. As the NHS and HPFS set each contained a single gender, we did not include gender as a covariate in analyses of the separate sets but included gender in the combined set.

In all analyses, odds ratio (OR) and 95% confidence intervals (CI) were computed using Plink (http://pngu.mgh.harvard.edu/purcell/plink/) [28].

**Results**

**T2DM SNPs and pancreatic cancer risk in the PanScan datasets**

All 38 T2DM susceptibility variants that had been reported in the literature were included in the analyses as either observed in the GWAS data ($n = 37$) or represented by SNPs in high LD ($n = 1$). The results from the combined PanScan datasets are shown in Table 1.
Table 1. Association between Type 2 diabetes (T2DM) susceptibility variants and pancreatic cancer risk.

| Chromosome | SNP   | Gene Region | T2DM odds ratio (OR) | Risk/non-risk allele frequency* | Combined PanScan 1 & 2~ (3360 cases and 3468 controls) |
|------------|-------|-------------|----------------------|---------------------------------|--------------------------------------------------------|
| 1          | rs2641348 | NOTCH2      | 1.13                 | C/T                             | 0.11 (0.92–1.15)                                       |
| 1          | rs340874  | PROX1       | 1.07                 | G/A                             | 1.00 (0.93–1.07)                                       |
| 2          | rs13414140 | THADA       | 1.15                 | C/T                             | 0.98 (0.88–1.09)                                       |
| 2          | rs243021  | BCL11A      | 1.08                 | T/C                             | 0.91 (0.84–0.97)                                       |
| 2          | rs2943641 | IRS1        | 1.11                 | C/T                             | 0.90 (0.84–0.97)                                       |
| 2          | rs780094  | GCKR        | 1.06                 | G/A                             | 0.99 (0.92–1.06)                                       |
| 3          | rs2877716 | ADCY5       | 1.12                 | C/T                             | 1.00 (1.0–1.17)                                        |
| 3          | rs4402960 | IGF2BP2     | 1.14                 | T/G                             | 0.81 (0.93–0.95)                                       |
| 3          | rs4411878 | ADAMTS9     | 1.08                 | C/T                             | 0.79 (0.95–1.12)                                       |
| 3          | rs6802898 | PPARG       | 1.14                 | C/T                             | 0.88 (0.95–1.17)                                       |
| 4          | rs10012946 | WFS1       | 1.12                 | C/T                             | 0.63 (0.93–1.07)                                       |
| 5          | rs7708285 | ZEBD3       | 1.08                 | G/A                             | 0.31 (0.97–1.13)                                       |
| 6          | rs7756992 | CDKAL1      | 1.14                 | G/A                             | 0.96 (0.89–1.04)                                       |
| 7          | rs13234407 | KLF14      | 1.07                 | G/A                             | 1.05 (0.98–1.13)                                       |
| 7          | rs1635852 | JAZF1       | 1.1                    | T/C                             | 0.46 (0.84–0.96)                                       |
| 7          | rs2191348 | DGKB-  | 1.06                 | T/G                             | 0.52 (0.93–1.07)                                       |
| 8          | rs13266634 | SLC30A8     | 1.15                 | C/T                             | 0.18 (1.01–1.21)                                       |
| 8          | rs896854  | TP53IMP1    | 1.06                 | A/G                             | 0.71 (0.95–1.10)                                       |
| 9          | rs10512085 | CHCHD9     | 1.11                 | A/G                             | 0.46 (0.95–1.09)                                       |
| 9          | rs2383208 | CDKN2A/B    | 1.20                 | A/G                             | 0.92 (0.96–1.27)                                       |

(Continued)
| Chromosome | SNP     | Gene Region | T2DM odds ratio (OR) | Risk/non-risk allele risk allele frequency* | Combined PanScan 1 & 2* (3360 cases and 3468 controls) |
|------------|---------|-------------|----------------------|-------------------------------------------|--------------------------------------------------|
|            |         |             |                      | Odds Ratio (95% C.I.)                      | p                                                |
| 10         | rs1111875 | HHEX/IDE    | 1.15                 | G/A                                       | 0.97 (0.90–1.04)                                 |
| 10         | rs11257655 | CDC123      | 1.11                 | T/C                                       | 1.06 (0.98–1.16)                                 |
| 10         | rs7903146 | TCF7L2      | 1.37                 | T/C                                       | 1.01 (0.93–1.09)                                 |
| 11         | rs13937153 | MTNR1B      | 1.15                 | T/C                                       | 1.05 (0.97–1.13)                                 |
| 11         | rs1552224 | CENTD2      | 1.14                 | T/G                                       | 1.03 (0.93–1.14)                                 |
| 11         | rs2237892 | KCNQ1       | 1.29                 | C/T                                       | 1.04 (0.90–1.20)                                 |
| 11         | rs2334499 | H19/IGF2    | 1.08                 | T/C                                       | 1.03 (0.96–1.10)                                 |
| 11         | rs5215    | KCNJ11      | 1.14                 | C/T                                       | 0.97 (0.91–1.05)                                 |
| 12         | rs1353362 | TSPAN8      | 1.09                 | C/T                                       | 0.98 (0.90–1.05)                                 |
| 12         | rs2612067 | HMGA2       | 1.10                 | C/A                                       | 1.04 (0.93–1.16)                                 |
| 12         | rs7965349 | HNF1A       | 1.07                 | C/T                                       | 0.95 (0.87–1.04)                                 |
| 15         | rs4778582 | ZFAND6      | 1.06                 | A/G                                       | 1.01 (0.94–1.08)                                 |
| 15         | rs8042680 | PRC1        | 1.07                 | A/C                                       | 0.99 (0.92–1.07)                                 |
| 16         | rs8050136 | FTO         | 1.17                 | A/C                                       | 1.08 (1.01–1.16)                                 |
| 17         | rs4430796 | HNF1B       | 1.10                 | G/A                                       | 1.05 (0.98–1.12)                                 |
| X          | rs5945326 | DUSP9       | 1.27                 | A/G                                       | 1.01 (0.89–1.13)                                 |
| X          | rs5945326m| DUSP9       | 1.27                 | A/G                                       | 0.93 (0.79–1.09)                                 |

**SNPs in high LD with susceptibility variants**

| Chromosome | SNP     | Gene Region | T2DM odds ratio (OR) | Risk/non-risk allele risk allele frequency* | Combined PanScan 1 & 2* (3360 cases and 3468 controls) |
|------------|---------|-------------|----------------------|-------------------------------------------|--------------------------------------------------|
|            |         |             |                      | Odds Ratio (95% C.I.)                      | p                                                |
| 11         | rs231362 | KCNQ1       | 1.11                 | G/A                                       | 1.02 (0.94–1.10)                                 |

* Risk/non-risk allele and risk allele frequency in Europeans
  – Covariates used in PanScan datasets include age, sex, study site, genotypic race (Eigenstrat principal components 1 and 2), and other significant principal components.
# Variant within the bracket is within high LD of the targeted SNP and is used to represent the association between the targeted variant and pancreatic cancer risk
f Association in females
m Association in males
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In the combined data, four SNPs were associated with PaC risk. These included two variants, FTO rs8050136 (OR = 1.08, 95% CI 1.01–1.16, p = 0.03) and BCL11A rs243021 (OR = 0.90, 95% CI 0.84–0.97, p = 0.005), which confirmed the reported results of the PanScan 1 data (same direction and similar effect size) [12]. The other two variants were newly identified as JAZF1 rs1635852 (OR = 0.9, 95% CI 0.84–0.96, p = 0.003) and GCK rs4607517 (OR = 1.11, 95% CI 1.01–1.21, p = 0.03). In the PanScan 2 dataset (data not shown), the three SNPs (rs1387153, rs243021, and rs8050136) previously identified in PanScan 1 [12] did not replicate.

After stratifying by diabetes status in the Mayo Clinic subset, we detected five significant associations at p = 0.05 level. Focusing on long-standing diabetic PaC cases and controls, we identified SLC30A8 rs13266634 (OR = 4.92, 95% CI 1.71–14.2, p = 0.003). Focusing on PaC cases and controls without diabetes, we identified DGKB-TMEM195 rs2191348 (OR = 1.23, 95% CI 1.03–1.47, p = 0.02), KCNQ1 rs231362 (OR = 1.24, 95% CI 1.00–1.53, p = 0.046), ADCY5 rs2877716 (OR = 1.28, 95% CI 1.05–1.58, p = 0.02) and BCL11A rs243021 (OR = 0.83, 95% CI 0.69–0.99, p = 0.04) (Table 2).

Overall, four associations in PanScan sets reached statistical significance at a threshold of p = 0.05. However, none of them were significant after correction for multiple comparisons using the Bonferroni correction and FDR correction.

Association with type 2 diabetes

Among the 14 reported PaC susceptibility variants, 11 were genotyped in the GENEVA diabetes GWAS (n = 5) or were represented by SNPs in high LD (n = 6). Variants ABO rs5059922, PDX1 rs9581943 and TERT rs2736098 were not captured in these datasets. Only the association between LINC-PINT rs6971499 and T2DM risk appeared significant at p = 0.05 level in the combined dataset of NHS and HPFS, however, it was no longer significant after correction for multiple comparisons (Table 3).

Discussion

Based on previous results that demonstrated a relationship between T2DM and PaC, we hypothesized a shared genetic etiology. Using published GWAS data, we tested the association between reported T2DM susceptibility variants and PaC risk, as well as the association between reported PaC susceptibility variants and T2DM risk. The analyses showed that only one PaC susceptibility variant was associated with T2DM risk at a weak significance level; similarly, there were only weak associations between T2DM susceptibility variants and PaC risk. These associations, found at a significance threshold of p = 0.05 became not significant after adjustment for multiple comparisons. We also did not replicate any of the three T2DM SNPs from the PanScan 1 dataset analysis in the PanScan 2 dataset.

One design strength of our study is that we could perform initial stratified analyses by diabetes status of PaC cases and controls to evaluate whether associations between T2DM susceptibility variants and PaC risk differ by diabetes history. We found no associations significant, despite one potential association showing a relatively large effect size (rs13266634, OR = 4.92). We discounted the large effect size for rs13266634 because it was likely due to the subgroup sample sizes of 63 cases and 23 controls, and the frequency of the minor allele (T) in the control subjects was not congruent with reports in the general population (0.46 vs 0.29). The sample size of the PaC cases and controls without diabetes (448 cases and 557 controls), was likely underpowered as well, but our findings on DGKB-TMEM195 rs2191348, KCNQ1 rs231362, ADCY5 rs2877716 and BCL11A rs243021 may warrant further evaluation from larger studies.

Our study has other limitations. We did not evaluate susceptibility variants from candidate gene association studies. Many biologically plausible candidate genes have been reported to be...
Table 2. Association analysis of Type 2 diabetes mellitus (T2DM) susceptibility variants and pancreatic cancer risk stratified by diabetes status using the Mayo Clinic subset.

| Chromosome | SNP    | Gene Region | T2DM Odds Ratio | Risk/non-risk allele frequency | Long-standing Diabetes (63 cases and 23 controls) | No Diabetes (448 cases and 557 controls) |
|------------|--------|-------------|-----------------|-------------------------------|-----------------------------------------------|------------------------------------------|
|            |        |             |                 |                               | Odds Ratio                                    |                                         |
|            |        |             |                 |                               | 95% C.I.                                      |                                         |
|            |        |             |                 |                               | p                                            |                                         |
|            |        |             |                 |                               | Odds Ratio                                    |                                         |
|            |        |             |                 |                               | 95% C.I.                                      |                                         |
|            |        |             |                 |                               | p                                            |                                         |
| SNPS observed in GWAS |
| 1          | rs2641348 | NOTCH2 | 1.13             | C/T                           | 0.92                                         | 0.40–2.12                                 |
|            |          |         |                  |                               | 0.85                                         | 1.04                                      |
|            |          |         |                  |                               | 0.79–1.37                                   | 0.79                                      |
| 1          | rs340874  | PROX1   | 1.07             | G/A                           | 1.35                                         | 0.60–3.02                                 |
|            |          |         |                  |                               | 0.47                                         | 1.05                                      |
|            |          |         |                  |                               | 0.88–1.26                                   | 0.56                                      |
| 2          | rs13414140 | THADA  | 1.15             | C/T                           | 0.43                                         | 0.10–1.76                                 |
|            |          |         |                  |                               | 0.24                                         | 0.89                                      |
|            |          |         |                  |                               | 0.68–1.15                                   | 0.36                                      |
| 2          | rs243021  | BCL11A  | 1.08             | T/C                           | 0.75                                         | 0.33–1.70                                 |
|            |          |         |                  |                               | 0.49                                         | 0.83                                      |
|            |          |         |                  |                               | 0.69–0.99                                   | 0.04                                      |
| 2          | rs2943641 | IRS1    | 1.11             | C/T                           | 1.54                                         | 0.63–3.77                                 |
|            |          |         |                  |                               | 0.34                                         | 1.10                                      |
|            |          |         |                  |                               | 0.91–1.32                                   | 0.31                                      |
| 2          | rs780094  | GCKR    | 1.06             | G/A                           | 1.44                                         | 0.70–2.97                                 |
|            |          |         |                  |                               | 0.33                                         | 1.02                                      |
|            |          |         |                  |                               | 0.84–1.22                                   | 0.87                                      |
| 3          | rs2877716 | ADCY5   | 1.12             | C/T                           | 0.79                                         | 0.30–2.10                                 |
|            |          |         |                  |                               | 0.64                                         | 1.28                                      |
|            |          |         |                  |                               | 1.05–1.58                                   | 0.02                                      |
| 3          | rs4402960 | IGF2BP2 | 1.14             | T/G                           | 1.56                                         | 0.63–3.86                                 |
|            |          |         |                  |                               | 0.34                                         | 1.03                                      |
|            |          |         |                  |                               | 0.85–1.24                                   | 0.80                                      |
| 3          | rs4411878 | ADAMTS9 | 1.08             | C/T                           | 1.02                                         | 0.44–2.35                                 |
|            |          |         |                  |                               | 0.97                                         | 0.89                                      |
|            |          |         |                  |                               | 0.72–1.10                                   | 0.28                                      |
| 3          | rs6802898 | PPARG   | 1.14             | C/T                           | 1.04                                         | 0.28–3.90                                 |
|            |          |         |                  |                               | 0.95                                         | 1.01                                      |
|            |          |         |                  |                               | 0.77–1.32                                   | 0.95                                      |
| 4          | rs10012946 | WFS1   | 1.12             | C/T                           | 0.44                                         | 0.18–1.04                                 |
|            |          |         |                  |                               | 0.06                                         | 0.91                                      |
|            |          |         |                  |                               | 0.76–1.09                                   | 0.31                                      |
| 5          | rs7708285 | ZEBD3   | 1.08             | G/A                           | 1.42                                         | 0.62–3.26                                 |
|            |          |         |                  |                               | 0.41                                         | 1.06                                      |
|            |          |         |                  |                               | 0.87–1.30                                   | 0.54                                      |
| 6          | rs7756992 | CDKAL1  | 1.14             | G/A                           | 1.62                                         | 0.68–3.83                                 |
|            |          |         |                  |                               | 0.28                                         | 0.96                                      |
|            |          |         |                  |                               | 0.78–1.19                                   | 0.73                                      |
| 7          | rs13234407 | KLF14  | 1.07             | G/A                           | 0.82                                         | 0.36–1.85                                 |
|            |          |         |                  |                               | 0.63                                         | 1.10                                      |
|            |          |         |                  |                               | 0.92–1.32                                   | 0.28                                      |
| 7          | rs1635852 | JAZF1   | 1.1              | T/C                           | 0.64                                         | 0.28–1.46                                 |
|            |          |         |                  |                               | 0.28                                         | 0.99                                      |
|            |          |         |                  |                               | 0.83–1.19                                   | 0.91                                      |
| 7          | rs2191348 | DGKB-TMEM195 | 1.06     | T/G                           | 2.15                                         | 0.97–4.78                                 |
|            |          |         |                  |                               | 0.06                                         | 1.23                                      |
|            |          |         |                  |                               | 1.03–1.47                                   | 0.02                                      |
| 7          | rs4607517 | GCK     | 1.07             | A/G                           | 1.55                                         | 0.55–4.43                                 |
|            |          |         |                  |                               | 0.41                                         | 1.17                                      |
|            |          |         |                  |                               | 0.92–1.48                                   | 0.20                                      |
| 8          | rs13266634 | SLC30A8 | 1.15             | C/T                           | 4.92                                         | 1.71–14.2                                 |
|            |          |         |                  |                               | 0.003                                        | 0.91                                      |
|            |          |         |                  |                               | 0.75–1.10                                   | 0.32                                      |
| 8          | rs896854  | TP53IMP1 | 1.06             | A/G                           | 0.87                                         | 0.40–1.91                                 |
|            |          |         |                  |                               | 0.73                                         | 0.90                                      |
|            |          |         |                  |                               | 0.75–1.07                                   | 0.22                                      |
| 9          | rs10512085 | CHCHD9 | 1.11             | A/G                           | 3.20                                         | 0.76–13.4                                 |
|            |          |         |                  |                               | 0.11                                         | 1.30                                      |
|            |          |         |                  |                               | 0.92–1.84                                   | 0.14                                      |
| 9          | rs2383208 | CDKN2A/B | 1.20             | A/G                           | 0.90                                         | 0.29–2.83                                 |
|            |          |         |                  |                               | 0.86                                         | 0.93                                      |
|            |          |         |                  |                               | 0.74–1.16                                   | 0.51                                      |
| 10         | rs1111875 | HHEX/IDE | 1.15             | G/A                           | 0.41                                         | 0.15–1.12                                 |
|            |          |         |                  |                               | 0.08                                         | 0.94                                      |
|            |          |         |                  |                               | 0.79–1.12                                   | 0.51                                      |

(Continued)
### Table 2. (Continued)

| Chromosome | SNP       | Gene Region | T2DM Odds Ratio | Risk/non-risk allele Risk allele frequency* | Long-standing Diabetes (63 cases and 23 controls) | No Diabetes (448 cases and 557 controls) |
|------------|-----------|-------------|-----------------|--------------------------------------------|-----------------------------------------------|------------------------------------------|
|            |           |             |                 | Odds Ratio 95% C.I. p                        | Odds Ratio 95% C.I. p                           |
| 10         | rs11257655| CDC123      | 1.11 T/C         | 0.55                                       | 0.94 0.76–1.16 0.57                             |
| 10         | rs7903146 | TCF7L2      | 1.37 T/C         | 0.24                                       | 1.06 0.86–1.29 0.60                             |
| 11         | rs1387153 | MTNR1B      | 1.15 T/C         | 0.31                                       | 1.09 0.90–1.32 0.38                             |
| 11         | rs1552224 | CENTD2      | 1.14 T/G         | 0.28                                       | 1.01 0.79–1.29 0.94                             |
| 11         | rs2237892 | KCNQ1       | 1.29 C/T         | 0.84                                       | 1.01 0.72–1.42 0.96                             |
| 11         | rs2334499 | H19/IGF2    | 1.08 T/C         | 0.93                                       | 1.13 0.94–1.37 0.19                             |
| 11         | rs5215    | KCNJ11      | 1.14 C/T         | 0.43                                       | 1.09 0.90–1.32 0.38                             |
| 12         | rs1353362 | TSPAN8      | 1.09 C/T         | 0.34                                       | 1.21 0.90–1.62 0.20                             |
| 12         | rs2612067 | HMG2A       | 1.10 C/A         | 0.12                                       | 1.21 0.90–1.62 0.20                             |
| 12         | rs7965349 | HNF1A       | 1.07 C/T         | 0.81                                       | 0.91 0.73–1.13 0.39                             |
| 15         | rs4778582 | ZFAND6      | 1.06 A/G         | 0.67                                       | 0.98 0.80–1.19 0.82                             |
| 15         | rs8042680 | PRC1        | 1.07 A/C         | 0.34                                       | 1.04 0.86–1.25 0.68                             |
| 16         | rs8050136 | FTO         | 1.17 A/C         | 0.42                                       | 1.05 0.87–1.26 0.64                             |
| 17         | rs4430796 | HNF1B       | 1.10 G/A         | 0.47                                       | 1.01 0.85–1.21 0.90                             |
| X          | rs5945326 | DUSP9       | 1.27 A/G         | 0.74                                       | 1.10 0.80–1.51 0.56                             |
| X          | rs5945326 | DUSP9       | 1.27 A/G         | 0.74                                       | 1.09 0.73–1.62 0.69                             |

**SNPs in high LD with susceptibility variants**

| Chromosome | SNP       | Gene Region | T2DM Odds Ratio | Risk/non-risk allele Risk allele frequency* | Long-standing Diabetes (63 cases and 23 controls) | No Diabetes (448 cases and 557 controls) |
|------------|-----------|-------------|-----------------|--------------------------------------------|-----------------------------------------------|------------------------------------------|
|            |           |             |                 | Odds Ratio 95% C.I. p                        | Odds Ratio 95% C.I. p                           |
| 11         | rs231362* | KCNQ1       | 1.11 G/A         | 0.51                                       | 1.00 0.99                                       |

* Risk/non-risk allele and risk allele frequency in Europeans
# Variant within the bracket is within high LD of the targeted SNP and is used to represent the association between the targeted variant and pancreatic cancer risk
† Association in females
‡ Association in males
NA: not available

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Table 3. Association between pancreatic cancer susceptibility variants with Type 2 diabetes (T2DM) risk in the GENEVA study.

| Chromosome | SNP       | Gene Region | Pancreatic Cancer Odds Ratio (95% C.I.) | Minor/Reference allele, MAF* | NHS dataset (1579 cases; 1801 controls) | Odds Ratio (95% C.I.) | p   | Odds Ratio (95% C.I.) | p   | Odds Ratio (95% C.I.) | p   |
|------------|-----------|-------------|----------------------------------------|-----------------------------|----------------------------------------|----------------------|-----|----------------------|-----|----------------------|-----|
|            |           |             |                                        |                             |                                        |                      |     |                      |     |                      |     |
| 1          | rs12029406| NR5A2       | 0.83 (0.78–0.89)                       | T/C                         | 0.99                                   | 0.83                 | 1.06 | 0.38                 | 1.02 | 0.62                 |     |
| 1          | rs3790843 | NR5A2       | 0.81 (0.75–0.87)                       | T/C                         | 0.95                                   | 0.40                 | 1.09 | 0.25                 | 1.01 | 0.86                 |     |
| 1          | rs3790844 | NR5A2       | 0.77 (0.71–0.84)                       | G/A                         | 1.03                                   | 0.70                 | 1.08 | 0.29                 | 1.06 | 0.27                 |     |
| 5          | rs401681  | CLPTM1-TERT | 1.19 (1.11–1.27)                      | T/C                         | 0.99                                   | 0.82                 | 1.06 | 0.36                 | 1.03 | 0.55                 |     |
| 16         | rs7190458 | BCAR1/CTR81/CTR82 | 1.46 (1.30–1.65) | A/G                         | 1.27                                   | 0.10                 | 0.86 | 0.32                 | 1.08 | 0.46                 |     |

SNPs observed in GWAS

1 rs12029406 NR5A2 0.83 (0.78–0.89) T/C 0.99 0.83 1.06 0.38 1.02 0.62
1 rs3790843 NR5A2 0.81 (0.75–0.87) T/C 0.95 0.40 1.09 0.25 1.01 0.86
1 rs3790844 NR5A2 0.77 (0.71–0.84) G/A 1.03 0.70 1.08 0.29 1.06 0.27
5 rs401681 CLPTM1-TERT 1.19 (1.11–1.27) T/C 0.99 0.82 1.06 0.36 1.03 0.55
16 rs7190458 BCAR1/CTR81/CTR82 1.46 (1.30–1.65) A/G 1.27 0.10 0.86 0.32 1.08 0.46

SNPs in high LD with susceptibility variants

1 rs10919791 NR5A2 0.77 (0.71–0.84) A/G 1.11 0.26 1.02 0.85 1.05 0.28
1 rs4465241 NR5A2 1.25 (1.14–1.37) T/C 1.11 0.26 1.02 0.85 1.05 0.28
1 rs9543325 near Fabp5L1 1.26 (1.18–1.35) C/T 1.48 0.18 1.07 0.80 1.20 0.35
1 rs9564966 near Fabp5L1 1.21 (1.13–1.30) A/G 1.44 0.23 0.80 0.44 0.96 0.45
7 rs6971499 LINC-PINT 0.79 (0.74–0.84) C/T 0.86 0.06 0.93 0.45 0.88 0.04
22 rs16986825 ZNRF3 1.18 (1.12–1.25) T/C 0.95 0.56 1.11 0.23 1.03 0.61

* Minor/Reference allele, minor allele frequency (MAF) in Europeans
# Variants within the bracket are within LD of the targeted SNP and are used to represent the association between the targeted variant and T2DM risk
~ NHS denotes Nurses' Health Study; HPFS denotes Health Professionals Follow-up Study

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associated with T2DM and PaC in different studies [29,30]. However, it is well known that the replication rate for SNPs derived using the candidate gene association design is relatively low [6]. Thus rather than test variants which were not always demonstrated to be associated with disease risk, we focused on GWAS derived susceptibility SNPs which were consistently replicated.

One possible explanation for these results is that the variants we analyzed from the GWAS studies account for only a modest genetic susceptibility to disease risk. There may still be genetic loci beyond these GWAS-derived SNPs that could play a role that link these two diseases. It is also likely that the majority of the shared etiology of PaC and T2DM involve other factors beyond genetic level, such as obesity, epigenetic or environmental factors. Shared family environment could potentially explain the observed association between family history of diabetes and pancreatic cancer risk. Complementary genetic methods, such as family-based linkage studies or high throughput sequencing studies, may offer alternatives to characterize the potential shared genetic etiology of the two conditions, and may reveal novel associations or interactions.

In conclusion, we found that GWAS-derived susceptibility variants do not explain the potential shared genetic etiology of PaC and T2DM. We do report interesting associations that may warrant further study using independent datasets with larger sample sizes.

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Author Contributions
Conceived and designed the experiments: LW GMP. Performed the experiments: LW KGR. Analyzed the data: LW. Contributed reagents/materials/analysis tools: KGR GMP. Wrote the paper: LW.

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