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Pain Experience in Pancreatitis: strong association of genetic risk loci for anxiety and PTSD in patients with severe, constant and constant-severe pain.

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Abstract

Background: Recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) are progressive inflammatory syndromes with variable features. Pain is the primary feature that contributes to low physical and mental quality of life with a third of patients reporting severe pain. Pain experience is worsened by depression. Here we tested the hypothesis that genetic risk for the psychiatric conditions of anxiety and post-traumatic stress disorder (PTSD) are associated with pain in CP and RAP+CP subjects.

Methods: The study cohort included phenotyped and genotyped RAP and CP patients from the North American Pancreatitis Study II (NAPS2) of European Ancestry. Candidate genetic association studies were based on the absence of pain versus pain that is constant, constant-severe, or severe. Twenty-eight candidate genetic loci for anxiety and PTSD risk were identified in the literature and were the focus of this study.

Results: We identified 24 significant pain-associated SNPs within 13 loci across the 3 pain patterns in CP and RAP+CP ($p<0.002$). Thirteen anxiety or PTSD genes were within these pain loci indicating non-random associations ($p<4.885\times10^{-23}$). *CTNND2* was associated with all pain categories and all pancreatitis etiologies. Implicated systems include Neuronal Signaling *(HTR2A, DRD3, NPY, BDNF)*, Hypothalamic-Pituitary-Adrenal Axis *(NR3C1, FKBP5*) and cell-cell interaction *(CTNND2, THBS2).*

Conclusion: A component of constant and severe pain in patients with RAP and CP is associated with genetic predisposition to anxiety and PTSD. Identification of patients at risk eligible for trials of targeted treatment as a component of a multidisciplinary pain management strategy should be formally evaluated.

Clinical Trials Registration: Clinicaltriasl.gov.# NCT01545167

Keywords

pain; pancreatitis; anxiety; PTSD; genetics

Introduction

Pancreatitis is an inflammatory syndrome that can become chronic resulting in irreversible destruction of the pancreas with variable levels of fibrosis, diabetes mellitus, exocrine

pancreatic insufficiency (EPI), and abdominal pain [1–3]. The complex etiology of acute pancreatitis (AP), recurrent AP (RAP) and chronic pancreatitis (CP) is associated with metabolic and toxic factors such as smoking, alcohol use, hypertriglyceridemia, hypercalcemia, obstructive etiologies, and genetic factors such as variants in or near *CASR, CEL, CFTR, CLDN2, CPA1, CTRC, PRSS1, SPINK1, TRPV6,* and *UBR1* among other genes [4–6]. Additional environmental factors and genetic variants also increase patients' risk for secondary complications such as diabetes [7–9] and pancreatic cancer [10–14]. AP and RAP typically occur before progressing to CP [1].

Severe, constant pain, a symptom seen in 1 in 3 CP patients, is the major driver of low quality of life (QOL) in these patients [1, 15–18]. However, even at the early stages of pancreatitis, pain negatively impacts physical and mental health and QOL [15–17]. Thus, the detriment in mental QOL in CP is not fully explained by pain alone and may be related, in part, to psychological determinants. Similarly, the reason for the variability of the pain experience by pancreatitis patients is unknown, but it may be influenced by a genetic predisposition to psychiatric disorders, given that psychiatric disorders and pain disorders often co-occur [19]. In fact, depression and anxiety are common in CP patients [18, 20].

Both children and adults with chronic abdominal pain commonly report comorbid psychological distress and trauma [21]. It is plausible that pain associated with a pancreatitis attack could be a sufficient stressor to induce psychopathology in genetically at risk patients [18]. Existing mental disorders could worsen and be worsened by the pain of the pancreatitis attack in a vicious cycle [19, 22, 23]. We have previously identified depression risk genes in pancreatitis patients with constant-severe pain; therefore, the focus of this investigation was on anxiety and post-traumatic stress disorder (PTSD) [23, 24].

The effectiveness of management for pain and poor QOL in patients with pancreatitis is often poor [25–27]. Recognition of the role of psychiatric risk in the pain experience may help develop more effective pain management for pancreatitis patients. To test the hypothesis that pain is associated with genetic risk loci for anxiety and PTSD, we investigated patients in the deeply phenotyped and genotyped North American Pancreatitis Study II (NAPS2) cohorts.

Methods

NAPS2

The NAPS2 cohort represents three sequential, cross-sectional, case-control studies of RAP and CP as previously described [28–30]. Standardized questionnaires were used for data collection and single nucleotide polymorphism (SNP) arrays (Illumina HumanOmniExpress BeadChip and HumanCoreExome) were used for genotyping [2], with supplemental, targeted genotyping as previously described [24, 31]. The subset of patients used for this analysis from the NAPS2 cohort was CP (N=818) and RAP+CP (N=1,277) subjects of European ancestry (EA). To reduce heterogeneity, the small sample of NAPS2 patients not of EA were excluded.

Pain Categories and Quality of Life

Patterns of pancreatitis pain were defined following Mullady's 6-category severity-frequency classification system with O = no pain; A = episodes of mild pain; B = constant mild to moderate pain; C = episodes of severe pain; D = constant mild and episodes of severe pain; and E = constant-severe pain during the year prior to recruitment [(1)]. Subjects responding with B, D or E were classified as *constant pain*, subjects responding with C, D and E were classified as *severe pain*, and subjects with D and E were *constant-severe pain*.

Anxiety and PTSD were not directly measured in the patient questionnaires; however, a mental component summary (MCS) score was calculated using responses from the Short Form 12 (SF-12) [(17)]. The MCS is as a measure of mental QOL, with higher scores correlating with better QOL and a score of 50 representing average health status [(1, 17)]. The MCS has previously been used as an indicator of mental health and measure of depressive disorders [(24, 32, 33)]. Thus, we used a lower than average MCS as a proxy indicator of poor mental health as had been done previously for depression [(24)].

Demographic and phenotypic data for patients in each pain category was compiled and analyzed using R version 3.6.2 [(34)]. Univariate comparisons were performed based on demographic variables using Pearson's chi-squared test for categorical data and the Wilcoxon rank test for continuous data. Two-tailed p-values < 0.05 were considered statistically significant (Tables 1–6) [(34)].

Variables

Two subsets of patients were tested independently, one group labeled RAP+CP, included both RAP patients and CP patients, and the other comprised of only patients with chronic pancreatitis (CP). All patients were classified as "case" or "control" based on the presence or absence of specific pain endophenotypes. A total of six studies were conducted looking at each of the three pain categories described above within both categories of pancreatitis patients. Both categories were used to compensate for a possible power reduction from assuming similarities of RAP and CP, even though RAP is a part of the CP pathogenesis and to increase sample sizes [(1, 2)]. A sample of only RAP patients (N=453) from NAPS2, and used in the RAP+CP group, was used to replicate major gene associations (See Tables S1 and S2, Supplemental Digital Content 1, which reports results from replication analysis).

Candidate Genes

A literature search was conducted in the summer of 2020 to compile a non-comprehensive list of candidate, autosomal risk genes for anxiety and PTSD (See Table S3, Supplemental Digital Content 2, for a list of candidate genes). These are genes implicated in or suggested as being associated with anxiety and/or PTSD, and genes also associated with depression or antidepressant response are labeled in Table S3 (See Table S3, Supplemental Digital Content 2, for a list of candidate genes). As a supplemental, the same candidate gene approach was repeated using a list of genes reported for anxiety and PTSD in the GWAS Catalog (See Tables S4 and S5, Supplemental Digital Content 3, which reports gene candidate results using GWAS Catalog) [(35)].

Genetic Data Analysis

The genetic analysis was constructed as a candidate gene review using data from pancreatitis subjects similar to what was done previously with depression [24]. This candidate gene review was conducted using PLINK 1.9 software [36]. Quality control methods for SNP data have been previously reported [2, 24]. Data was fit to a logistic regression to test for associations. The analysis was restricted to the list of candidate genes with a border of 50 kilobases (kb) added to each gene in PLINK 1.9. Since 28 gene regions instead of the whole genome was tested, the level of significance was relaxed to $p<0.002$ [37, 38]. To control for ancestry, the first four principal components of ancestry were included as covariates. Additional covariates were age, sex, body mass index (BMI), and a variable to control for differences across SNP chips. The minor allele frequency (MAF) threshold was set to 0.01.

SNPs meeting the required significance threshold were then combined into groups (likely haplotypes) based on linkage disequilibrium (LD) (± 250 kb from index SNP, $r^2 > 0.5$) in PLINK 1.9 [36]. The lead SNPs ($p \leq 0.002$) were annotated with genes within the borders of these LD regions based on genome build GRCh37/hg19.

The MAF for the lead SNPs was calculated using PLINK 1.9 (Table 7) [36]. Finally, GTEx (https://gtexportal.org/home/) was queried to determine if any of the lead SNPs were also expression quantitative trait loci (eQTLs) (See Table S6, Supplemental Digital Content 4, which reports eQTLs) [39].

We used an online exact hypergeometric probability calculator to test the probability that the Anxiety/PTSD gene loci were associated with pancreatitis pain loci by chance alone [40].

Results

Patient Characteristics (Tables 1–6)

All six tested categories of disease status and pain pattern show that higher pain levels are all significantly associated with lower average age ($p<1\times10^{-5}$). Additionally, higher pain levels are all significantly associated with lower mental QOL scores ($p<1\times10^{-5}$). Individually, constant pain is associated with smoking ($p=0.0027$) and EPI ($p=0.0009$) in CP patients, and with sex ($p=0.047$), smoking ($p=6.13\times10^{-5}$), EPI ($p<1\times10^{-5}$), and diabetes ($p=0.03$) in RAP+CP patients. Constant-severe pain is associated with smoking ($p=0.0018$) and EPI ($p=0.0085$) in CP, and sex ($p=0.028$), smoking ($p=0.0002$), and EPI ($p=2.24\times10^{-5}$) in RAP+CP patients. Finally, severe pain in CP is associated only with younger age ($p<1\times10^{-5}$) and MCS ($p<1\times10^{-5}$), while severe pain in RAP+CP patients is associated with smoking ($p=0.0065$) and EPI ($p=0.022$).

Candidate Anxiety/PTSD Genes Associated with Pain in CP/RAP+CP

Candidate gene studies were conducted within CP and RAP+CP patients across the three pain phenotypes. Resultant odds ratios (OR), 95% confidence intervals (CI), standard error (SE), and p-values for the 24 unique lead SNPs representing 13 loci across the 6 tested categories are reported in Table 7. The biological function of these known Anxiety/PTSD gene products and associated systems is described below.

CTNND2 was the anxiety and/or PTSD candidate gene most commonly associated with the various pain categories and was previously associated with depression [24]. Additionally, several genes have multiple loci with different effects. The OR's associated with specific SNPs within different loci suggest that some are protective (OR <1) and others risk (OR >1) for worse pain experience in pancreatitis, suggesting complex gene expression regulatory mechanism. Pain and Anxiety/PTSD risk SNPs in *DRD3* are associated with constant pain in the CP category, but we also identified a SNP that was protective for severe pain in the RAP+CP category.

The probability that these loci for psychiatric disorder genes overlapped with loci for severe pancreatic pain was tested. The probability that the loci were shared by chance alone was very low ($p<4.885\times10^{-23}$), indicating a statistically significant association.

Of the 24 lead SNPs, 6 have reported eQTLs from GTEx [39] (Table 7, See Table S6, Supplemental Digital Content 4, which reports eQTLs). The fact that these SNPs are seen in a variety of tissues indicates that the function of these genes is not pancreas-specific and reflects secondary disorders that make the experience of pancreatic disease worse.

Discussion

The poor QOL experienced by many patients with pancreatitis is linked to the pain experience, which is affected by pain signaling, central processing and the emotional response to those signals [1, 15–17, 41]. We previously noted that symptoms of depression in RAP and CP are associated with constant-severe pain and genetic loci containing depression risk genes [24]. We extended the findings of genetic predisposition to depression to investigate genetic predisposition to anxiety and PTSD and identified several candidate genes for anxiety and PTSD that deserve further targeted studies.

Both anxiety and PTSD interfere with daily life and relationships. A common model for understanding the variable etiology of these psychiatric disorders is "diathesis-stress" or rather genes and stress [23, 42]. This model predicts that after a combination of genes and outside stressors reaches a threshold stress-related psychopathology emerges [23].

Generalized anxiety disorder (GAD) is characterized by excessive and uncontrolled worry that is not appropriate to the actual risk posed by a stimulus or in the absence of the stimulus [42]. In addition to exposure to stress early in life, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis also plays a role in anxiety disorders [42, 43]. GAD overlaps phenotypically and is comorbid with other stress related disorders (such as other anxiety disorders, and depression) [42]. Twin studies produced a heritability estimate of 30–50% [23, 42]. About two thirds of children experiencing chronic pain also exhibit anxiety, and ~30–60% of patients with chronic pain will experience anxiety [22, 44]. Patients with chronic pain and anxiety tend not to respond well to treatment of their pain [22, 44]. One study even showed that although children with anxiety and pain were more likely to adhere to cognitive behavioral therapy for their pain, they were less likely to respond to it than other children with pain [44].

Posttraumatic Stress Disorder typically occurs in some individuals after experiencing traumatic events [23]. PTSD is characterized by four hallmark symptoms: hyper-arousal or reactivity, re-experiencing of the trauma, poor mood and thoughts related to the trauma, and avoidance of stimuli related to the trauma [23]. Twin studies have shown that both exposure to trauma (combat) and the symptoms of PTSD are heritable [23]. Additionally, PTSD can increase pain perception [45].

Clinical Implications

These findings further expand the opportunities to improve patient care through precision medicine [46]. Clinicians typically find it difficult to effectively treat CP pain due to the lack of precise therapies to relieve the different etiologies and severity patterns of pain in pancreatitis patients. In addition, the regulatory pressure to avoid opiates adds another challenge. The possibility of identifying pain-predominant symptoms linked to genetic risk for GAD, PTSD or depression at the point-of-care (including rural communities) provides a new precision medicine option for selecting specific medications for individual patients, educating them about how these psychological tendencies affect pain perception and QOL, and referring them for adjunctive therapy(ies) such as cognitive behavioral therapy that targets the specific aspect of pain. However, randomized, double blind, placebo-controlled trials are needed to determine the correlation between the genetic predictions and the utility of specific psychotropic medications and the magnitude of the effects, with and without additional psychiatric interventions.

Limitations

The limitations include relatively small sample size, including only people of EA, and lack of psychiatric phenotypic data [24]. An additional limitation of this study may be a non-exhaustive candidate gene list [47]. The candidate gene list was intended to capture the more established loci for anxiety and PTSD. However, we used a tool using exact hypergeometric probability to determine that the overlap (n=15) of our candidate genes (n=28) with pain genes (n=315) is not by random chance alone ($p<4.885\times10^{-23}$, 30,000 total genes) [40]. Refer to the Tables S4 and S5, Supplemental Digital Content 3, which reports gene candidate results using GWAS Catalog for more exhaustive results using genes reported in the GWAS Catalog as being associated with anxiety and/or PTSD [35].

Conclusion

Several established genes associated with anxiety and PTSD are also associated with pain in pancreatitis. Many of these genes are involved with dopamine biology: *DRD3*, *BDNF*, *SLC6A3*, and *NPY*. Other pathways that these candidate genes are associated with include neuronal signaling, prepulse inhibition, HPA axis, G protein-coupled receptor signaling, and cell-cell interaction (See Table 8 and Supplemental Digital Content 5, for a discussion of the significant candidate genes). The cell-cell interaction gene *CTNND2* has shown significant associations across all pain categories in CP and RAP+CP patients. These associations to pain phenotypes were also replicated in our cohort, using only RAP patients (See Tables S1 and S2, Supplemental Digital Content 1, which reports results from replication analysis). Pain in pancreatitis is subjective and a complex symptom. It is not predictably responsive to current therapies, and has a significant impact on QOL. As we showed previously

with depression, identifying patients at risk for psychiatric disorders may be beneficial in recommending alternative pain therapies [24]. Further studies into genotypic and phenotypic associations of pain and mental health are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AP	Acute Pancreatitis
BMI	Body Mass Index
BP	Base Pair
Chr	Chromosome
CI	Confidence Intervals
CP	Chronic Pancreatitis
EA	European Ancestry
EPI	Exocrine Pancreatic Insufficiency

eQTL	Expression Quantitative Trait Loci
GAD	Generalized Anxiety Disorder
HPA	Hypothalamic-Pituitary-Adrenal
Kb	Kilobases
LD	Linkage Disequilibrium
MAF	Minor Allele Frequency
MCS	Mental Component Summary
NAPS2	North American Pancreatitis Study II
OR	Odds Ratio
PTSD	Posttraumatic Stress Disorder
QOL	Quality Of Life
RAP	Recurrent Acute Pancreatitis
RAP+CP	Variable: RAP and CP Pancreatitis Patients
SD	Standard Deviation
SE	Standard Error
SF-12	Short Form 12
SNP	Single Nucleotide Polymorphism
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor

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Study Highlights:

WHAT IS KNOWN

- Pancreatitis pain is variable and can be severe, leading to a poor quality of life in some patients
- Current pain treatment strategies are often suboptimal or ineffective
- Depression risk loci overlap pancreatitis pain loci

WHAT IS NEW HERE

- Pancreatitis genetic loci associated with severe pain overlap with generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD) risk loci
- GAD and PTSD are pre-existing risk and are not necessarily only a response to chronic pain.
- Patients who experience constant and severe pancreatic pain may have several overlapping conditions that should be addressed individually as part of a complex disorder

Table 1.

Association of phenotypes within CP patients with constant pain.

Variable	Level	Controls[1] (N=443)	Cases[2] (N=375)	Total (N=818)	p-value
Age at Ascertainment	Mean (SD)	54.3 (16.7)	47.4 (13.2)	51.1 (15.6)	< 1e-05
Sex	Male	247 (55.8%)	185 (49.3%)	432 (52.8%)	0.08
	Female	196 (44.2%)	190 (50.7%)	386 (47.2%)	
Mental QOL	Mean (SD)	47.8 (10.5)	38.5 (11.8)	43.3 (12)	< 1e-05
	Missing	63	13	76	
Drinking	Never	90 (20.5%)	68 (18.1%)	158 (19.4%)	0.46
	Ever	350 (79.5%)	307 (81.9%)	657 (80.6%)	
	Missing	3	0	3	
Smoking	Never	143 (32.4%)	85 (22.7%)	228 (27.9%)	0.0027
	Ever	299 (67.6%)	290 (77.3%)	589 (72.1%)	
	Missing	1	0	1	
EPI	No	308 (69.5%)	218 (58.1%)	526 (64.3%)	0.00091
	Yes	135 (30.5%)	157 (41.9%)	292 (35.7%)	
Diabetes	No	308 (69.5%)	263 (70.1%)	571 (69.8%)	0.91
	Yes	135 (30.5%)	112 (29.9%)	247 (30.2%)	

Percentages shown next to the counts are column percentages within each variable.

[1]Patients without constant pain.

[2]Patients with constant pain.

CP, chronic pancreatitis; SD, standard deviation; QOL, quality of life; EPI, exocrine pancreatic insufficiency.

Table 2.

Association of phenotypes within CP patients with constant-severe pain.

Variable	Level	Controls[1] (N=488)	Cases[2] (N=330)	Total (N=818)	p-value
Age at Ascertainment	Mean (SD)	53.6 (16.4)	47.5 (13.4)	51.1 (15.6)	< 1e-05
Sex	Male	271 (55.5%)	161 (48.8%)	432 (52.8%)	0.068
	Female	217 (44.5%)	169 (51.2%)	386 (47.2%)	
Mental QOL	Mean (SD)	46.8 (10.9)	38.7 (11.9)	43.3 (12)	< 1e-05
	Missing	66	10	76	
Drinking	Never	102 (21.0%)	56 (17.0%)	158 (19.4%)	0.18
	Ever	383 (79.0%)	274 (83.0%)	657 (80.6%)	
	Missing	3	0	3	
Smoking	Never	156 (32.0%)	72 (21.8%)	228 (27.9%)	0.0018
	Ever	331 (68.0%)	258 (78.2%)	589 (72.1%)	
	Missing	1	0	1	
EPI	No	332 (68.0%)	194 (58.8%)	526 (64.3%)	0.0085
	Yes	156 (32.0%)	136 (41.2%)	292 (35.7%)	
Diabetes	No	337 (69.1%)	234 (70.9%)	571 (69.8%)	0.63
	Yes	151 (30.9%)	96 (29.1%)	247 (30.2%)	

Percentages shown next to the counts are column percentages within each variable.

[1]Patients without constant-severe pain.

[2]Patients with constant-severe pain.

CP, chronic pancreatitis; SD, standard deviation; QOL, quality of life; EPI, exocrine pancreatic insufficiency.

Table 3.

Association of phenotypes within CP patients with severe pain.

Variable	Level	Controls[1] (N=312)	Cases[2] (N=506)	Total (N=818)	p-value
Age at Ascertainment	Mean (SD)	55.4 (15.3)	48.5 (15.1)	51.1 (15.6)	< 1e-05
Sex	Male	170 (54.5%)	262 (51.8%)	432 (52.8%)	0.5
	Female	142 (45.5%)	244 (48.2%)	386 (47.2%)	
Mental QOL	Mean (SD)	46.2 (11.3)	41.8 (12.1)	43.3 (12)	< 1e-05
	Missing	61	15	76	
Drinking	Never	61 (19.7%)	97 (19.2%)	158 (19.4%)	0.91
	Ever	248 (80.3%)	409 (80.8%)	657 (80.6%)	
	Missing	3	0	3	
Smoking	Never	99 (31.8%)	129 (25.5%)	228 (27.9%)	0.06
	Ever	212 (68.2%)	377 (74.5%)	589 (72.1%)	
	Missing	1	0	1	
EPI	No	203 (65.1%)	323 (63.8%)	526 (64.3%)	0.78
	Yes	109 (34.9%)	183 (36.2%)	292 (35.7%)	
Diabetes	No	208 (66.7%)	363 (71.7%)	571 (69.8%)	0.15
	Yes	104 (33.3%)	143 (28.3%)	247 (30.2%)	

Percentages shown next to the counts are column percentages within each variable.

[1]Patients without severe pain.

[2]Patients with severe pain.

CP, chronic pancreatitis; SD, standard deviation; QOL, quality of life; EPI, exocrine pancreatic insufficiency.

Table 4.

Association of phenotypes within RAP+CP patients with constant pain.

Variable	Level	Controls[1] (N=770)	Cases[2] (N=507)	Total (N=1,277)	p-value
Age at Ascertainment	Mean (SD)	51.3 (16.9)	46 (13.4)	49.2 (15.8)	< 1e-05
	Missing	14	0	14	
Sex	Male	408 (53.0%)	239 (47.1%)	647 (50.7%)	0.047
	Female	362 (47.0%)	268 (52.9%)	630 (49.3%)	
Mental QOL	Mean (SD)	47.3 (10.7)	38.8 (11.6)	43.7 (11.8)	< 1e-05
	Missing	113	24	137	
Drinking	Never	156 (20.8%)	112 (22.1%)	268 (21.3%)	0.62
	Ever	595 (79.2%)	395 (77.9%)	990 (78.7%)	
	Missing	19	0	19	
Smoking	Never	288 (38.3%)	138 (27.3%)	426 (33.9%)	6.13e-05
	Ever	463 (61.7%)	368 (72.7%)	831 (66.1%)	
	Missing	19	1	20	
EPI	No	600 (79.4%)	332 (65.5%)	932 (73.8%)	< 1e-05
	Yes	156 (20.6%)	175 (34.5%)	331 (26.2%)	
	Missing	14	0	14	
Diabetes	No	589 (77.9%)	367 (72.4%)	956 (75.7%)	0.03
	Yes	167 (22.1%)	140 (27.6%)	307 (24.3%)	
	Missing	14	0	14	

Percentages shown next to the counts are column percentages within each variable.

[1]Patients without constant pain.

[2]Patients with constant pain.

CP, chronic pancreatitis; RAP, recurrent acute pancreatitis; SD, standard deviation; QOL, quality of life; EPI, exocrine pancreatic insufficiency.

Table 5.

Association of phenotypes within RAP+CP patients with constant-severe pain.

Variable	Level	Controls[1] (N=810)	Cases[2] (N=453)	Total (N=1,263)	p-value
Age at Ascertainment	Mean (SD)	50.9 (16.6)	46.1 (13.5)	49.2 (15.8)	< 1e-05
Sex	Male	431 (53.2%)	211 (46.6%)	642 (50.8%)	0.028
	Female	379 (46.8%)	242 (53.4%)	621 (49.2%)	
Mental QOL	Mean (SD)	46.6 (10.9)	39 (11.8)	43.7 (11.8)	< 1e-05
	Missing	104	19	123	
Drinking	Never	169 (21.0%)	99 (21.9%)	268 (21.3%)	0.77
	Ever	636 (79.0%)	354 (78.1%)	990 (78.7%)	
	Missing	5	0	5	
Smoking	Never	303 (37.6%)	123 (27.2%)	426 (33.9%)	0.00023
	Ever	502 (62.4%)	329 (72.8%)	831 (66.1%)	
	Missing	5	1	6	
EPI	No	630 (77.8%)	302 (66.7%)	932 (73.8%)	2.24e-05
	Yes	180 (22.2%)	151 (33.3%)	331 (26.2%)	
Diabetes	No	625 (77.2%)	331 (73.1%)	956 (75.7%)	0.12
	Yes	185 (22.8%)	122 (26.9%)	307 (24.3%)	

Percentages shown next to the counts are column percentages within each variable.

[1]Patients without constant-severe pain.

[2]Patients with constant-severe pain.

CP, chronic pancreatitis; RAP, recurrent acute pancreatitis; SD, standard deviation; QOL, quality of life; EPI, exocrine pancreatic insufficiency.

Table 6.

Association of phenotypes within RAP+CP patients with severe pain.

Variable	Level	Controls[1] (N=531)	Cases[2] (N=732)	Total (N=818)	p-value
Age at Ascertainment	Mean (SD)	52 (16.1)	47.1 (15.2)	49.2 (15.8)	< 1e-05
Sex	Male	265 (49.9%)	377 (51.5%)	642 (50.8%)	0.61
	Female	266 (50.1%)	355 (48.5%)	621 (49.2%)	
Mental QOL	Mean (SD)	46.7 (11)	41.8 (12)	43.7 (11.8)	< 1e-05
	Missing	90	33	123	
Drinking	Never	105 (20.0%)	163 (22.3%)	268 (2.3%)	0.36
	Ever	421 (80.0%)	569 (77.7%)	990 (78.7%)	
	Missing	5	0	5	
Smoking	Never	202 (38.3%)	224 (30.7%)	426 (33.9%)	0.0065
	Ever	326 (61.7%)	505 (69.3%)	831 (66.1%)	
	Missing	3	3	6	
EPI	No	410 (77.2%)	522 (71.3%)	932 (73.8%)	0.022
	Yes	121 (22.8%)	210 (28.7%)	331 (26.2%)	
Diabetes	No	407 (76.6%)	549 (75.0%)	956 (75.7%)	0.54
	Yes	124 (23.4%)	183 (25.0%)	307 (24.3%)	

Percentages shown next to the counts are column percentages within each variable.

[1]Patients without severe pain.

[2]Patients with severe pain.

CP, chronic pancreatitis; RAP, recurrent acute pancreatitis; SD, standard deviation; QOL, quality of life; EPI, exocrine pancreatic insufficiency.

Table 7.

Lead SNPS.

Candidate gene association results for lead SNPs for each group of pancreatitis and pain from NAPS2 data.

	Pain	Chr	SNP	OR (95% CI)	SE	P	Minor Allele	MAF	Gene
CP	Constant	3	rs79626250	2.97 (1.49, 5.92)	0.35	1.9×10^{-3}	A	0.036	*DRD3*
		5	rs111759924	0.51 (0.34, 0.75)	0.2	7.7×10^{-4}	T	0.054	*CTNND2*
		5	rs16901689	0.63 (0.47, 0.83)	0.15	1.4×10^{-3}	T	0.12	*CTNND2*
		5	rs59442633	2.01 (1.41, 2.88)	0.18	1.3×10^{-4}	C	0.12	*CTNND2*
		5*	rs72802806	1.59 (1.24, 2.03)	0.13	2.3×10^{-4}	A	0.26	*NR3C1*
		11*	rs1491851	1.38 (1.12, 1.69)	0.1	2.0×10^{-3}	T	0.49	Upstream *BDNF*
	Constant-Severe	2*	rs62132337	3.15 (1.55, 6.42)	0.36	1.5×10^{-3}	T	0.039	*CAMKMT*
		3	rs79626250	2.94 (1.51, 5.73)	0.34	1.6×10^{-3}	A	0.038	*DRD3*
		5	rs10054369	0.48 (0.31, 0.73)	0.22	6.3×10^{-4}	T	0.048	*CTNND2*
		5	rs12513857	1.41 (1.14, 1.75)	0.11	1.8×10^{-3}	T	0.35	*NR3C1*
		5	rs16901689	0.62 (0.46, 0.83)	0.15	1.5×10^{-3}	T	0.12	*CTNND2*
		5	rs59442633	2.23 (1.56, 3.18)	0.18	1.0×10^{-5}	C	0.13	*CTNND2*
		5	rs6865292	1.45 (1.17, 1.81)	0.11	8.1×10^{-4}	C	0.31	*NR3C1*
		6*	rs56977771	3.26 (1.56, 6.79)	0.37	1.6×10^{-3}	T	0.035	Downstream *FKBP5*
		13	rs1328677	0.69 (0.55, 0.86)	0.12	1.3×10^{-3}	A	0.24	*HTR2A*
		13*	rs731245	1.44 (1.18, 1.76)	0.1	4.1×10^{-4}	G	0.52	Upstream *HTR2A*
	Severe	2	rs189479791	0.2 (0.079, 0.51)	0.47	7.1×10^{-4}	C	0.0068	*PDE1A*
		5	rs142199704	0.37 (0.19, 0.69)	0.32	1.9×10^{-3}	A	0.018	*SLC6A3*
		5	rs76003244	3.83 (1.78, 8.24)	0.39	6.0×10^{-4}	A	0.05	*CTNND2*
		13	rs73175516	0.58 (0.41, 0.81)	0.17	1.6×10^{-3}	C	0.081	*HTR2A*
RAP+ CP	Constant	5	rs10054369	0.53 (0.38, 0.73)	0.17	1.3×10^{-4}	T	0.054	*CTNND2*
		5	rs16901689	0.63 (0.5, 0.80)	0.12	1.1×10^{-4}	T	0.13	*CTNND2*
		5	rs59442633	1.73 (1.3, 2.31)	0.15	2.0×10^{-4}	C	0.1	*CTNND2*

Pain	Chr	SNP	OR (95% CI)	SE	P	Minor Allele	MAF	Gene
	5*	rs72802806	1.4 (1.16, 1.7)	0.099	5.9×10^{-4}	A	0.24	*NR3C1*
	6*	rs9294969	1.82 (1.29, 2.56)	0.17	5.8×10^{-4}	A	0.078	Downstream *THBS2*
	7	rs148812933	2.15 (1.34, 3.46)	0.24	1.5×10^{-3}	T	0.043	Downstream *NPY*
	17	rs541569598	0.75 (0.63, 0.89)	0.088	1.2×10^{-3}	T	0.35	Upstream *SHMT1*
Constant-Severe	5	rs10054369	0.51 (0.36, 0.72)	0.17	1.2×10^{-4}	T	0.052	*CTNND2*
	5	rs16901689	0.62 (0.49, 0.8)	0.12	1.4×10^{-4}	T	0.12	*CTNND2*
	5	rs59442633	1.82 (1.36, 2.44)	0.15	6.0×10^{-5}	C	0.11	*CTNND2*
	5*	rs72802806	1.37 (1.13, 1.67)	0.1	1.6×10^{-3}	A	0.24	*NR3C1*
	6*	rs9294969	1.87 (1.33, 2.64)	0.18	3.6×10^{-4}	A	0.079	Downstream *THBS2*
	13*	rs731245	1.32 (1.12, 1.55)	0.082	8.9×10^{-4}	G	0.51	Upstream *HTR2A*
Severe	2	rs78195040	2.84 (1.47, 5.47)	0.34	9.3×10^{-4}	G	0.029	*CAMKMT*
	2	rs189479791	0.33 (0.17, 0.64)	0.33	1.9×10^{-3}	C	0.01	*PDE1A*
	3	rs111466137	0.52 (0.35, 0.76)	0.2	8.8×10^{-4}	T	0.036	*DRD3*
	5	rs56825733	0.48 (0.3, 0.75)	0.23	1.4×10^{-3}	T	0.024	*CTNND2*
	7	rs7357103	1.32 (1.11, 1.57)	0.089	1.9×10^{-3}	G	0.37	*NPSR1*

*SNP has an eQTL as reported in GTEx (39).

CP, chronic pancreatitis; RAP, recurrent acute pancreatitis; Chr, chromosome; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence intervals; SE, standard error; MAF, minor allele frequency.

Table 8.

Summary of Significant Candidate Genes.

Pathway	Candidate Genes	Protein Information
Neuronal Signaling	*HTR2A*	Serotonin receptor
	DRD3	Dopamine receptor
	NPY	Neuropeptide
	BDNF	Nerve growth factor
Prepulse Inhibition	*SLC6A3*	Dopamine transporter
	SHMT1	Cytosolic serine hydroxylmethyltransferase
HPA Axis	*NR3C1*	Glucocorticoid receptor
	FKBP5	Glucocorticoid receptor co-chaperone
G Protein-Coupled Receptor Signaling	*CAMKMT*	Class I protein methyltransferase
	PDE1A	Cyclic nucleotide phosphodiesterase
	NPSR1	G Protein-coupled receptor
Cell-Cell Interaction	*CTNND2*	Adhesive junction
	THBS2	Tumor growth inhibitor

HPA, Hypothalamic-Pituitary-Adrenal.