American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 15, No 1 (January), 2014: pp 68-80
Available online at www.jpain.org and www.sciencedirect.com

Biopsychosocial Influence on Exercise-Induced Injury: Genetic and Psychological Combinations Are Predictive of Shoulder Pain Phenotypes

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Abstract: **Chronic pain is influenced by biological, psychological, social, and cultural factors. The current study investigated potential roles for combinations of genetic and psychological factors in the development and/or maintenance of chronic musculoskeletal pain. An exercise-induced shoulder injury model was used, and a priori selected genetic (*ADRB2*, *COMT*, *OPRM1*, *AVPR1 A*, *GCH1*, and *KCNS1*) and psychological (anxiety, depressive symptoms, pain catastrophizing, fear of pain, and kinesiophobia) factors were included as predictors. Pain phenotypes were shoulder pain intensity (5-day average and peak reported on numerical rating scale), upper extremity disability (5-day average and peak reported on the QuickDASH), and shoulder pain duration (in days). After controlling for age, sex, and race, the genetic and psychological predictors were entered as main effects and interaction terms in separate regression models for the different pain phenotypes. Results from the recruited cohort (N = 190) indicated strong statistical evidence for interactions between the *COMT* diplotype and 1) pain catastrophizing for 5-day average upper extremity disability and 2) depressive symptoms for pain duration. There was moderate statistical evidence for interactions for other shoulder pain phenotypes between additional genes (*ADRB2*, *AVPR1 A*, and *KCNS1*) and depressive symptoms, pain catastrophizing, or kinesiophobia. These findings confirm the importance of the combined predictive ability of *COMT* with psychological distress and reveal other novel combinations of genetic and psychological factors that may merit additional investigation in other pain cohorts.**

Perspective:** **Interactions between genetic and psychological factors were investigated as predictors of different exercise-induced shoulder pain phenotypes. The strongest statistical evidence was for interactions between the COMT diplotype and pain catastrophizing (for upper extremity disability) or depressive symptoms (for pain duration). Other novel genetic and psychological combinations were identified that may merit further investigation.

Key words: *Chronic pain, muscle pain, pain candidate genes, psychological predictors, single nucleotide polymorphism,* COMT.

Received July 18, 2013; Revised September 13, 2013; Accepted September 24, 2013.
This study was completed with funding from the National Institutes of Health, NIAMS (AR055899) and NINDS (NS045551).
The authors have no financial or other conflict of interest to report for the data reported in this manuscript.
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1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.09.012

Chronic pain is widely acknowledged to be a multifactorial entity with input from various biological, psychological, social, and cultural factors.[26] This complexity makes it challenging to study the development of chronic pain conditions, but structure has been provided by recent theoretical models. In particular, Diatchenko et al[11] have proposed a model for idiopathic chronic pain conditions that takes into consideration many relevant factors involved in

the transition from acute to chronic pain. In this model, it was hypothesized that genetic factors provide a foundation for chronic pain development whereas specific interactions among environmental factors, psychological distress, and pain amplification further increase the chances of developing a chronic pain condition.[11]

In our previous studies, we have used this model as the framework for investigating variations in the catechol-*O*-methyltransferase (*COMT*) gene and psychological factors consistent with a fear-avoidance model of musculoskeletal pain (FAM).[30] Results from exercise-induced injury and surgical shoulder pain cohorts indicated that an interaction between a *COMT* gene diplotype that confers high pain sensitivity due to low enzyme activity and elevated pain catastrophizing resulted in higher shoulder pain intensity ratings.[16,17] Studies in patients with fibromyalgia have provided converging evidence to support an interaction between the *COMT* gene and pain-associated psychological distress.[8,14] For example, Finan et al[14] reported that patients with a *COMT* single nucleotide polymorphism (SNP) associated with low enzyme activity had higher pain on days coinciding with elevated pain catastrophizing.

The interactions between the *COMT* gene and pain-associated psychological distress are compelling because it has been observed in different pain conditions, where replication is rare in such studies involving genetic predictors. Given the consistent nature of these findings, there is a need to further investigate the development and maintenance of chronic pain conditions by exploring interactions between other relevant genetic and pain-associated psychological factors.[35] *COMT* has been the most studied gene,[35,45] but there are other candidates to consider for interactions with pain-associated psychological factors. In 2004, Belfer et al[2] identified 19 other high-priority candidate pain genes and since then many other promising genes have been identified in animal or human studies.[35,37] In addition, psychological factors other than pain catastrophizing merit further study in combination with candidate genes. For example, fear of pain, anxiety, and depressive symptoms have each been highlighted for their influence on the pain experience.[31]

The purpose of the current study was to investigate the influence of combinations of select genetic and psychological factors on different pain phenotypes. In addition to the *COMT* gene and pain catastrophizing, we studied other potential genetic and pain-associated psychological predictors to build on our previous studies.[16,17] An exercise-induced muscle injury model was used because it controls for mechanism of muscle injury and results in shoulder pain and disability that lasts for several days. We have successfully used this pain model in previous studies[3,4,15,16] and report on several pain phenotypes, including shoulder pain intensity, upper extremity disability, and duration of shoulder pain. These pain phenotypes were selected a priori, and each represents a different aspect of the pain experience.

Methods

Subjects

The University of Florida's institutional review board for human subjects approved this study, and all subjects provided informed consent before participating in this study. 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 18 and 85 years old 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) neurologic 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 exercise-induced shoulder injury studies.[15,16] Subjects received up to $160.00 compensation (prorated for each completed session) for their research participation for the time it took to complete the exercise protocol and data collection sessions.

Procedures

All subjects underwent 5 testing sessions on consecutive days. During the first session, subjects provided informed consent and completed a series of questionnaires assessing demographic and psychological data. Then subject DNA was collected via buccal swabs, and the concentric–eccentric isokinetic exercise-induced pain protocol was completed on their dominant shoulder. Subjects returned to the lab postinjury at 24-hour intervals for the next 4 days for collection of data related to their shoulder pain, including pain intensity and upper extremity disability. If shoulder pain continued after the fifth study day, subjects were sent an e-mail prompting them to report pain intensity via a web-based data collection tool. These procedures are explained in more detail in the subsequent sections.

Self-Report Questionnaires

Demographic and psychological data were captured by self-report. The demographic data included sex, age, race, dominant hand, height, and weight. The psychological data included general negative mood constructs and constructs specific to the FAM. These questionnaires are described below, and total scores were used for this study.

Negative Mood Measures

Depressive symptoms and anxiety were the negative mood constructs of interest for this study. The Patient Health Questionnaire (PHQ) is a 9-item measure that was used for assessment of depressive symptoms.[24,29] Anxiety was assessed with the State-Trait Anxiety Inventory (STAI), which is a 40-item measure for symptoms of anxiety.[43] Only the 20-item trait portion of the STAI