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Genetic associations of perinatal pain and depression

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Abstract

Underlying genetic influences may affect perinatal pain, depression, or both. We investigated the role of 59 single-nucleotide polymorphisms on 20 quantitative traits measured in perinatal women. Moreover, 183 pregnant women (28–37 weeks' gestation) were prospectively genotyped for single-nucleotide polymorphisms with known prior associations with either pain or depression in nonpregnant populations. Prenatal saliva samples were collected. Phenotypic data were gathered during prenatal, labor and delivery, and postpartum (six weeks and three months) periods, capturing labor pain, Edinburgh Postnatal Depression Score, and Brief Pain Inventories. Following quality control, genotypes were used as predictors and phenotypes as dependent variables in multiple linear regression analyses to detect associations. Three statistical models were tested: additive allele effects, deviation from dominant allele effects, and the joint test of both. rs4633 (a synonymous single-nucleotide polymorphism in *COMT*) associated with "pain right now" scores at six weeks postpartum. Single-nucleotide polymorphisms rs1135349 (a single-nucleotide polymorphism within a small noncoding RNA that has many prior associations for depression) and rs7548151 (intronic in *ASTN1*) were associated with the maximum pain unpleasantness score experienced during labor (a measure of the emotional valence of labor pain), controlling for the Holm–Bonferroni family-wise error rate. Sensory dimensions of labor pain (i.e., pain intensity) and postpartum depression scores were not associated with genotyped single-nucleotide polymorphisms. Identifying genomic components of these perinatal complex disorders may produce insights into relevant pathways or novel treatment options.

Keywords

Acute pain, childbirth pain, pain, psychology

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Introduction

Labor pain has been associated with postpartum depression,[1] but the biological basis of this relationship is unclear. Like other complex human traits, pain is multifactorial, mediated by environmental and genetic factors.[2] Pain heritability has been estimated by twin studies (heritability = 16%–50%).[3,4] Within DNA studies, patterns of genetic association for pain are apparent. Variants in chaperonin containing TCP1 subunit 5 (*CCT5*) and family with sequence similarity 173 member B (*FAM173B*) were associated with chronic widespread pain in a genome-wide association study (GWAS) performed on 7099 European subjects.[5] A GWAS performed on 11,891 European women found association of dysmenorrhea in a locus proximal to nerve growth factor (*NGF*).[6]

Genetic studies can potentially shed light on common factors between perinatal pain and depression. For example, catechol-O-methyltransferases (*COMT*)

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plays a role in degrading catecholamines, via methylation transfer, including neurotransmitters (dopamine, epinephrine, or norepinephrine) and has prior association with depression. Gene variants in *COMT* have been associated with opioid efficacy in pain studies and has prior association with pain.[7,8]

Comorbid chronic pain and depression is extremely common in the population (estimated at 30%–60%).[9] This comorbidity is strongly associated with females by approximately two-fold.[10] The public health burden is considerable, as the costs to treat depression or pain can be up to $560 billion.[11] Like pain, depression is a common, multifactorial disorder with a considerable element of heredity, evidenced by prior twin and family studies.[12] A case/control meta-analysis identified 44 loci associated with major depression in approximately one half-million research subjects using GWAS.[13]

A distinct group of depressive symptoms may arise in pregnant women before, during, and after labor and delivery. Past literature supports a potential genetic component. A linkage study for postpartum pain used microsatellite typing and found evidence of linkage in two genomic loci on chromosomes 1q and 9p.[14] One single-nucleotide polymorphism (SNP) from chromosome 1q was subsequently replicated in an independent sample.[15] In addition, several candidate gene studies identified SNPs associated with perinatal depression, including *COMT*.[16] Candidate gene studies focusing on labor pain have been undertaken with associative findings in *ADRB2* (β2-andrenergic receptor), *OPRM1* (μ-opioid receptor), and *GCH1* (guanosine triphosphate cyclohydrolase).[17]

Pain has also been linked to postpartum depression.[1,18–21] Furthermore, prior studies report the use of epidural analgesia with decreased postpartum depression; however, lack of association has also been reported.[22–25] Although the literature correlates chronic pain and depression with common genetic variants, we are unaware of any data that associates labor pain and postpartum depression with a common genetic explanation. Perinatal pain and postpartum depression possess biological and physiological characteristics that are distinct from chronic pain and depression outside of pregnancy and the postpartum period. Identifying common genetic components for pain and depression is important to inform the potential development of novel or innovative therapeutic targets in the perinatal period and to provide insights into risk stratification strategies for perinatal depression and pain management.

In this study, we explored genetic factors associated with pain and depression in perinatal women, to provide preliminary information identifying loci to target in larger genetic studies. We genotyped DNA variants previously associated with either pain or depression in nonpregnant populations, in a cohort of perinatal women who were prospectively phenotyped for prenatal, labor, and postpartum pain and depression. We hypothesized that SNPs associated with either pain or depression in nonpregnant populations are associated with clinical measures of pain or depression in perinatal women.

Methods

A prospective observational approach was chosen. Written informed consent was obtained from all research participants and this study was approved by the University of Pittsburgh Institutional Review Board. A convenience sampling of perinatal women aged 18 years or older were recruited at the third trimester prenatal clinic visit (28–40 weeks estimated gestational age), and prospectively followed throughout labor and delivery, six weeks postpartum, and three months postpartum. Participants were included if they were nulliparous, single gestation, vertex fetal presentation, English literate (due to the use of English language-validated surveys), and presented for spontaneous or induced labor and delivery at term gestation (estimated gestational age $\geq$37 weeks). Exclusion criteria included chronic pain, current opioid maintenance therapy, preeclampsia or emergency cesarean delivery, body mass index of $\geq$40 kg/m^2 (given data suggesting a relationship between obesity and depression[26]), and known fetal disease.

Self-reported demographic data included gravidity, parity, race, ethnicity, prenatal history of anxiety or depression, mental illness other than anxiety or depression, and marital status. Obstetric data included mode of delivery, perinatal lacerations, number of supplemental epidural dosing requirements during labor and delivery, and breastfeeding. Duration of labor was measured from labor and delivery data collected from the medical record (see below). Participants completed surveys at baseline (at the time of recruitment), six weeks postpartum, and three months postpartum.

Upon enrollment, depression was measured by the Edinburgh Postnatal Depression Scale (EPDS). Pain assessments were assessed with the pain catastrophizing (PCS) and pain inventory (Brief Pain Inventory, BPI). These instruments are validated and reliable for the constructs they are designed to measure.[27–30] For labor and delivery pain data collection, an electronic "pain diary" application was programmed and available via personal electronic device (Google Nexus 7, Android version 4.3 "Jelly Bean," Mountain View, CA). After admission into the labor and delivery unit, baseline assessment of pain intensity (sensory dimension) and pain unpleasantness (affective dimension) were established, each using a 100 mm horizontal visual analog scale for patient-reported ratings (e.g., "Over the last hour, how intense has your pain been?" and "Over the last hour, how

unpleasant has your pain been?"). Zero mm indicated "no intensity (or unpleasantness) at all" and 100 mm indicated "the most intense (or unpleasant) pain I can imagine." Pain ratings were assessed in this fashion every hour, and the application produced an audible reminder every hour for patients to capture these data. Pain unpleasantness is a measure of the emotional valence of pain[31]; this affective dimension of pain is distinct from the sensory aspect of pain and is differentially impacted by psychological factors.

Postpartum assessments occurred during hospitalization at zero to three days after childbirth (clinically important time points for acute pain and breastfeeding), at six weeks (this time period corresponds to persistent acute pain and is a common time point for postpartum depression screening), and at three months (this time period corresponds to diagnosis of chronic pain).[1,21,32,33] These surveys were sent by e-mail for assessment of pain (BPI) and breastfeeding (yes/no) at each time point. In-hospital postpartum pain and opioid requirement (in milligram morphine equivalents, MME) data were collected. Postpartum pain variables were calculated as described below.

Withdrawal criteria included incomplete baseline or follow-up survey responses, incomplete labor pain diaries for any reason, lack of electronic data transfer from pain diaries, and/or request and receipt of epidural labor analgesia prior to reporting first/baseline pain score in labor pain diary.

Pain and analgesia variables

Labor pain diary data were used to calculate the following pain and analgesia variables per individual patient: first labor and delivery pain score (mm); postepidural analgesia average pain score (mm); labor pain intensity max score (mm); labor pain unpleasantness max score (mm); labor pain intensity burden (area under curve, AUC); and labor pain unpleasantness burden (AUC). Pain AUC has been used to assess aspects of pain burden in multiple studies in obstetric, perioperative, and hospitalized patient populations.[34,35] For postpartum pain and analgesia assessments, the following data were collected and calculated. In-hospital opioid requirements were calculated as MME. Postpartum pain management strategies were unchanged from standard clinical care during the study period and were specifically comprised of acetaminophen 650–1000 mg oral every 6 h (vaginal and cesarean deliveries), ibuprofen 800 mg oral every 6 h (vaginal and cesarean deliveries), and oxycodone 5–10 mg orally every 4–6 h as needed for severe breakthrough pain (cesarean deliveries). Pain during the postpartum hospital stay was reported by nursing assessments in the context of routine clinical care and was assessed by an 11-point (0–10) numeric rating scale, where 0 is no pain and 10 is the worst pain imaginable. Pain scores in the postpartum period are expected to be measured at least twice per shift (every 4 h) by nursing staff. For variability in frequency of pain assessment sampling, time-weighted assessments of pain were calculated, as previously described by our group (percent change in pain and time-weighted percent change in pain).[1]

Labor epidural analgesia was protocolized for this study as follows. Epidural analgesia was initiated at time of patient request. Epidural space was localized by loss-of-resistance to saline and catheters were inserted at a 5 cm depth in the epidural space. Activation was by lidocaine 1.5% with 1:200,000 epinephrine (3 mL "test dose" followed by additional 2 mL), bupivacaine 0.0825% with fentanyl 2 mcg/mL (8 mL), and fentanyl 100 mcg. Continuous patient-controlled epidural analgesia was bupivacaine 0.0825% infusion with fentanyl 2 mcg/mL (8 mL/h), demand 8 mL, and lockout of 24 mL/h. Supplemental epidural dosing protocol included bupivacaine 0.125% with 10–15 mL in 5 mL increments at first request, lidocaine 1% 10 mL in 5 mL increments with adjustment to basal infusion rate to 11 mL/h at second request, and clinician judgment at third request. For women choosing not to use epidural labor analgesia, no other medications were used for pain relief during labor.

Candidate SNP selection

Given sample availability, this cohort was not sufficiently powered to perform GWAS for complex traits such as pain and depression; rather, the goal of this preliminary study is to generate hypotheses and inform future replication studies in larger cohorts. Given the recent wealth of knowledge obtained from pain and depression GWAS that used hundreds of thousands of subjects, we sought to replicate findings in our cohort of perinatal women, a population that has not had extensive genetic mechanistic evaluations for both labor pain and depression. In this study, we focused on genotyping SNPs that were previously associated with either pain or depression. Recently, a GWAS meta-analysis conducted on ~480,000 subjects revealed 44 risk loci significantly associated with major depression.[13] In addition, we considered SNPs that were previously associated with major depression in other studies.[13,36,37] Furthermore, prior studies associated several loci with pain perception or pain sensitivity, including *COMT*, sodium voltage-gated channel alpha subunit 9 (*SCN9A*), and GTP cyclohydrolase 1 (*GCH1*).[38,39] Based upon these prior associations demonstrated in the published literature, a total of 59 candidate SNPs associated with pain and/or depression were selected for testing and are completely listed in Supplemental Table 1.

DNA extraction and genotyping

Genomic DNA was extracted from saliva of n = 183 perinatal women (collected at 28–37 weeks estimated gestational age; Oragene Saliva Kit DNA Genotek, Inc., Ottawa, Canada) and quantified with PICOgreen dsDNA quantitation kit (ThermoFisher, Inc., Waltham, MA) using manufacturer's instruction. Subjects from the Centre d'Etude du Polymorphisme Humain (CEPH) were included as positive control DNAs. CEPH is a collection of European ancestry individuals and family members residing in Utah, USA, that were genotyped as part of the 1000 Genomes Project. Their SNP genotypes are freely available to the public (www.internationalgenome.org), and we used three subjects to check for genotype concordance (NA12778, NA12340, and NA12751; Coriell Institute for Medical Research).[40] Oligo pools were designed using Agena's Assay Design Suite (https://agenacx.com). The oligo pool design was able to accommodate n = 59 SNPs into two oligo pools: pool 1 contained 30 SNPs and pool 2 contained 29 SNPs (see Supplemental Table 1 for oligo sequences). SNPs were genotyped by Sequenom iPLEX MALDI-TOF mass spectrometric assays using manufacturer's protocols (Agena Bioscience, San Diego, CA). Genotyping was conducted by the Genomics Research Core at the University of Pittsburgh.

Genotyping quality control

SNP genotypes were converted into PLINK formatted files, and analysis was performed in PLINK v1.90b4.5 64-bit (25 July 2017).[41] SNPs were removed that had >5% failure rate (n = 11), failed Hardy Weinberg expectations ($P < 0.001$; n = 4), or were discordant for CEPH genotyping (n = 1). Individuals were removed if >5% of markers failed genotyping across both oligo pools (n = 11). Three individuals were chosen at random as duplicates per plate; concordance was 100%. Following quality control measures, there remained n = 173 subjects and 43 markers; the SNP genotyping rate was >99%.

Statistical methods

Linear regression was used to test the null hypothesis that the regression coefficient was not equal to zero across the three genotypes for each clinical phenotype, using race, ethnicity (due to known genetic heterogeneity across racial and ethnic groups), age, and a prior history of anxiety or depression as covariates. Variables were assessed for multicollinearity. PLINK software was used to assess additive gene effects (ADD), deviation from dominance effects (DOMDEV), and the joint effect of both ADD and DOMDEV (GENO-2DF). Each clinical measure was standardized using the "–standard-beta" command, which set the mean of each clinical variable to zero and unit variance. To reduce type I errors, multiple comparisons were addressed using Holm–Bonferroni method (H–B).[42] Tests were considered significant when the H–B family-wise error rate was less than 0.05. Furthermore, for any SNP reaching significance from the regression analysis, the mean differences were assessed using a one-way analysis of variance (ANOVA) in GraphPad Prism version 7. ANOVA was performed on the clinical variables among the three genotype groups (alpha level of significance = 0.05), and then a post hoc Tukey's test was used to assess the mean differences of each genotype group by comparing the mean of each genotype group to the means of the other two genotype groups. Significance for Tukey's testing was assessed for each comparison using family-wise significance level $P < 0.05$.

Missing data

We evaluated data for missingness. Where data were missing for labor pain, we evaluated the nature of missingness and compared demographic characteristics between participants who completed the study and participants who had missing data. Where patterns of missingness could be established or where uncertainty existed in type of missing data, a conservative assumption was made that the data was missing not at random.

Results

Cohort characteristics and quantitative traits

Of the 183 subjects genotyped, 173 perinatal women passed genotyping quality control filters and were included in the final analyses. Table 1 represents demographic characteristics of the study cohort. All women had not previously experienced childbirth (parity = 0). Of these, 65.3% (n = 113) planned to receive labor epidural analgesia; the remaining 30.6% (n = 53) planned not to use labor epidural analgesia. In this cohort, 62.4% had no history of depression or anxiety in the prenatal period, and 87.3% had no history of other mental illness. There was no significant relationship between history of anxiety or depression and postpartum pain intensity maximum score (estimate 4.27, 95% confidence interval −9.26 to 17.8, $P = 0.53$). Results for quantitative traits obtained before, during, and after labor and delivery are reported in Tables 1 and 2.

Multiple linear regression testing

We fit three regression models for each quantitative trait per SNP: (i) additive genetic effects (ADD), (ii) deviation from dominance (DOMDEV), and (iii) a two-degree-of-freedom joint test of ADD and DOMDEV

Table 1. Cohort demographics and obstetric, labor and delivery, and postpartum characteristics of the total cohort.

Variable	n = 173
Prenatal assessment	
Body mass index (kg/m^2)	31.9 (6.0)
Education (years)	15.3 (2.0)
Parity	
0	173 (100)
Race	
American Indian	1 (0.58)
Asian	12 (6.94)
African American	34 (19.65)
European/Caucasian	117 (67.63)
Other	1 (0.58)
Not reported	8 (4.62)
Ethnicity	
Hispanic or Latino	4 (2.31)
Not Hispanic or Latino	161 (93.06)
Not reported	8 (4.62)
Gravidity	
1	119 (68.79)
2	16 (9.25)
3	6 (3.47)
4	3 (1.73)
Not reported	29 (16.76)
Marital status	
Single	43 (24.85)
Married	117 (67.63)
Divorced	3 (1.73)
Not reported	10 (5.78)
Prenatal history of anxiety or depression	
Yes	57 (32.95)
No	108 (62.43)
Not reported	8 (4.62)
History of mental illness other than anxiety or depression	
Yes	12 (6.94)
No	151 (87.28)
Not reported	10 (5.78)
Plan to use labor epidural analgesia	
Yes	113(65.32)
No	53 (30.64)
Not reported	7 (4.05)
Childbirth/labor assessment	
Labor characteristics	
Estimated gestational age (weeks)	39.3 (1.3)
Duration of labor (hours)	16.0 (8.3)
Mode of delivery	
Normal spontaneous vaginal delivery	94 (54.34)
Assisted vaginal—vacuum	3 (1.73)
Cesarean—nonreassuring fetal tracing	7 (4.05)
Cesarean—arrest of dilation/descent	12 (6.93)
Cesarean—other	9 (5.20)
Not reported	48 (27.75)
Perineal lacerations	
None	41 (23.70)
First degree	19 (10.98)
Second degree	60 (34.68)
Third degree	3 (1.73)
Fourth degree	1 (0.58)
Not reported	49 (28.32)
Number of supplemental labor epidural analgesia doses	
0	84 (48.55)
1	13 (7.51)
2	5 (2.89)
3	1 (0.58)
4	1 (0.58)
5	0(0)
6	1 (0.58)
Not reported	68 (39.30)
Postpartum assessment	
Breastfeeding, postpartum days 1–2	
Yes	75 (43.35)
No	5 (2.89)
Not reported	93 (53.76)
Breastfeeding, six weeks postpartum	
Yes	67 (38.73)
No	9 (5.61)
Not reported	97 (56.07)
Breastfeeding, three months postpartum	
Yes	56 (32.37)
No	17 (9.83)
Not reported	100 (57.80)

Note: Data are reported as frequency (%) or mean (standard deviation).

(GENO-2DF). In the ADD model, increased quantitative phenotype scores (the dependent variables) as a function of the number of minor alleles counted is observed when the regression coefficient, β, is positive. The DOMDEV model tests whether a significant proportion of risk is attributable to the individuals who have a heterozygous genotype, that is, a "heterozygote advantage." The data are coded AA = 0, Aa = 1, and aa = 0, where a negative β (slope) in the DOMDEV model indicate the recessive allele is associated with increased quantitative trait scores. The GENO-2DF is a *t* test accounting for the slopes of both the ADD and DOMDEV together, where the two groups tested are homozygotes or heterozygotes versus homozygotes of the opposite allele. There were 69 SNP/phenotype pairs that were unable to be tested due to detection of multicollinearity.

SNP rs4633 is associated with "pain right now" score at 6 weeks postpartum (BPI #6)

Using the genotypes for rs4633 as predictors and "pain right now" score at 6 weeks postpartum as the dependent variable, we detected an association using linear regression analysis, considering race, ethnicity, age, and a

Table 2. Perinatal pain and depression phenotypes reported across prenatal, labor, and postpartum time points.

Pain and depression traits (units)	n	Mean (SD)	95% CI
Depression			
EPDS (baseline score)	167	5 (4)	4.4–5.6
EPDS (six weeks postpartum score)	82	4.1 (3.8)	3.3–5.0
EPDS (three months postpartum score)	74	4 (3.7)	3.1–4.8
Labor pain			
Initial labor pain score (mm)	88	6.4 (6)	5.1–7.6
Labor pain intensity max (mm)	88	77.8 (20.1)	73.5–82.1
Labor pain intensity burden (AUC)	88	429 (333.3)	358.4–499.7
Labor pain unpleasantness max (mm)	88	79.7 (19.5)	75.6–83.8
Labor pain unpleasantness burden (AUC)	88	443.1 (349.8)	369.0–517.2
Supplemental labor epidural analgesia doses (number)	106	2.8 (4.2)	2.0–3.6
Postpartum pain, zero to three days after delivery			
Postpartum opioid requirements (MME)[a]	106	30 (50.5)	20.3–39.7
Postpartum percent change in pain (%)[a]	118	−11 (47.1)	−19.6 to −2.4
Time-weighted postpartum percent change in pain (%)[a]	118	3.9 (1.5)	3.6–4.2
Postpartum pain, six weeks after delivery			
Pain at worst in last 24 h (score)	81	4.9 (2.7)	4.3–5.5
Pain at least in last 24 h (score)	81	5.4 (2.8)	4.8–6.0
Pain on average (score)	81	2.9 (2.3)	2.4–3.4
Pain right now (score)	80	2.9 (2.3)	2.4–3.4
Postpartum pain, three months after delivery			
Pain at worst in last 24 h (score)	71	1.1 (2)	0.6–1.5
Pain at least in last 24 h (score)	71	1.1 (2)	0.6–1.6
Pain on average (score)	71	0.7 (1.6)	0.3–1.1
Pain right now (score)	71	0.5 (1.5)	0.1–0.8

EPDS: Edinburgh Postnatal Depression Scale; AUC: area under curve; MME: milligram morphine equivalents; SD: standard deviation; CI: confidence interval.
[a]Measurements included in-hospital data only.

history of anxiety or depression as covariates, for additive genetic effects (ADD; $\beta = -0.33$, 95% confidence interval (CI) $= -0.54$ to -0.13, $P = 0.002$), for deviation from dominance genetic effects (DOMDEV; $\beta = -0.23$, 95% CI $= -0.43$ to -0.02, $P = 0.03$), and for the joint effects (GENO_2DF; unadjusted $P = 0.008$, H–B family-wise error rate $= 0.029$; Table 3). The slopes (β) of the regression lines were negative for both the ADD and the DOMDEV models, suggesting the major allele is associated with higher "pain right now" score at six weeks postpartum, and individuals with heterozygous genotypes have lower "pain right now" score at six weeks postpartum than individuals with either homozygous genotypes.

Furthermore, a one-way ANOVA was performed on "pain right now" score at six weeks postpartum for each of the three genotype groups and yielded a significant result ($F_{(2,76)}$=9.058, $P = 0.0003$; Figure 1(a)). A post hoc Tukey's test for "pain right now" score at six weeks postpartum showed group differences between the genotype groups (C/C vs. T/C, adjusted $P = 0.0002$ and C/C vs. T/T, adjusted $P = 0.0077$; Figure 1(a)). The T/C versus T/T group comparison did not have significantly different means (adjusted $P = 0.676$; Figure 1(a)). Indeed, as indicated by the regression analysis, the heterozygous individual group had the lowest mean value of "pain right now" score at six weeks postpartum (mean $= 2.189$, standard deviation (SD) $= 1.838$) compared to either homozygous group (C/C group mean $=$ 4.632, SD $= 2.543$ and T/T group mean $= 2.652$, SD $= 1.968$).

SNPs rs11135349 and rs7548151 are associated with labor pain unpleasantness maximum score

Using the genotypes for rs11135349 or rs7548151 as predictors and "labor pain unpleasantness maximum score" as the dependent variable, we detected an association using linear regression analysis, considering race, ethnicity, age, and history of anxiety or depression as covariates. SNP rs11135349 was significant for ADD ($\beta = -0.43$, 95% CI $= -0.65$ to -0.21, $P = 0.003$) and for GENO_2DF ($t = 16.69$, unadjusted $P = 0.0002$, H–B family-wise error rate $= 0.009$). The DOMDEV genetic effects model approached significance ($P = 0.062$; Table 3).

SNP rs7548151 was significant for ADD ($\beta = -0.60$, 95% CI $= -0.89$ to -0.31, $P = 0.001$), DOMDEV ($\beta = 0.59$, 95% CI $= 0.29$ to 0.88, $P = 0.0002$), and

Table 3. Multiple regression of phenotypes was performed on perinatal women, adjusted for race, ethnicity, age, and history of anxiety or depression, using coefficients from terms on additive gene effects (ADD), deviation from dominance (DOMDEV), and the joint effect of ADD and DOMDEV (GENO-2DF).

Clinical outcome	Chr: base (hg19)	SNP	Allele	Symbol	Transcript	global genomeAD MAF (n subjects)	Test	Coefficient					GENO_2DF		
								β	SE	95% CI	T	P	T	P	H–B
Pain right now (six weeks postpartum)	chr22: 19,950,485	rs4633	C/T	*COMT*	ENST 00000361682	0.4626 (140,690)	ADD	−0.33	0.11	−0.54 to −0.13	−3.18	0.002	14.35	0.0008	0.029
							DOMDEV	−0.23	0.10	−0.43 to −0.02	−2.19	0.03			
Labor pain unpleasantness max score (labor)	chr5: 164,523,472	rs11135349	A/C	Intergenic	ENST 00000519570	0.614 (15,683)	ADD	−0.43	0.11	−0.65 to −0.21	−3.83	0.0003	16.69	0.0002	0.009
							DOMDEV	0.20	0.10	−0.004 to 0.40	1.93	0.058			
	chr1: 177,026,733	rs7548151	G/A	*ASTN1*	ENST 00000361833	0.1345 (15,684)	ADD	−0.60	0.15	−0.89 to −0.31	−4.1	0.0001	18.8	8.3×10^{-5}	0.003
							DOMDEV	0.59	0.15	0.29 to 0.88	3.9	0.0002			

Note: These findings support that alleles increase risk for the pain phenotypes, specifically for additive gene effects (both "pain right now at six weeks postpartum" and "labor pain unpleasantness maximum score" phenotypes) and for DOMDEV effects ("pain right now at six weeks postpartum" phenotype). The relationships between rs4633 and "pain right now at six weeks postpartum" and rs11135349, rs7548151, and labor pain unpleasantness maximum score were significant for the joint test that accounted for both additive and dominant-deviance models, after considering multiple comparisons using Holm–Bonferroni family-wise error rate (H–B), where tests with H–B rate < 0.05 were considered significant.

H–B: Holm–Bonferroni family-wise error rate; CI: confidence interval; Chr: chromosome; SE: standard error; T: student t test; β: regression coefficient; ADD: additive gene effect model; DOMDEV: deviation from dominance effect model; GENO_2DF: joint test of the coefficients for ADD and DOMDEV models; SNP: single-nucleotide polymorphism; MAF: minor allele frequency.

GENO_2DF ($t = 18.8$, $P = 8.3 \times 10^{-5}$, H–B family-wise error rate = 0.003; Table 3).

The slopes (β) of the regression lines for the ADD models for rs11135349 or rs7548151 were negative, indicating the minor allele for each SNP was associated with an increased score for labor pain unpleasantness maximum.

For group differences, one-way ANOVA was performed on the labor pain unpleasantness maximum score values for each of the three genotype groups and yielded a significant finding for rs11135349 and rs7548151 ($F_{(2,84)} = 7.673$, $P = 0.0009$ and $F_{(2,84)}=7.182$, $P = 0.028$, respectively; Figure 1(b) and (c)). The post hoc Tukey's test for labor pain unpleasantness maximum score showed group differences between the genotype groups for rs11135349 and rs7548151 (A/A vs. A/C, adjusted $P = 0.0021$ and A/A vs. C/C, adjusted $P = 0.0013$; and A/A vs. A/G, adjusted $P = 0.005$ and A/A vs. G/G, adjusted $P = 0.02$; Figure 1(b) and (c)). The A/C versus C/C or A/G versus GG group comparisons for rs11135349 and rs7548151, respectfully, did not have significantly different mean differences (adjusted $P = 0.813$; Figure 1(b)).

Pertinent negative findings

We failed to reject the null hypothesis for the remaining quantitative traits across the genotyped SNPs in this cohort. Specifically, we note labor pain intensity traits (i.e., sensory components of pain), as well as the EPDS scores (at baseline, six weeks postpartum, and three months postpartum) were not significant following multiple comparisons correction for any of the genotyped SNPs. The full list of linear regression test results is available upon request.

Sensitivity analyses for missing data

There were missing data for "pain unpleasantness maximum score" (50%) and for "pain right now at six weeks" (54%). These variables are related to each other in that if a participant could not complete the labor pain diaries for any reason, she was withdrawn from the study, and subsequently "pain right now" assessments at six weeks were also missing. For the participants who did not compete the labor pain diaries (n = 61), whereby the "pain unpleasantness maximum score" was calculated, these data were conservatively judged to be missing not at random as they were logged as missing due to the following reasons: participants progressing through labor quickly (not enough time to complete the diary or incomplete entries; n = 42), pain diary data transfer problems (network issues; n = 7), requirement for cesarean delivery without labor for reasons of breech, development of

Figure 1. Box plot of clinical variables, BPI short 6pp (a) and pain unpleasantness max (b and c), by genotype of rs4633, rs11135349, and rs7548151, respectively, in perinatal women. Tukey's multiple comparisons post hoc test was performed on the clinical variables between each genotype group per SNP. $*P \leq 0.05$, $**0.005 < P < 0.01$, and $***P < 0.0005$.

preeclampsia, or other obstetric indications (n = 10), or receiving epidural analgesia prior to completing the diary (n = 2).

Results of the comparisons of demographic characteristics between missing and nonmissing data are shown in Supplemental Table 2. Groups of missingness were different for duration of labor (hours) and statistically, but not clinically, significantly different for level of education. Given the above considerations and these findings, we therefore assumed that the missing data for pain unpleasantness maximum score were missing not at random (MNAR). Given MNAR, coupled with the frequency of missing data exceeding 50%, it was judged that imputation was not appropriate, and results were interpreted within the context of the limitations presented with this information.

Discussion

In this study, we identified genetic factors contributing to depression and pain in perinatal women. Both pain and depression are complex, multifactorial disorders encompassing a wide range of symptoms and mechanisms: cognitive, emotional, and physical. While our cohort is a small, exploratory cohort, we were able to identify loci with modest associations. We identified three SNPs that were associated with two pain phenotypes: (1) rs4633 (a variant in the coding region of *COMT*) associated with "pain right now" at six weeks postpartum; (2) rs11135349 (a variant in an intergenic region previously associated with major depressive disorder) was associated with labor pain unpleasantness max score (a measure of the emotional valence or affective component of pain); and (3) rs7548151, an intronic SNP that maps to astroactin-1 (*ASTN1*), was previously associated with depression in a British study.[37]

Together, these data suggest that genetic variants are a common factor between depression and perinatal pain, and they provide a biological basis for continued research to explain the observed associations between perinatal pain and depression.

SNP rs4633 is a common (gnomeAD[43] global minor allele frequency (MAF) = 0.4626), missense variant in the coding region of *COMT* (EC2.1.1.6) on chromosome 22q11, resulting in increased translation rate.[44] COMT functions as a methyltransferase that mediates methyl group transfer from S-adenosylmethionine to catecholamines, including neurotransmitters like dopamine,[45] which can result in catecholamine transmitter degradation.[46] A total of 11 *COMT* transcripts have been described in GTEx[47] with transcripts ENST00000467943.1 and ENST00000406520.3 having nearly ubiquitous and high levels of expression across the 53 human body tissues analyzed.

In our study, the mean pain score (millimeters) value of "pain right now" at six weeks postpartum for individuals with C/C genotype (reference allele) was 4.6 mm (standard error of the mean (SEM) = 0.58), with T/C genotype (variant) was 2.2 mm (SEM = 0.30), with T/T genotype (variant) was 2.7 mm (SEM = 0.41). In other words, mutant alleles were associated with less pain than wild-type alleles. We know that rs4633 mutations result in CAC-CAT codon change, which has implications for molecular binding motifs (proteins, RNA, etc.). Altogether, this information points to required research to test what binding partners exist for rs4633 that could impact pain.

To our knowledge, this is the first study to find such an association between rs4633 and pain at six weeks postpartum. Our data suggest that individuals with C/C genotypes for rs4633 had higher mean pain scores when assessed at six weeks postpartum. A prior study found that rs4633 was associated with "longer" durations of latent labor (approximately 5 h)[48]; however, the association was for the opposite alleles than our study. A potential reason for observing opposite alleles may be due to differences in minor allele frequencies between study cohorts: our study was comprised of

individuals from North America (United States), while Terkawi's cohort was from Saudi Arabia. In that study, the duration of latent labor was dependent on the time of admission to the hospital. Presentation and admission to the hospital for childbirth may, in fact, have been driven by the degree of pain experienced by women during the early latent phase of labor. Therefore, it is possible that the findings of Terkawi et al. are not necessarily a function of latent labor duration, but rather a function of severity of pain in latent labor, that may then dictate a woman's presentation to the hospital for delivery. If it was in fact the pain (and not necessarily the duration of the latent phase of labor) that correlated with rs4633, then those findings are consistent with our finding of rs4633 associations with pain.

We found that two SNPs (rs11135349 and rs7548151) are associated with maximum labor pain unpleasantness score (a measurement of the emotional valence of pain). SNP rs11135349 maps to an intergenic region on chromosome 5q34 and was selected for genotyping in this cohort due to its prior association with major depressive disorder in the largest GWAS meta-analysis of major depression to date.[13] SNP rs11135349 is a common SNP (gnomeAD global MAF = 0.6155) across population groups, where it maps to a noncoding/antisense RNA locus, as supported by GTEx RNA-seq Gene Expression (ENSG00000241956.5) and Transcript Expression (ENST00000519267, ENST00000519570, ENST00000522646, and ENST00000522303) analyses performed on 570 participant donors (Figure 2).[47] These noncoding RNA transcripts, identified by GTEx, were present in CNS tissues.[47] When considering a 200 kb flanking region around rs11135349, there are a striking number of past GWAS that find significant association with depression,[36,37,49,50] neuroticism,[51,52] subjective well-being,[49] and neuropathic pain in post total joint replacement surgery for osteoarthritis (Figure 2).[53] Given these

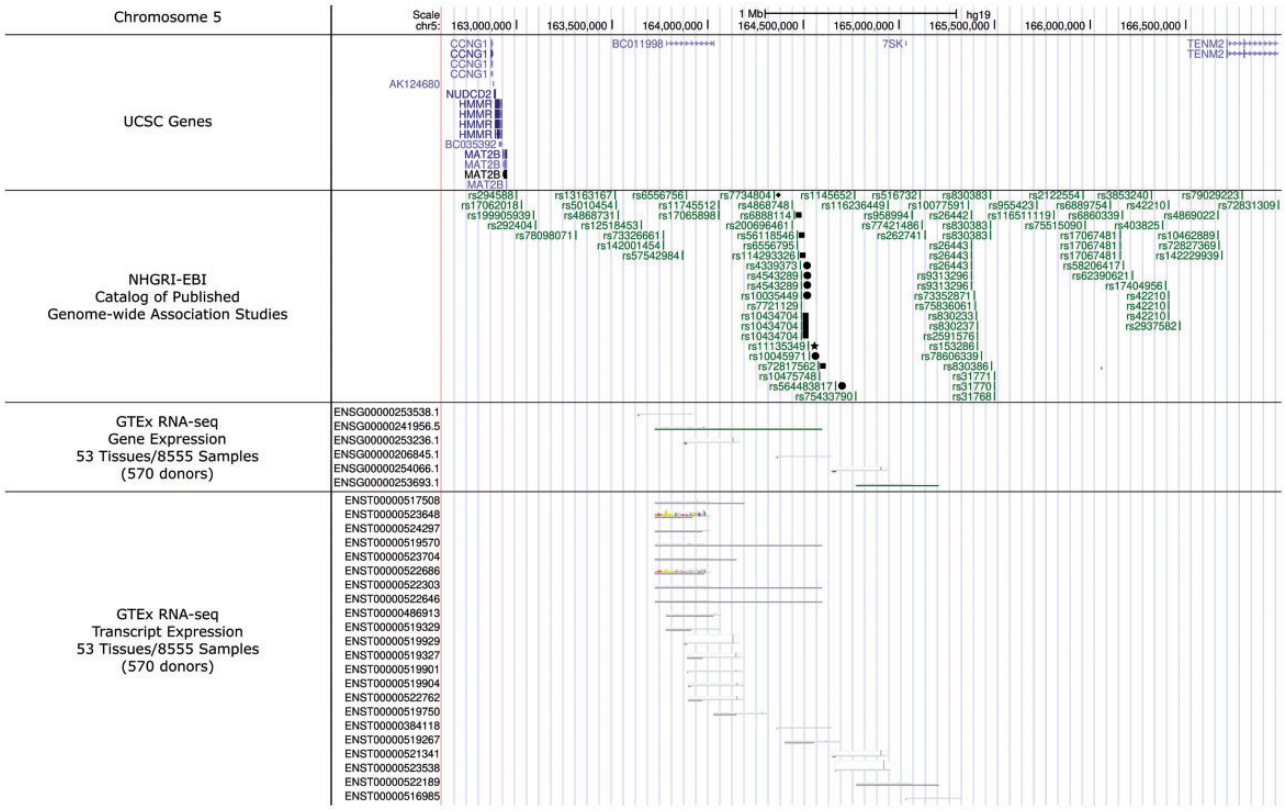

Figure 2. The 4.3 mega-base region of Chromosome 5 that flanks rs11135349 (filled star) (chr5:162614336–166985335). This area is absent of any known, documented UCSC gene coding loci (considered an intergenic region). Documented UCSC genes are mapped in the first panel "UCSC Genes." The second panel displays SNPs, within a 200 kb flanking region, that had prior association for depression (filled circle and filled star),[13,36,37,49,50] neuroticism (filled square),[51,52] subjective well-being (filled rectangle),[49] and pain (filled diamond).[53] GTEx RNA-sequencing analysis describes gene and transcript expression from this region, directly overlying the present SNP, rs11135349 (third and fourth panels, respectively), indicating rs11135349 maps to noncoding RNA species. In the present study, rs11135349 was associated with pain phenotype ("pain unpleasantness maximum score" measured during labor). In prior work,[13] rs11135349 was associated with depression. Image modified from the UCSC Genome Browser (assembly release date: Human Feb 2009 (GRCh37/hg19); http://genome.ucsc.edu/).[61]

considerations, this locus may be an important region that dictates associations between both phenotypes of pain and depression, not only in perinatal women but also in the broader population. Genetic studies examining pain phenotypes in larger cohorts are justified to establish this relationship.

Although this region is intergenic, it may be functional for noncoding RNAs, supported by the above studies, for pain and depression. Other disorders resulting from variation in noncoding RNAs have been documented, such as cancer, Alzheimer disease, Prader–Willi syndrome, Parkinson disease, and deafness.[54] However, the function of these noncoding RNA transcripts on 5q34 is presently unknown, and validation is warranted. The present study identifies a relationship between this noncoding RNA SNP (rs11135349) and labor pain unpleasantness; our own data have similarly found that labor pain unpleasantness is significantly associated with depression scores at six weeks postpartum, in women planning/receiving labor epidural analgesia ($R^2 = 0.41$; $P = 0.001$).[55] Together, these findings suggest that this noncoding RNA species may contribute to disease etiology not only for depression phenotypes but also for labor pain.

The other SNP associated with labor pan unpleasantness (the emotional valence of pain) was rs7548151. Both SNPs have been associated with depression phenotypes in GWAS studies.[37] SNP rs7548151 maps to astrotactin-1 (*ASTN1*), a neuronal adhesion molecule that functions in the migration of postmitotic neuroblasts.[56] While these SNPs do not map to an exonic region, they may be in linkage disequilibrium with and tagging truly causal variants. These findings provide further support for a central nervous system component that may underlie a relationship between depression and pain.

Notably, we did not find associations between SNPs that were previously associated with major depression, with the depression scores (EPDS) measures obtained at any time point (prenatal, six weeks postpartum, or three months postpartum). This failure to detect an association does not necessarily rule out a common genetic explanation for both perinatal pain and depression, but rather, may be due to (1) the small sample size of the current study and the small effect size of each SNP on phenotypic risk or (2) fundamental biological/mechanistic differences between perinatal depression and depression outside of pregnancy and the postpartum period. Prior association studies on major depression need sample sizes that contain hundreds of thousands of subjects.[13] Alternatively, perinatal depression may be unique and distinct from major depression. To our knowledge, there have been no GWAS findings for perinatal depression reported in The GWAS Catalog (accessed 12 August 2018).[57] This may be due to the temporal nature of depression onset, weaker biological evidence for SNP associations, or perhaps an etiological model that is epigenetic in nature.[58]

Some shortcomings of this study should be noted. The genotyping failure of some SNPs in *COMT* prevented us from performing haplotype analyses. Prior studies find associations of *COMT* haplotypes with metrics of pain[59] and pain experienced by female individuals diagnosed with major depressive disorder.[60] Furthermore, the use of self-reported ancestry cannot rule out type 1 error. Moreover, SNP MAFs were not compared in this study due to population stratification (i.e., MAF differences between groups may be due to group differences in ancestry and not due to a positive association of a SNP to a trait). Furthermore, introducing subgroups would have dramatically decreased the power to detect associations, and therefore we did not pursue these analyses for this study. Future studies incorporating an increased number of perinatal women and an increased number of SNP markers, including those missed in *COMT*, are justified and will add power to this study. Finally, there was missing data for labor pain. The missing data potentially may have biased our sample toward an underestimation of relationship due to omission of patients who had rapid labors (potentially short but intense periods of labor pain with subsequent omission of pain diary data), or who may have otherwise had immeasurably different characteristics with respect to risk for both pain and depression.

Conclusions

In conclusion, we have identified genetic loci that are associated with perinatal pain and which require replication in a larger cohort of obstetric patients. These identified loci have known associations with pain and depression in nonpregnant individuals, and they map to genetic regions that may have functional consequences, including to mechanisms underlying the relationships between perinatal pain and depression. Continued research to identify the genomic components of these complex disorders may produce insights into relevant pathways or novel treatment options in the obstetric population.

Summary Statement

SNPs in *COMT* (rs4633) and in an intergenic region associated with depression (rs1135349) are linked to pain experienced at six weeks postpartum and to the emotional valence of labor pain, respectively.

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Supplemental Material

Supplemental material for this article is available online.

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