Published in final edited form as:

Pancreas. 2011 November ; 40(8): 1188–1194. doi:10.1097/MPA.0b013e3182232975.

ABO blood group and chronic pancreatitis risk in the NAPS2 cohort

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Abstract

Objectives—A risk association has been observed between non-O blood groups and pancreatic adenocarcinoma. Chronic pancreatitis also increases risk for pancreatic cancer, raising questions as to whether non-O blood groups are a risk for chronic pancreatitis and whether the pathophysiologic pathways are linked. Our goal was to determine whether ABO blood group may affect the risk of chronic pancreatitis.

Methods—The study cohort included chronic pancreatitis patients (n=499) and healthy controls (n=631) from the NAPS2 study. Genotyping was performed using Sequenom assay of rs8176746 A/C and rs505922 C/T to classify participants into ABO blood groups.

Results—O blood group was non-significantly more common among cases (44.7% vs. 42.0%, P=0.36), particularly among cases with alcohol-related chronic pancreatitis (49.3% vs. 42%, P=0.060). Alcoholic patients without coexisting high-risk *PRSSI*, *CFTR* or *SPINK1* variants had a significant overrepresentation of O blood type when compared to controls (odds ratio 1.54, 95% Confidence interval 1.09-2.17; P=0.01).

Conclusions—A, B and AB blood groups were not associated with a greater likelihood of having chronic pancreatitis, and may decrease risk of chronic pancreatitis in individuals who are very heavy drinkers. These results suggest that the mechanism linking non-O blood type with pancreatic pathology is specific to carcinogenesis.

Keywords

ABO blood group; chronic pancreatitis; inflammation; blood type; genetic mutation; risk

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Introduction

In 2004, there were 277,000 hospitalizations and 475,000 ambulatory care visits due to pancreatic diseases (1). Chronic pancreatitis is a devastating pancreatic condition which is characterized histologically by the replacement of functional exocrine and endocrine tissue with fibrosis and clinically by weight loss, diabetes, steatorrhea, and severe abdominal pain (2, 3). The syndrome of chronic pancreatitis involves pancreatic inflammation and organ dysfunction and has been associated with multiple etiologies and unpredictable outcomes (2, 4-6). The incidence of chronic pancreatitis ranges from 1.6 to 23 cases per 100,000 per year worldwide (7, 8). The gradual rise in incidence of chronic pancreatitis that has been observed especially in developed countries may be attributed to increasing alcohol consumption and improvements in diagnostic methodology (5).

Chronic pancreatitis is a well-established risk factor for pancreatic cancer (9, 10), especially in patients with genetic etiologies such as those carrying mutations associated with hereditary pancreatitis (11-14). The risk of developing pancreatic adenocarcinoma for individuals with hereditary pancreatitis is further increased by cigarette smoking (15). Although most patients with chronic pancreatitis do not develop pancreatic adenocarcinoma, and the majority of individuals with pancreatic cancer were not previously diagnosed with chronic pancreatitis, the shared risk factors suggest that some pancreas-targeting pathogenic pathways which preclude to disease may be similar (10). While the genetic and environmental risk factors for chronic pancreatitis have been elucidated and reproduced in recent studies (4, 16-18), the etiological basis for pancreatic adenocarcinoma remains comparatively undefined. Additionally, the link between the two diseases has not been characterized molecularly.

Pancreatic adenocarcinoma is a highly lethal form of cancer which typically presents late and carries a 5-year survival rate of approximately 5% (19). As in chronic pancreatitis, there are multiple etiological risk factors for pancreatic cancer, although most of them have relatively small effects or are limited to a subset of patients, such as those with familial cancer syndromes [reviewed in (13, 20)]. The best documented environmental risk factors include cigarette smoking, obesity, diabetes mellitus, and diets with elevated fat or high-heat cooked meat content (21). Together, however, these factors do not confer sufficient risk to justify screening or intervention (22). The other major area of risk involves genetics, which was recently explored through a well-powered and validated genome-wide association study [GWAS] (23). The PanScan consortium performed single nucleotide polymorphism (SNP) array genotyping on 1896 cases with pancreatic cancer and 1939 controls. They identified a SNP (rs505922) in intron 1 of the ABO locus as the most significant genetic risk factor for pancreatic adenocarcinoma [odds ratio (OR) = 1.20; 95% confidence interval (CI): 1.12-1.28].

Using the PanScan cohort, Wolpin et al. assessed individual ABO blood group alleles and how each allele relates to pancreatic cancer risk (24). ABO genotypes were categorized as OO, AO, AA, AB, BO, and BB for 1,534 cases and 1,583 controls from 12 prospective cohorts in the multi-institutional PanScan study and logistic regression was implemented to determine adjusted ORs of pancreatic cancer. Compared to study participants with the OO genotype, those with AO and AA genotype had ORs of 1.33 (95% CI, 1.13-1.58) and 1.61 (95% CI, 1.22-2.18), while participants with BO and BB genotypes demonstrated ORs of 1.45 (95% CI, 1.14-1.85) and 2.42 (1.28-4.57). The population attributable fraction for non-O blood group was 19.5%. This finding verified previous observations that non-O blood groups were associated with pancreatic cancer risk (25-27).

We verified this finding using community-based blood donors in Pittsburgh. Among 708,842 donors to Pittsburgh's Central Blood Bank between 1979 and 2009, 274 pancreatic cancer cases with ABO blood group typing were identified (28). We found a statistically significantly higher frequency of blood group A amongst pancreatic cancer patients compared to its frequency amongst the regional blood donors [47.63% vs. 39.10%, odds ratio (OR) = 1.43, $P = 0.004$]; we also observed that the frequency of blood group O was significantly lower amongst pancreatic cancer patients relative to the community blood donors (32.12% vs. 43.99%, OR = 0.60, $P = 0.00007$). Thus, the effect of blood group is relevant to our patient populations.

In the current study, we compared the ABO blood group genotypes of participants with chronic pancreatitis and controls from the North American Pancreatitis Study 2 (NAPS2) cohort to determine whether blood group may influence the risk of developing chronic pancreatitis. We further evaluated cases according to etiology as an approach to understanding high-risk pathways (18) and to determine if the mechanisms involved in disease risk could overlap with those factors which play a role in pancreatic carcinogenesis or whether they are independent.

Materials and Methods

Study Population

The North American Pancreatitis Study 2 (NAPS2) is a multicenter consortium of 20 US centers which prospectively enrolled 1000 pancreatitis patients (540 chronic pancreatitis and 460 recurrent acute pancreatitis patients) and 695 controls between August 2000 and September 2006. Previous work has been published which describes the NAPS2 cohort in great depth (4, 29). In brief, the final NAPS2 dataset comprised all study participants who signed a consent form and completed a questionnaire; the majority of study participants also donated a blood sample. Data on patients was organized according to diagnosis, supporting documentation, etiological classification of disease, clinical signs and symptoms including pain patterns and quality of life, medication use and therapeutic interventions. Both patients and healthy control participants answered questions regarding past medical history, family history, and environmental exposures (including alcohol and tobacco use). Additionally, all treating physicians completed a comprehensive questionnaire assessing these same factors related to their individual patients, establishing etiologies for their pancreatitis as well as describing disease-related lifestyle factors. Upon achieving target enrollment, data was organized and classified to facilitate future analysis.

Chronic pancreatitis was confirmed based on patient history and findings on imaging studies and histological sample. Controls who were blood relatives of chronic pancreatitis patients were analyzed both as a whole and separately in our final analyses. Physicians were provided with a list of potential etiologies for each chronic pancreatitis patient's disease, including alcohol, cystic fibrosis, gallstones, hyperlipidemia, hyperparathyroidism, hereditary, medication-induced, pancreas divisum, trauma, idiopathic, or other (write in) and they could choose more than one etiology for each patient. Within the current study, chronic pancreatitis subgroups were further defined by their physicians as having alcohol as a singular or contributing cause of their chronic pancreatitis ($n=178$), non-alcohol related chronic pancreatitis ($n=254$), and idiopathic chronic pancreatitis ($n=133$), which was a subset of the non-alcohol related chronic pancreatitis patients. Within our study, certain patients were also evaluated separately who reported engaging in very heavy drinking (>60 grams of alcohol per day) ($n=97$).

Drinking categories based on alcohol consumption during the participants' heaviest drinking period were established. Study participants were classified as abstainers (no alcohol

consumption or < 20 drinks in lifetime), light drinkers (≤ 0.5 drinks per day or ≤ 3 drinks per week), moderate drinkers (> 0.5 to 1 drink per day or 4 to 7 drinks per week for women; > 0.5 to 2 drinks per day or 4 to 14 drinks per week for men), heavy drinkers (> 1 to < 5 drinks per day or 8 to 34 drinks per week for women; > 2 to < 5 drinks per day or 15 to 34 drinks per week for men), and very heavy drinkers (≥ 5 drinks per day or ≥ 35 drinks per week for both genders). Smoking status was classified as never (smoked ≤ 100 cigarettes in lifetime) or ever (smoked > 100 cigarettes). Ever smokers were categorized as past or current smokers. Amount of smoking was categorized as < 1 or ≥ 1 pack per day and pack-year history was calculated.

Genotyping Methods

For the purpose of the current study, cases and controls from NAPS2 who had low stock DNA were excluded from genotyping. Blood from a total of 499 chronic pancreatitis patients and 631 controls was evaluated for ABO blood group genotype. Genotyping was performed using Sequenom assay of rs8176746 A/C and rs505922 C/T to classify patients into ABO blood groups according to alleles of these two SNPs. Genotyping was done using a custom Mass ARRAY iPLEX Gold assay (Sequenom, Inc, San Diego, CA), a polymerase chain reaction (PCR) - based single nucleotide extension assay followed by mass measurement by matrix assisted laser desorption ionization – time of flight (MALDI-TOF). All cases and controls in the NAPS2 study were tested for the ABO alleles rs505922 and rs8176746. PCR and extension primers are detailed in table 1.

Comparisons of continuous variables between controls and pancreatitis cases were performed using 1-way analysis of variance and Kruskal-Wallis tests where applicable. If significant results were observed, appropriate 2-group comparisons were performed using the t test or Mann-Whitney test. Categorical data (ABO blood groups) were compared using the χ^2 test.

Results

Table 2 demonstrates how ABO blood group SNPs define blood group, both by biallelic blood group and simple recognized blood group. In table 3, demographic information on our chronic pancreatitis patients is presented. Age at recruitment, current body mass index at recruitment, race, alcohol consumption during the heaviest lifetime drinking period and cigarette smoking behavior were calculated; mean and standard deviation or percentage in each category are displayed. In our sample, chronic pancreatitis patients had significantly lower body mass index (BMI) than controls at the time of study enrollment. Chronic pancreatitis cases were also significantly more likely to be heavy or very heavy drinkers in comparison to controls and were more likely to be current smokers, and less likely to be past or never smokers, than controls. Table 4 shows the overall breakdown of ABO blood groups, in percentages, for all samples, for our controls (related and unrelated to cases) and for the total sample of chronic pancreatitis patients.

Table 5 displays information regarding simple ABO blood group among controls and chronic pancreatitis cases, sub-divided by diagnosis, drinking habits and the presence of pancreatitis-predisposing mutations. The rs8176746 minor allele was present in 7.4% of chronic pancreatitis cases vs. 6.1% of controls (P=non-significant [NS]) and the rs505922 minor allele was present in 34.1% of cases and 34.3% of controls (P=NS). Allele frequency among chronic pancreatitis subtypes was also similar to controls (P=NS). The O blood group was non-significantly more common among patients than controls (44.7% vs. 42.0%, P=0.36), a difference which was more pronounced among cases with alcohol-related chronic cases (49.3% vs. 42%, P=0.06). Patients with no known mutation in *PRSSI*, *SPINK1* or *CFTR* showed a similar trend in regards to blood group O compared with controls (47.4%

vs. 42.0%, $P=0.10$) Patients who were both alcoholic and who did not carry one of the chronic pancreatitis-predisposing mutations had a significant overrepresentation of the O blood type when compared to all controls, as shown in table 6 (OR 1.54, 95% Confidence interval [CI] 1.09-2.17; $P=0.01$). When comparisons of expected versus documented O blood group were made between chronic pancreatitis cases and unrelated controls only, the relationship between non-alcoholic, non-mutation status chronic pancreatitis and O blood group remained significant (OR 1.43, 95% CI 1.01-2.05; $P=0.047$; see table 7).

Discussion

This study extends our knowledge about the genetic risk of pancreatic diseases and potential mechanism by defining the risk of non-O blood groups to chronic pancreatitis. The primary finding was that the rs8176746 and rs505922 genotypes associated with the A, B or AB blood group are not associated with chronic pancreatitis, which distinguishes chronic pancreatitis risk from the established blood group risk for pancreatic cancer. An unexpected finding was that genotypes associated with non-O blood groups may protect individuals with alcohol-related chronic pancreatitis who do not carry pancreatitis-associated genetic mutations from developing their disease. This unexpected finding is hypothesis generating and must be validated or refuted in future studies.

While the mechanisms associated with the development of chronic pancreatitis are complex, several patterns are beginning to emerge. Autoimmune pancreatitis occurs in a small subset of patients with pancreatitis and the mechanisms are clearly distinct from the more typical forms of chronic pancreatitis. Episodes of severe acute pancreatitis resulting in pancreatic necrosis (necrosis-fibrosis pathway) account for another subset of patients. Hereditary pancreatitis from a gain-of-function cationic trypsinogen gene (*PRSSI*) mutation or two pancreatic secretory trypsin inhibitor gene (*SPINK1*) mutations comprises another distinct subset (30-32). Most patients with chronic pancreatitis, including alcohol-related chronic pancreatitis, appear to fall into a two-hit pathway that is initiated by an episode of acute pancreatitis and progresses to fibrosis subsequent to other stresses (6). This model has been further dichotomized by the effect *SPINK1*, with strong effects being linked to trypsin-activating etiologies and lesser effects being associated with alcohol-related pathways (18). From this perspective, non-O blood group genotypes appear to protect from progression along an alcohol-related pathway. Of note, patients with heavy drinking also tend to be heavy smokers, and the current study was not powered to determine which risk factor might have been affected by blood group-related mechanisms.

A large body of work has investigated the role of genetics and pancreatic diseases. Strong risk associations with chronic pancreatitis have been made between mutations in the cationic trypsinogen gene (*PRSSI*), the cystic fibrosis transmembrane receptor gene (*CFTR*) and serine protease Kazal type I gene (*SPINK 1*) (18, 30, 32-34). Additionally, studies—including our own recent, large-scale investigation—have documented that very heavy alcohol consumption (>5 drinks, or > 60 grams per day) as well as the amount of cigarette smoking significantly increase the risk of developing chronic pancreatitis, and the effects of alcohol and smoking appear to be more than additive (4). Furthermore, the interaction of genetic predisposing mutations and behavioral risk factors (alcohol and cigarettes) has demonstrated a compounding effect on the progression and severity of chronic pancreatitis (35-37).

Individuals who have been diagnosed with chronic pancreatitis are known to have a significantly greater likelihood of developing pancreatic adenocarcinoma (14, 38) and ABO blood group may affect pancreatic adenocarcinoma risk. In particular, in previous studies, individuals with blood group O have been shown to have gained protection from this highly

fatal form of cancer (23, 24, 27, 28). However, our own study shows that blood group O does not appear to be protective against chronic pancreatitis in the same way that it may reduce the likelihood of adenocarcinoma. Chronic pancreatitis is generally characterized by persistent intrapancreatic enzyme activation which causes a prolonged state of inflammation resulting in glandular destruction. Chronic pancreatitis and pancreatic cancer share a similar etiologic pathway involving recurrent pancreatic injury, DNA damage and cell cycling [reviewed in (39)]. Additionally, sustained inflammation drives the progression of each disease entity and influences the severity of chronic pancreatitis (38).

For over 200 years, a causative link between chronic inflammation and cancer has been recognized (40). Both infectious and non-infectious pathological inflammatory processes have recently been documented as playing an etiologic role in carcinogenesis, and many studies suggest that pancreatic cancer begins with the establishment of chronic inflammation (38, 41). Inflammatory mediators such as nuclear factor-kappa B (NF- κ B), cyclooxygenase-2 (Cox-2), and tumor necrosis factor alpha (TNF α), are known to facilitate tumor cell growth and metastasis (41). NF- κ B and interleukin-8 (IL-8) are important mediators of the inflammatory process in chronic pancreatitis and both have been implicated in the development of a variety of other malignancies (41, 42). One study observed that, while specific inflammatory components are specific either to chronic pancreatitis or tissue from pancreatic tumors, increased staining of the p50 NF- κ B subunit and IKK α kinase (a protein that permits activation of NF- κ B) was observed in both chronic pancreatitis and pancreatic neoplasia (43). The similar inflammatory components and downstream effectors which are present in chronic pancreatitis as well as in pancreatic cancer have warranted the investigation and cross-validation of singular risk factors such as ABO blood group.

ABO blood group is an established risk factor for gastric cancer (44-46) as well as non-gastrointestinal forms of cancer, such as ovarian cancer (47). In general, it appears that individuals with blood group O may be at diminished risk of developing particular forms of cancer, while individuals with blood groups A, B, and/or AB have heightened cancer risk. The relationship of blood group and pancreatic cancer may be a consequence of the effects of *Helicobacter pylori* (*H.pylori*) infection. Firstly, some studies have noted an association between *H.pylori* infection and the risk of pancreatic adenocarcinoma (48, 49), especially among certain cohorts, such as non-smokers and non-risk drinkers (48). Colonization of human hosts by *H.pylori* occurs due to binding to gastric mucins rather than to the mucosal epithelium (50) and the most efficient binding takes place on mucin Lewis (b) antigens (51). Lewis antigens comprise the same oligosaccharides that are part of the ABO antigens. A recent study of 373 case patients and 690 gender- and age-matched control subjects used enzyme-linked immunosorbent assay (ELISA) to determine seropositivity for *H. pylori* and its virulence protein CagA and to examine their relationship to ABO blood group (52). An association between pancreatic cancer risk and CagA-negative *H. pylori* seropositivity was observed among individuals with non-O blood group but not among those with O blood group (OR 2.78, 95% CI 1.49 -5.20, $P = .0014$; OR 1.28, 95% CI 0.62 - 2.64, $P = 0.51$, respectively).

In our study, blood group O was not protective against the development of chronic pancreatitis. In fact, chronic pancreatitis patients whose physicians included alcohol as part of their pancreatitis etiology and who did not carry one of the strongest disease-predisposing mutations, had a significantly greater likelihood of being of blood group O, suggesting it may be a risk factor among patients without other recognized genetic causes. It is widely recognized that only a small subset of individuals who are alcoholic progress to develop chronic pancreatitis while the majority of heavy drinkers do not develop irreversible pancreatic damage (4, 16). O-type blood may be a risk factor which drives this progression and affects the process in a mechanism that differs from the mechanism causing pancreatic

inflammation and fibrosis due to repeated trypsinogen activation. Conversely, most people with pancreatic cancer do not have a previous diagnosis of chronic, and, therefore, blood groups A and B may tip the balance in a different way to help initiate or promote pancreatic carcinogenesis. The strong effect of chronic pancreatitis on the risk of pancreatic adenocarcinoma is therefore most likely independent of an individual's ABO blood type.

Our study had some limitations. There were notable differences between our cases and controls; individuals with chronic pancreatitis had lower current BMI than controls, which is often related to diminished appetite, inefficient digestion, metabolic derangements involved in alcohol-induced chronic pancreatitis, and the effects of chronic pain (53). In addition, there were higher percentages of heavy drinkers and current smokers among chronic pancreatitis patients in contrast to the study controls. None of these factors is known to affect ABO blood group and therefore should not have biased our results in either a positive or negative direction. There were 176 unaffected control participants who were genetically-related to the cases. To avoid the effects of genetic bias in our results, we chose to evaluate ABO blood group for chronic pancreatitis cases and the 455 unrelated controls separately and our results maintained similar significance as when blood relatives were included in the control analyses. Including related controls in this study, however, would make our control and case groups more similar in reference to ABO blood group, which would be more likely to attenuate any associations, rather than to intensify them. Our study had numerous strengths. The adequately-powered study size and meticulous data collection on all participants adds credibility to our findings. Chronic pancreatitis cases were recruited from secondary or tertiary referral centers; therefore, their chronic pancreatitis diagnosis and disease course were well-documented. Additionally, many previous studies evaluating disease risk and ABO blood group have used self-reported blood group (blood type) in their comparisons; a particular strength of our study was the unequivocal results of ABO SNP genotyping and blood group classification.

In summary, our study does not implicate ABO blood group as a risk or protective factor for chronic pancreatitis, although a relationship between blood group O and non-genetic, alcohol-associated chronic pancreatitis warrants further investigation. The interactive roles of cigarette smoking and heavy drinking and blood group should also be evaluated in future, large-scale studies of multi-factorial pancreatic diseases.

Acknowledgments

We would like to acknowledge the other members of the NAPS2 consortium: Adam Slivka, Robert H. Hawes, Michelle A. Anderson, Mary E. Money, Peter A. Banks, Michele D. Bishop, John Baillie, Stuart Sherman, James DiSario, Frank R. Burton, Timothy B. Gardner, Stephen T. Amann, Andres Gelrud, Simon K. Lo, Mark T. DeMeo, William M. Steinberg, Michael L. Kochman, Babak Etemad, Christopher E. Forsmark, Janette Lamb, M. Michael Barmada, and Beth Elinoff.

Support: This publication was made possible by Grant Number RO1 DK061451 (DCW) and UL1 RR024153 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the NCRR or NIH.

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Table 1
PCR and extension primers

	ABO - O	ABO - B
SNP	rs505922	rs8176746
PCR1	TGGGTCAAGATGTATCCAGC	AAGGACGAGGGCGATTTC
PCR2	CTTGTTGGTCTTTGTTTCCC	ATCATGGCCTGGTGGCAG
extension primer	GTATCCAGCTGTACCTTT	CGAGGGCGATTCTACTAC
EXT1_CALL	C	C
EXT1_MASS	5687.7	6051
EXT2_CALL	T	A
EXT2_MASS	5767.6	6075

Table 2
ABO allele, blood group and simplified blood group

ABO B rs8176746	ABO O rs505922	Blood group	Simple blood group
C	C	A/A	A
C	CT	A/O	A
CA	C	A/B	AB
A	C	B/B	B
CA	CT	B/O	B
C	T	O/O	O

Table 3
Demographic information of healthy controls and chronic pancreatitis patients

	Controls (N=631)	Chronic pancreatitis patients (N=499)	P value
	Mean (standard deviation)	Mean (standard deviation)	
Average age	52 (14.5)	50 (15.9)	0.009
Body mass index (current)	28 (6.3) kg/m ²	25 (5.4) kg/m ²	0.009
	Number (percent)	Number (percent)	P value
Male gender	224 (35.5)	261 (53.3)	< 0.001
Race			
Caucasian	552 (87.8)	431 (86.5)	
African-American	36 (5.7)	47 (9.4)	
Other	41 (6.5)	20 (4.0)	0.014
Alcohol consumption [†]			
Abstain	162 (27)	116 (23.4)	
Light/moderate	330 (55.1)	192 (38.8)	
Heavy	71 (11.9)	62 (12.5)	
Very heavy	36 (6.0)	125 (25.3)	<0.001
Cigarette smoking			
Never	310 (49.7)	142 (28.7)	
Past	181 (29)	121 (24.4)	
Current	133 (21.3)	232 (46.9)	<0.001

[†] Alcohol consumption during the heaviest lifetime drinking period

Table 4
Overall blood group percentages for controls and chronic pancreatitis patients

Blood Group	Number	A	AB	B	O
All Samples	1130	41.1%	5.0%	10.6%	43.2%
Controls (all)	631	42.6%	5.5%	9.8%	42.0%
Unrelated controls	455	42.2%	5.1%	9.0%	43.7%
Related controls *	176	43.8%	6.8%	11.9%	37.5%
Chronic pancreatitis cases	499	39.3%	4.4%	11.6%	44.7%

* Related = blood relatives

All P values comparing chronic pancreatitis cases to controls are non significant

Table 5
Blood group stratified by alcohol consumption and mutation status

Blood Group		A	AB	B	O
All Samples	1130	465 (41.2%)	57 (5.0%)	120 (10.6%)	488 (43.2%)
	Number	Number (Percent)			
Controls (all)	631	269 (42.6%)	35 (5.5%)	62 (9.8%)	265 (42.0%)
Unrelated controls	455	192 (42.2%)	23 (5.1%)	41 (9.0%)	199 (43.7%)
Related Controls	176	77 (43.8%)	12 (6.8%)	21 (11.9%)	66 (37.5%)
Chronic Pancreatitis Patients Only					
	Number	Number (Percent)			
Chronic pancreatitis (CP)	499	196 (39.3%)	22 (4.4%)	58 (11.6%)	223 (44.7%)
Idiopathic CP	145	64 (44.1%)	5 (3.4%)	15 (10.3%)	61 (42.1%)
Alcohol-related/heavy drinking subgroups	Number	Number (Percent)			
Alcohol-related (per physician's diagnosis) [†]	219	76 (34.7%)	10 (4.6%)	25 (11.4%)	108 (49.3%)
Not alcohol-related	280	120 (42.9%)	12 (4.3%)	33 (11.8%)	115 (41.1%)
Very heavy drinkers [‡] with CP	125	45 (36.0%)	6 (4.8%)	14 (11.2%)	60 (48.0%)
Not very heavy drinkers with CP	374	151 (40.4%)	16 (4.3%)	44 (11.8%)	163 (43.6%)
Predisposing mutation status					
Mutation carriers with CP [*]	151	64 (42.4%)	8 (5.3%)	21 (13.9%)	58 (38.4%)
Non-mutation carriers with CP	348	132 (37.9%)	14 (4.0%)	37 (10.6%)	165 (47.4%)

Alcoholism/heavy drinking subgroups

[†] Alcohol-related = either the singular or a contributing etiology, as per physician reporting

[‡] Very heavy drinkers = ≥5 drinks per day or ≥35 drinks per week for men or women

^{*} Mutations in any of the following genes: PRSS1 (cationic trypsinogen), CFTR (cystic fibrosis transmembrane receptor) and SPINK1 (serine protease Kazal type I)

Table 6
Odds ratios (OR) that a case or control would be of blood group O, including related controls

All CP and all controls	Cases	Controls	Case non-carriers	Control non-carriers	OR	95 % CI	P-value
O all CP	223	265	276	366	1.12	0.88- 1.41	0.36
O (VHD* CP)	60	265	65	366	1.27	0.87-1.87	0.22
O (Alcohol-related [†] CP)	108	265	111	366	1.34	0.99-1.83	0.06
O (Alcohol-related CP) vs. VHD controls	108	13	111	23	1.72	0.83-3.57	0.14
O (Genetic mutation +) [‡]	58	265	93	366	0.86	0.60-1.24	0.42
O (Genetic mutation -)	165	265	183	366	1.25	0.96-1.62	0.10
O (Alcohol-related, Genetic mutation-)	88	265	79	366	1.54	1.09-2.17	0.01
O (Genetic mutation -, VHD)	49	265	47	366	1.44	0.94-2.21	0.10

CP = chronic pancreatitis patients; 95% CI=confidence interval

* VHD = very heavy drinkers

[†] Alcohol-related =either the singular or a contributing etiology, as per physician reporting

[‡] Mutations in any of the following genes: PRSS1 (cationic trypsinogen), CFTR (cystic fibrosis transmembrane receptor) and SPINK1 (serine protease Kazal type I)

Table 7
Odds ratios (OR) that a case or control would be of blood group O, unrelated controls only

All CP, unrelated controls only	Cases	Controls	Case non-carriers	Control non-carriers	OR	95 % CI	P-value
O all CP	23	199	276	256	1.04	0.81-1.34	0.77
O (VHD CP)	60	199	65	256	1.19	0.80-1.77	0.40
O (Alcohol-related CP)	108	199	111	256	1.25	0.91-1.73	0.17
O (Alcohol-related) vs. VHD controls	108	11	111	15	1.33	0.58-3.02	0.50
O (Genetic mutation +)	58	199	93	256	0.80	0.55-1.17	0.25
O (Genetic mutation -)	165	199	183	256	1.16	0.88-1.54	0.30
O (Alcohol-related, Genetic mutation)	88	199	79	256	1.43	1.01-2.05	0.04
O (Genetic mutation -, VHD)	49	199	47	256	1.34	0.86-2.08	0.19

CP = chronic pancreatitis patients; 95% CI=confidence interval

* VHD = very heavy drinkers
† Alcohol-related =either the singular or a contributing etiology, as per physician reporting
‡ Mutations in any of the following genes: PRSS1 (cationic trypsinogen), CFTR (cystic fibrosis transmembrane receptor) and SPINK1 (serine protease Kazal type I)