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Biopsychosocial influence on shoulder pain: risk subgroups translated across preclinical and clinical prospective cohorts

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Abstract

Tailored treatment based on individual risk factors is an area with promise to improve options for pain relief. Musculoskeletal pain has a biopsychosocial nature, and multiple factors should be considered when determining risk for chronic pain. This study investigated whether subgroups comprised genetic and psychological factors predicted outcomes in preclinical and clinical models of shoulder pain. Classification and regression tree analysis was performed for an exercise-induced shoulder injury cohort ($n = 190$) to identify high-risk subgroups, and a surgical pain cohort ($n = 150$) was used for risk validation. Questionnaires for fear of pain and pain catastrophizing were administered before injury and preoperatively. DNA collected from saliva was genotyped for a priori selected genes involved with pain modulation (*COMT* and *AVPR1A*) and inflammation (*IL1B* and *TNF/LTA*). Recovery was operationalized as a brief pain inventory rating of 0/10 for current pain intensity and <2/10 for worst pain intensity. Follow-up for the preclinical cohort was in daily increments, whereas follow-up for the clinical cohort was at 3, 6,

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Conflict of interest statement

None of the authors have conflicts of interest to declare.

and 12 months postoperatively. Risk subgroups comprised the *COMT* high pain sensitivity variant and either pain catastrophizing or fear of pain were predictive of heightened shoulder pain responses in the preclinical model. Further analysis in the clinical model identified the *COMT* high pain sensitivity variant and pain catastrophizing subgroup as the better predictor. Future studies will determine whether these findings can be replicated in other anatomical regions and whether personalized medicine strategies can be developed for this risk subgroup.

Keywords

Chronic shoulder pain; Catastrophizing; *COMT*; Postoperative pain

1. Introduction

In 2011, the Institute of Medicine identified chronic musculoskeletal pain as a nervous system disease that is a high-priority public health problem.²⁸ Treatment tailored to validated individual risk factors (ie, personalized medicine) holds promise to markedly improve options for pain relief. Personalized medicine based on genetic risk factors has had success in selected areas of cardiovascular medicine^{29,42,43,45} and oncology.^{1,5,9} However, to achieve similar successes for chronic pain, further studies are needed to identify and target specific mechanisms involved in chronic pain development. Given the complex biopsychosocial nature of pain, multiple factors (ie, genetic, psychological, social, and environmental) must be considered when determining risk for developing chronic musculoskeletal pain conditions.^{11,37}

Shoulder pain is the focus of this study because it is the fifth most frequently reported type of musculoskeletal pain, affecting 9.0% of all U.S. adults aged more than 18 years. In addition to high prevalence, poor outcomes and continued disability characterize shoulder pain. For example, in 1 cohort, 40% of the individuals did not recover by 1 year after a new episode of shoulder pain.⁵⁰ Individuals with shoulder pain also commonly report difficulty with basic (17.7%) and complex (21.4%) daily activities.²⁸ These epidemiological data justify the study of shoulder pain as a way to better understand mechanisms and risk factors involved in the development of chronic musculoskeletal pain. Ideally, better understanding of clinically relevant risk factors will lead to treatment strategies that limit the development of chronic shoulder pain and have application to other musculoskeletal pain conditions.

In previous studies, we investigated genetic and psychological factors that improved prediction of preclinical exercise-induced injury shoulder pain phenotypes.^{19,20} We selected a priori candidate genes known to be involved in pain modulation (eg, *COMT* and *AVPR1A*) or proinflammatory (eg, *TNF/LTA* and *IL1B*) responses and psychological constructs (eg, fear of pain and pain catastrophizing) that are established precursors to chronic pain conditions. Our preclinical findings identified multiple interactions between genes and psychological factors that improved prediction of exercise-induced shoulder pain beyond each individual factor.^{19,20} These findings spurred interest in risk subgroups comprised genetic and psychological factors to determine the clinical relevance of these preclinical

findings. Previous studies were completed in this preclinical model because it allowed for controlled muscle injury to the rotator cuff, which is a frequent target for shoulder surgery.

Persistent postoperative pain is a common and undesirable outcome of surgery that remains difficult to predict.³⁰ In particular, continued postoperative shoulder pain (POSP) commonly occurs after orthopedic surgery, even when arthroscopy is used.⁴⁶ This study was designed to determine whether risk subgroups comprised genetic and psychological factors that identified heightened pain responses in this preclinical model also predicted 12-month surgical outcomes. We hypothesized that this preclinical model would have high translational potential for POSP due to muscle injury in the same anatomical region of surgery. Translation from the preclinical model to a clinical model would indicate that the identified risk subgroup was robust and could be considered in future studies for developing personalized medicine approaches.

2. Methods

2.1. Overview

This study was reported following STREGA extension³³ of STROBE guidelines⁵¹ and registered prospectively at <http://clinicaltrials.gov/ct2/show/NCT00187863>. The University of Florida's Human Subject Institutional Review Board (IRB-01) approved this study, and all participants provided informed consent before enrollment. This study reports on 2 cohort studies performed in sequence, with parallel methods. Participants were recruited into a preclinical exercise-induced shoulder injury (EISI) or clinical POSP cohort as appropriate. The EISI cohort has been described in our previous preclinical studies,^{19,20} while this study is the first to report postoperative outcomes from the POSP cohort.

2.2. Procedures for risk subgroups

The purpose of this study was to determine whether risk subgroups that identified heightened pain responses in the EISI cohort were also predictive of clinical outcomes in the POSP cohort. Genetic and psychological factors that comprised the risk subgroups were identified in an a priori manner based on the results from our previous preclinical studies.^{19,20}

2.2.1. Risk subgroup composition—Fear of pain and pain catastrophizing consistently interacted with genes in our previous studies^{19,20} and were included as psychological components of the risk subgroups. Fear of pain was assessed with the Fear of Pain Questionnaire (FPQ), a 30-item instrument that measures fear of specific situations that normally produce pain.^{2,36,40} For sake of brevity, we used a shortened 9-item version of the FPQ consisting of #3, 9, 10, 14, 17, 19, 21, 23, and 24 from the original 30-item version. The 9 items selected allow for ease of application, correlate highly with the original 30-item scale ($r = 0.94-0.97$ from our pilot studies), and have demonstrated predictive validity.⁴¹ Study-specific internal consistency for the shortened FPQ was acceptable for the EISI (intraclass correlation coefficient = 0.85) and POSP (intraclass correlation coefficient = 0.86) cohorts. Pain catastrophizing was assessed with the Pain Catastrophizing Scale (PCS), which is a 13-item measure to quantify pain catastrophizing characterized by magnification,

rumination, and helplessness pain beliefs.^{47,49} Total scores from these questionnaires were used in the data analysis for this study.

Originally, 19 single-nucleotide polymorphisms (SNPs) from 10 pain candidate genes (*OPRM1*, *COMT*, *ADRB2*, *AVPR1A*, *GCH1*, *KCNS1*, *TNF/LTA*, *TNF-308*, *IL1B*, and *IL6*) were considered in our preclinical analyses.^{19,20} These genes were selected because of their established links with pain sensitivity, musculoskeletal pain, or the potential to develop chronic pain. The 4 a priori identified genes reported in this article were selected because they consistently interacted with psychological constructs to improve prediction of heightened pain responses from exercise-induced shoulder pain.^{19,20} Therefore, these genes were considered appropriate for further investigation as the genetic components of the risk subgroups. Conceptually, *COMT* and *AVPR1A* were investigated as pain modulatory genes¹⁹ and *TNF/LTA* region and *IL1B* were investigated as proinflammatory genes.²⁰ Genotyping of the selected SNPs at these genes was performed as described in our previous reports using subject DNA extracted from buccal epithelial cells.^{19,20} Hardy–Weinberg equilibrium was calculated and found acceptable for each SNP.

2.3. Subjects

In the EISI cohort, subjects were recruited and screened for eligibility by 1 of the study authors (J.J.P.) between 2009 and 2010. After consent was obtained, muscle injury was caused by an isokinetic exercise protocol that caused microtrauma to the rotator cuff musculature by fatiguing to 50% of the initial maximum voluntary isometric contraction.⁸ This protocol has been described in more detail in our previous studies.^{17–20} Subjects returned to the laboratory after injury at 24-hour intervals for the next 4 days for collection of data related to their shoulder pain. If shoulder pain continued after the fifth study day, subjects were sent an e-mail prompting them to report pain intensity through a web-based data collection tool. A total of 190 subjects were recruited into the EISI cohort.

2.3.1. Eligibility for exercise-induced shoulder injury cohort—Subjects were otherwise healthy men and women of any racial/ethnic background recruited by fliers from undergraduate and graduate courses and from the surrounding community. Inclusion criteria included (1) being between the ages of 18 and 85 years and (2) not currently performing strength training exercises for the upper extremity (operationally defined as no resistance exercise during the previous 6 weeks). Exclusion criteria included any 1 of the following: (1) currently experiencing neck or shoulder pain, (2) neurological impairment of the upper extremity (eg, loss of sensation, muscle weakness, or reflex changes), (3) currently taking pain medication, or (4) previous history of shoulder surgery. These eligibility criteria are the same as used in our previous EISI studies.^{17–20}

For the POSP cohort, consecutive individuals with shoulder pain were evaluated by orthopedic surgeons between 2009 and 2012. Surgical candidacy was determined by poor response to conservative treatment, diagnostic imaging, and physician examination. Individuals who were surgical candidates were then further screened by 1 of the authors (W.H.G.) for study eligibility. Eligible participants were then consented and scheduled for a baseline study session within 1 week of surgery. Participants underwent shoulder

arthroscopy and returned for study sessions at 3 months, 6 months, and 1 year postoperatively. Postoperative outcome assessment included shoulder pain intensity at each of those time points. A total of 150 subjects were recruited into the POSP cohort.

2.3.2. Eligibility for postoperative shoulder pain cohort—Patients were recruited consecutively from University of Florida's Orthopaedics Sports Medicine. Inclusion criteria for being a study participant were (1) between 18 and 85 years of age, (2) complaints of pain limited to anterior, lateral, or posterior shoulder, and (3) scheduled for arthroscopic surgery. Additionally, participants met 1 of the following criteria: (4) documented or suspected rotator cuff tendinopathy (evidence from clinical examination or imaging studies) including small (<1 cm), medium (1-3 cm), and large (3-5 cm) tears, or (5) documented or suspected adhesive capsulitis (evidence from clinical examination or imaging studies), or (6) documented or suspected superior labrum from anterior to posterior lesion or isolated anterior/posterior labral tears (evidence from clinical examination or imaging studies).

Exclusion criteria were (1) current complaints of pain lasting longer than the past 3 months involving neck, elbow, hand, low back, hip, knee, or ankle, or (2) massive rotator cuff tear (>5 cm), or (3) documented shoulder osteoarthritis or rheumatoid arthritis, or (4) previous shoulder surgery within the past year or currently complaining of pain from previous shoulder surgery, or (5) current shoulder fracture, tumor, or infection, or (6) previously diagnosed chronic pain disorder (including, but not limited to irritable bowel syndrome, fibromyalgia, temporomandibular disorder, chronic low back pain, etc), or (7) current psychiatric management, or (8) current gastrointestinal or renal illness.

2.4. Descriptive measures

Demographic and psychological data were captured by self-report questionnaires. The demographic data included sex, age, and race. The dominant arm was recorded for EISI and POSP cohorts, while information on surgical side was collected for the POSP cohort. Other information collected only from the POSP cohort included medication status, rotator cuff tear size, and depressive symptoms through the Patient Health Questionnaire, which is a 9-item measure.^{24,32} These data were collected in the POSP cohort because of their potential importance as co-founders to a risk subgroup's predictive ability for clinical outcomes. For example, depressive symptoms are often comorbid with pain catastrophizing and fear of pain¹⁴; therefore it was important to determine whether depressive symptoms impacted the risk subgroups. Also, integrity of the rotator cuff (typically measured with rotator cuff size) has been linked with postoperative outcomes;^{15,26,27} therefore it was important to account for this measure in the risk subgroups.

2.5. Outcome measures

All outcome assessments were completed by research assistants blinded to the risk subgroup status. The Brief Pain Inventory (BPI) is a widely accepted measure of pain intensity that has good test–retest reliability over short intervals.³¹ The BPI consists of rating pain intensity on an 11-point numerical rating scale ranging from 0 (no pain) to 10 (worst pain imaginable). The BPI was used as the primary outcome for the preclinical EISI and the clinical POSP cohorts, with the specific use for each cohort described below.

In the EISI cohort, the BPI was used to identify subjects who had a heightened response to the injury protocol by reporting very high pain intensity or longer-lasting effects of the injury. Therefore, the BPI outcomes for the EISI cohort were *peak pain intensity* (highest worst pain intensity recorded during the 5-day period) and *duration of shoulder pain* (number of days until subjects rated their current pain at 0/10 and their worst pain was rated <2/10). To facilitate the identification of risk subgroups, peak pain intensity was dichotomized into $\geq 7/10$ and duration was dichotomized into ≥ 7 days for purposes of the data analysis.

In the POSP cohort, the BPI was used to identify patients who had continued pain intensity after their arthroscopic surgery and met 12-month recovery criterion for pain intensity. Therefore, the BPI outcomes for the POSP cohort were *average pain intensity* at 3, 6, and 12 months (arithmetic mean of the current, worst, and best BPI ratings as per our previous study).²¹ Recovery was operationally defined as a rating of current pain intensity at 0/10 and rating of worst pain intensity as <2/10. Recovery was assessed at 3, 6, and 12 months with the overall rate collated at 12 months.

In addition, the Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH) was used to assess upper-extremity disability in the POSP cohort.²⁵ We used a validated abridged version of the DASH (the QuickDASH) that consists of 11 functional items with total scores ranging from 0 (not disability) to 100 (complete disability).²² An outcome for upper-extremity disability was used because shoulder pain can also affect distal function of the arm and hand, and we wanted to obtain an assessment of upper-extremity disability to aid in interpretation of the specificity of the risk subgroups. Similar to the BPI, QuickDASH outcomes were obtained at 3, 6, and 12 months postoperatively.

2.6. Sample size

Sample size was determined a priori for the 2 cohorts using a power analysis based on data collected from preliminary studies. These data provided estimation of effect parameters for the genetic and psychological factors as well as their interactions on outcomes, which were specified in terms of R-square of the full model and R-square difference between the full and the reduced models. The SAS POWER procedure was adopted to evaluate the required sample sizes to achieve a target power of 80% to test each effect at a type I error level of 0.005. We found that the proposed sample size of 360 for both cohorts would enable us to detect all but 2 observed effect sizes. However, for pragmatic reasons, we recruited 190 into the EISI cohort and 150 into the POSP cohort ($n = 340$ in total). This alteration in sample size did not adversely affect power because the number of predictor variables included in analyses was reduced. Specifically, based on our previous findings,^{19,20} we reduced the number of pain candidate genes that would be considered in risk subgroups from 10 to 4.

2.7. Data analysis

All statistical comparisons were 2-sided with an alpha level of 0.05. First, we conducted explorative analysis of pain duration and intensity (dichotomized as BPI $\geq 7/10$ and duration ≥ 7 days) using Classification and Regression Tree based on the EISI cohort. Classification and regression tree analysis is a modeling technique that constructs a decision tree for

predicting outcomes. Among selected genetic and psychological risk factors, Classification and Regression Tree analysis identified the best predictors to divide the sample into 2 branches. This process continued until additional branches could not be further divided to improve outcome prediction. Then, a group of the leaf nodes (ie, additional branching defined by the predictive factors) was designated as high risk, whereas the other leaf nodes were low risk. Only these predictive factors were regarded as associated with the outcomes of interest and included in the next step for risk subgroup formation. Second, for each predictive variable, we identified cutoff points that further divided the EISI cohort into high- and low-risk subgroups with smallest P value in χ^2 test that dichotomized outcomes for each gene by psychological combination. Third, for the risk subgroups that identified significantly heightened pain responses in the EISI cohort, we tested whether they were associated with the 12-month outcomes in the POSP cohort. Specifically, we provided Kaplan–Meier estimates for the probability of meeting the recovery criterion at 12-month follow-up as the primary analysis. In addition, we reported subgroup differences in pain and disability measures for 3-, 6-, and 12-month outcomes based on independent t tests.

Sensitivity analyses (with the use of Cox regression) were performed to determine whether demographic variables (age, sex, and race) influenced the prediction of 12-month recovery outcomes from risk subgroups. These sensitivity analyses also considered potentially important confounding variables, including depressive symptoms,¹⁴ rotator cuff tear size,^{15,26,27} and medication status. Finally, the sensitivity analyses considered whether the high-risk subgroup findings changed when *COMT* genotype was represented with an established 4 SNP diplotype,^{12,13} as opposed to the rs6269 SNP used in the primary analysis.

3. Results

Descriptive statistics are summarized in **Table 1**, while recruitment and follow-up summary for the POSP cohort are reported in **Figure 1**.

3.1. Risk subgroup preclinical identification

The 8 (4 genes $\times$ 2 psychological factors) risk subgroups investigated in the EISI cohort for prediction of peak pain intensity (dichotomized BPI 7/10) and duration of shoulder pain (dichotomized 7 days) are reported in **Table 2**. This analysis indicated that high-risk subgroups comprised *COMT* rs6269 AA genotype and FPQ or PCS were predictive of both higher pain intensity and duration of shoulder pain. No other risk subgroups considered were predictive of heightened pain responses in the EISI. Therefore, only the *COMT* rs6269–based risk subgroups were carried forward in the POSP cohort.

3.2. Risk subgroup clinical relevance

The 2 *COMT* rs6269–based risk subgroups were investigated for prediction of 3-, 6-, and 12-month POSP and upper-extremity disability outcomes (**Table 3**). Importantly, these 2 risk subgroups reported statistically similar levels of pain intensity and upper-extremity disability during the preoperative session. The *COMT* rs6269 and FPQ high-risk subgroup had higher average pain intensity at 6 months ($P < 0.05$) and was less likely to meet the

recovery criterion at 12-month follow-up (hazard ratio [HR] for time to recovery = 0.69, log-rank test $P = 0.043$). The *COMT* rs6269 and PCS high-risk subgroup had higher pain intensity ratings at 3 and 6 months and was also less likely to meet the recovery criterion at 12-month follow-up (HR = 0.51, log-rank test $P = 0.002$). There were no concurrent risk subgroup differences in the upper-extremity disability measure.

3.3. Sensitivity analysis for clinical relevance findings

The results of sensitivity analyses are presented in **Table 4**. These analyses indicated some attenuation of FPQ subgroup prediction when considering demographic and confounding variables. For PCS subgroups, the sensitivity analyses indicated no change in predictive outcomes. Furthermore, predictive results for either subgroup were not affected when *COMT* rs6269 was substituted with the established *COMT* diplotype.^{12,13}

Overall, the sensitivity analyses indicated that the *COMT* and PCS risk subgroup was the stronger predictor. This phenomenon is because the PCS risk subgroup consistently predicted 12-month recovery beyond chance, alone, or when other potential confounding variables were considered (**Table 4**). **Figure 2** shows the difference in time to shoulder pain recovery for the high- and low-risk subgroups based on *COMT* genotype and PCS score. In contrast, the prediction of the FPQ risk subgroup was no better than chance, as 95% confidence intervals for the HR consistently included 1.0.

4. Discussion

Implementation of personalized medicine for chronic musculoskeletal pain is predicated on validated risk subgroups that allow for application of tailored treatment.²⁸ This study investigated risk subgroups comprised genetic and psychological factors for translation from preclinical to clinical shoulder pain models. This is the first study we are aware of to investigate risk for persistent postoperative pain in this manner. Our principal findings were (1) risk subgroups containing *COMT* and either pain catastrophizing or fear of pain were predictive of heightened shoulder pain responses in the preclinical model and (2) the *COMT* and pain catastrophizing high-risk subgroup was the better predictor of POSP outcomes. Effect sizes indicated that risk subgroup differences in postoperative pain intensity were largest at 3 months and smallest at 12 months. However, in predictive analyses, the high-risk subgroup was approximately half as likely to report pain recovery 12 months postoperatively. The collective results from both cohorts provide strong evidence that *COMT*-based risk subgroups are robust predictors of persistent shoulder pain when combined with pain catastrophizing.

Catechol-*O*-methyltransferase is a ubiquitously expressed detoxifying enzyme involved in a number of important biochemical pathways, including adrenergic receptor activation that can cause release of proinflammatory cytokines^{23,39} and metabolism of neurotransmitters (eg, dopamine).⁵³ *COMT* encodes a membrane-bound form that is 50 residues longer at the amino-terminus than the soluble form, and the relative levels of each residue seem to have temporal and tissue specificity. This study found additional evidence for the *COMT* SNP rs6269 as a risk group predictor, consistent with a previous study that documented reduced *COMT* enzyme activity and increased pain sensitivity with the “A” allele at rs6269.³⁸

Specifically, rs6269 is in the promoter region of the soluble isoform of the gene and thus could theoretically affect expression of the soluble form. Alternatively, SNP rs6269 can be a genetic marker that differentiates *COMT* haplotypes coding for high-activity enzyme variants from low-activity variants, consistent with other studies that found an association with rs6269 SNP in general neurological^{7,52} and pain-specific⁴⁴ phenotypes. Single-nucleotide polymorphism rs6269 “G” allele is indicative of lower pain sensitivity in the established *COMT* 4-SNP pain sensitivity diplotypes.^{12,13} This association was confirmed with sensitivity analyses that used *COMT* diplotypes to define risk subgroups in the clinical cohort, which produced similar predictive results (**Table 4**). Therefore, we expect our risk subgroup to be applicable at the SNP and diplotype level for *COMT*.

Consistent with a biopsychosocial framework for pain, we considered combinations of genetic and psychological factors in this study and pain catastrophizing was the other part of this high-risk subgroup. Pain catastrophizing is a maladaptive coping style that perpetuates the experience of musculoskeletal pain.¹⁴ As expected, a genetic predisposition for diminished endogenous pain modulation and a coping approach consistent with pain catastrophizing were predictive of heightened pain responses and postoperative pain recovery outcomes. This risk subgroup did not predict upper-extremity disability, indicating that the associated biopsychosocial mechanisms involved were specific to pain-related processes with less of an impact on upper-extremity function.

The primary strength of this study was the use of sequential cohorts. This design allowed for efficient translation of key findings from the preclinical to the clinical setting because the same methods were used. Furthermore, embedding a prospective cohort study with 12-month postoperative outcomes within this sequential cohort design allowed for immediate determination of the clinical relevance of our preclinical findings. Another strength of this study is that it includes human subjects in both the preclinical and clinical models. This successful example provides evidence that inducing muscle injury in humans can serve as a viable alternate route for translational pain research, which is important because challenges exist for translation of nonhuman preclinical models.^{34,35} The primary weakness of this study was the lack of mechanistic or metabolic measures to further describe the risk subgroups. *COMT* has established links with multiple biological systems involved in pain processing,⁴ and the psychological factors studied also have empirical precedence for their influence on pain perception.¹⁴ However, their combined effects have not been previously described at a neurobiological level. Therefore, further research will be needed to confirm the mechanistic aspects of this high-risk subgroup. An additional limitation is the loss of variability inherent in dichotomizing the psychological measures for risk subgroup determination. A related limitation is that the pain catastrophizing level for the high-risk subgroup (PCS = 5) is not typical of elevated scores.¹⁴ This finding is likely because the PCS level used for this study was specific to *COMT* high pain sensitivity variation and therefore cannot be directly compared with previous studies that did not account for genetic variation when reporting elevated pain catastrophizing levels.

Links to other studies in the literature are limited because of the small number of studies. Previous studies investigating genetic and psychological predictors have used regression approaches to determine an association with outcomes. In our earlier studies, regression

analyses were used to first report that the interaction between the *COMT* gene diplotype and elevated pain catastrophizing scores resulted in higher shoulder pain intensity ratings in surgical and exercise-induced shoulder pain.^{18,21} Converging evidence came from studies in patients with fibromyalgia that also supported an interaction between the *COMT* gene and pain-associated psychological distress.^{10,16} These studies provided a conceptual support for this study but used analytical approaches that did not directly test translational potential. This study distinguishes itself as an important advancement from the previous work by sequentially testing the robustness and clinical relevance of risk subgroups identified in the preclinical cohort for prediction of postoperative outcomes in a clinical cohort.

This study has implications for providers and policy makers interested in identifying individuals at risk for experiencing persistent musculoskeletal or postoperative pain.²⁸ Continued or persistent postoperative pain occurs in 10% to 50% of surgical procedures and is an undesirable outcome that is difficult to predict.³⁰ Higher rates of persistent postoperative pain occur in orthopedic populations but are not dependent on whether a major or minor procedure was completed.⁴⁶ Predictive models for identifying risk of persistent postoperative pain have been published³ but typically have not incorporated genetic variation, although this risk factor has been highlighted as a priority.³⁰ Our results indicated large decrease (adjusted HR = 0.44) in the likelihood of reaching the 12-month recovery criterion. This finding has high potential for clinical relevance because this risk subgroup's predictive capability persisted even after adjusting for depressive symptoms, medication status, and rotator cuff tear size. Additional clinical relevance comes from the magnitude of risk, which is large enough to potentially alter standard of care. Furthermore, it seems plausible that this high-risk subgroup has application beyond postoperative settings. Indeed, the high-risk subgroup was identified in a preclinical model, which involved the transition from a pain-free to acute pain state. Thus, it is conceivable that this subgroup may confer increased risk for developing persistent musculoskeletal pain in general.

The results of this study provide important directions for future research. An immediate research question is related to replication in other anatomical regions that commonly experience surgery for musculoskeletal pain (eg, back, neck, and knee). We hypothesize that this high-risk subgroup would be useful for predicting postoperative outcomes in these other musculoskeletal pain categories because there is nothing specific to the shoulder for these genetic and psychological factors. However, future research is necessary to test this hypothesis and determine how the magnitude of risk differs depending on the anatomical region. Importantly, these data also indicated that individualized treatment may require more than generation of a genetic profile. Individualized treatment for pain conditions will ideally address multiple factors to account for the biopsychosocial nature of musculoskeletal pain. Therefore, another research question with immediacy is related to whether the genetic and psychological components of the risk subgroup validated in this study can be used to develop effective personalized medicine strategies. Specific to our findings, there are treatment options that could address the *COMT* variation (eg, propranolol⁴⁸) and the psychological components (eg, cognitive/behavioral approaches for catastrophizing⁶). However, the efficacy of these treatment options needs to be tested in randomized trials that compare outcomes of personalized and standard approaches for those in the high-risk

subgroup. Finally, future research should be focused on additional factors that could be added to this newly established risk subgroup. The theoretical model on which this work was based includes not only genetic and psychological factors but also social and environmental factors.¹¹ These unmeasured factors should be considered in future risk stratification studies to determine whether prediction of chronic musculoskeletal pain development is improved.

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Figure 1.
Recruitment and follow-up for postoperative shoulder pain cohort.

Figure 2.
Twelve-month shoulder pain recovery based on risk subgroup status.

Table 1

Descriptive summary of EISI and POSP cohorts.

Variable	EISI (preclinical model)		POSP (clinical model)	
	Mean $\pm$ SD or frequency	Median (minimum-maximum) or %	Mean $\pm$ SD or frequency	Median (minimum-maximum) or %
Age	23.0 $\pm$ 6.0	21 (18-58)	42.7 $\pm$ 17.4	42 (18-81)
Gender				
Female	116	61	51	34
Male	74	39	99	66
Race				
White	153	81	127	85
Black or African American	12	6	11	7
Other	24	13	12	8
Dominant hand				
Right	171	90	132	88
Left	19	10	18	12
Surgical side				
Right			75	50
Left			75	50
<i>COMT</i> rs6269				
AA	55	30	55	37
GA	97	53	61	42
GG	30	17	31	21
<i>AVPR1A</i> rs1042615				
AA	31	17	22	15
AG	84	45	58	39
GG	71	38	67	46
<i>TNF/LTA</i> rs2229094				
CC	15	9	12	8
CT	69	39	69	47
TT	90	52	66	45
<i>IL1B</i> rs1143627				
AA	21	13	63	43
AG	70	41	65	44
GG	78	46	20	13
Baseline FPQ	23.4 $\pm$ 5.8	24 (9-38)	20.9 $\pm$ 6.0	21 (9-36)
Baseline PCS	9.9 $\pm$ 7.7	10 (0-38)	10.8 $\pm$ 8.6	9 (0-42)
Baseline BPI			3.3 $\pm$ 2.4	3 (0-10)

BPI, Brief Pain Inventory; EISI, exercise-induced shoulder injury; FPQ, Fear of Pain Questionnaire; PCS, Pain Catastrophizing Scale; POSP, postoperative shoulder pain.

Table 2

Identification of risk subgroups predictive of heightened pain response in EISI cohort.

Gene	High-risk subgroup	High risk		Low risk		<i>P</i>	
		N	Percent outcome	N	Percent outcome		
Outcome = duration 7d							
<i>COMT</i>	rs6269 = “AA” and FPQ	15	52	36.5	130	21.5	0.037
	rs6269 = “AA” and PCS	5	42	40.5	140	21.4	0.013
<i>AVPR1A</i>	rs1042615 = “AA” and FPQ	15	28	35.7	158	24.1	0.194
	rs1042615 = “AA” and PCS	5	22	36.4	164	24.4	0.228
<i>TNF/LTA</i>	rs2229094 = “CT” and FPQ	15	64	31.3	110	23.6	0.272
	rs2229094 = “CT” and PCS	5	50	32.0	124	24.2	0.291
<i>IL1B</i>	rs1143627 = “GG” and FPQ	15	41	19.5	142	26.8	0.346
	rs1143627 = “GG” and PCS	5	72	20.8	111	27.9	0.280
Outcome = peak BPI 7/10							
<i>COMT</i>	rs6269 = “AA” and FPQ	15	52	48.1	130	23.1	0.001
	rs6269 = “AA” and PCS	5	42	52.4	140	23.6	<0.001
<i>AVPR1A</i>	rs1042615 = “AA” and FPQ	15	28	25.0	158	29.7	0.610
	rs1042615 = “AA” and PCS	5	22	27.3	164	29.3	0.847
<i>TNF/LTA</i>	rs2229094 = “CT” and FPQ	15	64	25.0	110	34.5	0.189
	rs2229094 = “CT” and PCS	5	50	24.0	124	33.9	0.203
<i>IL1B</i>	rs1143627 = “GG” and FPQ	15	41	31.0	142	29.3	0.834
	rs1143627 = “GG” and PCS	5	72	31.5	111	31.6	0.735

All statistical comparisons were made with χ^2 tests with a significance level of 0.05; the values in bold indicate that risk subgroup predicts heightened pain response ($P < 0.05$) investigated in clinical cohort.

BPI, Brief Pain Inventory; EISI, exercise-induced shoulder injury; FPQ, Fear of Pain Questionnaire; PCS, Pain Catastrophizing Scale.

Table 3

Comparison of risk subgroups on descriptive parameters and prediction of 12-month postoperative outcomes.

	<i>rs6269</i> and FPQ subgroup			<i>rs6269</i> and PCS subgroup		
	High risk (n = 50)	Low risk (n = 98)	<i>P</i> [*] (ES)	High risk (n = 41)	Low risk (n = 106)	<i>P</i> [*] (ES)
Descriptive						
Age, mean ± SD	36.5 ± 15.6	45.9 ± 17.6	0.002	40.0 ± 16.6	43.8 ± 17.6	0.205
Sex, no. of females (%)	15 (30)	35 (36)	0.487	11 (27)	39 (36)	0.268
Race, no. of whites (%)	40 (80)	85 (87)	0.317	31 (76)	94 (88)	0.097
Rotator cuff tear size, no. of tears (%)	33 (67)	44 (45)	0.204	23 (56)	54 (51)	0.339
Pain medication, no. of pain medications (%)	28 (56)	37 (38)	0.149	22 (54)	43 (40)	0.610
Depressive symptoms, mean ± SD	4.3 ± 4.4	3.1 ± 3.6	0.023	4.9 ± 4.6	3.0 ± 3.5	0.003
Preoperative outcome						
Average pain intensity, mean ± SD	3.3 ± 2.5	3.3 ± 2.3	0.982	3.6 ± 2.3	3.2 ± 2.4	0.218
Upper-extremity disability, mean ± SD	36.2 ± 18.9	33.2 ± 17.3	0.306	38.6 ± 17.8	32.5 ± 17.7	0.051
3-mo postoperative outcome						
Average pain intensity, mean ± SD	1.8 ± 1.6	1.3 ± 1.5	0.071 (0.33)	2.4 ± 2.0	1.2 ± 1.2	<0.001 (0.82)
Upper-extremity disability, mean ± SD	24.8 ± 15.3	24.4 ± 14.2	0.908 (0.03)	27.9 ± 16.9	23.2 ± 13.3	0.204 (0.33)
6-mo postoperative outcome						
Average pain intensity, mean ± SD	1.8 ± 1.9	1.1 ± 1.3	0.035 (0.46)	1.9 ± 2.0	1.1 ± 1.3	0.025 (0.52)
Upper-extremity disability, mean ± SD	15.7 ± 11.9	14.2 ± 11.4	0.434 (0.13)	15.5 ± 12.4	14.4 ± 11.3	0.721 (0.09)
12-mo postoperative outcome						
Average pain intensity, mean ± SD	1.2 ± 1.6	1.0 ± 1.7	0.229 (0.12)	1.5 ± 1.9	1.0 ± 1.5	0.101 (0.31)
Upper-extremity disability, mean ± SD	13.6 ± 16.3	11.4 ± 13.1	0.436 (0.15)	14.3 ± 17.5	11.3 ± 12.9	0.433 (0.21)
12-mo shoulder pain not recovered, %	39	18	0.048 (0.48)	46.1	17.2	0.002 (0.67)

ES, effect size; FPQ, Fear of Pain Questionnaire; PCS, Pain Catastrophizing Scale.

* *P* values were obtained from χ^2 tests for categorical variables and independent *t* tests for continuous variables. ESs were calculated for postoperative outcomes based on mean difference divided by pooled SD. All statistical comparisons were made with a significance level of 0.05.

Table 4

Sensitivity analyses for 12-month postoperative pain recovery outcome.

	FPQ subgroup			PCS subgroup		
	HR	Wald's 95% CI	P	HR	Wald's 95% CI	P
<i>COMT rs 6269</i>						
Not adjusted	0.69	0.44-1.07	0.096	0.51	0.31-0.84	0.009
Partially adjusted model	0.66	0.42-1.05	0.077	0.53	0.32-0.88	0.013
Fully adjusted model	0.61	0.37-1.00	0.050	0.44	0.25-0.77	0.004
<i>COMT diplotype</i>						
Not adjusted	0.69	0.45-1.07	0.095	0.52	0.32-0.83	0.006
Partially adjusted model	0.68	0.43-1.08	0.100	0.56	0.34-0.92	0.021
Fully adjusted model	0.64	0.40-1.04	0.072	0.46	0.27-0.80	0.006

Partially adjusted model included demographic variables (age, sex, and race); Fully adjusted model included demographic variables, depressive symptoms, medication status, and rotator cuff tear size; All statistical comparisons were made with $\alpha = 0.05$.

CI, confidence interval; FPQ, Fear of Pain Questionnaire; HR, hazard ratio; PCS, Pain Catastrophizing Scale.