nature genetics

Genome-wide association study identifies variants in the *ABO* locus associated with susceptibility to pancreatic cancer

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We conducted a two-stage genome-wide association study of pancreatic cancer, a cancer with one of the lowest survival rates worldwide. We genotyped 558,542 SNPs in 1,896 individuals with pancreatic cancer and 1,939 controls drawn from 12 prospective cohorts plus one hospital-based case-control study. We conducted a combined analysis of these groups plus an additional 2,457 affected individuals and 2,654 controls from eight case-control studies, adjusting for study, sex, ancestry and five principal components. We identified an association between a locus on 9q34 and pancreatic cancer marked by the SNP rs505922 (combined $P = 5.37 \times 10^{-8}$; multiplicative per-allele odds ratio 1.20; 95% confidence interval 1.12–1.28). This SNP maps to the first intron of the *ABO* blood group gene. Our results are consistent with earlier epidemiologic evidence suggesting that people with blood group O may have a lower risk of pancreatic cancer than those with groups A or B.

Pancreatic cancer has one of the highest mortality rates of any cancer, with an estimated 5-year relative survival rate of <5% (refs. 1,2). Currently, there is not an effective screening test for this malignancy, and by the time of initial diagnosis, metastatic disease is commonly present. Established risk factors include a family history of pancreatic cancer, a medical history of type 2 diabetes and cigarette smoking[3]. Studies have also suggested an increased risk of pancreatic cancer within families with hereditary pancreatitis[4,5]. In addition, it has been estimated that a small proportion of pancreatic cancers are due to highly penetrant germline mutations[6]. Prior studies have suggested a genetic contribution to pancreatic cancer, but there has been limited success in replicating common variants reported to be associated with this disease. Here we report a genome-wide association study (GWAS) to identify common variants associated with pancreatic cancer.

We conducted a GWAS in 1,896 individuals with pancreatic cancer and 1,939 controls drawn from 12 prospective cohorts (the American Cancer Society Cancer Prevention Study II (ref. 7), the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study[8]; the European Prospective Investigation into Cancer and Nutrition[9]; CLUE II (ref. 10); the Health Professionals Follow-up Study[11]; the New York University Women's Health Study[12]; the Nurses' Health Study[11]; the Physicians' Health Study I (ref. 11); the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial[13]; the Shanghai Men's and Women's Health Study[14,15]; the Women's Health Initiative[16] and

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Received 25 March; accepted 8 July; published online 2 August 2009; doi:10.1038/ng.429

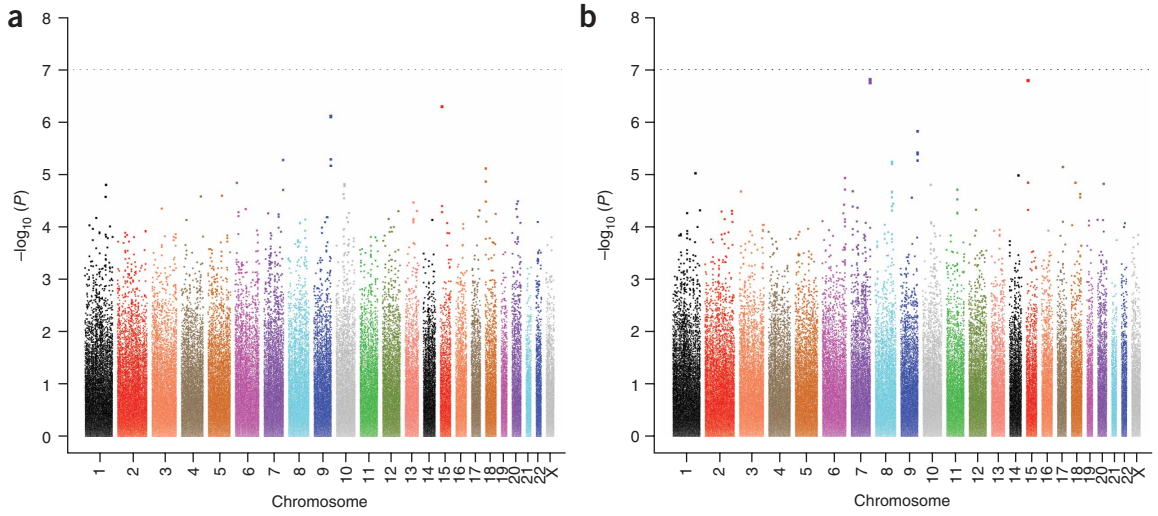

Figure 1 Manhattan plot of the *P* values in the pancreatic cancer GWAS. (**a**) Association with pancreatic cancer for the entire GWAS (12 cohort studies and the Mayo case-control study; Online Methods). (**b**) Results of the GWAS including only the 12 cohorts studies. Association was assessed using unconditional logistic regression adjusted for study, arm, age, sex, ancestry and the top five principal components of the population stratification analysis. The *x* axis represents chromosomal locations and the *y* axis shows *P* values on a logarithmic scale.

the Women's Health Study[17]; **Supplementary Table 1**) plus one hospital-based case-control study (the Mayo Clinic Molecular Epidemiology of Pancreatic Cancer Study[18]). Eight case-control studies participated in the independent rapid follow-up, known as a fast-track replication phase, of 2,457 cases and 2,654 controls (the University of Toronto[19], University of California San Francisco[20], the Johns Hopkins University, M.D. Anderson Cancer Center[21], PACIFIC Study of Group Health and Northern California Kaiser Permanente, Memorial Sloan-Kettering Cancer Center[22], Yale University[23], and the Mayo Clinic Molecular Epidemiology of Pancreatic Cancer Study[18]; **Supplementary Table 2**).

After quality control of genotypes using the HumanHap500 chip, 558,542 SNPs were available for analysis. We fit a logistic regression model for genotype trend effects (1 degree of freedom (d.f.)), adjusting for study, age, sex, ancestry and the top five principal components of population stratification (Online Methods). The quantile-quantile plot did not demonstrate a systematic deviation from the expected distribution, minimizing the likelihood of systematic genotype error or bias due to underlying population substructure (**Supplementary Fig. 1**). The results of the GWAS are shown in **Figure 1a**. Because of the potential for survivor bias in case-control studies owing to rapid mortality, we also analyzed the GWAS for the cohort studies alone (that is, excluding the Mayo participants) (**Fig. 1b**).

We conducted a fast track replication of SNPs from three regions (9q34, 7q36 and a gene desert on 15q14) in eight case-control studies (four hospital-based and four population-based). At least two SNPs per region ranked among the lowest 25 *P* values in the initial GWAS: (i) rs505922, rs495828, rs657152 and rs630014 (ranked 2, 3, 8 and 17) on 9q34, which includes the *ABO* gene, (ii) rs167020, rs172310 and rs288746 (ranked 6, 10 and 89) on 7q36, which includes *SHH* (sonic hedgehog homolog), and (iii) rs8028529, rs4130461 and rs4459505 (ranked 1, 18 and 26) in the gene desert on 15q14 (**Table 1**).

In a combined analysis of individuals of European background[24], the strongest association with pancreatic cancer below the threshold for genome-wide significance[25] was for a locus marked by rs505922 on chromosome 9q34, located within the first intron of *ABO*, a well-described blood group gene ($P = 5.37 \times 10^{-8}$, trend model; heterozygous odds ratio (OR_{Het}) = 1.20, 95% confidence interval (c.i.) 1.12–1.28; homozygous odds ratio (OR_{Hom}) = 1.44, 95% c.i. 1.26–1.63). We observed a comparable result when we included all ethnic groups in stage 1 ($P = 2.61 \times 10^{-8}$; **Supplementary Table 3**). In the case-control replication set, we genotyped a second SNP, rs687621 ($r^2 = 1$ with rs505922 in HapMap CEU and $r^2 = 0.91$ in stage 2 controls), located 12 kb centromeric in intron 2; this confirmed the signal at the locus ($P = 1.57 \times 10^{-4}$ in the stage 2 case-control studies only). In the combined analysis, we observed a comparably strong signal for rs630014 ($P = 1.58 \times 10^{-7}$; $OR_{Het} = 0.85$, $OR_{Hom} = 0.71$), which resides within 500 bp of rs505922 and is in linkage disequilibrium (LD) ($r^2 = 0.52$ in HapMap CEU and 0.40 in PanScan GWAS European controls). After adjusting for rs505922, none of the remaining SNPs in *ABO* was significant at $P < 0.01$. The SNPs reside in a haplotype block that encompasses the proximal promoter and introns 1 and 2 (**Fig. 2**).

Blood groups were first described by Karl Landsteiner in 1900, but the structure of the ABO antigens and their biosynthesis remained elusive until after 1950. The *ABO* gene encodes a glycosyltransferase that catalyzes the transfer of carbohydrates to the H antigen, forming the antigenic structure of the ABO blood groups. The proteins encoded by the A and B alleles of *ABO* differ minimally in amino acid sequence but catalyze the transfer of different carbohydrates (N-acetylgalactosamine or galactose) onto the H antigen to form the A or B antigens. Individuals with the O blood group do not produce either the A or B antigens because of a single-base deletion.

Our findings are notable because multiple studies, mainly from the 1950s and 1960s, reported an association between ABO blood type and gastrointestinal cancers, most strongly for gastric cancer but also for pancreatic cancer[26,27]. The protective allele T for rs505922 is in complete LD ($r^2 = 1.0$) with the O allele of the *ABO* locus, consistent with earlier reports showing increased risk of gastric and pancreatic cancer for individuals of the A and B blood groups. It is plausible that the single-base deletion that generates the O blood group underlies the association signal, but further mapping and laboratory work will be required to determine which variant(s) account for the observed association.

Genetic variation in the first intron of the *ABO* gene has also been associated with circulating levels of serum tumor necrosis factor alpha

(TNFα)[28], circulating levels of soluble intracellular adhesion molecule 1 (sICAM-1)[29] and plasma levels of alkaline phosphatase[30]. Although higher TNFα levels are associated with the common allele of rs505922, which is protective for pancreatic cancer in our study, the data concerning the relationship between blood groups and TNFα levels are inconsistent[28]. Furthermore, this region could be important for regulating circulating levels of sICAM-1, as rs507666 and rs505922 (located 170 bp apart) were recently reported to be associated with the amount of circulating ICAM-1 (ref. 29). In addition, SNPs in the *ABO* locus, including rs657152, have been associated with plasma levels of liver-derived alkaline phosphatase[30]. Last, ABO antigen expression is altered in primary and metastatic pancreatic cancers compared with normal pancreatic tissues[31].

For rapidly fatal conditions, case-control studies are prone to distortion because they include survivors disproportionately. For variants unrelated to survival, case-control data are suitable for discovery and replication of risk-related markers. However, for variants related to survival, case-control studies yield biased estimates of

Table 1 Association of SNPs on chromosomes 9q34, 7q36 and 15q14 with risk of pancreatic cancer

Marker[a], alleles[b], chromosome[c], location[c] and gene[d]	Subset[e]	MAF		Number of participants		χ^{2f}	*P* value[f]	OR_{Het} (95% c.i.)	OR_{Hom} (95% c.i.)[g]
		Controls	Cases	Controls	Cases				
rs505922 (T, C)	Stage 1 (cohorts)	0.357	0.417	1,462	1,406	21.11	4.33×10^{-6}	1.29 (1.16–1.43)	1.66 (1.33–2.05)
9q34	Stage 1 (all)	0.357	0.411	1,805	1,771	22.18	2.48×10^{-6}	1.26 (1.14–1.39)	1.59 (1.31–1.92)
135139050	Stage 2	0.343	0.375	2,127	2,120	9.50	2.06×10^{-3}	1.15 (1.05–1.26)	1.32 (1.11–1.58)
ABO	Stage 1 + 2	0.349	0.392	3,932	3,891	29.58	5.37×10^{-8}	1.20 (1.12–1.28)	1.44 (1.26–1.63)
rs495828 (G, T)	Stage 1 (cohorts)	0.192	0.236	1,423	1,362	18.11	2.08×10^{-5}	1.35 (1.18–1.55)	1.82 (1.38–2.41)
9q34	Stage 1 (all)	0.194	0.236	1,755	1,717	21.37	3.78×10^{-6}	1.34 (1.18–1.51)	1.79 (1.40–2.29)
135144688	Stage 2	0.223	0.238	1,786	1,718	2.10	1.47×10^{-1}	1.09 (0.97–1.21)	1.18 (0.94–1.47)
ABO	Stage 1 + 2	0.209	0.237	3,541	3,435	17.93	2.30×10^{-5}	1.19 (1.10–1.30)	1.43 (1.21–1.68)
rs657152 (G, T)	Stage 1 (cohorts)	0.380	0.437	1,463	1,408	18.05	2.15×10^{-5}	1.26 (1.13–1.40)	1.59 (1.28–1.97)
9q34	Stage 1 (all)	0.380	0.430	1,806	1,773	18.13	2.06×10^{-5}	1.23 (1.12–1.35)	1.51 (1.25–1.83)
135129086	Stage 2	0.374	0.404	1,791	1,729	7.24	7.13×10^{-3}	1.14 (1.04–1.26)	1.30 (1.07–1.58)
ABO	Stage 1 + 2	0.377	0.417	3,597	3,502	24.29	8.28×10^{-7}	1.19 (1.11–1.27)	1.41 (1.23–1.61)
rs630014 (C, T)	Stage 1 (cohorts)	0.475	0.421	1,463	1,408	18.04	2.16×10^{-5}	0.80 (0.72–0.88)	0.63 (0.51–0.78)
9q34	Stage 1 (all)	0.473	0.427	1,805	1,773	16.74	4.28×10^{-5}	0.82 (0.75–0.90)	0.67 (0.56–0.81)
135139543	Stage 2	0.479	0.441	2,196	2,118	11.83	5.84×10^{-4}	0.86 (0.79–0.94)	0.74 (0.63–0.88)
ABO	Stage 1 + 2	0.477	0.435	4,001	3,891	27.49	1.58×10^{-7}	0.85 (0.79–0.90)	0.71 (0.63–0.81)
rs167020 (G, A)	Stage 1 (cohorts)	0.250	0.313	1,462	1,408	27.28	1.76×10^{-7}	1.37 (1.22–1.54)	1.88 (1.48–2.38)
7q36	Stage 1 (all)	0.259	0.307	1,805	1,773	20.06	7.52×10^{-6}	1.27 (1.15–1.41)	1.62 (1.31–2.00)
155312494	Stage 2	0.278	0.294	1,802	1,734	2.39	1.22×10^{-1}	1.09 (0.98–1.20)	1.18 (0.96–1.45)
SHH	Stage 1 + 2	0.269	0.301	3,607	3,507	18.12	2.07×10^{-5}	1.17 (1.09–1.26)	1.38 (1.19–1.60)
rs172310 (C, A)	Stage 1 (cohorts)	0.272	0.336	1,454	1,399	27.02	2.01×10^{-7}	1.36 (1.21–1.53)	1.85 (1.47–2.34)
7q36	Stage 1 (all)	0.282	0.329	1,796	1,763	17.43	2.98×10^{-5}	1.25 (1.12–1.38)	1.56 (1.26–1.92)
155308388	Stage 2	0.305	0.323	1,768	1,699	2.80	9.45×10^{-2}	1.09 (0.99–1.21)	1.19 (0.97–1.46)
SHH	Stage 1 + 2	0.293	0.326	3,564	3,462	17.04	3.66×10^{-5}	1.17 (1.08–1.25)	1.36 (1.17–1.57)
rs288746 (T, C)	Stage 1 (cohorts)	0.109	0.144	1,458	1,403	14.57	1.35×10^{-4}	1.37 (1.16–1.61)	1.87 (1.36–2.59)
7q36	Stage 1 (all)	0.114	0.138	1,800	1,768	8.08	4.48×10^{-3}	1.23 (1.07–1.42)	1.52 (1.14–2.02)
155299433	Stage 2	0.116	0.128	1,805	1,735	2.59	1.08×10^{-1}	1.12 (0.97–1.30)	1.26 (0.95–1.68)
SHH	Stage 1 + 2	0.115	0.133	3,605	3,503	10.14	1.45×10^{-3}	1.18 (1.07–1.30)	1.39 (1.13–1.70)
rs8028529 (T, C)	Stage 1 (cohorts)	0.198	0.255	1,457	1,404	25.92	3.55×10^{-7}	1.38 (1.22–1.56)	1.91 (1.49–2.45)
15q14	Stage 1 (all)	0.202	0.249	1,800	1,768	23.13	1.51×10^{-6}	1.31 (1.17–1.47)	1.72 (1.38–2.15)
34441889	Stage 2	0.231	0.229	1,800	1,736	0.02	8.92×10^{-1}	0.99 (0.89–1.11)	0.98 (0.79–1.23)
None	Stage 1 + 2	0.217	0.239	3,600	3,504	11.12	8.53×10^{-4}	1.14 (1.06–1.24)	1.31 (1.12–1.53)
rs4130461 (G, T)	Stage 1 (cohorts)	0.224	0.273	1,463	1,408	18.71	1.53×10^{-5}	1.31 (1.16–1.47)	1.70 (1.34–2.17)
15q14	Stage 1 (all)	0.231	0.272	1,806	1,773	16.64	4.52×10^{-5}	1.25 (1.12–1.39)	1.56 (1.26–1.94)
34439130	Stage 2	0.256	0.250	1,802	1,736	0.39	5.32×10^{-1}	0.97 (0.87–1.08)	0.93 (0.75–1.16)
None	Stage 1 + 2	0.243	0.261	3,608	3,509	6.15	1.32×10^{-2}	1.10 (1.02–1.19)	1.21 (1.04–1.41)
rs4459505 (G, A)	Stage 1 (cohorts)	0.177	0.218	1,455	1,402	15.51	8.21×10^{-5}	1.30 (1.14–1.49)	1.70 (1.30–2.21)
15q14	Stage 1 (all)	0.178	0.214	1,796	1,765	14.92	1.12×10^{-4}	1.26 (1.12–1.42)	1.59 (1.26–2.01)
34443314	Stage 2	0.196	0.198	1,803	1,737	0.08	7.81×10^{-1}	1.02 (0.90–1.14)	1.03 (0.82–1.31)
None	Stage 1 + 2	0.187	0.206	3,599	3,502	8.52	3.51×10^{-3}	1.13 (1.04–1.23)	1.28 (1.08–1.51)

Results from the unconditional logistic regression of the genotypes generated in the initial GWAS and the follow-up studies in a total of 3,891 individuals with pancreatic cancer and 4,001 controls. The analysis was adjusted for age in 10-year categories, sex, study, arm, ancestry and five principal components of population stratification. OR, odds ratio; Het, heterozygous; Hom, homozygous for minor allele.
[a]NCBI dbSNP identifier. [b]Major allele, minor allele. [c]Chromosome and NCBI Human Genome Build 36 location. [d]Gene neighborhood within 20 kb upstream and 10 kb downstream of SNP. [e]Stage 1: initial GWAS; stage 2: replication. [f]1-d.f. score test. [g]Estimate assuming multiplicative odds model.

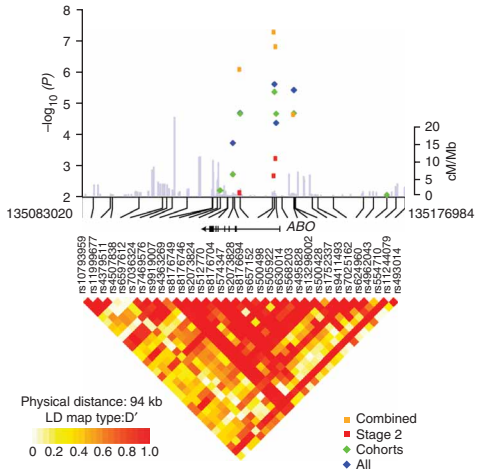

Figure 2 Association and linkage disequilibrium plot of the 9q34 locus. Association results are shown for all GWAS studies (blue diamonds), GWAS cohorts (green diamonds), replication studies (red circles) and all studies combined (yellow circles). Overlaid on the association panel is a plot of estimated recombination rates (cM/Mb) across the region from HapMap Phase II. The LD plot shows a region of chromosome 9 marked by SNPs, rs505922 and rs630014 ($r^2 = 0.52$ in HapMap CEU and 0.40 in PanScan European control individuals) and bounded by SNPs between chromosome 9 135083020 and 135176984 (NCBI Human Genome Build 36). Linkage disequilibrium (LD) is depicted for SNPs with mean allele frequency (MAF) >5% within PanScan. rs505922 and rs630014 are located in the first intron of the *ABO* gene, shown above the LD plot. Only SNPs genotyped in both the GWAS and 'fast track' replication are shown.

the association with pancreatic cancer risk. *ABO* variants seem to be unrelated to survival and show strong, similar signals in both cohort and case-control data.

We observed a genome-wide association with *SHH* ($P = 1.76 \times 10^{-7}$) among cohorts that was not replicated in the follow-up in case-control studies ($P = 0.12$), raising three possibilities: that the cohort finding is due to chance, that *SHH* is related to both survival and to risk or that the SNPs failed to replicate because of chance (**Table 1**). Because there is substantial evidence that *SHH* has a role in pancreatic carcinogenesis, further work is required to investigate this region[32].

Pancreatic cancer is among the deadliest of cancers, with mortality rates approaching incidence rates[1]. As there are few known risk factors, improved diagnostics and a finer understanding of the molecular pathogenesis are urgently needed. Our findings have identified the contribution of genetic variation in the *ABO* locus of 9q34 to pancreatic carcinogenesis, a finding that supports an epidemiologic observation first made a half-century ago and recently confirmed[33]. We are now conducting a GWAS in the eight studies from stage 2 of this study and anticipate that this will bring the identification of additional loci associated to pancreatic cancer. The discovery of additional genetic risk variants for this highly lethal cancer could contribute to improvements in risk stratification, prevention, early detection and therapeutic approaches to pancreatic cancer.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Data access. The Cancer Genetic Markers of Susceptibility (CGEMS) data portal provides access to data for 558,542 SNPs in 3,835 individuals. Investigators from certified scientific institutions may access the portal after approval of their submitted Data Access Request.

Note: Supplementary information is available on the Nature Genetics website.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the energy and contribution of our late colleague, Robert Welch. Additional acknowledgments are found in the **Supplementary Note**.

AUTHOR CONTRIBUTIONS

L.A., P.K., R.Z.S.-S., C.S.F., G.M.P., K.B.J., S.M.L., J.B.M., G.S.T., S.J.C., P.H. and R.N.H. organized and designed the study. L.A., A.H., K.B.J., G.T. and S.J.C. supervised genotyping of samples. L.A., P.K., R.Z.S.-S., C.S.F., K.B.J., C.K., K.Y., S.J.C., P.H. and R.N.H. contributed to the design and execution of statistical analysis. LA., S.J.C., P.H. and R.N.H. wrote the first draft of the manuscript. R.Z.S.-S., C.S.F., G.M.P., A.A.A., H.B.B.-d.-M., M.G., K.H., E.J.J., A.L., W.Z., D.A., W.B., C.D.B., F.B., S.B., J.E.B., P.M.B., F.C., F.C.-C., S.C., M.C., M.d.A., E.J.D., J.W.F., S.G., J.M.G., E.L.G., M.G., C.A.G., G.H., S.E.H., M.H., E.A.H., D.J.H., R.J., M.J., R.K., A.P.K., C.K., R.C.K., D.L., M.M., R.R.M., D.S.M., S.H.O., K.O., A.V.P., P.H.M.P., A.R., E.R., H.A.R., X.-O.S., D.T., S.K.V.D.E., J.V., J.W.-W., B.M.W., H.Y. and A.Z.-J. conducted the epidemiologic studies and contributed samples to the PanScan GWAS and/or replication. All authors contributed to the writing of the manuscript.

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ONLINE METHODS

Study participants. Participants in stage 1 of the GWAS were drawn from 12 cohort studies and one case-control study (**Supplementary Table 1**) in the Pancreatic Cancer Cohort Consortium Genome-Wide Association Study (PanScan1) and are part of a larger international consortium, the National Cancer Institute–sponsored Cohort Consortium. They include the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC)[8], CLUE II (ref. 10), the American Cancer Society Cancer Prevention Study II (CPS-II)[7], the European Prospective Investigation into Cancer and Nutrition (EPIC, comprising cohorts from Denmark, France, Germany, the UK, Greece, Italy, the Netherlands, Spain and Sweden)[9], the Health Professionals Follow-up Study (HPFS)[11], Nurses' Health Study (NHS)[11], the New York University Women's Health Study (NYUWHS)[12], the Physicians' Health Study I (PHS I)[11], the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)[13], the Shanghai Men's and Women's Health Study (SMWHS)[14,15], the Women's Health Initiative (WHI)[16], and the Women's Health Study (WHS)[17]. Each cohort that participated in PanScan had a defined population from whom blood or buccal cells were collected before the diagnosis of pancreatic cancer. Incident primary pancreatic adenocarcinoma cases were identified by self-report with subsequent medical record review, linkage with a cancer registry or both. Cases were defined as primary adenocarcinoma of the exocrine pancreas (ICD-O-3 code C250–C259). Non-exocrine pancreatic tumors (histology type 8150, 8151, 8153, 8155 and 8240) were excluded.

We identified 1,770 incident cases among the cohorts as part of a nested case-control study. We selected an equal number of controls within their respective cohort. One control was matched per case based on calendar year of birth (±5 years), sex, broad category of race and ethnicity and DNA (blood or buccal cell). Each control was alive and free of pancreatic cancer on the calendar date that his or her matching case was diagnosed with pancreatic cancer. The NHS, HPFS, WHS and PHS cohorts also matched cases and controls based on smoking status. Four hundred individuals with pancreatic adenocarcinoma and 400 controls were included from the Mayo Clinic Molecular Epidemiology of Pancreatic Cancer Study[18]. The Molecular Epidemiology of Pancreatic Cancer study was initiated in 2000 and used an 'ultrarapid' case ascertainment system in which >95% of patients at the Mayo Clinic from Minnesota, Iowa, and Wisconsin who were suspected to have pancreatic cancer were approached. Among those with pancreatic cancer, 72% provided consent and a blood sample. Clinic controls were drawn from patients seeking general medical care and were frequency matched to cases on age, race, gender, and area of residence.

Eight case-control studies from the PANC4 consortium participated in a replication of promising SNPs from the initial scan: University of Toronto[19], University of California San Francisco[20], Johns Hopkins University, M.D. Anderson Cancer Center[21], PACIFIC Study of Group Health and Northern California Kaiser Permanente, Memorial Sloan-Kettering Cancer Center[22] and Yale University[23] and distinct cases and controls from the Mayo Clinic Molecular Epidemiology of Pancreatic Cancer Study[18] (**Supplementary Table 2**).

Each participating study obtained informed consent from study participants and approval from its Institutional Review Board. Each cohort study and the Mayo Clinic case-control study obtained Institutional Review Board certification, permitting data sharing in accordance with the US National Institutes of Health (NIH) Policy for Sharing of Data Obtained in NIH-Supported or -Conducted Genome-Wide Association Studies.

Genotyping and quality control. We selected 4,063 DNA samples (including 311 from buccal cells) for genotyping (representing 3,932 individuals). One hundred twenty-nine DNA samples were analyzed in duplicate.

Owing to the multitude of studies of varying sample sizes in PanScan, we compared the results of genotype clustering to verify goodness of fit, detect genotype discordances and monitor potential cluster heterogeneity. The genotype models evaluated included (i) default cluster definitions provided by Illumina, (ii) clusters estimated from each study separately, (iii) clusters estimated from each study separately using samples with >98% completion rates, calling the 'low-completion' samples using those cluster models, (iv) clusters estimated from all studies together using all samples, (v) clusters estimated from all studies together using samples with >98% completion rates, then calling the low-completion samples using those cluster models and (vi) clusters estimated from each study separately using samples with >98% completion rates, followed by grouping and reclustering studies that showed similar cluster metrics. Genotypes for low-completion samples were called using the corresponding cluster model. On the basis of completion rates and low discordance between known duplicate samples, the most rigorous clustering methods were (iii), (v) and (vi). Model (v) was chosen on the basis of parsimony.

We attempted 561,466 SNP genotype assays on the 4,063 DNA samples using the Human Hap500 Infinium Assay (Illumina). Samples with <98% completion after the second attempt were subsequently excluded. SNP assays with call rates <90% were excluded. We observed an average discordance rate of 0.017% for 139 pairs of duplicate DNA assays (including 129 plated duplicate samples).

Deviation from Hardy-Weinberg proportions were tested[34] in control samples (with CEU ancestry >0.80 by STRUCTURE) of each study (**Supplementary Fig. 2**). No SNPs were excluded from analysis, as the tests for association are valid in the presence of departure from Hardy-Weinberg proportions.

Some participants with valid genotypes were excluded because of (i) unanticipated interstudy duplicates ($n = 14$), (ii) completion rates <98% ($n = 219$ samples corresponding to 74 participants), (iii) unexpected within-study duplicate ($n = 1$) and (iv) ineligible samples ($n = 8$). The final count of participants for the stage 1 association analysis was 1,896 cases and 1,939 controls (**Supplementary Table 4**).

Assessment of population structure was performed with STRUCTURE[35] by seeding the genotypes from the PanScan studies with the reference HapMap genotypes (based on Build 22 for HapMap II with MAF >5% in any of three HapMap populations)[36]. A set of 9,405 SNPs with $r^2 < 0.004$ was selected for this analysis[37–39]. A total of 59 participants (29 cases and 30 controls) were estimated to be of admixed origin with <80% similarity to CEU. No participants were excluded based on results from STRUCTURE but were assigned to the following categories for adjustment in the association analysis: European if CEU admixture portion was >80%, Asian if JPT/HCB admixture portion was >80% and 'other' if admixture with no one continental group was >80% (**Supplementary Fig. 3**). African American ancestry was defined based on self-report, with similarity to YRI ranging from 41% to 96%.

A principal component analysis (PCA) of DNA samples in this study (excluding inferred sib and half-sib pairs) was performed with EIGENSTRAT[40]. Five principal components were effective[41] for distinguishing significant population groups and were included as quantitative covariates to correct for genetic admixture.

Genotype data for the full scan was used to identify 144 participants with 60%–99% identity by state as potential relatives. Two sets of SNPs with pairwise $r^2 < 0.004$ were selected separately for Asian (13,905 SNPs) and non-Asian studies (9,405 SNPs) and run on PREST[42] to identify five unexpected full-sib pairs and two unexpected half-sib pairs (seven cases and seven controls), who were excluded from PCA but included in the association analysis.

TaqMan assays (ABI) were designed and optimized for ten SNPs in the three notable regions as well as for a technical replica assay for rs505922 (rs687621) because this SNP could not be optimized (96% genotype concordance with HapMap samples) as per SNP500Cancer.

For the fast-track replication study, 5,845 samples were genotyped, including 180 duplicate DNA samples for quality control purposes. Genotyping was performed using a multiplex integrated fluidic technology (Fluidigm Biomark) and individual TaqMan assays (ABI). During the follow-up replication genotyping, the opportunity arose to conduct a GWAS with the Illumina Infinium 610Quad. Because the same SNPs would be later genotyped, we completed genotyping only for the top ten ranked SNPs (a second GWAS is ongoing). Consequently, genotyping of some of the samples for the fast-track replication was performed with low quantities of DNA (reserving sufficient DNA for the GWAS). Sample completion ranged from 28.90% to 99.40% per study, and genotype completion rates per locus ranged from 57.7% to 99.8%. Overall genotype concordance between duplicate samples was 96.52%, indicating the reliability of the current fast-track replication results. Discordant genotypes between duplicates were set to 'missing'. A small proportion (0.2%) of samples genotyped in stage 2 were excluded, as they were unanticipated interstudy or intrastudy duplicates or had incomplete covariate data. The

corresponding Infinium cluster plots for the ten SNPs are shown in **Supplementary Figure 4**.

Association analysis. All association analyses were conducted using logistic regression, adjusted for age (in 10-year categories), sex, study, arm (for WHI, intervention versus observation), ancestry and five principal components of genetic structure. Each SNP genotype was coded as a count of minor alleles, with the exception of X-linked SNPs among males, which were coded as '2' if the participant carried the minor allele and '0' if he carried the major allele[25]. This log-linear odds model has near-optimal power across a wide range of alternative hypotheses, the main exception being rare recessive variants, for which we have limited power regardless of genotype coding[43]. A score test was performed on all genetic parameters in each model to determine statistical significance, with 1 d.f.

We analyzed each study separately and conducted two analyses pooling multiple studies: the first included all cohorts ('cohorts'); the second included all studies ('all'). We assessed heterogeneity in genetic effects across study using the Q and I^2 statistics[44].

We selected for replication ten SNPs from the three most notable regions from the GWAS (based on two or more SNPs per region ranking in the top 25 SNPs) based on the results of the two pooled analyses. We tested association between pancreatic cancer and the replication SNPs by fitting logistic regression models and testing the estimated genetic effects using the GLU software package. We analyzed each study separately in addition to pooling all eight studies. Models were adjusted for age in 10-year intervals as well as for sex, self-reported race and study. Genotypes were coded as counts of minor alleles (1-d.f. trend test). Combined single-SNP analyses pooled stage 1 and stage 2 data sets and adjusted for study, arm, age, sex, race and top five principal components of population stratification. In stage 2 studies, principal components could not be calculated and were set to 0. **Supplementary Table 5** provides the results of the stage 2 association analysis.

Data analysis and management used GLU (Genotyping Library and Utilities version 1.0), a suite of tools available as an open-source application for management, storage and analysis of GWAS data.

URLs. CGEMS portal, http://cgems.cancer.gov/; Core Genotyping Facility, http://cgf.nci.nih.gov/; EIGENSTRAT, http://genepath.med.harvard.edu/~reich/EIGENSTRAT.htm; GLU, http://code.google.com/p/glu-genetics/; SNP500Cancer, http://snp500cancer.nci.nih.gov/; STRUCTURE, http://pritch.bsd.uchicago.edu/structure.html; Tagzilla, http://tagzilla.nci.nih.gov/; PANC4, http://panc4.org.

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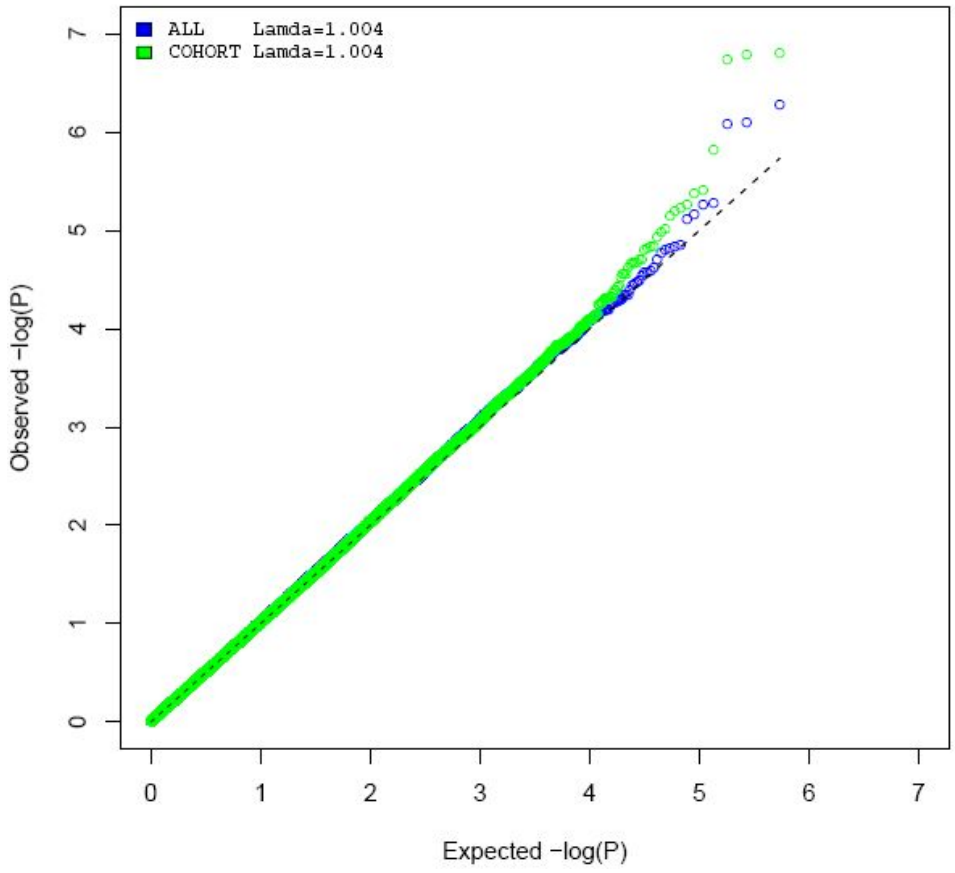
Supplementary Material

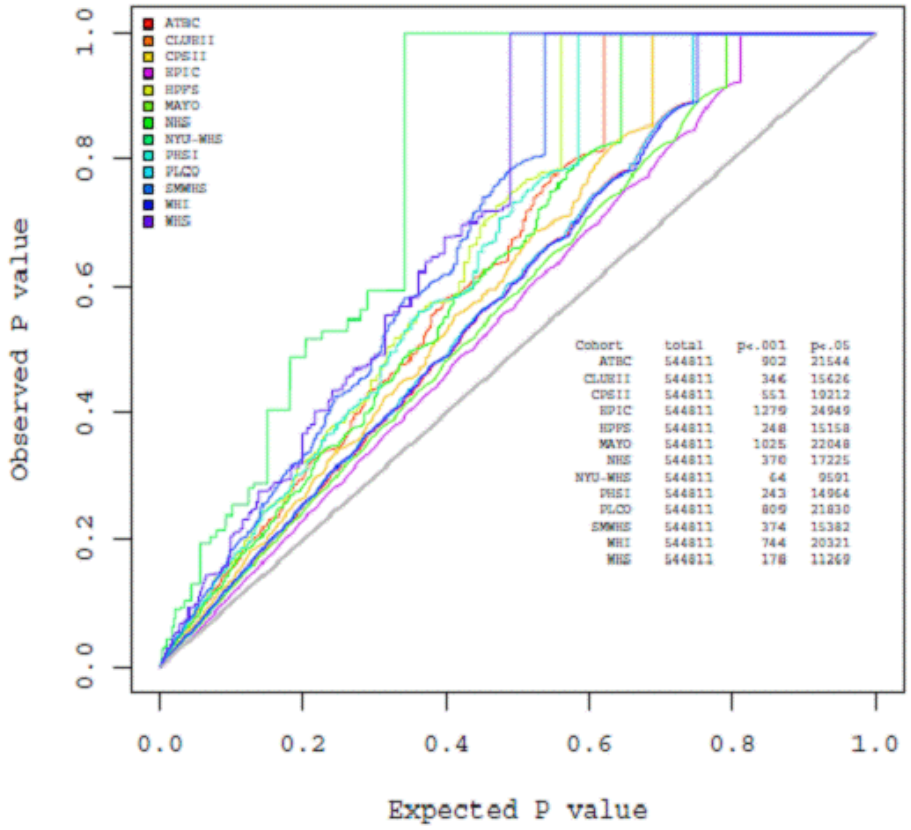
for

"Genome-Wide Association Study Identifies *ABO* Blood Group Susceptibility Variants for Pancreatic Cancer"

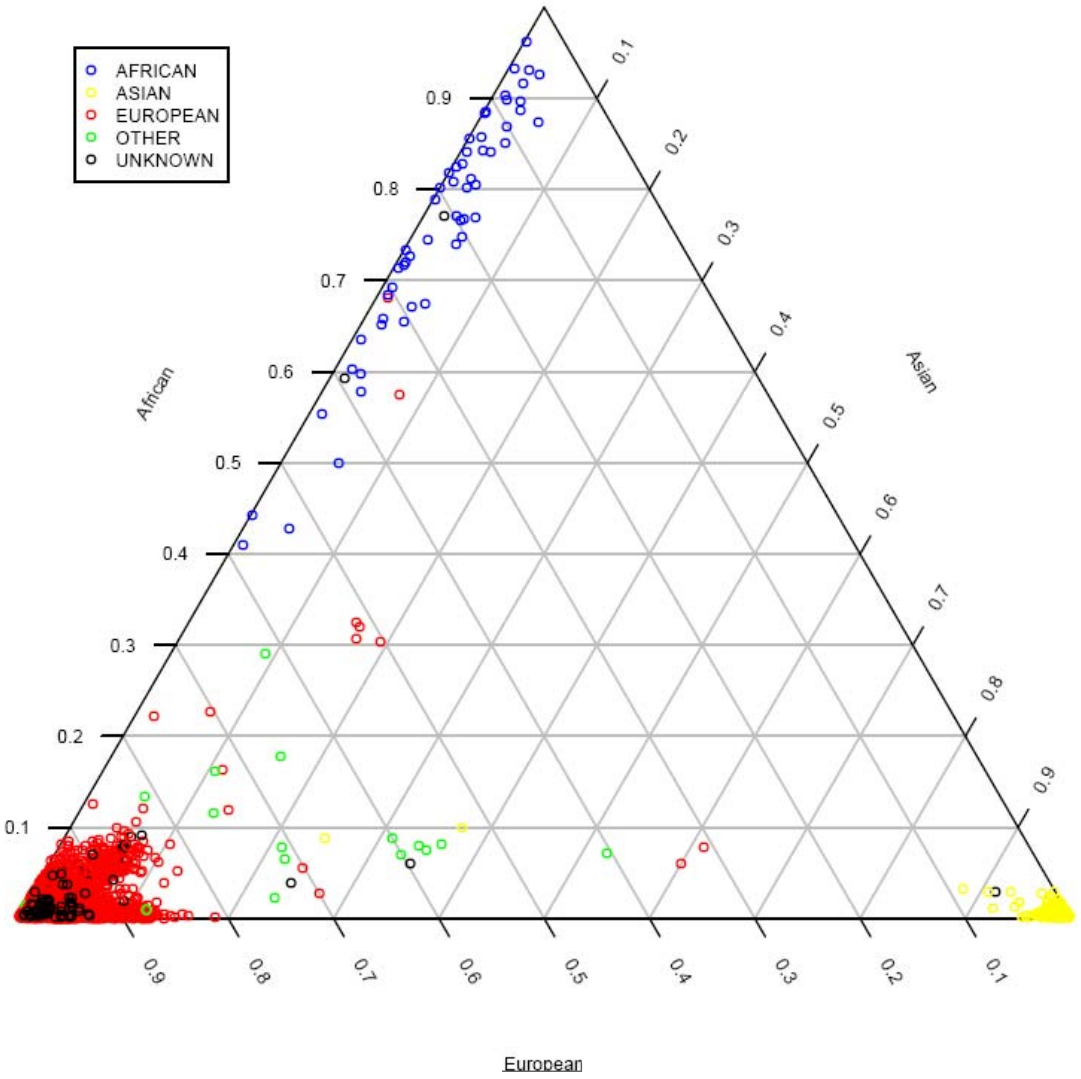
Supplemental Figure 1: Quantile-Quantile (QQ) plot of observed vs. expected P values for PanScan 1 Genome Wide Association Study.



Supplemental Figure 2: Test for deviation from Hardy-Weinberg proportions.

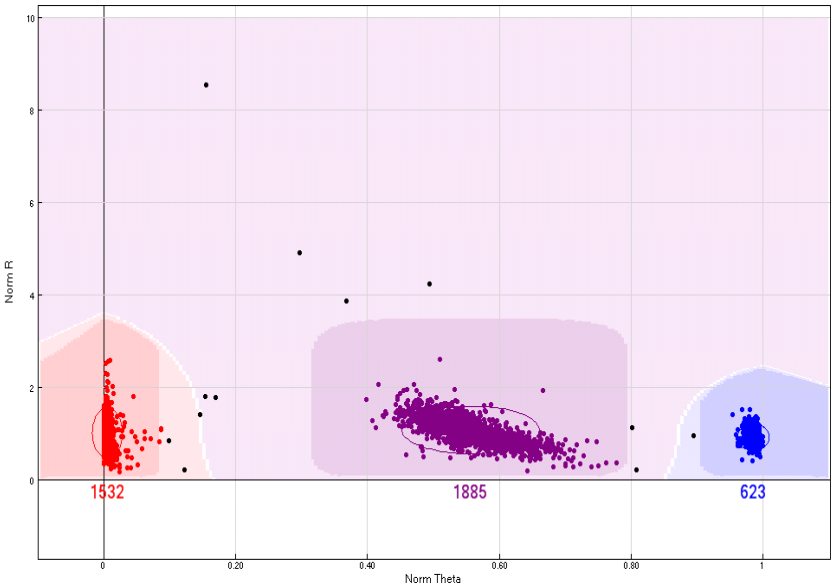


Supplemental Figure 3. Plot of admixture defined by analysis with STRUCTURE.

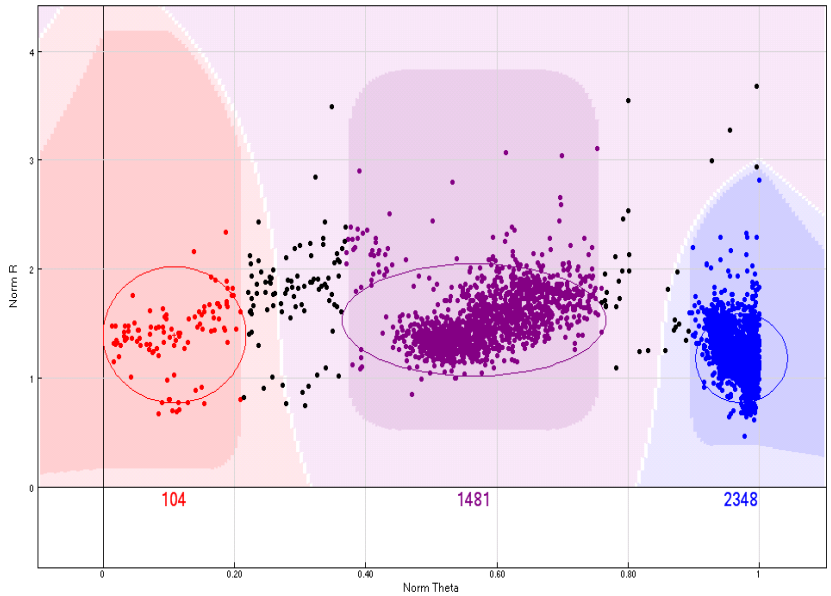


Supplemental Figure 4. Illumina HumanHap550 genotype clustering for the 10 SNPs selected for replication.

rs505922



rs495828



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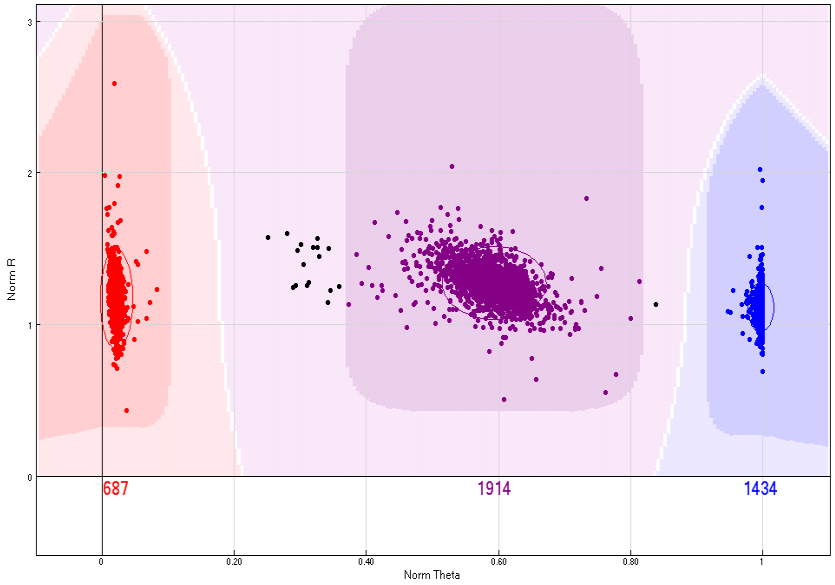

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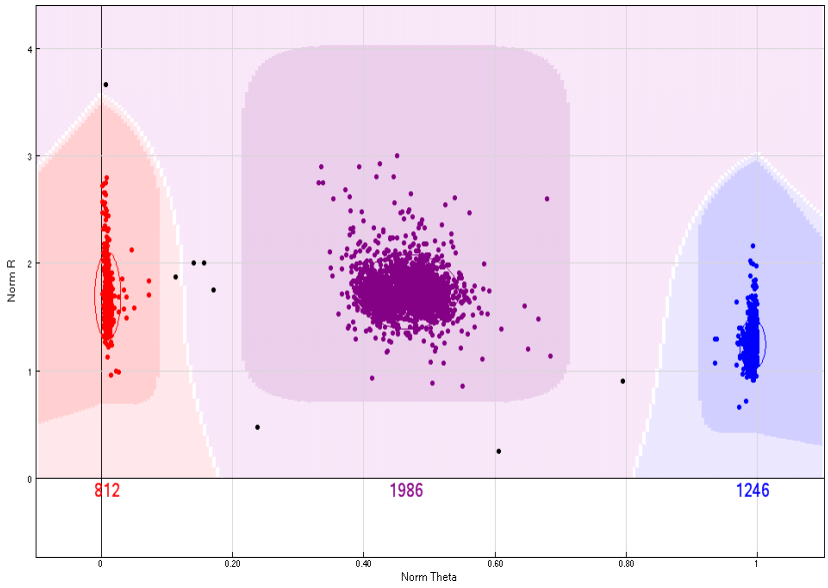

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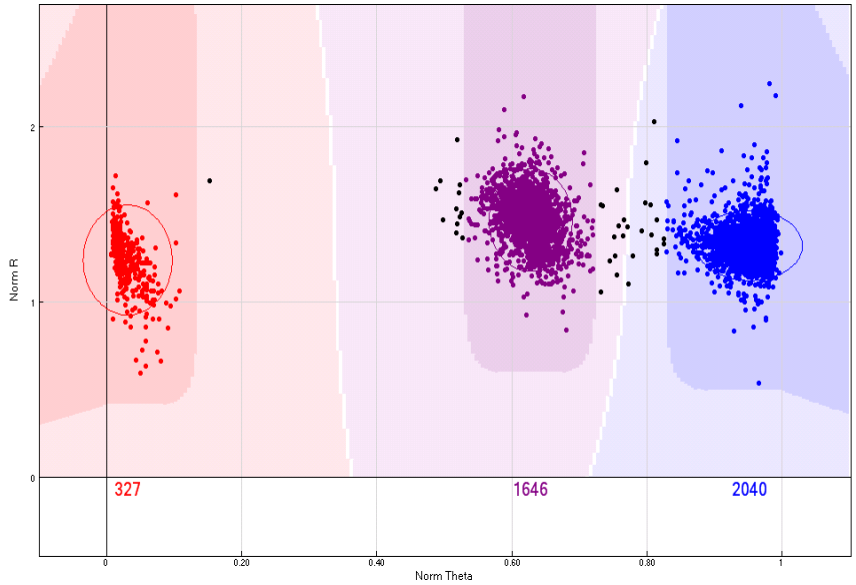

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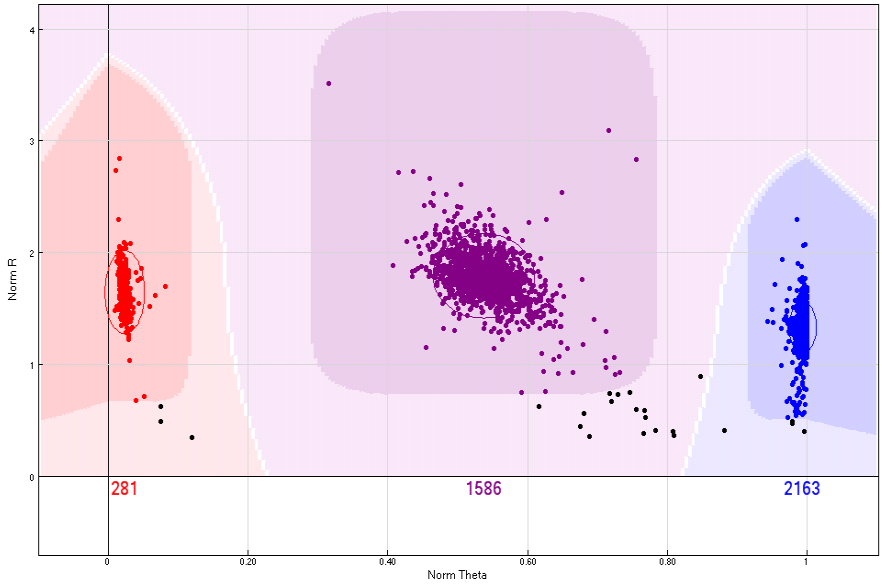

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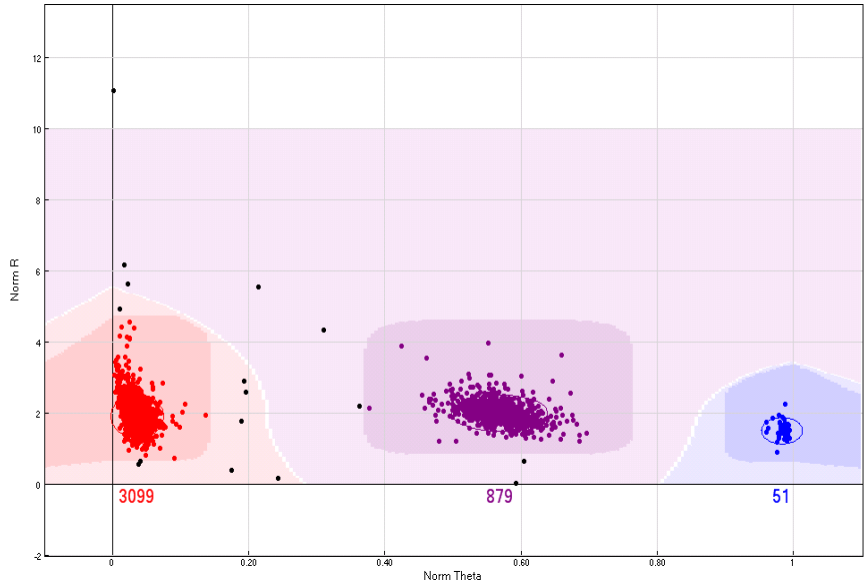

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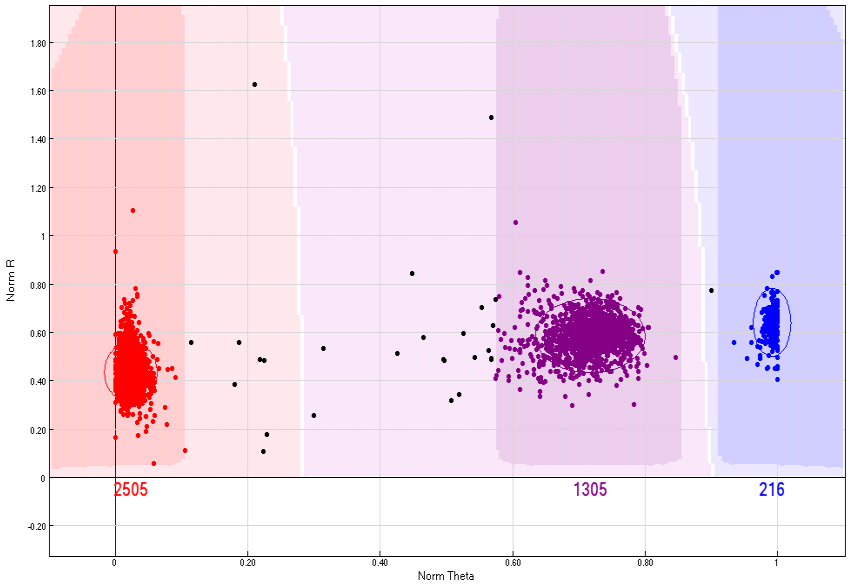

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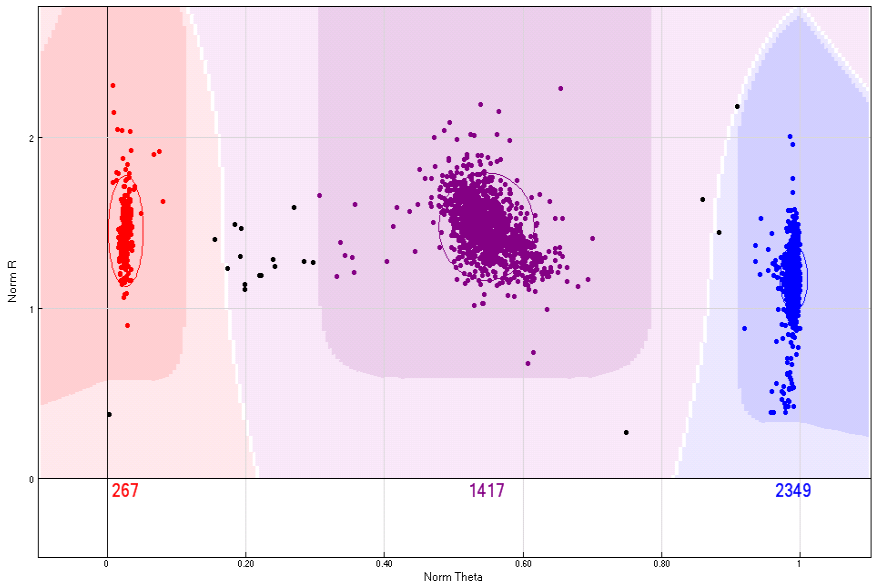

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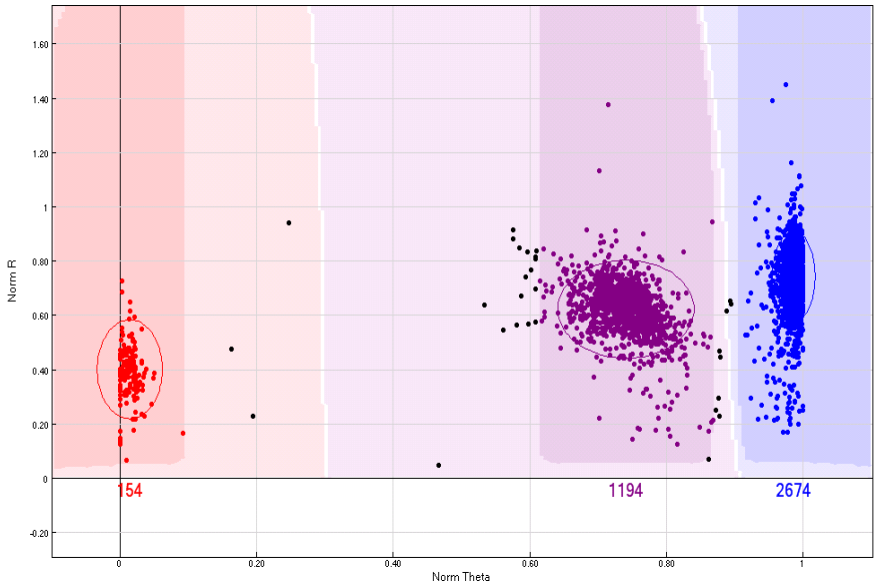

Supplemental Table 1. Nested case control studies from twelve cohorts and one clinic based case control study in PanScan1 GWAS.

Cohort	*Cases, n*	*Controls, n*	Location	Enrollment [1]	DNA, year	Mean time to case diagnosis (years) [2]	Case diagnosis age, mean (SD)	Male, %	Race, Caucasian (%)	Matching of controls to cases
The Alpha-Tocopherol, Beta-Carotene Prevention Study (ATBC) [1]	194	208	Finland	1985-1988	1992-1993	6.6	70.5 (5.6)	100	100	Race, sex, age, date of blood draw, follow-up time
Give Us a Clue to Cancer and Heart Disease Study (CLUEII)[2]	68	71	Washington County MD, USA	1989	1989	8.5	69.7 (11.3)	46.0	100	Race, sex, age, date of blood draw, follow-up time
Cancer Prevention Study (CPS II)[3]	120	118	USA	1992-1993	1998-2002	2.0	74.9 (5.7)	56.7	97.9	Race, sex, birth year, DNA source (blood or buccal), follow-up time
European Prospective Investigation Into Cancer and Nutrition Study (EPIC)[4]	421	426	Europe	1987-2002 (varied by center)	1988-2002	5.0	62.1 (7.8)	46.6	100	Sex, center, age, date of blood draw, follow-up time
Health Professionals Follow-up Study (HFPS)[5]	54	51	USA	1986	1993-1995	5.2	71.3 (7.9)	100	100	Sex, age, date of blood draw, follow-up time, smoking status (never/former/current)
Nurse's Health Study (NHS)[5]	82	84	USA	1976	1989-1990	8.0	69.6 (6.4)	0	91.6	Race, sex, age, date of blood draw, follow-up time, smoking status (never/former/current)
The New York University Women's Health Study (NYU-WHS)[6]	13	13	USA	1985-1990	1988-1990	8.5	67.9 (10.0)	0	76.9	Race, sex, age, date of blood draw, follow-up time, menopausal status at enrollment
Physicians Health Study (PHS)[5]	49	54	USA	1982-1983	1982-1983	13.4	70.4 (10.0)	100	79.6	Race, sex, age, date of blood draw, follow-up time, smoking status (never/former/current)
Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO)[7]	199	220	USA	1994-2001	1994-2001	6.0	71.7 (5.9)	60.6	91.7	Race, sex, age, birth year, date of blood draw, follow-up time, DNA source (blood or buccal cell), study arm, and center
Shanghai Men's and Women's Health Study (SMWHS) [8, 9]	58	65	China	1996 (F) 2001 (M)	1997-2004	3.4	66.0 (7.5)	21.1	0	Sex, age, birth year, menopausal status at baseline, date of blood draw, follow-up time
Women's Health	245	242	USA	1992-1998	1992-2001	4.1	71.8 (7.4)	0	85.2	Race, sex, age, center, enrollment date, study

Initiative (WHI)[10]										arm, hysterectomy status, menopausal status, follow-up time
Womens' Heath Study (WHS)[11]	25	32	USA	1992-1993	1993-1994	3.9	61.9 (8.4)	0	94.7	Race, age, birth year, smoking status (never/former/current) date of blood draw, follow-up time
Mayo Clinic Molecular Epidemiology Case-Control Study[12]	368	345	Upper Mid-West: Minn., Iowa, Wisconsin, USA	2000-2007	Cases, 2000-2006 Controls, 2004-2007	0	66.4 (9.8)	56.7	99.0	Clinic based controls, frequency matched to cases on age, race, sex, and residence.
Cohort total	1594	1528		1976-2004	1982-2004	5.5	68.5 (8.5)	47.7	91.1	
Phase 1 total	1,896	1,939		1976-2007	1982-2007	5.5	68.1 (8.8)	49.3	92.5	

1. Refers study baseline and enrollment
2. Refers to years of follow-up after DNA collected.

Supplemental Table2. Eight case control studies used in rapid replication for PanScan1

Case control study	***Cases, n***	***Controls, n***	**Location**	**Source of cases**	**Source of controls**	**Matching method and variables**	**Date of case diagnosis**	**Date of control recruitment**	**Case diagnosis age, mean (SD)**	**Sex Male, %**	**Race, Caucasian, %**
UCSF[13]	**272**	**274**	San Francisco Bay Area, USA	Population-based cancer registry	Random digit-dial within six SF Bay Area counties, no history pancreatic cancer	Frequency matched by sex and age	1993-1999	1995-1999	64.9 (10.7)	54.2	85.0
Yale[14]	**246**	**523**	Connecticut, USA	Population-based cancer registry	Block list-directed Random digit-dial, no personal history of cancer (except non-melanoma of skin)	Frequency matched by age and sex	2004-2008	2005-2008	66.8 (9.9)	55.1	94.7
Toronto[15]	**298**	**301**	Ontario (cases) Greater Toronto (controls), Canada	Population-based cancer registry	Spouse or unrelated family member control from same generation or Random digit dialing property assessment rolls	Age, gender, and ethnicity. no personal history of colorectal cancer	2000-2008	1999-2003	63.8 (10.0)	54.6	94.8
MD Anderson[16]	**496**	**412**	Texas, USA	Hospital	Friends and spouses of non-pancreatic cancer patients at MDA, no personal history of cancer (except non-melanoma of skin)	Frequency matched by age, race, and sex	1996-2007	2004-2007	61.9 (9.9)	60.8	95.4

Johns Hopkins Hospital	**136**	**220**	Baltimore, USA	JHU Clinic	Spouse (in-Law) of Pancreatic Cancer Patient, no history pancreatic cancer	None	1996-2007	1996-2007	64.3 (10.2)	43.3	95.6
Mayo Clinic Molecular Epidemiology Case-Control Study[12]	**585**	**500**	Upper Mid-West: Minn., Iowa, Wisconsin, USA	Clinic	General Medical Evaluation (primary care) patients, no personal history of cancer (except non-melanoma of skin)	Frequency matched by age, race, sex, and residence	1993-2008	2004-2007	66.1 (10.9)	53.7	98.7
Memorial Sloan Kettering[17]	**140**	**149**	NYC, USA	Clinic	Spouses of patients; visitors accompanying patients, no personal history of cancer (except non-melanoma of skin)	None	2000-2008	2004-2008	59.3 (10.7)	48.8	95.9
PACIFIC Study	**284**	**275**	Seattle, WA and Northern California, USA	Group Health (Seattle Pufet Sound) and Kaiser Permanente Northern CA)	Group Health (Seattle Pufet Sound) and Kaiser Permanente Northern CA	Frequency matched by race, age, enrollment duration in HMO, and sex	2005-2008	2005-2008	68.9 (11.0)	49.7	100
Total	2457	2654					1993-2008	1995-2008	64.8 (10.7)	53.9	95.3

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Supplemental Table 3. Association of SNPs on chromosomes 9q34, 7q36 and 15q14 to risk of pancreatic cancer in all ethnic groups

Marker[a], Alleles[b], Chr[c], Location[c] and Gene[d]	Subset[e]	MAF[f]	Subjects[g]	χ^{2} [h]	*P* value[h]	OR_{Het} (95% CI)	$OR_{Hom\ (95\%\ CI)}$ [i]
rs505922 (T, C)	Stage 1 Cohorts	0.362|0.422	1592|1526	23.11	1.53E-06	1.29 (1.16-1.43)	1.65 (1.35-2.03)
9q34	Stage 1 All	0.360|0.415	1937|1894	24.37	7.95E-07	1.26 (1.15-1.39)	1.59 (1.32-1.92)
135139050	Stage 2	0.343|0.376	2185|2210	9.45	2.11E-03	1.15 (1.05-1.25)	1.31 (1.10-1.57)
ABO	Stage 1 + 2	0.351|0.394	4122|4104	30.97	2.61E-08	1.20 (1.12-1.28)	1.43 (1.26-1.63)
rs495828 (G, T)	Stage 1 Cohorts	0.189|0.234	1550|1478	21.19	4.17E-06	1.37 (1.20-1.56)	1.87 (1.43-2.44)
9q34	Stage 1 All	0.192|0.235	1884|1836	24.3	8.23E-07	1.35 (1.20-1.52)	1.82 (1.43-2.32)
135144688	Stage 2	0.222|0.236	1824|1770	1.93	1.65E-01	1.08 (0.97-1.21)	1.17 (0.94-1.46)
ABO	Stage 1 + 2	0.207|0.236	3708|3606	19.94	8.00E-06	1.20 (1.11-1.30)	1.44 (1.23-1.70)
rs657152 (G, T)	Stage 1 Cohorts	0.384|0.441	1593|1528	20.64	5.53E-06	1.27 (1.14-1.40)	1.60 (1.31-1.97)
9q34	Stage 1 All	0.383|0.434	1938|1896	20.73	5.28E-06	1.24 (1.13-1.36)	1.53 (1.27-1.84)
135129086	Stage 2	0.376|0.405	1829|1781	6.36	1.16E-02	1.13 (1.03-1.24)	1.28 (1.06-1.55)
ABO	Stage 1 + 2	0.379|0.420	3767|3677	25.35	4.79E-07	1.19 (1.11-1.27)	1.41 (1.23-1.60)
rs630014 (C, T)	Stage 1 Cohorts	0.472|0.415	1593|1528	21.3	3.92E-06	0.79 (0.71-0.87)	0.62 (0.51-0.76)
9q34	Stage 1 All	0.471|0.422	1937|1896	20.19	7.00E-06	0.81 (0.74-0.89)	0.66 (0.55-0.79)
135139543	Stage 2	0.478|0.440	2256|2211	10.8	1.02E-03	0.87 (0.80-0.95)	0.76 (0.64-0.89)
ABO	Stage 1 + 2	0.475|0.432	4193|4107	29.28	6.27E-08	0.84 (0.79-0.90)	0.71 (0.63-0.81)
rs167020 (G, A)	Stage 1 Cohorts	0.236|0.294	1592|1528	27.48	1.59E-07	1.37 (1.21-1.53)	1.86 (1.48-2.36)
7q36	Stage 1 All	0.246|0.293	1937|1896	20.68	5.43E-06	1.27 (1.15-1.41)	1.62 (1.32-2.00)
155312494	Stage 2	0.274|0.289	1840|1787	2.3	1.29E-01	1.08 (0.98-1.20)	1.17 (0.95-1.45)
SHH	Stage 1 + 2	0.260|0.291	3777|3683	18.12	2.07E-05	1.17 (1.09-1.26)	1.38 (1.19-1.59)
rs172310 (C, A)	Stage 1 Cohorts	0.257|0.317	1583|1519	27.21	1.82E-07	1.36 (1.21-1.52)	1.84 (1.46-2.31)
7q36	Stage 1 All	0.269|0.314	1927|1886	18.18	2.01E-05	1.25 (1.13-1.38)	1.56 (1.27-1.92)
155308388	Stage 2	0.301|0.318	1806|1748	2.65	1.04E-01	1.09 (0.98-1.20)	1.18 (0.97-1.45)
SHH	Stage 1 + 2	0.285|0.316	3733|3634	17.1	3.55E-05	1.16 (1.08-1.25)	1.36 (1.17-1.57)
rs288746 (T, C)	Stage 1 Cohorts	0.105|0.138	1588|1523	15.05	1.05E-04	1.37 (1.17-1.60)	1.87 (1.36-2.56)

7q36	Stage 1 All	0.111|0.134	1932|1891	8.94	2.80E-03	1.24 (1.08-1.43)	1.54 (1.16-2.04)
155299433	Stage 2	0.115|0.126	1843|1788	2.01	1.56E-01	1.11 (0.96-1.28)	1.23 (0.92-1.63)
SHH	Stage 1 + 2	0.113|0.130	3775|3679	9.76	1.78E-03	1.17 (1.06-1.30)	1.37 (1.13-1.68)
rs8028529 (T, C)	Stage 1 Cohorts	0.188|0.241	1587|1524	27.4	1.66E-07	1.39 (1.23-1.57)	1.93 (1.50-2.46)
15q14	Stage 1 All	0.193|0.240	1932|1891	25.17	5.25E-07	1.32 (1.19-1.48)	1.75 (1.41-2.19)
34441889	Stage 2	0.230|0.233	1838|1788	0.01	9.32E-01	1.00 (0.89-1.11)	0.99 (0.79-1.24)
none	Stage 1 + 2	0.211|0.237	3770|3679	12.58	3.91E-04	1.15 (1.06-1.24)	1.32 (1.13-1.55)
rs4130461 (G, T)	Stage 1 Cohorts	0.218|0.262	1593|1528	18.8	1.46E-05	1.30 (1.15-1.47)	1.69 (1.33-2.15)
15q14	Stage 1 All	0.224|0.264	1938|1896	16.84	4.07E-05	1.25 (1.12-1.39)	1.56 (1.26-1.93)
34439130	Stage 2	0.257|0.257	1840|1789	0.8	3.70E-01	0.95 (0.86-1.06)	0.91 (0.73-1.12)
none	Stage 1 + 2	0.240|0.261	3778|3685	5.62	1.78E-02	1.10 (1.02-1.18)	1.20 (1.03-1.39)
rs4459505 (G, A)	Stage 1 Cohorts	0.168|0.207	1585|1521	16.53	4.80E-05	1.31 (1.15-1.49)	1.71 (1.32-2.22)
15q14	Stage 1 All	0.170|0.206	1928|1887	16.33	5.31E-05	1.27 (1.13-1.43)	1.62 (1.28-2.04)
34443314	Stage 2	0.195|0.202	1841|1790	0.11	7.43E-01	1.02 (0.91-1.15)	1.04 (0.82-1.31)
none	Stage 1 + 2	0.182|0.204	3769|3677	9.78	1.76E-03	1.14 (1.05-1.24)	1.30 (1.10-1.53)

Association of SNPs on chromosomes 9q34, 7q36 and 15q14 to risk of pancreatic cancer in all ethnic groups.
The results from the unconditional logistic regression of the genotypes generated in the initial GWAS and the follow-up studies in a total of 3,891 pancreatic cancer cases and 4,001 controls. The analysis was adjusted for age in ten-year categories, sex, study, arm, ancestry and five principal components of population stratification.
[a]NCBI dbSNP identifier.
[b]Major allele, minor allele.
[c]Chromosome and NCBI Human genome Build 36 location.
[d]Gene neighborhood within 20 kb upstream and 10 kb downstream of SNP.
[e]Stage 1 is the initial GWAS and stage 2 the replication.
[f]Minor allele frequency in control and case participants.
[g]Controls, cases.
[h]1 d.f. score test.
[i]Estimate assuming multiplicative odds model
OR, Odds ratio; Het, heterozygous; Hom, homozygous for minor allele. CI, 95% confidence interval.

Supplemental Table 4. Final Participant Counts for Stage I (GWAS) Association Analysis

Cohort/Study	Cases	Controls
ATBC	194	208
CLUE II	68	71
CPS II	120	118
EPIC	421	436
HPFS	54	51
MAYO	368	345
NHS	82	84
NYU-WHS	13	13
PHS I	49	54
PLCO	199	220
SMWHS	58	65
WHI	245	242
WHS	25	32
Grand Total	1,896	1,939

Supplemental Table 5. Final Participant Counts for Stage 2 (Replication) Association Analysis

STUDY	CASES	CONTROLS
Pacific/Group Health	284	275
JHU	136	220
Mayo	585	500
MDA	496	412
MSKCC	140	149
Toronto	298	301
UCSF	272	274
Yale	246	523
Grand Total	2,457	2,654

Nature Genetics: doi:10.1038/ng.429

Supplemental Note

PanScan Steering Committee

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Acknowledgements

The NYU Women's Health Study is supported by research grants R01CA034588, R01CA098661, center grant P30CA016087 from the NCI and the center grant ES000260 from the National Institute of Environmental Health Sciences.

The WHI program is funded by the National Heart, Lung, and Blood Institute, NIH, through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221.

The Mayo Clinic Molecular Epidemiology of Pancreatic Cancer study is supported by the Mayo Clinic SPORE in Pancreatic Cancer (P50 CA102701). The authors would like to acknowledge Kari Rabe, Traci Hammer, Jodi Cogswell, Hugues Sicotte, Janet Olson, Martha Matsumoto, and Dennis Robinson.

Nature Genetics: doi:10.1038/ng.429

The Yale University study was supported by grant number 5R01CA098870 from the NCI, NIH. The cooperation of 30 Connecticut hospitals, including Stamford Hospital, in allowing patient access, is gratefully acknowledged. This study was approved by the State of Connecticut Department of Public Health Human Investigation Committee. Certain data used in this study were obtained from the Connecticut Tumor Registry in the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data.

The PHS, NHS, HPFS and WHS at Harvard were supported by the NCI, NIH (Grants No. P01 CA87969, P01 CA55075, P50 CA127003, R01 CA124908).

The work at Johns Hopkins University was supported by the NCI (Grants P50CA62924 and R01CA97075) and the Lustgarten Foundation for Pancreatic Cancer Research.

The Shanghai Men's Health Study was supported by the National Cancer Institute extramural research grant [R01 CA82729]. The Shanghai Women's Health Study was supported by the National Cancer Institute extramural research grant [R01 CA70867] and, partially for biological sample collection, by the Intramural Research Program of National Cancer Institute (Division of Cancer Epidemiology and Genetics).
We are in debt to the contributions of Drs. Yu-Tang Gao and Yong-Bing Xiang in these two cohort studies. The studies would not be possible without the continuing support and devotion from the study participants and staff of the SMHS and SWHS.

Nature Genetics: doi:10.1038/ng.429

Memorial Sloan Kettering Cancer Center acknowledges the work of Jennifer A. Simon and Irene Orlow.

The work at MD Anderson was supported by NIH grant RO1 CA98380.

The UCSF study was supported in part by National Cancer Institute grants CA59706, CA108370, CA109767, CA89726 (E.A. Holly, PI) and CA98889 (E.J. Duell, PI) and by the Rombauer Pancreatic Cancer Research Fund.

The University of Toronto study was supported by grants from the NIH (R01 CA97075, as part of the PACGENE consortium), The Lustgarten Foundation for Pancreatic Cancer Research and the Ontario Cancer Research Network. We acknowledge the Pancreatic Cancer Canada Foundation (www.pancreaticcancercanada.ca) for their continued support of research into the early detection of pancreatic cancer, and the Pancreas Cancer Screening Study at Mount Sinai Hospital and Princess Margaret Hospital. The authors acknowledge Ayelet Borgida and Heidi Rothenmund for their dedicated contributions towards data collection and study co-ordination.

PLCO was supported by individual contracts from the NCI to the University of Colorado Denver NO1-CN-25514, Georgetown University NO1-CN-25522, Pacific Health Research Institute NO1-CN-25515, Henry Ford Health System NO1-CN-25512, University of Minnesota, NO1-CN-25513, Washington University NO1-CN-25516, University of Pittsburgh NO1-CN-25511, University of Utah NO1-CN-25524,

Nature Genetics: doi:10.1038/ng.429

Marshfield Clinic Research Foundation NO1-CN-25518, University of Alabama at Birmingham NO1-CN-75022, Westat, Inc. NO1-CN-25476, University of California, Los Angeles NO1-CN-25404

The ATBC Study was supported by funding provided by the Intramural Research Program of the NCI, NIH, and through U.S. Public Health Service contracts (N01-CN-45165, N01-RC-45035, and N01-RC-37004) from the NCI.

For the EPIC cohorts, all coauthors coordinated the initial recruitment and management of the studies. All authors contributed to the final paper. The authors thank all of the participants who took part in this research and the funders and support and technical staff who made this study possible. The work described in this paper was carried out with the support of the European Commission: Public Health and Consumer Protection Directorate 1993-2004; Research Directorate-General 2005-."; Ligue contre le Cancer, Societé 3M, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center, Federal Ministry of Education and Research (Germany); Danish Cancer Society (Denmark); ISCIII RETIC (RD06/0020) of the Spanish Ministry of Health, The participating regional governments and institutions (Spain); Cancer Research UK, Medical Research Council, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, the Wellcome Trust (United Kingdom); Greek Ministry of Health and Social Solidarity, Hellenic Health Foundation and Stavros Niarchos Foundation (Greece); Italian Association for Research on Cancer (AIRC) (Italy); Dutch

Nature Genetics: doi:10.1038/ng.429

Ministry of Public Health, Welfare and Sports, Dutch Prevention Funds, LK Research Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF) (the Netherlands); Swedish Cancer Society, Swedish Scientific Council, Regional Government of Skane and Västerbotten (Sweden).

CLUE II was supported by National Institute of Aging grant (5U01AG018033) and National Cancer Institute grants (CA105069, CA73790). The authors express their appreciation to the participants of the CLUE II cohort and thank the staff at the George W. Comstock Center for Public Health Research and Prevention for their dedication and contributions to the study: Judy Hoffman-Bolton, Clara Krumpe, Kitty Spoonire and Betty Miner.

The Cancer Prevention Study II Nutrition Cohort is supported by the American Cancer Society. The authors thank all of the men and women in the Cancer Prevention Study II Nutrition Cohort for their many years of dedicated participation in the study.

The authors wish to thank Debbie Winn, Daniela Seminara and Scott Rogers for assisting with funding coordination for the project and Donghui Li for supporting the study with supplemental grant CA98380.

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the

Nature Genetics: doi:10.1038/ng.429

views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

The authors acknowledge the contribution of the staff of the Core Genotyping Facility, specifically, Zhaoming Wang, Chenwei Liu, Xiang Deng, Laurie Burdett, Aurelie Vogt, Belynda Hicks and Jesus Gonzalez-Bosquet.

Nature Genetics: doi:10.1038/ng.429