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Constant-Severe Pain in Chronic Pancreatitis is Associated with Genetic Loci for Major Depression in the NAPS2 Cohort

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Abstract

Background: Pain is the most debilitating symptom of recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) and often requires chronic opioids or total pancreatectomy with islet autotransplantation to manage. Pain is a complex experience that can be exacerbated by depression and vice versa. Our Aim was to test the hypothesis that depression-associated genes are associated with a constant-severe pain experience in RAP/CP patients.

Study: A retrospective study was done using North American Pancreatitis Study II (NAPS2) genotyped RAP and CP patients with completed case report forms (n=1,357). Subjects were divided based on pattern of pain and pain severity as *constant-severe pain* (n=787) versus *not constant-severe pain* (n=570) to conduct a nested genome wide association study. The association between reported antidepressant medication use and depression gene loci was tested.

Results: Constant-severe pain was reported in 58% (n=787) of pancreatitis patients. No differences in sex or alcohol consumption were found based on pain severity. Antidepressant use was reported in 28% (n=223), and they had lower SF-12 mental quality of life (MCS, $p < 2.2\times10^{-16}$). Fifteen loci associated with constant-severe pain ($p<0.00001$) were found to be in or near depression-associated genes including: *ROBO2, CTNND2, SGCZ, CNTN5* and *BAIAP2*. Three of these genes respond to antidepressant use (*SGCZ, ROBO2,* and *CTNND2*).

Conclusions: Depression is a major co-factor in the pain experience. This genetic predisposition to depression may have utility in counseling patients and in instituting early antidepressant therapy for pain management of pancreatitis patients. Prospective randomized trials are warranted.

Keywords

pain chronic; chronic pancreatitis; depression; antidepressants; Human Genetics

Introduction

Chronic pancreatitis (CP) is a syndrome of inflammatory destruction of the pancreas ending in irreversible damage with variable degrees of exocrine pancreatic insufficiency (EPI), diabetes mellitus (DM) and constant-severe pain.[1–3] Progression to CP typically begins with acute pancreatitis (AP) and recurrent AP (RAP), but even at these earlier stages, there are negative effects on physical and mental health and quality of life (QOL). [4–6] The etiology of AP, RAP and CP is complex and associated with toxic and metabolic factors such as alcohol, smoking, hypercalcemia, hypertriglyceridemia, genetic factors such as DNA sequence variants in or near *CASR, CEL, CFTR, CLDN2, CPA1, CTRC, PRSS1, SPINK1, TRPV6, UBR1* and others, and obstructive etiologies. [7–9] Additional genetic variants and environmental factors predispose to secondary complications such as diabetes [10–12] and pancreatic cancer.[13–17] The major disabling feature that drives low quality of life is severe, constant pain, a condition that develops in 1 in 3 CP patients.[1, 5, 6] The reason for variability of this feature among pancreatitis patients is unknown, but may include genetic factors.

Pain is a subjective experience that encompasses the generation of pain signals from the injured organ, the physiological and pathological reflex responses, and higher brain responses linked to regions associated with emotion and motivation (prefrontal region, limbic system, and midbrain periaqueductal gray) to the pain signals.[18] Depression is recognized as a comorbid diagnosis in a variety of pain disorders and antidepressants have been empirically used in patients with CP to manage pain.[19] However, the effects of depression on the pain experience may be overlooked, and it is unclear as to who is likely to respond to antidepressant medications or other therapies in the management of the constant-severe pain experience in CP and the mechanisms implicated in treatment response.

Major Depressive disorder (e.g. ICD-10 F33.2) is characterized by recurrent episodes of depression lasting at least two weeks and can include lowered energy and enjoyment of activities, depressed mood, different patterns of sleeping and eating, anxiety, lack of focus, guilt, and medically unexplainable symptoms.[20] Depression can be influenced by environmental factors—such as illness, financial instability, and childhood trauma—and genetic factors across many loci.[21, 22] The heritability of depression has been estimated to be between 30% and 40% based on twin studies.[21, 23] Individuals of both sexes with depression are also at an increased risk for certain physical disorders such as diabetes mellitus, stroke, and heart disease.[21, 24] Patients with depression tend to have higher inflammatory immune responses; similarly, cytokines can induce depression and depression-like symptoms in patients.[25] Therefore, it is possible that some RAP/CP patients that are genetically prone to depression are also susceptible to altered inflammation and more severe pain.

We conducted an exploratory study in a well phenotyped and genotyped cohort of patients with RAP and CP to determine whether genetic loci that have previously been demonstrated to be associated with depression were overrepresented in the pancreatitis patients who also reported the most constant-severe pain. Our findings of associations between the constant-severe pain experience and several depression risk loci that are known to be responsive to antidepressant medications, and may respond to other therapies, establish this approach as a pathway toward more effective, personalized treatment of the most disabling complication of pancreatitis.

Materials and Methods

Study Population

CP and RAP patients and controls were ascertained from the North American Pancreatitis II (NAPS2) studies (NCT01545167).[1, 6, 26–29] NAPS2 was launched in 1999 to determine the contribution of known risk factors (alcoholism and smoking) to CP and to discover new genetic risk factors.[26, 28, 29] The concept was to prospectively ascertain 1000 subjects with RAP and CP and spouse-friend controls with detailed demographic information and family history to define and quantify pancreatic disease-associated risk factors and exposures (based on TIGAR-O [30]), disease onset and progression to test the Sentinel Acute Pancreatitis Event (SAPE) hypothesis, [31, 32] and the prevalence and timing of secondary complications including pain, exocrine pancreatic insufficiency (EPI), diabetes (before or after AP), quality of life, etc. Biomarker results from the medical records were recorded to determine disease features and stages (e.g. pancreas imaging, list of secondary diagnoses, special tests, etc) and blood was collected to measure serum biomarkers and DNA for genetic variants).

NAPS2 occurred in three phases, the original NAPS2 cohort (2000-2006) designed to ascertain 1000 RAP/CP patients, the NAPS2-continuation and validation study (NAPS2-CV) (2008-2012) designed to ascertain an additional 500 CP patients for GWAS studies, and NAPS2-ancillary study (NAPS2-AS) designed to ascertain 250 CP patients and 250 controls of African ancestry). Between sub-studies minor changes were made to the case report forms to clarify ambiguities or uncertainties in previous versions (e.g. the physician was asked whether the patient was on pancreatic enzyme replacement therapy, but initially they were not asked if it was for EPI or pain). The result was over 50 direct and secondary publications including defining the role of alcohol and smoking in CP, [27, 33, 34] pain patterns and their effect on quality of life,[6, 35, 36] differences among patients based on age,[6, 35, 36] sex[37] and ancestry, [11, 28, 38] and multiple genetic findings including the first CP genome wide association study (GWAS) identifying *PRSS1-2* and *CLDN1* risk loci, [2] a new cystic fibrosis related syndrome,[39] complex genetic risks, [38–41] establishing the foundation for a new mechanistic definition of CP[3] and providing the rationale for precision medicine for pancreatic diseases.[42–44]

The final subset of the NAPS2 cohort used in this study included RAP and CP subjects (n=1,357). The diagnosis of RAP was based on two or more documented episodes of acute pancreatitis. CP was diagnosed based on validated imaging studies or histology.[26, 36] The study was constructed as a cross-sectional study including questionnaires described

later. Only patients of European ancestry (EA) were included in the analysis to reduce heterogeneity since the majority of subjects recruited for NAPS2 were of EA. Previous genotyping was done on the Illumina HumanOmniExpress BeadChip.[2] Genotype data was prepared for imputation using the McCarthy Group pre-imputation checking tools and imputed against the 1000 genomes phase-3 reference panel on the Sanger imputation server using EAGLE2 for pre-phasing and PBWT for imputation.[45–47] Resultant imputed files were filtered based on the INFO score ≥0.5, renamed based on position, filtered for biallelic positions only, and filtered for genotype completeness at 90% leaving a total of 9,251,575 SNPs with a MAF >0.01 for our analysis.

Questionnaires

Two sets of questionnaires were used to collect detailed information; one administered to patients by a trained research coordinator and the other completed by the enrolling physician. The patient questionnaires collected information on demographics (including current and maximal weight and height to calculate body mass index (BMI)), diabetes, EPI, personal and family history, exposure to alcohol and tobacco, medication use, mental and physical quality of life using Short Form-12 (SF-12), pain experience using a visual analogue scale, pain frequency and severity, and McGill pain score.[1, 6]. The questionnaires in NAPS2 original and NAPS2-CV were identical in the core elements, but additional questions on the use of specific medication for pancreatic disease (rather than a list of all medicines) and their perceived utility were used in NAPS2-CV and NAPS2-AS so that not all information was available in all patients, resulting in missing information on antidepressants from those individuals (n=547).

The enrolling physician provided information on age at onset and diagnosis of CP, exocrine and endocrine insufficiency, disease etiology, TIGAR-O risk factors, imaging findings, treatments tried and their perceived effectiveness.[48] The detailed assessment of alcohol and smoking in the NAPS2 cohort has been previously reported.[26] “Never drank” is less than 20 drinks in a lifetime. Smoking history was obtained from the patients’ case report forms (CRF) with “never smoked” being less than 100 cigarettes in a lifetime.

Pain, Depressive Symptoms, and Antidepressant Use

Patterns of pain were defined following Mullady[1] using a 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; E = constant-severe pain.[1] For this study, subjects responding with D or E were classified as *constant-severe pain*, while subjects responding with O, A, B, or C were classified as *not constant-severe pain*. This combination of constant and severe pain had the highest impact on QOL.

Depression was not directly measured by the SF-12; however, a self-reported symptom of depression and a mental component summary (MCS) was gathered and reported as proxies in this study. The depressive symptom (“Felt Blue”) was assessed using the SF-12 question “Have you felt downhearted and blue?” with reference to the previous 4 weeks and rated on a Likert scale of 1 “All of the time” to 6 “None of the time.” The “Felt Blue” variable

was a dichotomized version of the Likert responses with responses 1, 2, or 3 corresponding to “Yes” and 4, 5, or 6 corresponding to “No.” The MCS was used as a measure of mental QOL, with a higher score indicating a greater QOL. [35] The MCS has been used previously as a measure of mental health and depressive disorders. [49, 50]

Antidepressant use was reported in free-text format in the patient and/or physician case report forms. Text mining procedures in R were used to extract the antidepressants.[51] A list of the queried drugs, both brand name and corresponding generic names, can be found in Supplemental Table 1. The antidepressant variable was binary, with 1 meaning antidepressants were reported in the CRF and not used as pain medication and 0 meaning no antidepressants were reported. The majority of CP and RAP patients from the original NAPS2 cohort that were taking antidepressants were taking selective serotonin reuptake inhibitors (SSRIs, 56%), followed by tricyclic antidepressants (TCAs, 19%), serotonin and norepinephrine reuptake inhibitors (SNRIs, 16%), and norepinephrine-dopamine reuptake inhibitor (NDRIs, 10%) (Supplemental Table 1).

Genetic Data Analysis

The genetic analysis was constructed as a candidate gene review within a nested genome wide association study (GWAS) data set of subjects with RAP/CP subjects based on pain patterns. The RAP and CP patients were combined, then classified as one of two groups: *constant-severe pain* (cases) or *not constant-severe pain* (controls). The nested GWAS was conducted using PLINK 1.9 software.[52] Quality control methods have been previously reported.[2] Data was fit to a logistic regression to test for associations. To control for ancestry, the first 4 principle components of ancestry were included as covariates. The minor allele frequency (MAF) was set to 0.01. Single nucleotide polymorphisms (SNPs) with a p-value of less than 1×10^{-4} were chosen to continue in the analysis.

SNPs meeting the required significance threshold were then clumped into groups based on linkage disequilibrium (LD) (± 250 kb from index SNP, $r^2 > 0.5$) using the “clump” command in PLINK.[52] The lead SNPs (p-value ≤ 0.0001) for each clump were annotated with gene names based on build GRCh37/hg19. These genes were then compared to a list of genes associated with unipolar depression and antidepressant response obtained from the GWAS Catalog in October 2019.[53] Odds ratios (OR) for the lead pain SNPs stratified by the binary antidepressant usage variable were calculated with Cochran-Mantel-Haenszel (CMH) statistics using the “within” and “mh” commands in PLINK.[52]

Demographic data was compiled and analyzed using R version 3.6.0. Univariant comparisons were performed based on the demographic variables using Pearson chi-squared test for categorical data. Two-tailed p-values <0.05 were considered statistically significant (Table 1).[51] Zoom plots were created using the online platform LocusZoom, and exported using Gapplin (Supplemental Figures 1–5).[54, 55]

Results

Patient characteristics

The characteristics of the RAP and CP subjects classified as *constant-severe pain* or *not constant-severe pain* and the associations between constant-severe pain and general risk factors or depression-associated features are summarized in Table 1. Age, smoking, "Felt Blue", and MCS are all associated with *constant-severe pain*. Antidepressant usage was associated with lower MCS (Wilcoxon rank sum test with continuity correction, W=208590, $p < 2.2x10^{-16}$).

Genetic associations between constant-severe pain and depression genes.

There were a total of 1,357 genotyped individuals of European ancestry with pancreatitis and core pain/depression information in the dataset. Candidate chromosomal loci for depression-associated genes in patients with a *constant-severe pain* phenotype were identified using PLINK by comparing *not constant-severe pain* with *constant-severe pain*. Candidate loci were identified by lead SNPs ($p < 0.0001$), clumped with other SNPs within 250 kb and with r^2 greater than 0.5 with the lead SNP.[52] Genes associated with the lead SNPs of the clumps were compared to genes associated with depression and reported in the GWAS Catalog identifying 15 pain loci containing depression genes.[53] The SNP most significantly associated with pain and with a depression-associated gene was rs12449867 on chromosome 17 near *BAIAP2-AS1* (OR 1.44, $p=2.0x10^{-5}$ for pain) (Table 2). Additionally, three genes (*ROBO2, CTNND2,* and *SGCZ* (Table 2)) were also reported in the GWAS Catalog as being associated with antidepressant response.[53] Individual zoom plots of the leading loci are in Supplemental Figures 1–5. The LD regions shown in the zoom plots were based on EA.

The use of antidepressants in patients with pain was assessed using Cochran-Mantel-Haenszel analysis. The result for each SNP associated with constant-severe pain was correlated with antidepressant usage (Table 3). The most significantly associated locus after stratification by antidepressant use is at Chromosome 8:14,471,243, rs11300774 (OR 0.636, $p=4.38x10^{-6}$). Genotype counts for each SNP in cases and controls are reported in Table 4.

Discussion

Depression is a major, worldwide problem. It is estimated that at least 1 in every 6 individuals worldwide will experience depression during their lifetime, making depression the top cause of disability in the world.[23] Depression often starts during the teen years, persisting into adulthood. Like most psychiatric disorders, depression is a syndrome diagnosed using observation and self-report methods.[22]

Pain and depression are comorbid and reciprocal, with the severity of one increasing the severity of the other.[56, 57] Severe depression affects an estimated 85% of patients with chronic pain.[58] Chronic pain has a heritability of approximately 30%.[57] Patients with depression and a chronic pain disorder were less likely to recover from their pain, and future episodes of pain were predicted by the presence of severe depression. Patients with severe depression before surgery suffered more pain after surgery than patients without

depression. Conversely, antidepressants may not be as effective at treating depression in patients with higher pain levels at baseline, with 94% of relapsing depression occurring in patients with mild to moderate pain. Fortunately, when treatment of depression is successful some symptoms of pain are also alleviated.[56]

Pain is the most important clinical feature associated with disability and poor mental and physical quality of life in patients with RAP and CP.[1, 6] The connection between pain in chronic pancreatitis and depression is known. For example, one study found that in patients with chronic pancreatitis, not caused by alcoholism, severe depression was associated with higher intensity of pain.[59] Additionally, depression was a predictor of hospital readmissions at 30 days in patients with chronic pancreatitis.[60] Pain is a predictor of relapsing depression, it is therefore reasonable to suggest that a longer duration of pancreatic pain would influence the severity of depression; although duration was not associated with the "Felt Blue" variable (Supplemental Table 2).[29] Thus, this is a major problem that must be addressed. Here we evaluated the possible role of underlying genetic risk of depression to the experience of constant-severe pain. Our approach was an exploratory study to determine whether depression-associated genes that were already discovered and well characterized were within regions associated with constant-severe pain in patients with RAP and CP.

Pain and depression genes in pancreatitis

Fifteen candidate loci with known depression-associated genetic risk variants that were associated with constant-severe pain phenotype loci ($p<0.00001$) were identified in our NAPS2 cohort. Additionally, the use of antidepressant medications indicates that over a quarter of patients were being treated with a trend toward higher use in constant-severe pain (30.2% *constant-severe* vs. 24.8% *not constant-severe*) but we could not determine if some patients initially had constant-severe pain that was improved with antidepressants and were therefore in the *not constant-severe pain* category at the time of ascertainment. We also saw an association with constant-severe pain and smoking (70% *constant-severe* vs. 61% *not constant-severe*, $p<0.01$); however, this result may be confounded by some subjects smoking to control pain.[34] Alcohol use was not significantly different between pain categories. However, patients in the *constant-severe* pain category had a lower MCS, indicative of a lower QOL associated with their pain. These data clearly indicate that depression is a major problem in patients with RAP and CP and that genetic loci with known depression-associated genetic risk variants are significantly associated with constant-severe pain.

Depression-associated genes

Multiple well-established depression-associated genes were associated with pain in pancreatitis patients including *ROBO2, CTNND2, SGCZ, CNTN5,* and *BAIAP2.* Three of these genes are also associated with response to antidepressants (*ROBO2*, *CTNND2*, *SGCZ*).[53] Further information on these genes can be found in the Supplemental Information. These findings may also provide mechanistic support to the empiric observation that some patients with CP respond to antidepressant medications. [19]

Clinical Implications

The identification of genetic risk variants for depression associated with the severe-constant pain phenotype may have important clinical implications. The data presented here is a retrospective, cross-sectional, observational cohort study that are not designed to study depression *per se*. Furthermore, genetic risks for complex conditions such as depression are not independently causal as multiple genetic, epigenetic, environmental, emotional and other contextual factors (e.g. childhood abuse) also contribute to the phenotype. Thus, further longitudinal studies that are designed to address issues of pain and depression in pancreatitis —including interventional studies—are still needed. Nevertheless, the associations identified here were strong, and some immediate applications should be considered.

Recognition by the physician that a patient with pancreatitis and pain has genetic risks for depression can be useful for providing patient education that they are more likely to have biology-based components to depression, that depression makes pain worse, and that addressing these symptoms may augment pain treatment. Furthermore, there may be benefit in early interventions such as cognitive behavioral therapy and, in some cases, detection of genetic risks in specific genes such as *SGCZ, ROBO2,* and *CTNND2* may provide rationale for a trial of specific medications that are known to improve symptoms in patients with depression from other etiologies.

Limitations and future directions

This nested study has a small sample size, which reduces power to discover genetic variants associated with a phenotype using the accepted genome-wide significance threshold of $5x10^{-8}$.[61] Although no SNPs reached genome-wide significance as an independently associated factor, the study design was to identify previously validated depression genes within loci that were marginally associated with pain in RAP/CP. Thus, we do not believe that stringent thresholds for new genetic associations with correction for genome wide associations apply here. Since depression analysis was not a goal of the NAPS2 studies, the depression phenotype(s) were not well defined, and slight changes in the CRFs may have affected study precision and power (e.g. missing data). The text mining process used to identify antidepressants is limited by spelling errors present in the case report forms, recall bias, as well as the number of subjects that contained full pharmacologic data. However, the NAP2 phenotypes and CRFs were completed by expert clinicians so the accuracy of the overall data set is fundamentally superior to administrative data sets and most of the unclear text data was easily resolved. The temporal relationship between severe pain and use of antidepressants was also not ascertained. Thus, the relationships between pain, depression, and antidepressants could not be fully assessed in this study, but should be addressed in future studies.

Summary and conclusions

Pain is the most debilitating symptom of chronic pancreatitis and one of the most difficult to treat.[1, 62] Approximately 18% of patients with chronic pancreatitis also experience depression.[60] Pain can increase the severity of depression, and vice versa.[56] GWAS data has been used to study the comorbidity and overlapping risk alleles of depression in diseases like type 2 diabetes, metabolic syndrome, and inflammatory bowel disease, and

now in pancreatitis.[23, 24, 63] Our findings suggest that there is an overlap of depression associated genes and constant-severe pancreatic pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations.

AP	Acute pancreatitis
BAIAP2-AS1	the BAIAP2 divergent transcript gene (or BAIAP2-DT)
BMI	body mass index
CMH	Cochran-Mantel-Haenszel statistic
CP	chronic pancreatitis
CRF	case report form
CTNND2	the catenin delta 2 gene (or GT24; NPRAP)
DM	diabetes mellitus
EPI	exocrine pancreatic insufficiency
EA	European ancestry
GWAS	genome wide association study
LD	linkage disequilibrium
MAF	minor allele frequency
MCS	mental component summary
NAPS2	North American Pancreatitis Study II
NDRI	antidepressant drug class of norepinephrine-dopamine reuptake inhibitors

OR	odds ratio
QOL	quality of life
RAP	recurrent acute pancreatitis
ROBO2	the roundabout guidance receptor 2 gene (or *SAX3*)
SGCZ	the sarcoglycan zeta gene (or ZSG1)
SF-12	Short form 12
SNP	Single nucleotide polymorphism
SSNRI	antidepressant drug class of serotonin and norepinephrine reuptake inhibitors
TIGAR-O	common risk and etiology list for pancreatitis including Toxic, Idiopathic, Genetic, Autoimmune, Recurrent Acute and Severe Acute pancreatitis, and Obstructive

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Table 1.
Association of demographic and depression phenotypes with constant-severe pain.

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

Variable	Level	Not Constant-severe Pain (n=570)	Constant-severe Pain (n=787)	Total (n=1357)	p-value
Age [1]	Mean (sd)	51.7 (16.3)	46.5 (15.4)	48.7 (16.0)	***
Sex	Male	281 (49.3%)	407 (51.7%)	688 (50.7%)	
	Female	289 (50.7%)	380 (48.3%)	669 (49.3%)	
Alcohol	Never	118 (20.9%)	171 (21.8%)	289 (21.4%)	
	Ever	447 (79.1%)	615 (78.2%)	1062 (78.6%)	
	Missing	5	1	6	
Smoking	Never	220 (38.8%)	237 (30.3%)	457 (33.9%)	
	Ever	347 (61.2%)	546 (69.7%)	893 (66.1%)	**
	Missing	3	4	7	
Antidepressant Use	No	300 (75.2%)	287 (69.8%)	587 (72.5%)	
	Yes	99 (24.8%)	124 (30.2%)	223 (27.5%)	
	Missing	171	376	547	
“Felt Blue”	No	281 (86.5%)	312 (76.3%)	593 (80.8%)	
	Yes	44 (13.5%)	97 (23.7%)	141 (19.2%)	***
	Missing	245	378	623	
EPI	No	335 (71.9%)	501 (69.6%)	836 (70.5%)	
	Yes	131 (28.1%)	219 (30.4%)	350 (29.5%)	
	Missing	104	67	171	
Diabetes	No	354 (72.7%)	568 (74.6%)	922 (73.9%)	
	Yes	133 (27.3%)	193 (25.4%)	326 (26.1%)	
	Missing	83	26	109	
Mental QOL	Mean (sd)	46.8 (11)	41.8 (12)	43.7 (11.9)	***
	Missing	96	35	131	

Stars indicate level of significance within each variable and with pain severity

* p<0.05,

** p<0.01,

*** p<0.001.

Footnote: 1. Age of ascertainment.

Table 2.

GWAS results for 15 depression SNPs associated with pain in the NAPS2 data.

Chromosomal locations are based on build GRCh37/hg19.

Chr	Location (bp)	SNP	P	A1/A2[1]	OR (A1)	95% CI	Freq. A1	Gene
2	15,686,142	rs141909432	$4.8x10^{-5}$	A/G	3.97	2.04,7.71	0.02	NBAS
2	55,331,982	rs2968817	$7.6x10^{-5}$	A/G	0.69	0.57,0.83	0.29	RTN4
3	12,816,143	rs113388258	$2.4x10^{-5}$	C/T	2.03	1.46,2.82	0.06	CAND2, TMEM40
3	77,151,787	rs4624600	$5.5x10^{-5}$	C/T	1.36	1.17,1.59	0.35	ROBO2 *
5	11,187,984	rs59442633	$2.9x10^{-5}$	C/T	1.81	1.37,2.38	0.08	CTNND2 *
5	146,034,762	rs458909	$9.4x10^{-5}$	A/C	3.44	1.85,6.39	0.02	PPP2R2B
8	14,471,243	rs11300774	$6.1x10^{-5}$	T/TA	0.68	0.56,0.82	0.25	SGCZ *
11	100,059,361	rs2123323	$7.0x10^{-5}$	T/C	1.39	1.18,1.64	0.46	CNTN5
11	100,126,103	rs36106152	$7.9x10^{-5}$	G/GA	0.71	0.59,0.84	0.33	CNTN5
12	118,024,434	rs71450224	$5.1x10^{-5}$	A/AAAAG	0.68	0.56,0.82	0.26	KSR2
17	79,004,271	rs12449867	$2.0x10^{-5}$	C/T	1.44	1.22,1.71	0.34	BAIAP2-AS1
17	79,031,825	rs9898347	$9.6x10^{-5}$	A/G	0.71	0.60,0.84	0.35	BAIAP2
17	79,036,107	rs34176221	$5.9x10^{-5}$	AT/A	1.39	1.19,1.64	0.45	BAIAP2
18	49,961,950	rs1619323	$4.2x10^{-5}$	C/T	0.66	0.54,0.81	0.22	DCC
22	45,353,108	rs8137390	$4.3x10^{-5}$	G/A	1.50	1.24,1.82	0.20	PHF21B

* Indicates regions associated with antidepressant response.

Footnote 1: A1 is the minor allele, A2 is the major allele.

Table 3.

CMH results for lead SNPs when genotype and pain are grouped by antidepressant use.

Chr	SNP	A1	MAF	A2	CHISQ	P	OR	SE	L95	U95
2	rs141909432	A	0.016	G	15.16	$9.89x10^{-5}$	3.221	0.327	1.698	6.113
2	rs2968817	A	0.291	G	16.32	$5.36x10^{-5}$	0.691	0.092	0.578	0.828
3	rs113388258	C	0.059	T	18.73	$1.51x10^{-5}$	2.077	0.17	1.489	2.898
3	rs4624600	C	0.347	T	18.13	$2.06x10^{-5}$	1.435	0.085	1.215	1.695
5	rs59442633	C	0.082	T	18.43	$1.76x10^{-5}$	1.84	0.144	1.388	2.439
5	rs458909	A	0.017	C	17.48	$2.90x10^{-5}$	3.581	0.323	1.9	6.748
8	rs11300774	T	0.246	TA	21.09	$4.38x10^{-6}$	0.636	0.099	0.524	0.771
11	rs2123323	T	0.461	C	11.96	$5.44x10^{-4}$	1.326	0.082	1.13	1.555
11	rs36106152	G	0.329	GA	16.44	$5.03x10^{-5}$	0.699	0.089	0.588	0.831
12	rs71450224	A	0.262	AAAAG	16.62	$4.56x10^{-5}$	0.677	0.096	0.561	0.817
17	rs12449867	C	0.336	T	16.68	$4.43x10^{-5}$	1.415	0.085	1.197	1.672
17	rs9898347	A	0.355	G	12.4	$4.30x10^{-4}$	0.737	0.087	0.622	0.874
17	rs34176221	AT	0.445	A	11.19	$8.23x10^{-4}$	1.315	0.082	1.12	1.543
18	rs1619323	C	0.217	T	17.35	$3.10x10^{-5}$	0.653	0.103	0.534	0.799
22	rs8137390	G	0.202	A	15.99	$6.37x10^{-5}$	1.485	0.099	1.223	1.804

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Table 4.

Genotypic distribution among cases and controls.

Counts represent number of individuals.

Chr	rsID	Gene	A1 (minor)	A2 (major)	Total	*Not Constant-severe Pain*				*Constant-severe Pain*			
						A1/A1	A1/A2	A2/A2	Control	A1/A1	A1/A2	A2/A2	Cases
2	rs141909432	NBAS	A	G	1355	0	9	560	569	0	33	753	786
2	rs2968817	RTN4	A	G	1356	47	274	248	569	59	303	425	787
3	rs113388258	CAND2,TMEM40	C	T	1357	0	51	519	570	4	100	683	787
3	rs4624600	ROBO2	C	T	1347	72	193	300	565	155	287	340	782
5	rs59442633	CTNND2	C	T	1355	1	74	495	570	11	123	651	785
5	rs458909	PPP2R2B	A	C	1357	0	10	560	570	0	36	751	787
8	rs11300774	SGCZ	T	TA	1356	43	301	225	569	46	478	263	787
11	rs2123323	CNTN5	T	C	1356	97	300	173	570	182	392	212	786
11	rs36106152	CNTN5	G	GA	1357	65	231	274	570	82	381	324	787
12	rs71450224	KSR2	A	AAAAG	1354	41	234	295	570	45	303	436	784
17	rs12449867	BAIAP2-AS1	C	T	1355	49	239	281	569	99	376	311	786
17	rs9898347	BAIAP2	A	G	1356	72	296	202	570	91	340	355	786
17	rs34176221	BAIAP2	AT	A	1354	88	284	197	569	177	391	217	785
18	rs1619323	DCC	C	T	1355	31	195	343	569	36	260	490	786
22	rs8137390	PHF21B	G	A	1356	20	177	372	569	35	262	490	787