

Association of Common Susceptibility Variants of Pancreatic Cancer in Higher-Risk Patients: A PACGENE Study

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Abstract

Individuals from pancreatic cancer families are at increased risk, not only of pancreatic cancer, but also of melanoma, breast, ovarian, and colon cancers. While some of the increased risk may be due to mutations in high-penetrance genes (i.e., *BRCA2*, *PALB2*, *ATM*, *p16/CDKN2A* or DNA mismatch repair genes), common genetic variants may also be involved. In a high-risk population of cases with either a family history of pancreatic cancer or early-onset pancreatic cancer (diagnosis before the age of 50 years), we examined the role of genetic variants previously associated with risk of pancreatic, breast, ovarian, or prostate cancer. We genotyped 985 cases (79 early-onset cases, 906 cases with a family history of pancreatic cancer) and 877 controls for 215,389 SNPs using the iSelect Collaborative Oncological Gene-Environment Study (iCOGS) array with cus-

tom content. Logistic regression was performed using a log-linear additive model. We replicated several previously reported pancreatic cancer susceptibility loci, including recently identified variants on 2p13.3 and 7p13 (2p13.3, rs1486134: OR = 1.36; 95% CI, 1.13–1.63; $P = 9.29 \times 10^{-4}$; 7p13, rs17688601: OR = 0.76; 95% CI, 0.63–0.93; $P = 6.59 \times 10^{-3}$). For the replicated loci, the magnitude of association observed in these high-risk patients was similar to that observed in studies of unselected patients. In addition to the established pancreatic cancer loci, we also found suggestive evidence of association ($P < 5 \times 10^{-5}$) to pancreatic cancer for SNPs at *HDAC9* (7p21.1) and *COL6A2* (21q22.3). Even in high-risk populations, common variants influence pancreatic cancer susceptibility. *Cancer Epidemiol Biomarkers Prev*; 25(7); 1185–91. ©2016 AACR.

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Introduction

Pancreatic cancer has a 5-year survival rate of 7%. It is currently the fourth leading cause of cancer-related death in the United States (1) and projected to be second by 2030 (2). Approximately 5% to 10% of individuals with pancreatic cancer have a family history of the disease (3). Familial pancreatic cancer (FPC) is defined as a kindred with at least two first-degree relatives (FDR) diagnosed with pancreatic cancer. Population-based studies have estimated that having a single FDR with pancreatic cancer increases one's risk 1.7- to 13-fold (4, 5). Prospective studies of FPC have shown a 6.5- to 18-fold risk of pancreatic cancer for individuals with two or more affected FDRs (6, 7).

Age is a strong predictor of pancreatic cancer risk with the median age at diagnosis of pancreatic cancer in the United States being 72 years (8). However, 5% to 10% of all pancreatic cancer cases present with early-onset pancreatic cancer (EOPC) defined as the occurrence of a cancer before the age of 50 years (8). While it has been suggested that this group of patients may have an underlying genetic predisposition to pancreatic cancer (9), not all studies report an increased risk of pancreatic cancer among the relatives of EOPC patients (7, 10).

Individuals with inherited mutations in genes including *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *STK11*, *CDKN2A*, *PRSS1*, and DNA mismatch repair genes (11–15) are at increased risk of pancreatic cancer. We have shown that FDRs of FPC probands have an

increased risk of dying from breast [weighted standardized mortality ratio (wSMR) = 1.36; 95% CI, 1.02–1.79] and ovarian (wSMR = 1.66; 95% CI, 1.04–2.53) cancers (16). Relatives of EOPC probands have an increased risk of mortality due to cancers of the breast (wSMR = 1.98; 95% CI, 1.01–3.52), colon (wSMR = 2.31; 95% CI, 1.30–3.81), or prostate (wSMR = 2.31; 95% CI, 1.14–4.20; ref. 16). These findings suggest the possibility of an overlapping genetic etiology among breast, ovarian, prostate, colon, and pancreatic cancers, only a fraction of which are likely explained by mutations in established hereditary cancer genes.

Genome-wide association studies (GWAS) have been successful in identifying common genetic variants (SNPs) associated with many cancers. In a series of three GWAS studies, the Pancreatic Cancer Case–Control Consortium (PanC4, PanScan II) and the Pancreatic Cancer Cohort Consortium (PanScan I-III) identified SNPs associated with pancreatic cancer at the following loci in the non-Hispanic white population: rs505922 on 9q34 (*ABO*; ref. 17), rs9543325 on 13q21 (18), rs3790844 on 1q31 (18), at least two independent loci on 5p15.33 [rs401681 (*CLPTM1L*; ref. 18) and rs2736098 (*TERT*; ref. 19)], rs6971499 on 7q32.3 (19), rs7190458 on 16q23.1 (*BCAR1/CTRB1/CTRB2*; ref. 19), rs9581943 on 13q12.12 (*PDX1*; ref. 19), and rs16986825 on 22q12.1 (*ZNRF3*; ref. 19). PanC4 recently identified additional significantly associated loci [rs1486134 on 2p13.3 (near *ETAA1*), rs9854771 on 3q29 (*TP63*), rs17688601 on 7p13 (*SUGCT*), and rs11655237 on 17q25.1 (*LINC00673*); ref. 20].

GWAS have identified many loci that harbor common susceptibility alleles for common cancers such as breast, colon, ovarian, and prostate cancer (21). The iCOGS array (22) was designed to capture genetic variation associated with risk for breast, ovarian, and prostate cancer as well as all regions found to have highly suggestive evidence of association with other phenotypes (as indicated in the NHGRI genome browser as of May 2010).

Because individuals with EOPC or with a strong family history of pancreatic cancer may differ in underlying genetic susceptibility to pancreatic cancer, we sought to examine the role of common pancreatic cancer-associated variants in our high-risk population using samples from the Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium (23). We further sought to identify novel pancreatic cancer candidate loci by interrogating genomic regions with known associations to other cancers.

Materials and Methods

Subjects

A total of 1,862 individuals (985 pancreatic cancer cases and 877 controls) from six PACGENE study sites (23) were included (Supplementary Table S1). Cases were eligible if they had either a family history of pancreatic cancer or were diagnosed with pancreatic cancer at the of age 50 years or younger. PACGENE sites include Dana-Farber Cancer Institute (Boston, MA), Johns Hopkins Hospital (Baltimore, MD; www.nfptr.org), Karmanos Cancer Institute (Detroit, MI), Mayo Clinic (Rochester, MN), MD Anderson Cancer Center (Houston, TX), and University of Toronto (Ontario, Canada). Controls were kindred-based unrelated individuals (i.e., spouse or other unrelated individual in the kindred) from each of the participating sites. All participants completed risk factor and family history questionnaires and provided a blood or saliva sample from which DNA was extracted for genotyping. Informed consent was obtained from each study participant and

each study site received its respective Institutional Review Board approval.

Genotyping

Samples were genotyped at the Johns Hopkins Genetic Resource Genotyping Core using the iCOGS Illumina genotyping array, consisting of 211,155 SNPs plus custom content of 4,234 SNPs. The iCOGS array (22), designed as part of the Collaborative Oncological Gene-Environment Study, is a custom Illumina iSelect genotyping array. Our custom SNP content included 1,283 SNPs selected for prior evidence of association with pancreatic cancer [based on $P < 0.001$ in PanScan I (17) or PanScan II (18)]. We also included SNPs found to be highly correlated with these target SNPs, based on r^2 values greater than 0.4 in Hapmap2, Hapmap3, or 1000 Genomes Pilot 1 data, for a total of 4,234 custom SNPs. Genotyping quality was excellent with a blind duplicate reproducibility rate of 99.99% (based on 23 duplicate sample pairs) and a concordance rate of 99.65% from HapMap control samples that were genotyped on this array along with our samples. No individuals had a missing call rate greater than 2%.

Quality control metrics were applied to all samples and SNPs prior to statistical analyses (See Supplementary Figs. S1A and S1B). Samples were removed if their reported sex did not match genetic sex. If identity-by-descent (IBD) sharing analysis determined that a pair of samples shared more alleles than expected by chance (>0.185), the sample with the largest missing call rate was removed. SNPs with minor allele frequencies less than 0.02, missing call rate greater than 5%, evidence of departure from Hardy–Weinberg equilibrium ($P < 5.7 \times 10^{-7}$), or a missing rate that differed significantly between cases and controls ($P < 1 \times 10^{-5}$) were excluded. After quality control, 199,677 SNPs (195,720 iCOGS SNPs and 3,957 custom SNPs) and 1,825 samples (963 cases and 862 controls) remained for analyses.

Statistical analysis

Logistic regression using an additive genetic model was performed with PLINK v.1.07 (24) for each SNP. Sex and the first three eigenvectors from principal components analysis were included as covariates to control for population structure (Supplementary Fig. S2). A Bonferroni threshold of $P < 2.5 \times 10^{-7}$ (0.05/199,677) was used to assess statistical significance.

SNPs with significant evidence of association ($P < 5 \times 10^{-8}$) in prior GWAS were tested for association in the PACGENE samples. To identify any overlapping or related individuals between PACGENE and prior GWAS [PanScan I (17), PanScan II (18), and PanC4 (20)], IBD sharing was carried out to identify pairs of individuals who share more of their genome than would be expected by chance. For any pair that shared greater than 0.185, the PACGENE individual was excluded from analysis. PanScan I and PanScan II data were downloaded from dbGAP (dbGaP study accession: phs000206.v4.p3). Z-tests were used to determine if the effect size in our study was statistically different from the effect size estimates identified in prior GWAS for the same SNP.

Results

A total of 1,862 samples (985 cases, 877 controls) were available for genotyping (Table 1). Of these 985 cases, 79 were EOPC cases (age < 50 at diagnosis) and 906 cases had a family history of pancreatic cancer, averaging 2.44 affected family members.

Table 1. Description of cases with EOPC, family history, and unrelated controls from the PACGENE consortium

	Subset ^a	N	Age ^b (SD)	Familial cases ^c	Average number of affected family members (range)	% Male	% Non-Hispanic white
Cases	Early onset	79	40.56 (3.93)	0	1 (1-1)	54	95
	Family history	906	64.31 (10.82)	685	2.44 (2-11)	50	93
	All	985	62.62 (12.13)	685	2.33 (1-11)	50	93
Controls		877	62.24 (10.96)	0	0.0046 (0-1)	44	96

^aEarly onset, diagnosed with pancreatic cancer before the age of 50 years. Family history, has a family history of pancreatic cancer.

^bAverage age of onset for cases; average age at study enrollment for controls.

^cCases belonging to a FPC kindred, defined as a confirmed diagnosis of pancreatic cancer in a pair of FDRs.

Among these 906 cases, 684 were from kindreds that met the definition of FPC. Mean age at onset was 40.6 in the EOPC cases and 64.3 in the cases with a family history. Individuals were predominantly non-Hispanic white based on self-reported ancestry. Approximately 50% of cases were male and 44% of controls were male.

A total of 195,720 SNPs genotyped on the iCOGS array passed quality control and were analyzed using a logistic regression model with an additive genetic effect (Supplementary Figs. S3 and S4). No loci were significant after Bonferroni correction ($P < 2.5 \times 10^{-7}$). Two novel regions showed suggestive evidence of association to pancreatic cancer ($P < 5 \times 10^{-5}$) and merit further study: 7p21.1 (*HDAC9*, rs12531908; OR = 1.43; 95% CI, 1.23–1.66; $P = 3.88 \times 10^{-6}$) and 21q22.3 (*COL6A2*, rs4458293; OR = 0.75; 95% CI, 0.65–0.86; $P = 3.33 \times 10^{-5}$; see Fig. 1).

By design, the 4 SNPs that reached genome-wide significance from PanScan I (17) and PanScan II (18) were included on the custom panel. Results from PanScan III (19) and PanC4 (20) were not available at the time of SNP selection, therefore not all genome-wide significant SNPs in PanScan III and PanC4 were genotyped on the custom panel. Of the 9 SNPs on the custom panel that were previously associated with pancreatic cancer risk at the genome-wide level, 6 were significantly associated with pancreatic cancer in this high-risk population ($P < 0.05$; see Table 2; Supplementary Fig. S5): 9q34 (ref. 17; *ABO*, rs505922, OR = 1.29; 95% CI, 1.12–1.48, $P = 4.37 \times 10^{-4}$), 13q21.32 (ref. 18; *KLF5*, rs9543325, OR = 1.25, 95% CI, 1.08–1.45, $P = 3.58 \times 10^{-3}$), 5p13.33 (ref. 18; *CLPTM1L*, rs401681, OR = 1.31, 95% CI, 1.14–1.52, $P = 2.26 \times 10^{-4}$), 7q32.3 (ref. 19; *LINC-PINT*, rs6971499, OR = 0.72, 95% CI, 0.58–0.88, $P = 1.73 \times 10^{-3}$), 2p13.3 (ref. 20; *ETAA1*, rs1486134, OR = 1.36, 95% CI, 1.13–1.63; $P = 9.88 \times 10^{-4}$), and 7p13 (ref. 20; *SUGCT*, rs17688601, OR = 0.77; 95% CI, 0.64–0.94; $P = 1.05 \times 10^{-2}$). For the 3 remaining SNPs, the point estimates and direction of effect were consistent with the previously reported association: 1q32.1 (ref. 18; *NR5A2*, rs3790844, OR = 0.87; 95% CI, 0.73–1.03; $P = 9.48 \times 10^{-2}$), 13q12.12 (ref. 19; *PDX1-AS1*, rs9581943, OR = 1.11; 95% CI, 0.96–1.29; $P = 1.50 \times 10^{-1}$), and 3q29 (*TP63*, rs9854771, OR = 0.92; 95% CI, 0.77–1.09; $P = 3.14 \times 10^{-1}$). For all 9 SNPs, the Z-tests were not significant ($P > 0.05$), confirming that the observed effect sizes in our cohort do not differ significantly from those observed in prior GWAS. The control allele frequencies in our study population were consistent with those reported in the prior studies ($P > 0.1$). We also observed strong evidence supporting association to SNPs at 16q23.1 (*BCAR1/CTRB1/CTRB2*; ref. 19; rs7202877, OR = 1.72; 95% CI, 1.40–2.11; $P = 2.3 \times 10^{-7}$) which was identified as a pancreatic cancer susceptibility locus by PanScan III. Two sensitivity analyses were conducted: (i) the analysis was repeated using only non-Hispanic

white samples; and (ii) PACGENE study site was included as an additional covariate in the analysis. For both sensitivity analyses, results were essentially unchanged (results not shown).

Discussion

Our findings support a role for common genetic variants that increase pancreatic cancer risk among a cohort of patients with a family history or early onset of the disease. Understanding the full spectrum of genetic changes that predispose to pancreatic cancer may improve our understanding of the biology of the disease and lead to strategies for its early detection and treatment. Our results confirm a role for variation at 9q34 (*ABO*), 13q21.32 (*KLF5*), 5p13.33 (*CLPTM1L*), 7q32.3 (*LINC-PINT*), 16q23.1 (*BCAR1/CTRB1/CTRB2*), 2p13.3 (*ETAA1*), and 7p13 (*SUGCT*) in the development of pancreatic cancer, specifically among high-risk patients. Our study represents the first independent report to replicate association at 7p13 and 2p13.3 (20), providing further evidence supporting a role for variation at these two loci in the development of pancreatic cancer.

Our study suggests that variation at 7p21.1, driven by SNP rs12531908 intronic to *HDAC9* (histone deacetylase 9; Fig. 1A), may be associated with pancreatic cancer. HDACs play a role in regulation of acetylation of histone proteins and several HDAC inhibitors are currently being studied in preclinical or clinical studies for pancreatic cancer (25).

Our study was underpowered to detect associations of modest effect sizes. A power analysis for our discovery stage where 963 cases and 862 controls were analyzed across 200,158 SNPs showed our study to have >80% power to detect an effect size of 1.5 at a locus with a MAF of 0.4. When replicating the previously identified SNPs, our smallest sample size of 565 cases and 606 controls had >80% power to detect an effect of 1.3 for a SNP with a MAF > 0.25. In our study, we were therefore insufficiently powered to detect most of the SNPs with reported modest effect sizes (~1.15). In addition, the sparse genome coverage of the iCOGS array prevented us from addressing important questions related to polygenic risk scores and heritability; these questions are better left for a study with genome-wide coverage.

We analyzed a high-risk population of pancreatic cancer patients including subjects with either early-onset diagnosis (age < 50 years) or a family history of the disease. SNPs associated with pancreatic cancer in prior GWAS are associated in this high-risk population, and the effect sizes do not differ significantly. This does not rule out the likely possibility of separate, unique, genetic risk factors and/or gene-by-environment interactions in this specific population. Our work supports a role for common variants in pancreatic cancer susceptibility, even among defined high-risk subgroups.

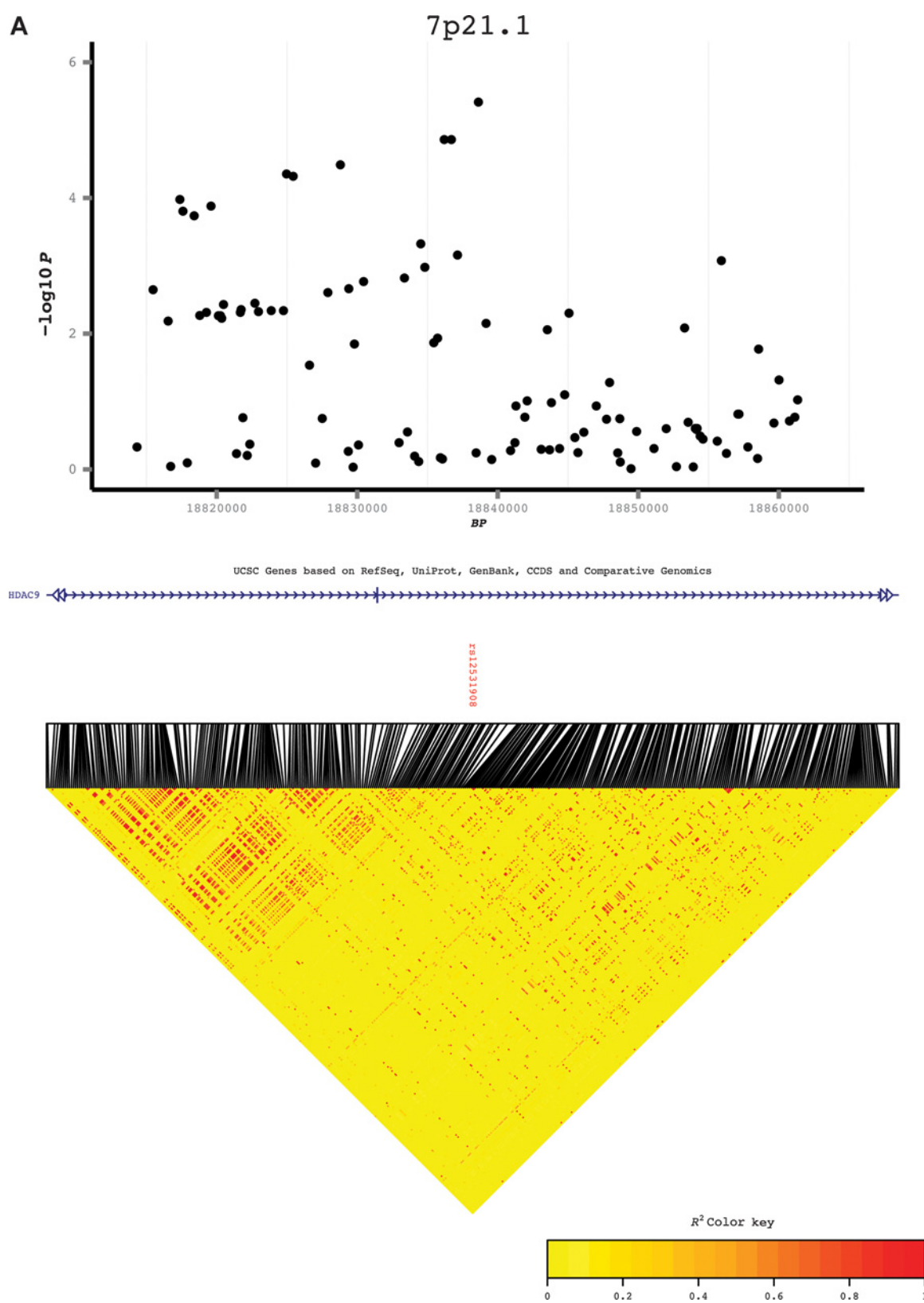


Figure 1. Regional association and linkage disequilibrium (LD) plots for two regions suggestive for association with pancreatic cancer: 7p21.1 (A); 21q22.3 (B). LD plots are based on 1,000 Genomes European samples. (Continued on the following page.)

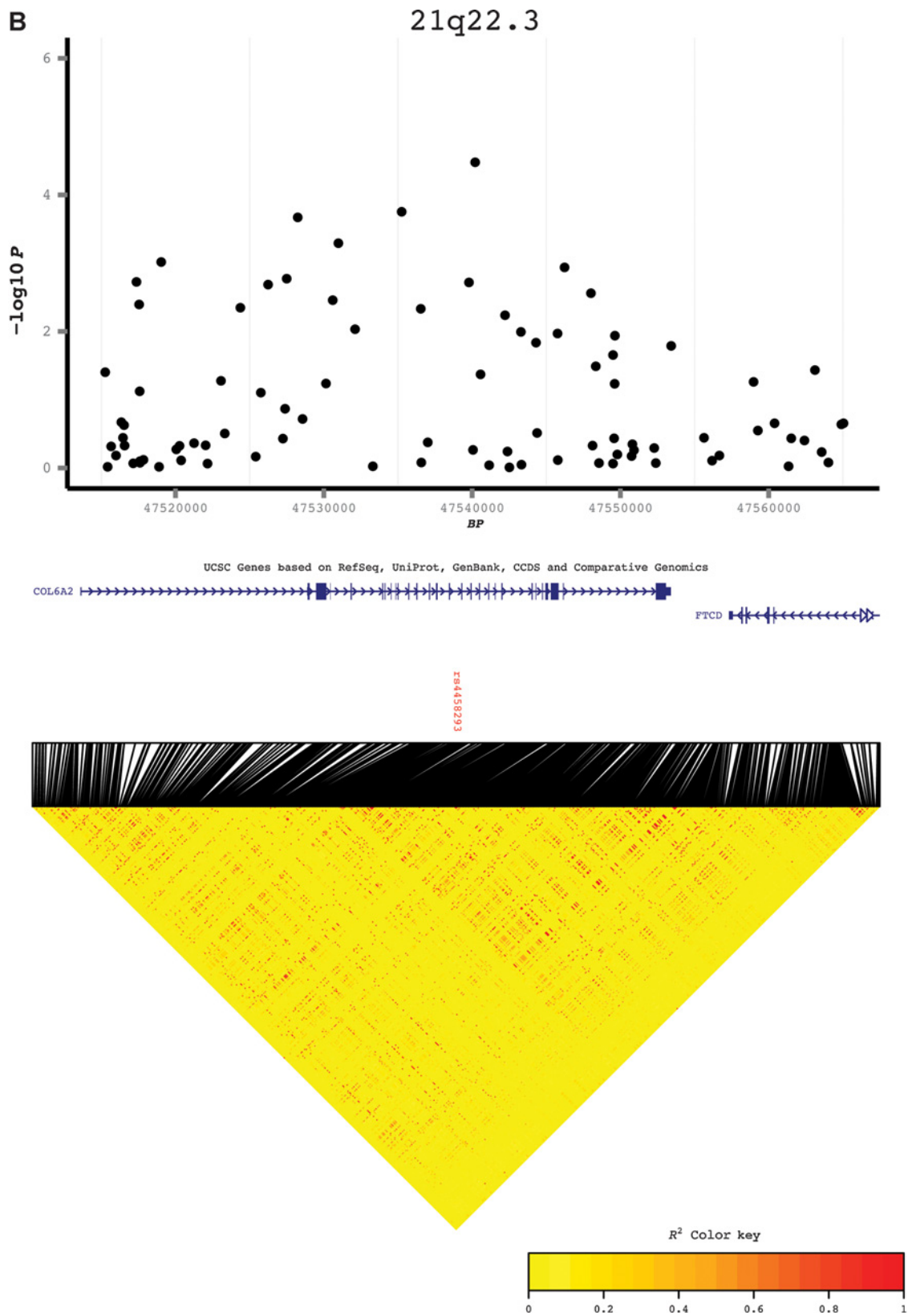


Figure 1.
(Continued.)

Table 2. Association results for nine previously reported pancreatic cancer susceptibility loci and current PACGENE data

Chromosome ^a SNP ^b gene ^c position ^d	Study ^e	Published ^f			PACGENE ^g			MAF (cases; controls)	MAF (cases; controls)
		OR (95% CI)	P	MAF (cases; controls)	OR (95% CI)	P	N ^h		
9q34.3 rs505922(C/T) ABO 136,149,229	PanScan I (17)	1.20 (1.12-1.28)	5.37 × 10 ⁻⁸	0.39;0.35	1.29 (1.12-1.48)	4.37 × 10 ⁻⁴	903 cases, 847 controls	0.40; 0.342	
13q21.32 rs9543325(C/T) KLF5 73,916,628	PanScan II (18)	1.26 (1.18-1.35)	3.27 × 10 ⁻¹¹	0.42;0.37	1.25 (1.08-1.45)	3.58 × 10 ⁻³	863 cases, 707 controls	0.44;0.38	
1q22.1 rs790844(C/T) NR5A2 200,007,432	PanScan II (18)	0.77 (0.71-0.84)	2.45 × 10 ⁻¹⁰	0.20;0.24	0.87 (0.73-1.03)	9.48 × 10 ⁻²	863 cases, 707 controls	0.22;0.25	
5p15.33 rs401681(T/C) CLPTMIL 1,322,087	PanScan II (18)	1.19 (1.11-1.27)	3.66 × 10 ⁻⁷	0.49;0.45	1.31 (1.14-1.52)	2.26 × 10 ⁻⁴	863 cases, 707 controls	0.50;0.43	
7q32.3 rs6971499(C/T) LINC-PINT 130,680,521	PanScan III (19)	0.79 (0.74-0.84)	2.98 × 10 ⁻¹²	0.12;0.15	0.72 (0.58-0.88)	1.73 × 10 ⁻³	803 cases, 693 controls	0.12;0.16	
13q12.12 rs9581943(A/G) PDX1-AS1 28,493,997	PanScan III (19)	1.15 (1.10-1.20)	2.35 × 10 ⁻⁹	0.43;0.41	1.11 (0.96-1.29)	1.50 × 10 ⁻¹	803 cases, 693 controls	0.42;0.40	
2p13.3 rs1486134(G/T) E7AA1 67,639,769	PanC4 (20)	1.14 (1.09-1.19)	3.36 × 10 ⁻⁹	0.30;0.28	1.36 (1.13-1.63)	9.88 × 10 ⁻²	564 cases, 606 controls	0.31; 0.26	
7p13 rs17688601(A/C) SUGCT 40,866,663	PanC4 (20)	0.88 (0.84-0.92)	1.41 × 10 ⁻⁸	0.24;0.27	0.77 (0.64-0.94)	1.05 × 10 ⁻²	564 cases, 606 controls	0.22;0.28	
3q29 rs9854771(A/G) TP63 189,508,471	PanC4 (20)	0.89 (0.85-0.92)	2.35 × 10 ⁻⁸	0.33;0.36	0.92 (0.77-1.09)	3.14 × 10 ⁻¹	564 cases, 606 controls	0.33;0.35	

Abbreviation: MAF, minor allele frequency.

^aCytogenetic region according to NCBI genome build 37 and NCBI's Map Viewer.

^bEffect allele/reference allele.

^cThe closest RefSeq gene.

^dSNP position according to NCBI genome build 37 (Hg19).

^eThe study where the association was originally identified and published.

^fThe OR and P value reported in the publication referred to in the "Study" column.

^gThe OR and P value observed in the PACGENE study.

^hThe number of individuals included for each association test. As individuals that were present in PACGENE and the prior studies were removed, the number of individuals analyzed varies.

Disclosure of Potential Conflicts of Interest

R.H. Hruban has provided expert testimony for Myriad Genetics Inc. No potential conflicts of interest were disclosed by the other authors.

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