Genome-wide association study data reveal genetic susceptibility to chronic inflammatory intestinal diseases and pancreatic ductal adenocarcinoma risk

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Abstract

Registry-based epidemiologic studies suggest associations between chronic inflammatory intestinal diseases and pancreatic ductal adenocarcinoma (PDAC). As genetic susceptibility contributes to a large proportion of chronic inflammatory intestinal diseases, we hypothesize that the genomic regions surrounding established genome-wide associated variants for these chronic inflammatory diseases are associated with PDAC. We examined the association between PDAC and genomic regions (+/− 500 kb) surrounding established common susceptibility variants for ulcerative colitis, Crohn's disease, inflammatory bowel disease, celiac disease, chronic pancreatitis, and primary sclerosing cholangitis. We analyzed summary statistics from genome-wide association studies data for 8,384 cases and 11,955 controls of European descent from two large consortium studies using the summary data-based adaptive rank truncated product method to examine the overall association of combined genomic regions for each inflammatory disease group. Combined genomic susceptibility regions for ulcerative colitis, Crohn's disease, inflammatory bowel disease, and chronic pancreatitis were associated with PDAC at P-values < 0.05 (0.0040, 0.0057, 0.011, and 3.4×10^{-6}, respectively). After excluding the 20 PDAC susceptibility regions (+/− 500 kb) previously identified by GWAS, the genomic regions for ulcerative colitis, Crohn's disease, and inflammatory bowel disease remained associated with PDAC (P-values = 0.0029, 0.0057, and 0.0098, respectively). Genomic regions for celiac disease (P-value = 0.22) and primary sclerosing cholangitis (P-value = 0.078) were not associated with PDAC. Our results support the hypothesis that genomic regions surrounding variants associated with inflammatory intestinal diseases, particularly, ulcerative colitis, Crohn's disease, inflammatory bowel disease, and chronic pancreatitis are associated with PDAC.

Introduction

Pancreatic cancer, characterized by its increasing incidence and high fatality, is the 3rd leading cause of cancer-related mortality in the United States (US) (1). Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer (2). In addition to risk factors, such as cigarette smoking, excess weight and diabetes, genetic susceptibility contributes to the disease with an estimated heritability of up to 21% (3).

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Chronic inflammation plays an important role in PDAC pathogenesis. The most direct link between inflammation and pancreatic cancer is derived from known associations with chronic pancreatitis, with risks being particularly strong for hereditary pancreatitis (4). Swedish registry-based studies have identified significant excess incidence of PDAC in patients with ulcerative colitis (5), Crohn's disease (6), and primary sclerosing cholangitis (7) compared with the general Swedish population, albeit based on a relatively small number of PDAC cases. Ulcerative colitis and Crohn's disease are characterized as idiopathic, immune-mediated recurrent or chronic inflammatory disorders of the gastrointestinal tract and are collectively classified as inflammatory bowel disease. Primary sclerosing cholangitis is a chronic autoimmune disease with progressive inflammation and fibrosis in the intrahepatic and extrahepatic biliary ducts and has also been associated with inflammatory bowel disease (8). Celiac disease, an autoimmune disorder characterized by chronic inflammation in small intestine, has been variably associated with PDAC (9,10). A limitation of registry-based studies and epidemiologic studies that rely on self-report is chronic inflammatory intestinal diseases may not be accurately ascertained (e.g., misdiagnosed with irritable bowel syndrome due to overlapping symptoms) (11,12), and thus affect risk estimates. Genetic susceptibility is known to contribute to each inflammatory disease mentioned above (13–16).

In this study, we examined the association between genomic regions surrounding common susceptibility variants identified from published genome-wide association studies (GWAS) of ulcerative colitis, Crohn's disease, inflammatory bowel disease, celiac disease, chronic pancreatitis and primary sclerosing cholangitis, and risk of PDAC using GWAS data from two large PDAC consortia (17–21). We hypothesize that combined genomic susceptibility regions for each chronic inflammatory intestinal disease group will be associated with PDAC. The statistical approach we employed considers the joint association of multiple genomic regions with PDAC risk (22), and thus has the potential to detect associations that could be overlooked by traditional single-marker approaches.

Materials and Methods

Study sample

Our study was based on 9,038 primary PDAC cases (ICD-O-3 code C250-C259) and 12,389 controls of European ancestry from four GWAS conducted in the Pancreatic Cancer Cohort Consortium (PanScan I, II, III) and the Pancreatic Cancer Case Control Consortium (PanC4) (17–21). Participants with non-exocrine pancreatic tumors (histology types 8150, 8151, 8153, 8155 and 8240) were excluded because their etiologies are thought to be different. The details of the cases, controls and study design have been previously described (17–21). The three PanScan GWAS included participants from 16 cohorts [Alpha-Tocopherol, Beta-Carotene Study (ATBC, Finland), Agricultural Health Study (US), Give us a Clue to Cancer and Heart Disease Study (CLUE II, US), Cancer Preventions Study II (CPS-II, US), European Prospective Investigation into Cancer and Nutrition Study (EPIC, which comprises cohorts from Denmark, France, Germany, Great Britain, Greece, Italy, The Netherlands, Spain, and Sweden), Health Professional Follow-Up Study (HPFS, US), Multiethnic Cohort (US), Melbourne (MCCS, Australia), Nurse's Health Study (NHS, US),

New York University Women's Health Study (US), Physician's Health Study I (PHS, US), Prostate Lung Colorectal Ovarian Cancer Cohort (PLCO, US), Selenium and Vitamin E Cancer Prevention Trial (US), Vitamins and Lifestyle Cohort (US), Women Health Initiative Cohort (US), Women's Health Study (WHS, US)] from the National Cancer Institute's cohort consortium, 9 case-control studies and 1 case series (Gastrointestinal Cancer Clinic of Dana-Farber Cancer Institute, US). PanC4 included 9 case-control studies. The case-control studies included in either PanScan II or PanC4 were the Central Europe study coordinated by IARC (hospital-based, EU), Johns Hopkins Hospital (clinic-based, US), Mayo Clinic (clinic-based, US), MD Anderson Cancer Center (hospital-based, US), Memorial Sloan Kettering Cancer Center (clinic-based, US), PANDoRA- pancreatic cancer case-control study (clinic-based, EU), PACIFIC Study of Group Health and Northern California Kaiser Permanente (HMO, US), QIMR Berghofer Medical Research Institute (population-based, Australia), Spanish Pancreatic Cancer Study (hospital-based, Spain), University of California San Francisco (population-based, US), University of Toronto (population-based, Canada), and Yale University (population-based hospitals, US) (17–21). Controls for PanScan I and II and PanC4 were matched to cases by age, sex, self-reported race, area of residence (case-control studies) and/or smoking (HPFS, PHS, NHS, WHS cohorts only) and incidence density sampled within each respective cohort studies. PanScan III used previously genotyped controls, mostly from cohort studies (ATBC, CPS-II, EPIC, HPFS, MCCS, MEC, NHS, PLCO, WHI). To facilitate stratified analyses by study design (cohort versus case-control) and evaluate potential survival bias, we excluded 654 cases and 434 controls from PanScan III studies because they did not have comparable controls or cases by study designs because PanScan III used previously genotyped controls (e.g., exclusion of cases from case-control or case series studies that used cohort controls). We only included participants of European ancestry to avoid confounding by population stratification. Our final analytic data set included 8,384 (2,320 cohort, 6,064 case-control) PDAC cases and 11,955 (6,121 cohort, 5,834 case-control) controls.

Each participating study obtained written informed consent from participants and approval from their local Institutional Review Board. The National Cancer Institute's Special Studies Institutional Review Board approved the consortia study.

GWAS summary statistics

Genotype imputation across the four study phases was based on the 1000 Genomes Project (Phase 3, v1) reference dataset (23) and IMPUTE2 (http://mathgen.stats.ox.ac.uk/impute/impute_v2.html) (24) as previously described (21). Due to the large overlap of variants on the arrays (Illumina HumanHap550 Infinium II, Human 610-Quad) used for PanScan I and II, these studies were combined and jointly analyzed, whereas PanScan III (OmniExpress, Omni1M, Omni2.5M and Omni5M) and PanC4 (Illumina HumanOmniExpressExome-8v1) were each analyzed separately. For quality control, SNPs with minor allele frequency (MAF) < 5% and low-quality imputation score (IMPUTE2 INFO score < 0.3) were excluded (21). For each GWAS phase, SNPTEST (http://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html) (25) was used to perform association analysis and generate summary statistics based on probabilistic genotype values from IMPUTE2. The analysis was adjusted for age (10-year categories, ($\leq$50, 51-60, 61-70, 71-80, and $\geq$81)), sex, top eigenvectors for each

study phase, study (PanScan), and geographic region (PanScan Ⅲ) as previously described (17–21). PanScan Ⅲ was adjusted for geographic region (US, central and northern Europe, and southern Europe) because of the use of the previously genotyped controls that were not necessarily from the same study or region as the cases (20).

SNP selection

We identified "index-" single-nucleotide polymorphisms (SNPs) associated with ulcerative colitis, Crohn's disease, inflammatory bowel disease, celiac disease, chronic pancreatitis and primary sclerosing cholangitis at genome-wide association level (P-value $< 5×10^{-8}$) using the most recent and largest studies curated by NHGRI-EBI Catalog of published GWAS (https://www.ebi.ac.uk/gwas/) as of October 9, 2017 (Supplementary Table S1). As some GWAS had inflammatory bowel disease as an outcome alone, we defined inflammatory bowel disease as a unique disease group rather than combining GWAS regions for ulcerative colitis and Crohn's disease. We reviewed the original GWAS publications and added additional SNPs that met the significance level criterion (26). For SNPs that were not genotyped or imputed in our data set (i.e., genotyped on different platforms), we selected an alternative index-SNP in high linkage disequilibrium (LD, r^2 0.74) using LDlink (https://ldlink.nci.nih.gov) (27). We then included genomic regions +/− 500 kb surrounding each index-SNP and applied LD filtering to highly correlated SNP pairs ($r^2 > 0.80$) in each disease group. In total, our analysis included the following number of index-SNP defined regions (SNPs in regions): 99 (728) for ulcerative colitis, 151 (997) for Crohn's disease, 211 (1,403) for inflammatory bowel disease, 21 (148) for celiac disease, 11 (35) for chronic pancreatitis, and 15 (109) for primary sclerosing cholangitis. Fifty-five index-SNP defined regions associated with inflammatory bowel disease did not overlap with ulcerative colitis or Crohn's disease.

Statistical analysis

We first conducted a meta-analysis combining SNP-level summary statistics from the four GWAS using an inverse-variance fixed-effects model. To eliminate the effect of population stratification, the square root of the genomic inflation factors for each study phase ($\lambda = 1.02$, 1.02, 1.01 and 1.06 for PanC4, PanScan I and II case-control, PanScan I and II cohort, and PanScan III cohort, respectively) was used to rescale the standard error of the estimated log odds ratio at each SNP before the meta-analysis. We then applied the summary data-based adaptive rank truncated product (sARTP) method (22) to the meta-analysis result. The genomic region surrounding an index-SNP was treated as a "gene", and the disease-level analysis was the gene-set/pathway analysis by combining the signals across multiple regions defined by the index-SNPs for a given inflammatory intestinal disease group (22). The sARTP analysis selected up to five of the most significant outcome (PDAC)-associated SNPs within each index-SNP defined region and adjusted for multiple comparison through a resampling procedure. The disease-level sARTP adjusted for multiple comparison for tests done around all considered index-SNP/regions within a disease group through a similar resampling procedure. One-hundred million resampling steps were used to estimate the P-value of each index-SNP region and disease-level associations. A panel of 503 European subjects (population codes: CEU, TSI, FIN, GBR, IBS) in the 1000 Genomes Project (phase

3, v1) was used in sARTP to estimate the LD between SNPs. We considered a disease-level *P*-value less than or equal to 0.05 statistically significant. All statistical tests are two-sided.

We also conducted a sensitivity analysis excluding the 20 PDAC-associated risk signals identified by previous GWAS at 1q32.1 (*NR5A2*), 1p36.33 (*NOC2L*), 2p14 (*ETAA1*), 3q28 (*TP63*), 5p15.33 (*CLPTM1L-TERT*), 7p14.1 (*SUGCT*), 7q23.2 (*LINC-PINT*), 8q21.11 (*HNF4G*), 8q24.21 (*MYC*), 9q34.2 (*ABO*), 13q12.2 (*PDX1*), 13q22.1 (non-genic), 16q23.1 (*BCAR1*), 17q12 (*HNF1B*), 17q24.3 (*LINC00673*), 18q21.32 (*GRP*), and 22q12.1 (*ZNRF3*) (17–21,28) and genomic regions within +/− 500kb (22).

LD score regression

To estimate the genetic correlation between the disease groups and PDAC, we performed LD score regression (29) using summary statistics (excluding major histocompatibility complex regions) from PDAC GWAS (21) and GWAS for ulcerative colitis, Crohn's disease, inflammatory bowel disease, chronic pancreatitis and primary sclerosing cholangitis with comparable HapMap3 genotype imputation (30–32). Celiac disease was excluded from the analysis because the originating study did not have imputed genotyping data.

Pairwise LD analysis, functional annotation and eQTL analysis

We performed a pairwise LD analysis to evaluate haplotype patterns between alleles of the index-SNPs and sARTP-selected SNPs using LDlink (27). We conducted an exploratory analysis of expression quantitative trait locus (eQTL) data to assess the *cis* effects of the most statistically significant sARTP-selected SNPs (*P*-value   0.002) and their corresponding index-SNPs on gene expression in pancreas tissue and determined whether the same gene(s) were expressed in gastrointestinal tract, and whole blood tissues using data from the NIH Genotype-Tissue Expression (GTEx) v8 (33). We also examined the regulatory potential of these SNPs (and SNPs in LD) using experimental data and information from Ensembl (34), HaploReg v4.1 (35), and RegulomeDB v1.1 (36).

Data Availability

The majority of the data that support the findings of this study are available in dbGAP at https://www.ncbi.nlm.nih.gov/gap/, reference number [phs000206.v5.p3 and phs000648.v1.p1]. Biomedical research scientists from recognized research institutions can request data as bona fide researchers from dbGAP or by contacting the corresponding author.

Results

Table 1 shows the characteristics of our study population by genotyping phase and study design. The age and sex distribution of cases compared to controls within each study phase (PanScan I and II, PanC4) was similar except for PanScan Ⅲ which used previously genotyped controls. Overall, the majority of cases were diagnosed after age 60 years (74.1%), 39.1% of the cases were diagnosed after age 70 years, and 54.3% of the cases were men. A higher proportion of the cases from the cohort studies were diagnosed at older ages (87.7% > 60 years and 53.0% > 70 years) compared to the case-control studies (68.9% > 60

years and 33.8% > 70 years). The proportion of female cases was greater among the cohort studies (51.8%), while the proportion of male cases was greater in the case-control studies (56.6%).

Disease group and PDAC

Genetic susceptibility to the ulcerative colitis, Crohn's disease, inflammatory bowel disease, and chronic pancreatitis groups (P-values = 0.0040, 0.0057, 0.011, and 3.4×10^{-6}, respectively) was significantly associated with PDAC while that to the celiac disease and primary sclerosing cholangitis groups (P-values = 0.22 and 0.078) was not (Table 2). After excluding the previous PDAC GWAS risk signal regions, the associations for ulcerative colitis, Crohn's disease, and inflammatory bowel disease remained (P-values = 0.0029, 0.0057, and 0.0098), but that for chronic pancreatitis did not (P-value = 0.073). Associations for ulcerative colitis, Crohn's disease, inflammatory bowel disease, chronic pancreatitis and primary sclerosing cholangitis (P-values = 0.022, 0.0069, 0.014, 3.2×10^{-6}, and 0.018) were present in the case-control studies but not in the cohort studies (Supplementary Table S2).

The PDAC associations for the index-SNP defined regions, and for SNPs selected by sARTP within each region are shown in Supplementary Table S3 and Supplementary Table S4, respectively. The index-SNPs were highly correlated with their sARTP-selected SNPs, with LD r^2 value   0.78 among all SNP pairs.

In total, 32 out of 99 index-SNP defined regions for ulcerative colitis, 28 out of 151 regions for Crohn's disease and 30 out of 211 regions for inflammatory bowel disease were selected by sARTP and contributed to the associations between disease groups and PDAC (Table 3). There was some overlap of the regions across these disease groups. For example, 6 index-SNP defined regions were in common for ulcerative colitis and Crohn's disease (rs2872507, rs12946510, rs2413583, rs7517847, rs9868809, rs3766606) (Figure 1). The most significant index-SNP defined regions associated with PDAC (P-value < 0.01) and corresponding gene (location) contributing to the associations included rs9858542 (*BSN*, 3p21.31; Crohn's disease, inflammatory bowel disease), rs6651252 (*LINC00824*, 8q24.21; Crohn's disease, inflammatory bowel disease), rs2872507 (intergenic variant, 17q21.1; ulcerative colitis, Crohn's disease, inflammatory bowel disease), rs10883365 (*LINC01475*, 10q24.2; Crohn's disease, inflammatory bowel disease), rs9988642 (*IL23R*, 1p31.3; Crohn's disease, inflammatory bowel disease), rs4256018 (*FERMT1*, 20p12.3; inflammatory bowel disease), rs7809799 *(KPNA7*, 7q22.1; ulcerative colitis, inflammatory bowel disease), rs9822268 (*APEH*, 3p21.31; ulcerative colitis), rs4409764 (intergenic variant, 10q24.2; ulcerative colitis), rs80174646 (*IL23R*, 1p31.3; ulcerative colitis), and rs568617 (*FIBP*, 11q13.1; Crohn's disease).

Five out of 21 index-SNP defined regions for celiac disease, 1 out of 11 regions for chronic pancreatitis, and 1 out of 15 regions for primary sclerosing cholangitis contributed to the associations. The index-SNP defined region for chronic pancreatitis that contributed to the chronic pancreatitis-PDAC association was rs8055167 (*CTRB1, CTRB2*, 16q23.1, P-value = 1.0×10^{-7}). The index-SNP defined region that contributed to the primary sclerosing cholangitis-PDAC association was rs3197999 (*MST1*, 3p21.31, P-value = 0.0028).

LD score regression

The genetic correlation r_g (standard error, se) of each disease group with PDAC was 0.08 (*P*-value = 0.42, se = 0.10) for ulcerative colitis, −0.16 (*P*-value = 0.055, se = 0.08) for Crohn's disease, −0.07 (*P*-value = 0.39, se = 0.08) for inflammatory bowel disease, 0.28 (*P*-value = 0.49, se = 0.41) for chronic pancreatitis, and −0.13 (*P*-value = 0.25, se = 0.12) for primary sclerosing cholangitis.

eQTL and functional annotation

The exploratory eQTL results for select index-SNPs and their corresponding sARTP-selected SNPs with the strongest evidence of association with PDAC are shown in Table 3 and Supplementary Table S5. Their functional annotations were shown in Supplementary Table S6 and Supplementary Table S7. In three regions defined by correlated index-SNPs (r^2 0.95) associated with ulcerative colitis, Crohn's disease, inflammatory bowel disease, or primary sclerosing cholangitis, variants rs9858542-A, rs9822268-A, rs3197999-A were associated with increased *UBA7* expression in normal tissues of pancreas, transverse colon, and small intestine (*P*-values 6.0×10^{-6}). These SNPs were associated with increased *UBA7* expression in esophageal mucosa, stomach, and whole blood (Supplementary Table S5). In the region defined by the chronic pancreatitis index-SNP rs8055167, variant rs8055167-C was associated with lower *CTRB2* expression and increased *CTRB1* expression in normal pancreatic tissue (*P*-values 2.0×10^{-6}). In the region defined by ulcerative colitis/Crohn's disease/inflammatory bowel disease index-SNP rs2872507, variant rs2872507-A was associated with decreased *PGAP3* expression in normal pancreatic, transverse colon and small intestine tissues (*P*-values 2.5×10^{-7}). Similar eQTL effects were present in the esophagus-gastroesophageal junction, stomach, and whole blood.

Discussion

Our analysis of GWAS data showed that the joint effects of common variants in genomic regions containing susceptibility loci for ulcerative colitis, Crohn's disease, inflammatory bowel disease, and chronic pancreatitis were associated with PDAC. After excluding the previously established PDAC-associated regions, the genomic regions for ulcerative colitis, Crohn's disease, and inflammatory bowel disease remained associated with PDAC, but the association for chronic pancreatitis was no longer significant. No significant associations were observed for genetic susceptibility to celiac disease or primary sclerosing cholangitis. Our results are consistent with the previous Swedish registry-based studies of patients previously diagnosed with ulcerative colitis and Crohn's disease that found positive associations with PDAC compared with the general population (5,6), and the known association between chronic pancreatitis and PDAC (4).

Although previous GWAS suggest overlap of genetic susceptibility between ulcerative colitis and Crohn's disease (37), a connection with PDAC remains to be elucidated. In this study, we observed that multiple common regions between ulcerative colitis and Crohn's disease are associated with PDAC, suggesting some shared underlying biology between the two inflammatory diseases that contributes to the risk of PDAC. Of note, index-SNP rs7517847 (ulcerative colitis, Crohn's disease) resides in *IL23R* (Supplementary Table S3),

which encodes a subunit of the receptor for interleukin-23 (IL-23). The IL-23 signaling pathway mediates intestinal inflammation (38) and promotes inflammation-induced tumorigenesis in colon in murine models (39). In addition, expression of IL-23 was significantly higher in pancreatic tumor compared with normal adjacent tissue (40).

With regard to the three inflammatory bowel disease groups, susceptibility variants residing at loci 3p21.31 and 17q12-q21 are of interest due to their associations with PDAC (Supplementary Table S4), and significant *cis*-eQTL effects in pancreas, transverse colon and small intestine (Table 3). Index-SNPs rs9858542 (Crohn's disease, inflammatory bowel disease), rs9822268 (ulcerative colitis) and rs3197999 (primary sclerosing cholangitis) reside at 3p21.31 (Supplementary Table S3), a region in which multiple susceptibility loci for chronic inflammatory intestinal diseases have been identified (26,31,37,41). The three index SNPs and their sARTP-selected SNPs are eQTLs for *UBA7*. Previous studies suggested a tumor suppressive effect of UBE1L (the protein encoded by *UBA7*) in both lung cancer and acute promyelocytic leukemia (42,43). Index-SNP rs2872507 is an intergenic variant located at 17q12-q21, a locus found to be associated with many immune-mediated diseases (44). rs2872507 and its sARTP-selected SNPs are associated with decreased *PGAP3* expression in pancreas, transverse colon and small intestine. *PGAP3* is frequently coamplified with the oncogene *ERBB2* in breast and gastric cancer (45,46), and co-silencing of *PGAP3* with *ERBB2 in vitro* results in an additive inhibition of cell viability and induced apoptosis (47). In an agnostic pathway analysis, we previously identified *PGAP3* as a top contributing gene associated with PDAC within the Nikolsky breast cancer chr17q11-q21 amplicon gene set with four SNPs associated with decreased *PGAP3* expression (48). In a separate transcriptome-wide association study, genetically predicted expression of *PGAP3* was found to be associated with PDAC risk (49). Our findings based on eQTL analysis are suggestive and further colocalization analysis may help identify a shared etiology between inflammatory bowel disease and PDAC.

Our sensitivity analyses suggest that the associations we observe between ulcerative colitis, Crohn's disease, inflammatory bowel disease groups and PDAC are not driven by previously identified PDAC GWAS loci. The chronic pancreatitis group, however, was no longer associated with PDAC. The association observed in the primary analysis was driven by the PDAC-associated SNP rs8051363, which is in close proximity to the PDAC risk signal rs7190458 (*BCAR1/CTRB1/CTRB2*) at 16q23.1 (20,21).

Our analysis is based on regions surrounding established susceptibility variants from GWAS of each inflammatory intestinal disease. As a result, we may not be able to observe an association for disease groups with only few established GWAS loci (e.g., primary sclerosing cholangitis). In contrast to Mendelian randomization and polygenic risk scores that sum trait-associated single SNPs from GWAS weighted by their effect sizes to provide an overall measure of an individual's genetic risk to develop disease (50), our approach uses genomic regions surrounding established gastrointestinal disease SNPs from GWAS and selects only SNPs associated with PDAC in those regions to examine trait-disease associations. These aforementioned approaches rely on previous GWAS and may overlook a significant portion of heritability, given that heritability is often distributed over thousands of genetic variants with small effects in complex traits (29). To complement our current

approach, we performed LD score regression which took the effect of all SNPs into account, regardless of their genome-wide significance level. The LD regression analyses did not show significant genome-wide shared heritability between inflammatory intestinal diseases and PDAC, which might be due to limited number of participants in the originating studies and lack of power to observe associations, particularly for pancreatitis and primary sclerosing cholangitis. Our results suggest that only selective regions surrounding established susceptibility variants for inflammatory intestinal diseases are associated with PDAC.

Strengths of the study include the large number of PDAC cases and controls, and our statistical approach using GWAS data. Our associations are based on genomic regions identified from GWAS of inflammatory intestinal diseases, which provides the opportunity to identify susceptibility to chronic intestinal inflammation, beyond that of questionnaires or registry data with variable accuracy. sARTP allowed us to discover disease group-PDAC associations that would not be detected by studies using traditional single-marker approaches. One limitation of the study is that although we highlighted individual PDAC-associated SNPs that contributed to the overall associations of inflammatory intestinal diseases with PDAC, none of them alone was statistically significant after correction for multiple comparisons. We observed more significant associations in the case-control studies compared with cohort studies. This is most likely due to the larger number of cases in the case-control compared to the cohort studies (n = 6,064 versus n = 2,320), and thus increased power to detect associations. Alternatively, the differences might be related to selection bias of either the cases (e.g., referral bias, IBD-related, survival bias) or controls (e.g., participation bias) from the case-control studies particularly as many of the studies were clinic or hospital based. Lastly, our study lacks clinical diagnosis of inflammatory intestinal diseases and information on important environmental factors (e.g., gluten exposure for celiac disease) that play a role in the etiology of these diseases.

In conclusion, our results support the hypothesis that variants within genomic regions surrounding susceptibility variants for ulcerative colitis, Crohn's disease, inflammatory bowel disease, and chronic pancreatitis are associated with PDAC. Further investigations are warranted to replicate our findings and examine these associations in populations of non-European ancestry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance:

The joint effects of common variants in genomic regions containing susceptibility loci for inflammatory bowel disease and chronic pancreatitis are associated with PDAC and may provide insights to understanding pancreatic cancer etiology.
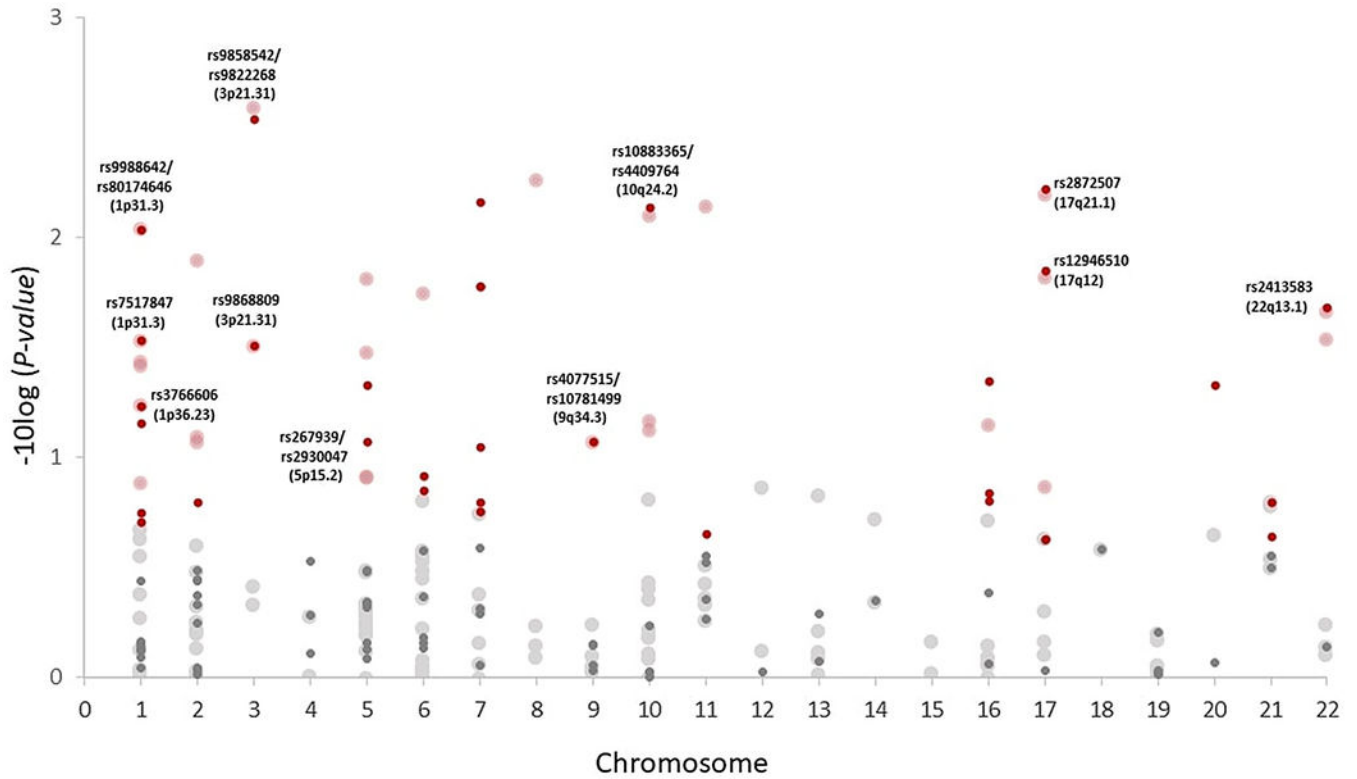
Figure 1.
Index-SNP defined regions contributing to the associations of Crohn's disease and ulcerative colitis with PDAC. Index-SNP defined regions associated with PDAC in ulcerative colitis (small circle) and Crohn's disease (large circle). Circles highlighted in red are regions contributing to each disease group-PDAC association. Circles labeled with SNP IDs and locations represent index-SNP defined regions that are in common between Crohn's disease and ulcerative colitis. The analysis (N=8,384 cases and 11,955 controls) is adjusted for age, sex, study, geographic region, and the top eigenvectors for the PanScan studies and age, sex, and the top eigenvectors for the PanC4 studies. All statistical tests are two-sided. PDAC = pancreatic ductal adenocarcinoma; sARTP = summary data-based adaptive rank truncated product.

Table 1.

Number of cases and controls, case diagnosis age, control enrollment age, and sex distribution by study phase and study design from PanScan and PanC4 studies[a]

Characteristic	Study Phase				Total		
	PanScan I Case / control 1,746 / 1,812	PanScan II Case / control 1,768 / 1,841	PanScan III Case / control 937 / 4,651	PanC4 Case / control 3,933 / 3,651	Cohort Case / control 2,320 / 6,121	Case-control Case / control 6,064 / 5,834	Combined Case / control 8,384 / 11,955
Case diagnosis age, > 60 years, n (%)	1,419 (81.3)	1,168 (66.0)	880 (93.9)	2,744 (69.7)	2,034 (87.7)	4,177 (68.9)	6,211 (74.1)
Age[b], years, n (%)							
50	63 (3.6) / 44 (2.4)	157 (8.9) / 181 (9.8)	6 (0.6) / 104 (2.2)	357 (9.1) / 389 (10.6)	44 (1.9) / 125 (2.0)	539 (8.9) / 593 (10.2)	583 (6.9) / 718 (6.00)
51-60	264 (15.1) / 226 (12.5)	443 (25.1) / 422 (22.9)	51 (5.5) / 687 (14.8)	832 (21.2) / 910 (24.9)	242 (10.4) / 849 (13.9)	1,348 (22.2) / 1,396 (23.9)	1,590 (19.0) / 2,245 (18.8)
61-70	673 (38.6) / 724 (40.0)	605 (34.2) / 599 (32.6)	256 (27.3) / 2,450 (52.7)	1,401 (35.6) / 1,225 (33.6)	805 (34.7) / 3,053 (49.9)	2,130 (35.1) / 1,945 (33.3)	2,935 (35.0) / 4,998 (41.8)
71	746 (42.7) / 818 (45.1)	563 (31.8) / 639 (34.7)	624 (66.6) / 1,410 (30.3)	1,343 (34.1) / 1,127 (30.9)	1,229 (53.0) / 2,094 (34.2)	2,047 (33.8) / 1,900 (32.6)	3,276 (39.1) / 3,994 (33.4)
Sex, n (%)							
Male	892 (51.1) / 925 (51.0)	945 (53.45) / 965 (52.4)	433 (46.2) / 3,422 (73.6)	2,280 (57.97) / 2,038 (55.8)	1,118 (48.2) / 4,154 (67.9)	3,432 (56.6) / 3,196 (54.8)	4,550 (54.3) / 7,350 (61.5)
Female	854 (48.9) / 887 (49.0)	823 (46.55) / 876 (47.6)	504 (53.8) / 1,229 (26.4)	1,653 (42.03) / 1,613 (44.2)	1,202 (51.8) / 1,967 (32.1)	2,632 (43.4) / 2,638 (45.2)	3,834 (45.7) / 4,605 (38.5)

[a]The analysis (N=8,384 cases and 11,955 controls) was restricted to participants of European ancestry from the PanScan and PanC4 consortia.

[b]Age at pancreatic cancer diagnosis or age when selected to be a control. PanScan III used previously genotyped controls.

Table 2.

Association of genetic susceptibility to inflammatory intestinal disease groups and risk of PDAC in participants of European ancestry from PanScan and PanC4 studies[a]

Disease group	Index-SNP defined region			Excluding previous PDAC GWAS loci[c]		
	n	SNP[b], n	P-value	n	SNP, n	P-value
Ulcerative colitis	99	728	0.0040	96	716	0.0029
Crohn's disease	151	997	0.0057	151	997	0.0057
Inflammatory bowel disease	211	1,403	0.011	208	1,393	0.0098
Celiac disease	21	148	0.22	21	148	0.22
Chronic pancreatitis	11	35	3.4×10^{-6}	10	32	0.073
Primary sclerosing cholangitis	15	109	0.078	15	109	0.078

Abbreviations: GWAS, genome-wide association study; PDAC, pancreatic ductal adenocarcinoma; SNP, single-nucleotide polymorphism.

[a]The analysis (N=8,384 cases and 11,955 controls) was adjusted for age, sex, study, geographic region, and the top eigenvectors for the PanScan studies and age, sex, and the top eigenvectors for the PanC4 studies.

[b]These SNPs are within +/− 500kb genomic regions around index-SNPs and correlated with index-SNPs at $r^2 > 0.80$.

[c]Results were obtained after excluding +/− 500kb genomic regions of 20 PDAC GWAS risk signals.

Table 3.

Expression quantitative trait loci (eQTL) for select index-SNPs[a] in normal tissues of pancreas, traverse colon and small intestine from GTEx[b]

Index-SNP	Location	Position[c]	Gene	r[d]	eQTL gene	GTEx pancreas (n=305)		GTEx colon-transverse (n=368)		GTEx small intestine-terminal ileum (n=174)	
						P-value	Effect size (β)[e]	P-value	Effect size (β)	P-value	Effect size (β)
rs9858542 [‖#]	3p21.31	49701983	BSN	Ref.	UBA7	2.4×10^{-9}	0.29	1.2×10^{-12}	0.26	5.5×10^{-6}	0.17
rs9822268 [≠]	3p21.31	49719729	APEH	1.00	UBA7	7.4×10^{-10}	0.30	6.9×10^{-13}	0.26	6.0×10^{-6}	0.16
rs3197999 [¶]	3p21.31	49721532	MST1	0.95	UBA7	2.7×10^{-9}	0.29	1.2×10^{-12}	0.26	3.9×10^{-6}	0.17
rs8055167 [§]	16q23.1	75254889	CTRB1, CTRB2	—	CTRB2	3.4×10^{-17}	−0.50	—	—	—	—
rs2872507 [‖##]	17q21.1	38040763	—	—	PGAP3	5.6×10^{-10}	−0.23	2.8×10^{-8}	−0.11	2.5×10^{-7}	−0.16

Abbreviations: Chr., chromosome; eQTL, expression quantitative trait loci; PDAC, pancreatic ductal adenocarcinoma; sARTP, summary data-based adaptive rank truncated product; SNP, single-nucleotide polymorphism; TSS, transcription start site.

[a] Only index-SNPs whose corresponding sARTP-selected SNPs show the strongest association with PDAC (P-value 0.002) are presented in the table.

[b] cis-acting eQTLs are examined by using +/− 1 Mb cis-window around a gene's TSS.

[c] SNP position according to NCBI Human Genome Build 37.

[d] Linkage disequilibrium r[2] values are obtained from NCI LDlink EUR population data.

[e] Effect size (β) denotes the directional effect for alternative allele relative to the reference allele. The magnitude has no direct biological interpretation.

[‖] Crohn's disease

[≠] Ulcerative colitis

[#] Inflammatory bowel disease

[§] Chronic pancreatitis

[¶] Primary sclerosing cholangitis