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Contribution of *COMT* and *BDNF* Genotype and Expression to the Risk of Transition From Acute to Chronic Low Back Pain

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Objectives: A number of factors, including heritability and the environment, contribute to risk of transition from acute low back pain to chronic low back pain (CLBP). The aim of this study was to (1) compare somatosensory function and pain ratings at low back pain (LBP) onset between the acute low back pain and CLBP conditions and (2) evaluate associations between *BDNF* and *COMT* polymorphisms and expression levels at LBP onset to acute and chronic pain burden and risk for transition to the chronic pain state.

Methods: In this longitudinal study, 220 participants were enrolled following recent onset of LBP and data were collected until the LBP resolved or until the end of the study at 6 months. Forty-two participants' pain resolved before 6 weeks from onset and 42 participants continued to have pain at 6 months. Patient-reported pain burden, somatosensory function (quantitative sensory testing), and blood samples were collected at each study visit.

Results: CLBP is associated with greater pain burden and somatosensory hypersensitivity at the time of LBP onset. *COMT* rs4680 genotype (GG) was associated with acute cold pain sensitivity and with the risk for transition to CLBP while *COMT* expression was independently associated with risk for transition.

Discussion: CLBP was characterized by higher reported pain burden and augmented hypersensitivity at LBP onset. *COMT* expression and genotype were associated with acute pain burden and likelihood of transition to CLBP.

Key Words: low back pain, chronic pain, genetics, quantitative sensory testing

(*Clin J Pain* 2020;36:430–439)

Low back pain (LBP) is responsible for one-third of work-related disability claims, is one of the top 10 most expensive conditions in the United States, and affects nearly 1 in 10 people worldwide.[1,2] For most individuals with an acute low back pain (ALBP) episode, the pain resolves within 4 to 6 weeks and patients regain the ability to resume normal activities (acute resolving LBP; ALBP). However, an estimated 20% of individuals with acute pain will continue to have pain beyond 12 weeks (chronic low back pain; CLBP) at a level that negatively impacts normal activities, function, and quality of life.[3] The transition to CLBP raises the risk of long-term disability and comorbidities including other pain disorders.[4]

In ~ 90% of individuals who seek health care for LBP there is no identifiable etiology and the pain is presumed to be of mechanical or nonspecific origin.[5] Even though the origin of the pain is unclear, as the prevalence of CLBP increases there has been a concomitant increase in health care utilization including spinal injections, surgical procedures, and use of opioid medications.[6] Early identification and intervention for those individuals with the highest risk for CLBP may provide a more effective method for prevention and management. Prior studies have identified a number of factors that contribute to a profile of risk for CLBP, including psychological health, poorer general health, functional impairment, increased inflammatory tone, and heritable factors,[7–9] but there remains a lack of consensus regarding key variables in predicting those that will eventually transition to a chronic pain state. This paucity in the literature prevents the development of precision health care strategies directed at the mechanisms of risk.

As with many complex health conditions, LBP likely represents a disorder of complex etiology comprised of multigenic

Received for publication September 26, 2019; revised January 16, 2020; accepted February 6, 2020.

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Supported by the National Institute of Nursing Research, Storrs, CT (Starkweather, PI; R01 NR013932). Drs Dorsey, Baltimore, MD (P30 NR011396; R01 NR013601; P30 NR014129) and Baumbauer, Storrs, CT (R03 NS096454) are currently receiving grants. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Nursing Research (NINR) or the National Institutes of Health (NIH). The authors declare no conflict of interest.

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DOI: 10.1097/AJP.0000000000000819

contributions as well as environmental factors. Heritability of LBP is estimated to range from 30% to 60% with higher familial incidence associated with increased severity of LBP.[10,11] A number of studies have focused on genetic contributions to physical degeneration of the vertebral discs or to development of nerve injury-pain following sciatic compression due to herniation of a disc.[12,13] Degenerative disc disease (DDD) is often cited as a cause of LBP although disc degeneration is ubiquitous among adults and characterized by increased desiccation of the spinal disc matrix, proteoglycan degradation, and elevated disc tissue levels of proinflammatory cytokines.[14] Given that the degree of DDD does not correlate well with pain severity or duration, surgical options are typically reserved only after conservative measures have failed to improve function and quality of life. More recent work by Pinheiro et al[9] confirmed a relationship between CLBP and anxiety/depression with further support for a shared heritable mechanism, though a list of proposed candidate genes in this shared mechanism were not identified. For the present study, we identified 2 high priority candidate genes, *Catechol-O-Methyltransferase* (*COMT*) and *Brain Derived Neurotrophic Factor* (*BDNF*), based on prior work by ourselves and others suggesting that these 2 genes (1) encode products that are potent mediators of pain processing,[15–21] (2) play an important role in the early steps of nervous system sensitization leading to enhanced pain sensitivity,[22–25] and (3) may contribute to the etiology of depression and/or anxiety leading to exacerbation of pain.[26,27] *COMT* encodes the catechol-o-methyltransferase enzyme responsible for catecholamine metabolism and thus modulation of adrenergic, noradrenergic, and dopaminergic signaling. *COMT* is one of the most frequently studied "pain genes" and has been associated with differential pain sensitivity under normal and pathologic conditions.[28–33] Single nucleotide polymorphisms (SNP) and haplotypes within *COMT* have been shown to alter both the structure and function of the resulting COMT enzyme and, subsequently, modulate levels of the neurotransmitters that are degraded downstream.[28,29,34–39]

Given the number and nature of the neurotransmitters metabolized by COMT, it is, perhaps, not surprising that it has been found to play a role in pain sensitivity/susceptibility as well as mood and other psychological outcomes.[40,41] When considered as part of the biopsychosocial model of pain, *COMT* genotype is associated with psychological outcomes including anxiety and depression but also interacts with other psychological traits like pain catastrophizing to determine pain outcomes in other clinical populations.[42] This complexity is illustrated by the mixed conclusions in the literature regarding the role of *COMT* in clinical and experimental pain outcomes. *BDNF* encodes the protein brain-derived neurotrophic factor (BDNF), a regulator of synaptic transmission and plasticity at adult synapses and in response to injury, and a number of polymorphisms have been shown to affect the availability and activity of BDNF.[13,14]

Cortical pain processing is associated with large-scale changes in neuronal connectivity, resulting from neural plasticity phenomena of which BDNF is a central driver. Noxious stimulation also increases BDNF production in the spinal dorsal horn[43–45] and in the brainstem[45,46] leading to increased pain signaling and manifestations of enhanced pain sensitivity such as hyperalgesia and allodynia.[47]

On the basis of previous findings, our hypothesis was that the CLBP group would have higher pain burden early on, increased sensitivity to painful stimulation, and increased frequency of *BDNF* and *COMT* risk alleles compared with the ALBP group. The primary aim of the study was to (1) compare somatosensory function and pain ratings at LBP onset between the patients in the ALBP condition and those in the CLBP condition and (2) evaluate the potential contribution of *BDNF* and *COMT* polymorphisms and gene expression levels at LBP onset to higher pain burden during ALBP and risk for developing CLBP.

METHODS

Participants

Men and women between the ages of 18 to 50 years of age with recent onset of LBP (<2 weeks at time of recruitment) and able to read and write in English were invited to participate from primary health care clinics, college campuses, and the general community through advertisements. This age range was selected to provide a more homogenous sample in terms of general health, work status, and contributing factors of CLBP. An acute nonspecific LBP episode was defined as pain anywhere in the region of the low back bound superiorly by the thoraco-lumbar junction and inferiorly by the lumbo-sacral junction, which had been present for >24 hours but <4 weeks duration and was preceded by at least 1 pain-free month.[48] Recruitment took place at 2 urban university health systems after approval from the Institution Review Board. All participants provided written consent before study participation.

Volunteers with LBP were excluded for the following: (1) pain at another site or associated with a painful condition (eg, DDD, herniated lumbar disc, fibromyalgia, neuropathy, rheumatoid arthritis, sciatica); (2) previous spinal surgery; (3) presence of neurological deficits; (4) history of comorbidities that affect sensorimotor function (eg, multiple sclerosis, spinal cord injury); (5) pregnant or within 3 months postpartum; (6) taking opioid, or anticonvulsant medication; and, (7) history of diagnosed psychological disorders (bipolar disorder, schizophrenia).

After collection of data at the baseline visit, participants who continued to have pain ≥2 on the numeric rating scale were followed up every 6 weeks until either the patient reported that their pain had resolved in the time since their previous visit or until 24 weeks (end of the study). Participants whose pain had resolved as indicated by a visual analogue scale (VAS) rating of 1 or below by the 6-week time-point were classified as ALBP. Participants who had chronic pain at the 6-month visit were classified as CLBP.

Procedures

After obtaining informed consent, participants were scheduled to undergo baseline data collection as soon as possible but no longer than 1 week from the time of consent. Data collection took place in a private research suite to complete questions about age, sex, socioeconomic status, educational attainment, lifestyle behaviors (smoking, exercise), comorbidities, and past episodes of LBP. Following completion of the questionnaires, participants underwent venipuncture for collection of blood samples and quantitative sensory testing (QST). The sequence of data collection was followed for all participants.

Pain Measures

The Brief Pain Inventory (BPI) is a pain assessment tool that has well-established reliability and validity for adult patients with LBP, and is sensitive to change over time.[49] The BPI assesses the severity of pain, location of pain, pain

medications, amount of pain relief in the past 24 hours and the past week, and the impact of pain on daily functions.

The McGill Pain Questionnaire (MPQ) short form is a reliable self-report measure of pain perception.[50,51] It entails 15 verbal descriptors of sensory and affective dimensions of pain and is scored on a 4-point scale (0-none to 3-severe) by adding the numeric value of each pain dimension. Higher scores indicate higher levels of sensory and affective components of pain (range, 0 to 45).

QST

QST was used to evaluate responses to experimental pain and uses standardized stimuli to test both nociceptive and non-nociceptive systems.[52] Quantitative sensory testing was performed on the lumbar region and the dominant forearm (remote area). A standardized protocol of administration, including examination room conditions and instructions provided for the participant, were strictly followed from the same protocol described in the preliminary analysis reported by our group.[53,54] Participants completed a confirmation trial on the nondominant forearm to verify the participant's understanding of the procedures.

Genotyping

Genomic DNA (gDNA) was extracted from buffy coat using standard protocols (DNA mini kit, Qiagen). All samples were genotyped for 3 *COMT* SNPs (rs4633, rs4818, rs4680) and 1 *BDNF* SNP (rs6265) using predesigned TaqMan primers and universal genotyping master mix (Life Technologies, Thermo Fisher) (Table 1). The global minor allele frequencies for all SNPs were ≥ 0.20 based on data from 1000 Genomes. Genotyping assays were performed according to the manufacturer's protocol using an Applied Biosystems (ABI) StepOne Plus PCR machine and ABI allelic discrimination software.

Gene Expression Analysis

Whole blood was collected by venipuncture into one 5-mL EDTA vacutainer and one 10-mL Paxgene blood RNA tubes (PreAnalytix, Qiagen), labeled with a unique study identification label, and transported directly to the laboratory for processing. RNA isolation was performed using the PAXgene total RNA isolation system (Qiagen, Valencia, CA) according to the manufacturer's protocol and was reverse transcribed using RT^2 cDNA kit (Qiagen). The mRNA expression of 84 genes involved in the transduction, maintenance, and modulation of pain was determined (Neuropathic & Inflammatory RT2 Profiler PCR Array; Sabio Sciences, Valencia, CA) using qPCR performed on the ABI StepOne Plus PCR machine. After an initial incubation step, 40 cycles (95°C for 15 seconds and 1 minute at 60°C) of PCR were performed. Relative gene expression levels were quantified for *COMT* and *BDNF* using the $2^{-\Delta\Delta}$CT method which normalizes data of the genes of interest to the average of 3 housekeeping genes β-actin (*ACTB*), *GAPDH*, and Beta-microtubulin (*B2M*) and determines the expression level relative to normal controls.

TABLE 1. Details on Candidate SNPs Assessed in Low Back Pain Participants

Gene	SNP ID	VIC/FAM	HapMap	1000 Genome	African American
BDNF	rs6265	C/T	20/80 (t/c)	20/80	5/95 (t/c)
COMT	rs4818	C/G	30/70 (g/c)	Not available	31/69 (g/c)
COMT	rs4633	C/T	37/63 (t/c)	48/52 (t/c)	27/73 (t/c)
COMT	rs4680	A/G	37/63 (a/g)	48/52	27/73

FAM indicates 6-carboxyfluorescein; SNP, single nucleotide polymorphism; VIC, 2′-chloro-7′phenyl-1,4-dichloro-6-carboxy-fluorescein.

Statistical Analyses

The results from the current sample are part of larger funded NIH study (NCT01981382, clinicaltrails.gov). We have already examined differences in demographic variables as well relationship between genetic variation of the *FAAH* gene and pain sensitivity in this population.[55] Student *t* tests were used to test for group differences in QST variables that were normally distributed, χ^2 was used to identify differences in genotype frequency between ALBP and CLBP conditions and multiple stepwise linear regression analyses using an additive genetic model to explore the contributions of the candidate gene SNPs to each outcome measure as a separate dependent variable. In the first step, we entered biological predictors influential to health outcomes (age, sex, race, and ethnicity). The subsequent step(s) of the model consisted of individual SNP genotype and/or candidate gene expression values. In order to correct for multiple comparisons (total of 4 for the 4 individual SNPs evaluated), the adjusted *P*-value necessary for significant associations is $P \leq 0.0125$. Given the sample size and our desire not to dismiss potential clinically relevant associations, we present findings and their associated *P*-values. We have used the uncorrected *P*-value ≤ 0.05 throughout the manuscript to identify statistical significance. This approach allows for the most robust generation of testable hypotheses for future studies into the mechanisms underlying any associations.

RESULTS

Demographics and Genetic Variation

A total of 220 participants were recruited; the final sample for analysis was comprised of first 42 participants that had resolution of their pain within 6 weeks from onset and the first 42 participants who continued to have pain for 6 months (termination of the study). The remaining participants resolved at some point after 6 weeks and before 6 months and were not included in the present analysis. These participants were successfully genotyped at 4 SNPs (rs6265 [*BDNF*] and rs4680, rs4633, and rs4818 [*COMT*]). We previously reported a preliminary analysis of baseline demographic, psychological, and self-report pain scores among ALBP and CLBP participants and relationship between *FAAH* genotype.[55] As shown in Table 2, we observed some heterogeneity in age, sex, race, and ethnicity within our sample and between the 2 groups (ALBP and CLBP). As a result, we loaded these factors as the first step in the stepwise regression to remove potential confounding effects and identify significant effects based on the proportion of the variance (R^2 change, *F* change, *P* change) explained by genotype and/or gene expression.

Comparing Pain at the Time of Onset for ALBP Versus CLBP Participants

A pattern of increased pain burden was found for the participants that would go on to develop CLBP compared with the ALBP participants across multiple measures and outcomes assessed at the time of recruitment. Mean comparisons using independent samples *t* tests revealed that CLBP participants reported significantly higher ratings for the pain

TABLE 2. Pain Self-report at the Time of Low Back Pain Onset by Group

	CLBP (N = 42)	Acute Resolved (N = 42)	*P*
BPI (scale), mean (SE)			
Average	5.24 (0.29)	3.57 (0.25)	**0.000***
Worst	6.83 (0.34)	4.43 (0.31)	**0.000***
Least	3.52 (0.35)	1.52 (0.21)	**0.000***
Now	4.98 (0.40)	3.05 (0.25)	**0.000***
Interference	4.50 (0.35)	2.54 (0.27)	**0.000***
McGill Pain Questionnaire, mean (SE)			
Affective	2.45 (0.41)	1.69 (0.23)	0.109
Sensory	11.05 (0.91)	8.54 (0.86)	**0.048***
VAS	50.87 (3.99)	25.72 (2.92)	**0.000***

Bold indicates $P \leq 0.05$ for analysis.
*Level of significance set at 0.05.
BPI indicates Brief Pain Inventory; CLBP, chronic low back pain; VAS, visual analogue scale.

severity and pain interference subscales of the BPI (Worst Pain, Least Pain, Average Pain, Pain Now and Pain Interference; all $P < 0.001$) (Fig. 1). Participants also completed the MPQ at the time of recruitment and, for those that would go on to develop CLBP, at their 6-month follow-up. Analysis with independent samples *t* test revealed that CLBP participants reported higher sensory ($P < 0.05$) and present pain intensity (PPI) scores ($P < 0.001$) on the MPQ at the time of recruitment (Fig. 2). Analysis of somatosensory function (QST) assessments conducted on the lower back at the time of initial recruitment revealed lower average cold pain threshold (CPT; $P = 0.010$), lower mechanical pain threshold (MPT; $P = 0.021$), and greater dynamic mechanical allodynia (DMA; $P = 0.018$) in the CLBP group compared with the ALBP group (Fig. 3A, B, and D). Pressure pain thresholds (PPT) did not differ between the acute and chronic groups when stimulation occurred on the back (Fig. 3C). When remote somatosensory function was assessed by stimulating the nondominant forearm, only CPT ($P = 0.012$) and PPT ($P = 0.041$) differed between CLBP and ALBP groups with

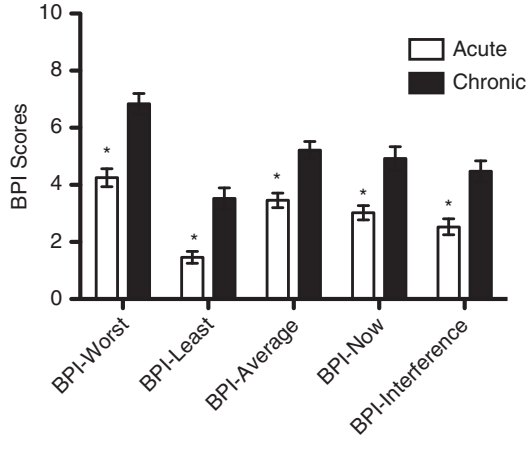

FIGURE 1. Pain burden is higher early on for those who will go on to develop chronic low back pain (CLBP) compared with those with acute resolving LBP. Within 2 weeks of LBP onset, those that will develop CLBP score higher on all subscales of the Brief Pain Inventory (BPI) assessed, all $P < 0.001$. *Statistical significance.

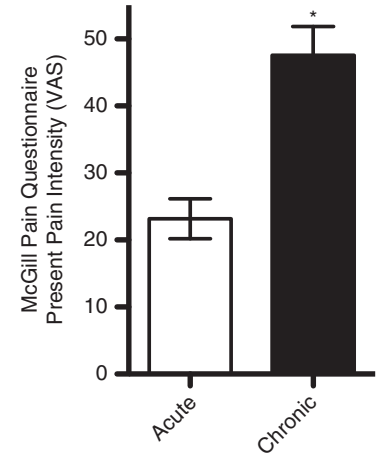

FIGURE 2. McGill Pain Questionnaire Present Pain Intensity (VAS) Ratings are higher early on for those who will develop chronic low back pain (CLBP) compared with those with acute resolving LBP. CLBP participants reported higher present pain intensity at the time of recruitment ($P < 0.001$). *Statistical significance. VAS indicates visual analogue scale.

CLBP participants exhibiting CPT to higher temperatures and PPT to lower force stimulation (for summary of all QST at both locations included in this analysis, see Table 3). No other significant differences were found in QST measures (ie, heat pain threshold and windup ratio).

Those with CLBP exhibited significant stability in their responses to painful stimulation (ie, QST) as well as in their pain self-report (BPI and MPQ). Paired samples *t* tests for all BPI subscales indicated that only pain interference (BPI-Int) changed from the time of recruitment to 6 months postrecruitment ($t_{39} = 2.637$, $P < 0.05$), with a reduction in BPI-Int at 6 months suggesting that while reported pain intensity remained unchanged the patients' perceived interference with daily function decreased over time, potentially reflecting effective coping in the face of chronic pain. All other self-report measures, BPI-Worst, BPI-Least, BPI-Average, and MPQ, were stable and showed no significant change between the time points (all $P < 0.05$). Moreover, paired samples *t* tests showed no significant change in QST measures of MPT, CPT, PPT, MST, or DMA (all $P > 0.05$) indicating significant stability in QST over time for those who would go on to develop CLBP with no change detected from recruitment to study completion at 6 months. These analyses are in agreement with prior reports that more severe acute pain increases risk for development of chronic pain states.[56,57]

Candidate Gene Polymorphisms are Associated With Susceptibility to CLBP

COMT Genotype and CLBP Susceptibility

χ^2 test was performed to determine whether the genotypic frequencies differed between acute and chronic pain conditions, that is, those that would resolve quickly and those that would go on to develop CLBP. The genotypic frequencies of *COMT* SNP rs4680 differed significantly between the groups (AR and CLBP) ($\chi^2_{(2,\ N=79)} = 10.223$, $P = 0.006$) (Fig. 4A) with more participants homozygous for the major allele at rs4680, corresponding to a valine substitution at codon 158, known to result in the more functionally active form of the resulting COMT enzyme, in the CLBP group

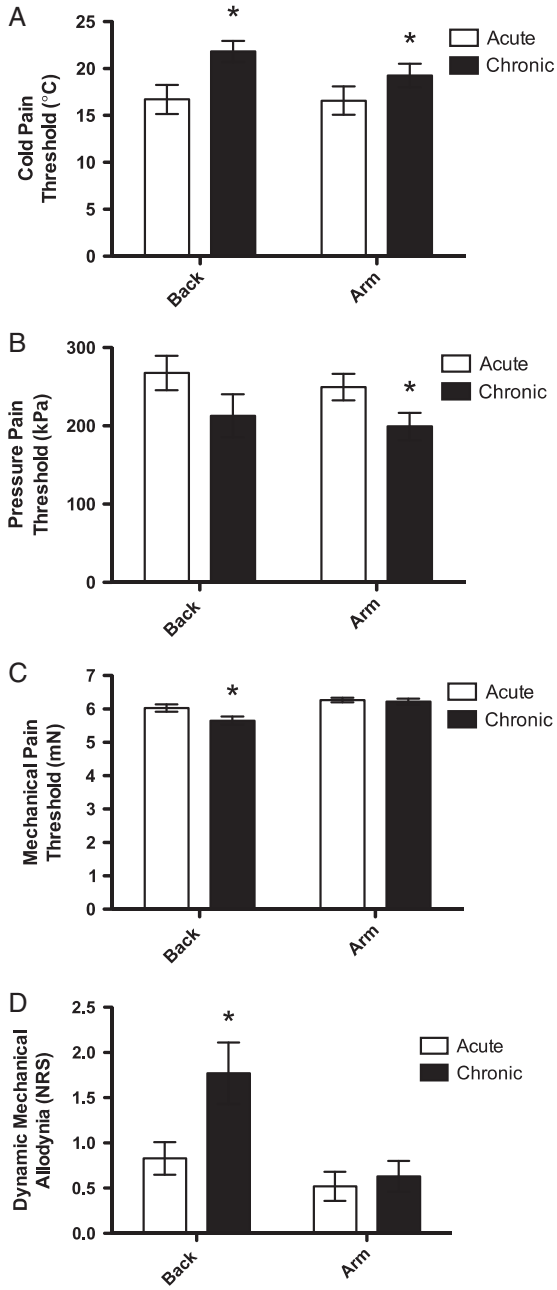

FIGURE 3. Somatosensory function is altered in those who will develop chronic low back pain (CLBP) compared with those with acute resolving LBP. When testing was conducted on the lower back (the painful area), cold pain threshold (CPT, $P=0.010$; A), mechanical pain threshold (C, $P=0.021$), and dynamic mechanical allodynia to brush stroke (D, $P=0.018$) was exacerbated in those that would go on to develop CLBP while pressure pain threshold (PPT, $P>0.05$; B) did not differ between groups. When testing was conducted on a remote location on the nondominant forearm only CPT (A, $P=0.012$) and PPT (B, $P=0.041$) were significantly different between CLBP and acute resolving LBP groups. *Statistical significance.

compared with the ALBP group. Two additional *COMT* SNPs, rs4633 and rs4818, showed no significant differences in frequency for ALBP and CLBP conditions (data not shown). In agreement with the χ^2 analysis presented above, multiple

TABLE 3. Quantitative Sensory Testing Time of Low Back Pain Onset Between Groups

Test	CLBP (N = 42)	Acute Resolved (N = 42)	*P*
Cold pain threshold, mean (SEM) (°C)			
Remote area	19.27 (1.25)	16.58 (1.51)	**0.012**
Back area	21.82 (1.13)	16.71 (1.56)	**0.010**
Heat pain threshold, mean (SEM) (°C)			
Remote area	41.06 (0.66)	41.78 (0.63)	0.432
Back area	39.54 (0.45)	40.66 (0.56)	0.125
Pressure pain threshold, mean (SEM) (KPa)			
Remote area	199.31 (17.39)	249.55 (16.85)	**0.041**
Back area	212.92 (27.52)	267.55 (22.04)	0.125
Mechanical pain threshold, mean (SEM) (mN)			
Remote area	6.22 (0.09)	6.27 (0.07)	0.690
Back area	5.65 (0.12)	6.03 (0.11)	**0.021**
Mechanical sensitivity, NRS 0-10, mean (SEM)			
Remote area	1.40 (0.37)	1.73 (0.25)	0.137
Back area	3.87 (0.43)	2.82 (0.35)	0.060
Wind-up ratio, mean (SEM)			
Remote area	1.30 (0.10)	1.48 (0.13)	0.268
Back area	1.38 (0.09)	1.49 (0.11)	0.418
Dynamic mechanical allodynia, mean (SEM)			
Remote area	0.63 (0.17)	0.52 (0.16)	0.628
Back area	1.77 (0.34)	0.83 (0.18)	**0.018**

Bold indicates $P \leq 0.05$ for analysis.
CLBP indicates chronic low back pain; NRS, numeric rating scale.

stepwise linear regression revealed a significant association between rs4680 genotype and pain condition whereby genotype predicted ~5% of the variance in group ALBP vs. CLBP ($F_{change}=4.233$, $r^2_{change}=0.046$, $P_{change}=0.043$). Moreover, when *COMT* expression was subsequently added as the next step of the regression model, it was revealed that *COMT* expression was associated with transition to CLBP ($F_{change}=5.670$, $r^2_{change}=0.057$, $P_{change}=0.020$) and predicted an additional ~6% of the variance.

BDNF Genotype, Expression, and CLBP Susceptibility

As described above, χ^2 test was performed to determine whether the frequency for the 3 genotypes differed between the 2 pain conditions. The distribution of *BDNF* SNP rs6265 genotype differed significantly between the groups ($\chi^2_{(2, N=79)}=9.60$, $P=0.009$) (Fig. 4B) with a smaller proportion of patients in the CLBP group homozygous for the minor allele at rs6265, corresponding to a methionine substitution at amino acid position 66, compared with ALBP participants. Multiple stepwise linear regression revealed an association between *BDNF* SNP rs6265 genotype and susceptibility to CLBP that approached significance ($F_{change}=3.908$, $r^2_{change}=0.042$, $P_{change}=0.052$) but, when *BDNF* expression was added to the model, we found no additional significant association between *BDNF* expression and susceptibility to CLBP above and beyond the relationship with *BDNF* genotype.

Associations of COMT Genotype and Expression With Acute LBP Pain Burden (BPI and MPQ)

When baseline BPI_{Int} was considered for all patients combined (AR and CLBP), multiple linear regression revealed that *COMT* SNP rs4680 genotype, but not *COMT* expression, was significantly associated with BPI_{Int} ($F_{change}=7.944$, $r^2_{change}=0.092$, $P_{change}=0.006$) and predicted ~9% of the variance. No other significant *COMT* SNP associations were

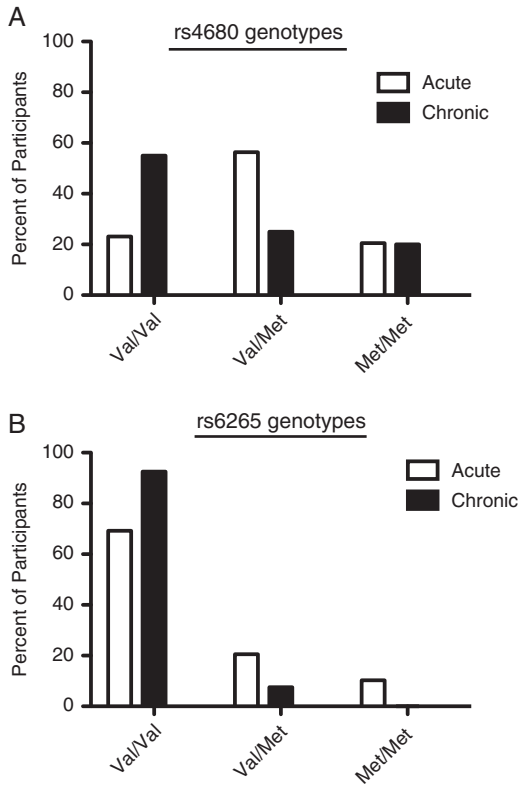

FIGURE 4. *COMT* and *BDNF* SNP genotypes are significantly associated with likelihood of transition to chronic low back pain (CLBP). A, The genotypic frequencies of *COMT* SNP rs4680 differed significantly between the groups (ALBP and CLBP) ($P = 0.006$) with more participants homozygous for the major allele (Met/Met) found in the CLBP group. B, Fewer subjects in the CLBP group were found to be homozygous for the minor allele at rs6265 *BDNF* ($P = 0.009$). SNP indicates single nucleotide polymorphism.

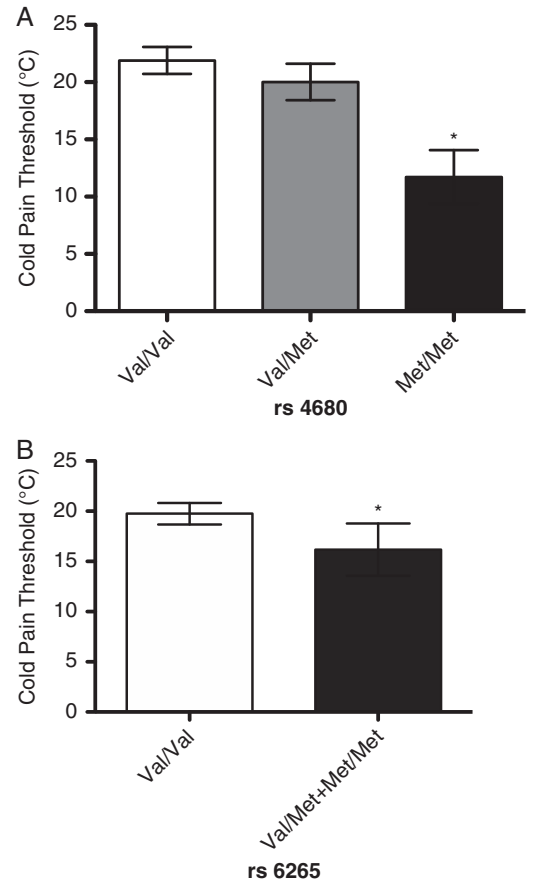

FIGURE 5. *COMT* SNP rs4680 genotype and *BDNF* SNP rs6525 genotype are significantly associated with cold pain threshold (CPT) at the time of initial recruitment regardless of whether they would go on to resolve quickly or to develop CLBP. A, Participants homozygous for the minor allele (Met/Met) at the *COMT* SNP rs4680 had increased sensitivity (lower threshold) for cold pain. B, Participants carrying at least 1 minor allele at *BDNF* rs6525 also exhibited lower CPT thresholds. *Statistical significance.

detected for BPI_{Int} or any other severity subscales of the BPI at the time of recruitment. While the sample size was not adequate to separately examine potential genetic associations with BPI_{Int} at 6 months, BPI_{Int} scores at the time of recruitment and at 6 months were highly positively correlated ($r_P = 0.618$, $P < 0.001$). Both *COMT* SNP rs4680 genotype ($F_{change} = 6.979$, $r^2_{change} = 0.085$, $P_{change} = 0.010$) and *BDNF* SNP rs6265 genotype ($F_{change} = 4.259$, $r^2_{change} = 0.050$, $P_{change} = 0.043$), but not *COMT* or *BDNF* expression, were significantly associated with VAS ratings of PPI on the MPQ, explaining ~9% and ~5% of the variance in PPI at the time of recruitment, respectively. MPQ VAS ratings of PPI at the time of initial recruitment and the 6-month follow-up were significantly positively correlated ($r_P = 0.445$, $P < 0.01$).

COMT and BDNF Genotype are Associated With Cold Hypersensitivity But Not Mechanical Pain Sensitivity at LBP Onset

Group differences in QST outcomes between the ALBP and CLBP conditions have been reported elsewhere,[55,58] however, the potential associations between *COMT* and *BDNF* SNP genotype and QST outcomes have not been evaluated. Multiple linear regression analysis on CPT revealed significant associations for both *COMT* SNP rs4680 genotype ($F_{change} = 12.674$, $r^2_{change} = 0.136$, $P_{change} = 0.001$) and *BDNF* SNP rs6525 genotype ($F_{change} = 4.707$, $r^2_{change} = 0.048$, $P_{change} = 0.033$) with CPT at the time of initial recruitment (Fig. 5A and B). Neither of the other 2 QST measures (MPT or PPT) were significantly associated with genotype or gene expression. Though the sample size for patients in the chronic condition was not sufficient to assess the presence of genotype associations with long-term outcomes, QST measures taken at the time of recruitment and at the 6-month follow-up were significantly correlated for CPT ($r_P = 0.698$, $P = 0.000$), MPT ($r_P = 0.352$, $P = 0.026$), and PPT ($r_P = 0.730$, $P = 0.000$), suggesting that these measures are stable over time and associations present in acute pain outcomes are likely relevant to predicting chronic pain burden for those that do not resolve.

DISCUSSION

While prognostic indicators for the development of chronic pain, whether following injury or surgery, remain incompletely understood, the value of being able to predict individual patient pain trajectories cannot be overstated. For LBP, a set of variables that could be applied early in an acute episode to reduce risk for CLBP, with its associated negative effects on function and quality of life, requires that

we first identify the highest priority variables playing a role in the acute to chronic transition.

The present study was designed to explore potential associations between polymorphisms and/or expression of 2 pain-relevant candidate genes (*COMT* and *BDNF*), acute pain sensitivity, and the transition to chronic pain in a population with idiopathic LBP. Our findings show that there are distinct somatosensory alterations present at the onset of LBP that differentiate those whose pain will resolve (ALBP) and those who will go on to develop CLBP. Significantly, we found that participants who developed CLBP showed selective pain sensitivity enhancement in both the area of pain and at a remote location at the time of pain onset compared with those who resolved. The CLBP group exhibited hyperalgesia to cold and mechanical stimuli as well as significant DMA to brush stimulation on the painful area of the lower back. Our findings are also in agreement with prior reports that widespread pressure and cold hypersensitivity co-occur in other chronic musculoskeletal disorders (eg, spinal pain, fibromyalgia, temporomandibular joint disorder, and whiplash associated disorder.[59–63] Importantly, widespread cold pain hypersensitivity may serve as a risk factor for increased central sensitization and risk for developing chronic pain, particularly neuropathic pain[64] and has previously been associated with COMT genotype elsewhere.[65] DMA to brush stimulation is a prevalent characteristic of neuropathic pain conditions resulting from peripheral sensitization of C-fibers and/or activation of sensory neurons responsive to low threshold mechanical stimulation (eg, Aβ fibers).[66–69] Overall, the QST profile of the CLBP group suggests engagement of a neuropathic process early on and may reflect a difference in the source of the LBP episode and/or individual differences in the nervous system response to an acute painful episode. While alterations in somatosensory function may be expected in a population already experiencing chronic pain, the present QST findings offer novel insight into the processes engaged early during the LBP episode that may increase risk for CLBP as these participants are recruited during an acute LBP episode and have not already developed a chronic pain disorder. This study extends findings from the literature measuring pain sensitivity differences between ALBP and CLBP patients.[70] Moreover, we provide evidence for a profile of pain hypersensitivity and increased pain burden beginning early in the pain episode, before any emergence of other indicators of persistence, suggesting a unique profile of somatosensory and self-report parameters that can help identify those at risk for CLBP.

While the mechanism underlying the relationship between this "neuropathic" profile and risk for CLBP remains to be fully elucidated, it does provide evidence in support of precision pain management strategies tailored specifically to combat the processes engaged in neuropathic pain and, potentially, prevent or reduce the likelihood of transition to CLBP. QST and molecular profiling have already been identified as relevant variables on which to base stratification of neuropathic pain patients for more precise diagnosis and treatment.[71] One benefit of the current findings is that they suggest an early profile of responding that could be used to stratify those with the greatest risk of CLBP for intervention with specific strategies targeting neuropathic processes early on.

COMT genotype was significantly associated with cold pain sensitivity (on the lower back and the remote area) and pain burden (BPI) as well as the development of CLBP while *COMT* expression was associated only with the likelihood of transitioning to CLBP and not with specific somatosensory alterations. The literature regarding *COMT* genotypic effects on pain sensitivity, susceptibility, and outcomes has been mixed but the present findings help to refine our understanding of the complex role of *COMT* in CLBP. Much of the relevant data for CLBP has focused on postsurgical outcomes following lumbar discectomy and other interventions while our study is restricted to patients with idiopathic LBP without a diagnosis of organic disease or malformation. Prior work by Rut et al[72] evaluated the relationship between polymorphisms of *COMT* (rs4680: A > G—Val158Met, rs6269: A > G, rs4633: C > T, rs4818: C > G) and pain sensitivity after lumbar discectomy. Minor allele carriers were characterized by the lowest preoperative scores related to pain intensity and lower pain intensity at 1 year after the surgery. Patients with *COMT* haplotype associated with low metabolic activity of the enzyme demonstrated significant clinical improvement in pain intensity score, lower disability and pain intensity at 1 year after the surgery. Another study examined *COMT* polymorphisms in patients with CLBP for duration of > 1 year resulting from discogenic disc disease who were treated with lumbar fusion or cognitive therapy and exercises.[73] SNPs adjusted for covariates revealed associations of rs4633 and rs4680 with posttreatment pain reduction, with a tendency for greater improvement among heterozygous patients compared with the homozygous. In contrast, some have failed to confirm associations among *COMT* polymorphisms and basic or clinical pain sensitivity, risk of chronic pain, or poor treatment outcomes.[74,75] For example, the *COMT* Val158Met SNP was not found to increase risk disc herniation in 1 report, however, Met/Met patients had more pain and slower recovery than those with Val/Met, which in turn also had more pain and slower recovery than those with Val/Val suggesting that genotype contributes to the progression of disc herniation symptoms.[76,77] In an 11-year follow-up study of patients who underwent lumbar fusion or nonoperative treatment for painful DDD, disability at baseline was significantly associated with *COMT* SNPs rs4818, rs6269, and rs4633. However, no significant associations were observed for *COMT* at long-term follow-up. The size and design of the present study cohort do not allow direct evaluation of relationships between long-term pain burden and *COMT* genotype; however, the present findings that *COMT* genotype was associated with acute pain burden, somatosensory functional differences, and risk for the development of CLBP as well as the presence of strong correlations between acute and chronic pain measures suggest that the relationships seen during acute pain may hold true for the chronic state as well.

Our phenotyping data suggest that a neuropathic process may be engaged early on in those that will go on to develop CLBP. The A allele, encoding the shift from valine to methionine at codon 158, is typically described as the "risk" allele for its associations with lower enzymatic activity, higher anxiety, decreased stress resilience, and increased pain sensitivity in normal and inflammatory conditions.[36,78] However, our findings are in agreement with reports that pharmacological inhibition of COMT enzymatic activity, a treatment that mimics the reduced activity seen in the presence of the A allele at rs4860, reverses neuropathic pain in a rat model of spinal nerve ligation.[79] This pattern of results would be expected if early engagement of a neuropathic mechanism contributes to the development of CLBP. The present findings are in

agreement with other reports of increased chronic pain risk following clinical and exercise-induced shoulder pain for participants with genotypes indicative of low COMT activity, though this association was only true for participants also reporting high levels of pain catastrophizing.[42,80] Taken together, these findings lend support to the hypothesis that inherited factors help shape an individual's profile of risk for chronic pain and also provide further evidence this profile is linked to the balance of neuropathic processes engaged during an acute pain episode. Further supporting this argument, the CLBP group were hypersensitive to painful mechanical and cold stimuli compared with the acute pain group, in direct agreement with the phenotype observed in the animal model of neuropathic pain for which COMT inhibition was therapeutic.

We also assessed associations between BDNF SNP genotype and pain outcomes. Presence of the minor allele for the common *BDNF* SNP rs6265 (Val66Met) is associated with reduced activity-dependent synaptic release of BDNF.[81,82] Carriers of the minor allele A, encoding the valine to methionine substitution, exhibit higher risk and severity for dysmenorrhea, increased analgesic need in medication-overuse headache, and increased sensitivity to experimental pain.[83–85] Moreover, A allele carriers with chronic pain exhibit augmented cortical pain responding to painful stimulation, suggesting that the effects of *BDNF* polymorphisms may be the result of alterations in central pain processing centers as opposed to peripheral, but this is an issue for further investigation. We evaluated *BDNF* mRNA expression in circulating peripheral blood, which may explain the lack of agreement between our data and the data reported by others evaluating relationships between *BDNF* expression in specific pain-relevant tissues and pain sensitivity. Recently, Dorsey and colleagues have shown that TrkB.T1, the truncated isoform of the BDNF receptor TrkB is upregulated in animal models following noxious stimulation and its presence is associated with the emergence of chronic pain.[86–88] However, as with *COMT*, the findings have been mixed with others failing to find a significant relationship between *BDNF* rs6525 genotype, *BDNF* expression and pain outcomes for fibromyalgia[89] and migraine.[90,91] The present findings suggest that the reduced *BDNF* activity linked to the presence of ≥ 1 minor alleles could reduce risk for CLBP, potentially through a reduction in BDNF signaling-dependent neuropathic pain processes.

CONCLUSIONS

Before health care professionals can deliver precision interventions and improve long-term health outcomes for CLBP patients, we must first understand the heritable (eg, genetic) and environmental factors that contribute to risk and/or susceptibility to CLBP. With the present findings, we contribute to a body of literature addressing the complex contribution(s) of *COMT* and *BDNF* to the heritability of chronic pain susceptibility. These potential mechanisms of risk may prove instrumental in identifying effective pharmacological and nonpharmacological precision pain management strategies.

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