Biopsychosocial influence on shoulder pain: genetic and psychological combinations are predictive of 12 month post-operative pain and disability outcomes

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Abstract

Objective—The current study identified novel combinations of genetic and psychological factors that predicted 12-month post-operative pain and disability outcomes following arthroscopic shoulder surgery.

Methods—A prospective pre-surgical cohort (n = 150) was recruited to complete validated psychological questionnaires and have their DNA collected from saliva. DNA was genotyped for *a priori* selected genes involved with pain modulation (*ADRB2, OPRM1, AVPR1A, GCH1, and KCNS1*) and inflammation (*IL1B, TNF/LTA,* and *IL6*). The outcome measures of interest were the Brief Pain Inventory (BPI) and Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire. Follow up for the cohort was at 3, 6, and 12 months post-operatively. After controlling for age, sex, race, and pre-operative status, genetic and psychological factors were entered as main effects and interaction terms in separate general linear models for predicting post-operative pain and disability outcomes.

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Conflict of Interest

The authors have no conflict of interest, financial or otherwise, to declare with submission of this manuscript.

Results—Seven interactions involving pain modulatory genes were identified. Three provided strong statistical evidence for different outcomes including; 1) *KCNS1* and kinesiophobia for pre-operative pain intensity, 2) *ADRB2* and depressive symptoms for post-operative course, and 3) *GCH1* and anxiety symptoms for 12 month pain intensity outcome. Ten interactions involving inflammatory genes were identified. Three provided strong statistical evidence for the 12 month post-operative course outcome including; 1) 2 different *IL6* SNP's and pain catastrophizing, and 2) *IL6* and depressive symptoms.

Conclusion—The current study identified novel genetic and psychological interactions that can be used in future studies to further understand the development of persistent post-operative pain and investigate the effectiveness of tailored treatment.

The etiology of chronic pain conditions is complex, influenced by many different biopsychosocial factors (i.e. genetic, psychological, social, and environmental) interacting to determine an individual's risk.[1, 2] Specific to the purposes of this study, persistent post-operative pain is a subset of chronic pain that results in undesirable surgical outcomes.[3] Persistent post-operative shoulder pain occurs following orthopedic surgery, even when arthroscopy is used.[4] Prediction of those at risk for persistent post-operative pain is difficult and improvement in this area has been highlighted as a research priority.[3]

We have investigated genetic and psychological factors in pre-clinical[5, 6] and clinical cohorts[7] with the overarching goal of improving prediction of post-operative outcomes. In our line of research we selected *a priori* candidate genes known to be involved in pain modulation (e.g. *COMT* and *AVPR1A*) or pro-inflammatory responses (e.g. *TNF/LTA* and *IL1B*), as well as psychological constructs (e.g. fear of pain and pain catastrophizing) that are established precursors to chronic musculoskeletal pain conditions. In our pre-clinical study involving 190 healthy adults we induced pain by eccentrically exercising the rotator cuff muscles to fatigue and then monitoring shoulder pain and upper-extremity disability ratings over several consecutive days. In this pre-clinical study we observed multiple interactions between genes and psychological factors that improved prediction of pain related phenotypes.[5, 6] From these pre-clinical analyses we identified risk subgroups, and one comprised of *COMT* SNP rs6269 and pain castastrophizing not only predicted heightened shoulder pain in the pre-clinical cohort but also predicted 12-month post-operative outcomes among patients undergoing shoulder surgery.[7]

The identification of a robust high-risk *COMT* and pain catastrophizing subgroup was encouraging, but there are many other genetic and psychological interactions that could improve prediction of post-operative outcomes. Our prior approach was translational in nature, with the goal being to first identify candidate interactions in a pre-clinical cohort and then carry those forward for validation in a clinical cohort.[7] This past approach, while rigorous, did not identify genetic and psychological interactions directly in a clinical cohort, which is traditionally how prognostic factors are identified. Therefore, further investigation of these interactions is warranted given that our pre-clinical pain model was not a perfect approximation of post-operative pain. Indeed, there is ample biological plausibility for additional genetic and psychological interactions influencing post-operative outcomes. Therefore, the purpose of the current analysis was to investigate whether combinations of *a*

priori selected genetic and psychological factors predicted 12-month post-operative outcomes for patients receiving arthroscopic shoulder surgery. These additional analyses are warranted because they will identify novel and potentially clinically relevant interactions that advance our understanding of shoulder pain conditions.

PATIENTS AND METHODS

Overview

This study was reported following STREGA extension [8] of STROBE guidelines[9] 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 prior to enrollment. The current paper is the primary analysis for identifying genetic and psychological predictors in the post-operative shoulder pain cohort.

Subjects

Consecutive individuals with shoulder pain were evaluated by orthopedic surgeons at the University of Florida's Orthopaedic and Sports Medicine Institute between 2009 and 2012. Surgical candidacy was determined by poor response to conservative treatment, diagnostic imaging, and physician examination. Individuals that were surgical candidates were then further screened by one of the authors (WHG) for study eligibility. Eligible participants were then consented, and scheduled for a baseline study session within 1 week of surgery. Demographic data were captured by self-report questionnaires and included sex, age, and race. Participants underwent shoulder arthroscopy, and returned for study sessions at 3 months, 6 months and 1 year post-operatively.

Inclusion criteria 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 one 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 OA or RA, or 4) prior shoulder surgery within the past year or currently complaining of pain from prior 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.

Predictive Measures

Genetic and psychological factors that were used as predictors in this study were *a priori* selected as briefly described below and in more detail in prior pre-clinical studies.[5, 6]

Genetic Measures—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 prior pre-clinical analyses.[5, 6] These genes were selected because of their established links with pain sensitivity, musculoskeletal pain, or the potential to develop chronic pain and there was an *a priori* plan to investigate them in pre-clinical and clinical cohorts. The genes reported in the current paper include 15 SNPs from 9 candidate genes not previously considered as predictors in the post-operative cohort. The COMT gene was not further considered because it has already been included in a validated risk subgroup, and this would be redundant with our prior study.[7] Each of the remaining genes is associated with biological process that could plausibly interact with psychological constructs to impact the reporting of shoulder pain. Therefore, these genes were considered appropriate for further investigation in the post-operative cohort. Conceptually, *OPRM1, ADRB2, AVPR1A, GCH1,* and *KCNS1* were investigated as pain modulatory genes and *TNF/LTA, TNF-308, IL1B,* and *IL6* were investigated as pro-inflammatory genes just as they were in our pre-clinical studies.[5, 6] Genotyping of the selected single nucleotide polymorphisms (SNPs) of these genes was performed as described in our previous reports using subject DNA extracted from buccal epithelial cells.[5, 6] Hardy-Weinberg equilibrium was calculated and found acceptable for each SNP.

Psychological Measures—Psychological measures were selected to represent constructs commonly identified as predictors of poorer outcome for musculoskeletal pain conditions. Depressive symptoms and anxiety were assessed with the Patient Health Questionnaire (PHQ)[10, 11] and the State-Trait Anxiety Inventory (STAI).[12] Fear of pain was assessed with the Fear of Pain Questionnaire (FPQ-III)[13-15] and for sake of brevity we used a shortened 9-item version that has performed similarly to the full scale.[16] Fear of movement was assessed with the shortened version of the Tampa Scale of Kinesiophobia (TSK-11).[17, 18] Finally, pain catastrophizing was assessed with the Pain Catastrophizing Scale (PCS).[19]

Outcome Measures

Pain and disability measures were collected pre-operatively and at 3, 6, and 12 months post-operatively. The Brief Pain Inventory (BPI) is a widely accepted measure of pain intensity that has good test-rest reliability over short intervals.[20] The BPI consists of rating pain intensity on an 11-point numerical rating scale ranging from 0 (no pain) to 10 (worst pain imaginable). In addition, the Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH) was used to assess upper-extremity disability.[21] We used a validated abridged version of the DASH (the QuickDASH) which consists of 11 functional items with total scores ranging from 0 (not disability) to 100 (complete disability).[22]

Sample Size

Sample size was determined *a priori* based on an 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 180 would enable us to detect all but two anticipated effect sizes based on estimates from our pilot data. However, for pragmatic reasons we recruited 150 into the post-operative cohort. 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, we reduced the number of covariates included in the regression models to exclude medication status and rotator cuff size as they did not impact findings in the clinical cohort.[7]

Data Analysis

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina). Summary statistics were calculated for all demographic, genetic, psychological, and outcome measures. For every gene, a general linear model was fitted to assess its main effect (genotype level) and a series of expanded models were fitted to study its interaction with the psychological factors for each shoulder pain outcome of interest. The predictors in the linear models included demographic variables (age, gender, and race), pain candidate genes as individual SNPs, psychological factors in their original continuous metric, and the gene × psychology interaction. Therefore, each linear model had the same structure with 4 increments including 1) demographic data, 2) genotype, 3) psychological factor, and 4) the gene by psychological factor interaction. The BPI and DASH were used as dependent variables in the linear models as a) pre-operative status; b) post-operative course by area under the curve (AUC, computed with 3, 6, and 12 month outcome scores); and c) 12 month outcome score. Three different versions of the outcome measures were used in the analysis to distinguish between factors predictive of pre-operative status, post-operative course, and final post-operative status respectively. Pre-operative values were used as covariates in linear models that included post-operative measures as dependent variables.

With this analytical approach the gene by psychological interaction effect was determined individually after accounting for other relevant predictor variables, thereby identifying unique prediction of variability for the dependent variable of interest. In our linear modeling, we conducted a total of 18 independent tests to determine if interactions (9 genetic factors by 2 psychological factors) improved prediction for each shoulder pain outcome. Bonferroni correction would yield a threshold alpha level of 0.0027 for each outcome. While this might be a conservative correction for genetic studies, the value of 0.0027 provides a convenient benchmark in assessing the outcome of the analyses. Specifically, interaction terms with p values <0.0027 were considered "strong" statistical evidence for predicting the pain phenotype of interest, while those with p values 0.0027 but <0.05 as showing "moderate" statistical evidence for predicting the pain phenotype of interest. Interaction terms with p values 0.05 were not reported in this paper. This same approach for p-value adjustment and interpretation was used in our pre-clinical studies.[5, 6]

Results

A total of 150 patients were consented, with 120 (80.0%), 123 (82.0%), and 120 (80.0%) providing follow up at 3, 6, and 12 months respectively. Descriptive data for this cohort are reported in Tables 1 and 2.

Pain Modulatory Genes—Regression analyses for the pain modulatory genes are reported in Table 3. The final models that contained interactions explained between 25% to 44% variance (p's < 0.005). Interactions that met our criterion for "strong" statistical evidence are depicted graphically in Figure 1.

In predicting pre-operative status one genetic and psychological interaction emerged with strong statistical evidence and one with moderate statistical evidence. These interactions both involved the *KCNS1* SNP interacting with the TSK-11 to predict worst and average pain intensity ratings. These interaction terms contributed an additional 7.1% (p = 0.001) and 5.5% (p = 0.004) variance to the full models for the strong and moderate evidence respectively. Increasing TSK-11 scores were more strongly associated with increasing pain intensity for the CT and TT genotypes in comparison with those in the CC genotype (Fig. 1A).

In predicting post-operative outcome course one genetic and psychological interaction showed strong statistical evidence, and three showed moderate statistical evidence. The strong statistical evidence was for an interaction between *ADRB2* and PHQ predicting post-operative upper-extremity disability AUC by adding 9.1% (p = 0.0001) variance to the final model. Increasing PHQ scores were more strongly associated with increasing upper-extremity disability for the AA genotype in comparison with those in the AG and GG genotypes (Fig. 1B). The *ADRB2* and PHQ interaction also added 5.8% variance (p = 0.0106) to peak post-operative upper-extremity disability scores. Pain intensity AUC was predicted by two different interactions that added significant variance to the final model. The first interaction was *ADRB2* and PHQ (4.8% and p = 0.0036) and the second interaction was *AVPR1A* and TSK-11 (3.6% and p = 0.0197).

In predicting 12-month post-operative status only one genetic and psychological interaction was detected and it met our criterion for strong statistical evidence. This interaction involved *GCH1* and the STAI and the term added 8.6% (p = 0.0025) variance to the full model. Increasing STAI scores were more strongly associated with increasing average pain intensity for the AA genotype in comparison with those in the AT and TT genotypes (Fig. 1C).

Inflammatory Genes—Regression analyses for the inflammatory genes are reported in Table 4. The final models that contained interactions explained between 21% to 45% variance (p's < 0.005). There were no genetic and psychological interactions that met our criterion for predicting pre-operative status. Interactions that met our criterion for "strong" statistical evidence are depicted graphically in Figure 2.

In predicting post-operative outcome course three genetic and psychological interactions showed strong statistical evidence, and 10 with moderate evidence. The interactions with strong statistical evidence were between *IL6* and the PCS and between IL6 and the PHQ for

two different outcomes. The interaction between IL6 and PCS added 7.7% variance (p = 0.0002) to the final model for pain intensity AUC and 8.1% variance (p = 0.0004) to the final model for upper-extremity disability AUC. The interaction between IL6 and PCS added 8.1% variance (p = 0.0004) and interaction between IL6 and PHQ added 6.7% variance (p = 0.0019) to the final model for upper-extremity disability AUC. For all three interactions, increasing PCS (or PHQ) scores were associated with increasing in pain outcomes intensity as follows: strongly positive for GG genotype, less but positive for CG, non-significant for CC. (Fig. 1D-F). A summary of the 10 other interactions for post-operative outcomes includes 7 interactions involving *IL6* SNPs with other psychological measures for predicting pain and disability, 2 interactions involving *IL1B* and the PHQ for predicting disability, and 1 interaction for *TNF/LTA* and the FPQ for predicting pain. These interactions are reported in detail in Table 3.

In predicting 12-month post-operative status two genetic and psychological interactions were detected and both met our criterion for moderate statistical evidence. Both of these interactions involved prediction of 12-month disability scores, with the *TNF/LTA* and STAI interaction adding 5.4% variance (p = 0.027) and the IL6 and FPQ interaction adding 7.3% variance (p = 0.009) to the final models respectively.

Discussion

In this study we identified novel interactions between genetic and psychological factors that improved prediction of 12 month post-operative clinical outcomes following arthroscopic shoulder surgery. These findings advanced our previous translational work by identifying interactions directly in a clinical cohort. Our results indicated strong statistical evidence for 3 different interactions between pain modulatory genes and psychological factors for predicting pre-operative, post-operative course, and 12 month outcomes (*KCNS1* × TSK-11, *ADRB2* × PHQ, and *GCH1* × STAI, respectively). Our results also indicated strong statistical evidence for 3 interactions involving an inflammatory gene for predicting post-operative course (2 for *IL6* × PCS and *IL6* × PHQ). These interactions added between 6-9% additional variance to full regression models, magnitude which suggests these findings may have clinical relevance for improving post-operative outcome prediction. Strong statements regarding the clinical implications of these findings must await future replication of the results; however, we believe this study has high potential clinical relevance in two areas. First, we expect these results to provide guidance on incorporating genetic and psychological factors to improve prediction of post-operative outcomes. Second, we expect the subgroups derived from these results will allow for the development and testing of the effectiveness of tailored treatment approaches based on genetic and psychological risk factors.

Interactions with Pain Modulatory Genes—The current analysis revealed additional interactions that improved prediction of post-operative outcomes beyond the previously identified *COMT* × PCS risk subgroup.[7] Our results suggest these interactions may have phenotypic specificity, as each interaction with strong statistical evidence predicted a different clinical outcome. In our parallel analysis for predicting pre-clinical shoulder pain phenotypes in healthy subjects following exercise-induced shoulder injury, *KCNS1* and

ADRB2 interacted with catastrophizing and depression, respectively, to predict disability and pain duration, respectively.[6] While the exact psychological factors involved with these interactions differed from those observed in the clinical cohort, the replication of these particular genes interacting with related psychological factors in separate cohorts suggests they are robust.

ADRB2 was the most frequent pain modulatory gene to interact with psychological factors and it was commonly coupled with a measure of depressive symptoms. This finding converges with previous research in which *ADRB2* haplotype was associated with psychological traits, and predictive of those developing temporomandibular disorder.[23] Furthermore, there is converging evidence that *ADRB2* genotype is associated with chronic widespread pain[24] and disabling neck and back pain.[25] The current study adds to the existing literature by indicating *ADRB2* has a role in the development of persistent post-operative disability via its interactions with psychological factors. The other pain modulatory genes identified in these interactions do not have as many comparison studies available. *KCNS1* was identified in peripheral neuropathic pain models that were further investigated and determined to increase risk of low back pain with the "C" risk allele.[26] Interestingly, our findings compliment this previous report by indicating increased risk with the "T" allele when combined with fear of movement. Previous research has identified pain protective genotypes/haplotypes of *GCH1* in preclinical and clinical models[27-29] and this study demonstrated that *GCH1* homogenous for the "A" allele interacted with anxiety to predict 12 month pain outcomes. The novelty and specificity of these findings for *KCNS1* and *GCH1* need further confirmation in future studies that predict post-operative outcomes.

Interactions with Inflammatory Genes—In contrast to the pain modulatory genes, there was notable consistency for inflammatory gene interaction findings. *IL6* was the only gene with strong statistical evidence for an interaction predicting post-operative course for pain and disability measures and the "G" allele was consistently predictive of higher risk. Furthermore *IL6* was included in 10/12 of gene × psychological interactions indicating robust findings with potential clinical relevance for improving outcome prediction by collecting this information pre-operatively.

Scant literature is available in patient populations to aid the interpretation of the inflammatory gene findings, but there are precedents in pre-clinical studies. For example, in healthy subjects experiencing experimental pain higher pain catastrophizing predicted increased *IL6* serum levels, providing biological plausibility for interactions between pain-related psychological constructs and inflammatory responses.[30] In our pre-clinical analyses predicting shoulder pain phenotypes we identified *TNF/LTA* and *IL1B* as interacting with psychological factors.[5] *IL6* was not predictive of any of the pre-clinical phenotypes, which was a stark contrast to the clinical findings. This lack of translation could be an indication that exercise-induced injury may be a better choice for general musculoskeletal pain processes, as evidenced by examples of translation for pain modulatory genes. A pre-clinical model of exercise-induced injury may not be a good choice for mimicking inflammatory processes that lead to the development of persistent post-operative pain and disability. Collectively these findings indicate that *IL6* polymorphisms indicating a pro-inflammatory predisposition should be considered in concert with psychological functioning as strong

candidates for having clinical relevance in future predictive models of post-operative pain and disability.

Future Research—These findings provide direction for future study. Models for predicting post-operative outcomes could start with the established $COMT \times$ PCS interaction, and then add other interactions identified in these analyses to determine if prediction improved. It is conceivable that consideration of both inflammatory and pain modulatory factors in prediction models would allow for more accurate prediction, but this approach has yet to be tested. Future study could also determine how prediction of specific outcomes changes when including the outcome specific gene by psychology interactions identified in this study. For example, a future study could determine if the addition of the $GCH1 \times$ TSK-11 interaction improves the precision of 12 month pain intensity outcome prediction after considering the $COMT \times$ PCS interaction. Investigation of these questions in an independent cohort would provide valuable information on what are the parameters for optimal outcome prediction when using such interactions. Finally, future research could add biological phenotypes so that a better understanding of the mechanisms underlying these interactions could be gained.

Limitations—The strengths of this study include the investigation of *a priori* selected genetic and psychological factors, the intentional link to a pre-clinical model, and 12 month follow up. There are, of course, limitations to consider. First, in our predictive models we did not control for pain medication or rotator cuff tear size. These factors were included in an earlier analysis[7] and did not impact outcomes so it was decided to not include them in the current analysis for sake of parsimony. Furthermore we did not consider any psychological $\times$ psychological interactions in the regression models even though there is likely interaction amongst the constructs included in this study. Second, we do not have associated biological measures so can't discuss physiological implications of these findings. This concern is mitigated by using genetic factors with known functional consequences but still limits what can be determined mechanistically from this study. Third, we can't interpret the identified interactions as being indicative of chronic pain per se because subjects had pre-operative pain that varied greatly in duration. Therefore, the interactions identified in this study are best interpreted as being predictive of persistent post-operative pain.

Conclusions—Persistent post-operative pain is a common and undesirable outcome of surgery that remains difficult to predict,[3] even when arthroscopy is used.[4] Given the complex nature of pain, multiple factors must be considered when determining risk for developing chronic or persistent pain conditions.[1, 2] The current study identified 6 interactions genetic and psychological interactions that improved prediction of pain and disability outcomes. Although clinical relevance of these interactions will ultimately be determined in future studies our findings indicate they can be used to improve the identification of persistent post-operative pain and to design tailored pain management strategies.

Acknowledgments

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Significance and Innovation

- In a planned follow up to our pre-clinical studies we identified interactions between genetic and psychological factors that improved prediction of 12 month pain and disability outcomes.

- Interactions with the pain modulatory genes were similar to those in our pre-clinical model, and each interaction was predictive of a different outcome measure.

- Interactions with the inflammatory genes differed from our pre-clinical model and consistently predicted the same outcome (12 month post-operative course).

- These results provide important direction for future prognostic studies involving post-operative outcomes and/or development of tailored pain management strategies.

Figure 1. Pain Modulatory Gene × Psychology Interactions that Strongly Predicted Pain and Disability Outcomes

Figure 1 Key: TSK-11 = Tampa Scale of Kinesiophobia; DASH = Disability of Arm, Shoulder, and Hand; AUC = Area Under the Curve; PHQ = Patient Health Questionnaire; STAI = State Trait Anxiety Inventory; BPI = Brief Pain Inventory
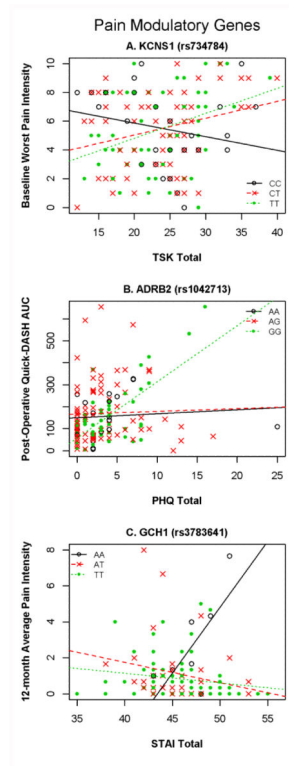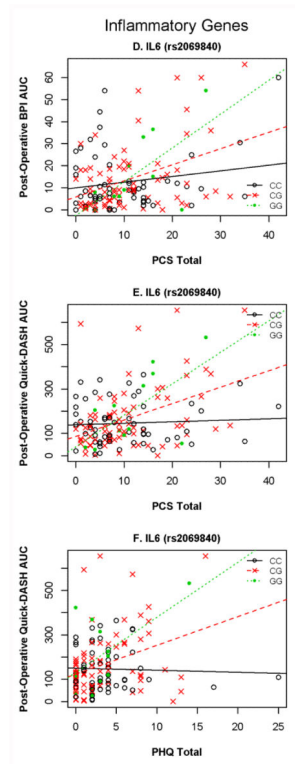
Figure 2. Inflammatory Gene × Psychology Interactions that Strongly Predicted Pain and Disability Outcomes
Figure 2 Key: PCS = Pain Catastrophizing Scale; DASH = Disability of Arm, Shoulder, and Hand; AUC = Area Under the Curve; PHQ = Patient Health Questionnaire; BPI = Brief Pain Inventory

Table 1

Description of Pain Modulatory and Inflammatory Genes

SNP		Frequency	Percent	SNP		Frequency	Percent
Pain Modulatory				**Inflammatory**			
ADRB2 rs1042713	AA	18	12.2%	IL1B rs16944	AA	20	13.5%
	AG	79	53.7%		AG	64	43.2%
	GG	50	34.0%		GG	64	43.2%
ADRB2 rs1042714	CC	52	35.1%	IL1B rs1143627	AA	63	42.6%
	CG	76	51.4%		AG	65	43.9%
	GG	20	13.5%		GG	20	13.5%
OPRM1 rs1799971	AA	109	73.7%	IL1B rs1143634	AA	10	6.8%
	AG	36	24.3%		AG	46	31.1%
	GG	3	2.0%		GG	92	62.2%
AVPR1 rs1042615	AA	22	15.0%	IL6 rs1800797	AA	16	10.8%
	AG	58	39.5%		AG	68	46.0%
	GG	67	45.6%		GG	64	43.2%
AVPR1 rs10877969	CC	5	3.4%	IL6 rs2069840	CC	56	38.6%
	CT	44	29.7%		CG	77	53.1%
	TT	99	66.9%		GG	12	8.3%
GCH1 rs3783641	AA	9	6.1%	TNF-308 rs1800629	AA	3	2.1%
	AT	44	29.9%		AG	38	26.0%
	TT	94	64.0%		GG	105	71.9%
KCNS1 rs734784	8	27	18.4%	TNF/LTA rs2229094	CC	12	8.2%
	CT	64	43.5%		CT	69	46.9%
	TT	56	38.1%		TT	66	44.9%
				TNF/LTA rs1800683	AA	17	11.6%
					AG	70	47.6%
					GG	60	40.8%

Table 2

Descriptive Summary of Operative Shoulder Pain Cohort

Variable		Pre-Operative		3 months		6 months		12 months	
		Mean±SD or Frequency	Median [Min, Max] or Percent	Mean±SD or Frequency	Median [Min, Max] or Percent	Mean±SD or Frequency	Median [Min, Max] or Percent	Mean±SD or Frequency	Median [Min, Max] or Percent
Age		42.7±17.4	42 [18,81]						
Gender	Female	51	34%						
	Male	99	66%						
Race	White	127	85%						
	Black or African American	11	7%						
	Other	12	8%						
Dominant Hand	Right	132	88%						
	Left	18	12%						
Surgical Side	Right	75	50%						
	Left	75	50%						
FPQ		20.9±6.0	21 [9, 36]						
PCS		10.8±8.6	9 [0, 42]						
PHQ		3.6±4.0	2 [0, 25]						
STAI		45.9±3.4	46 [35, 56]						
TSK-11		23.7±6.1	24 [12, 40]						
Average BPI		3.3±2.4	3 [0, 10]	1.5±1.5	1 [0, 8.7]	1.3±1.5	0.7 [0, 7.3]	1.1±1.6	0.5 [0, 8]
Worst BPI		5.4±2.6	6 [0, 10]	3.0±2.2	3 [0, 0]	2.6±2.4	2 [0, 10]	2.0±2.3	1 [0, 10]
Average DASH		34.3±17.9	31.8 [2.3, 79.5]	24.4±14.5	21.5 [0, 75]	14.6±11.6	11.4 [0, 50]	12.0±14.1	6.8 [0, 81.8]
Peak DASH		37.6±12.4	36.5 [13, 74]	30.9±12.1	28.0 [13, 68]	25.1±8.8	24.0 [13, 49]	23.7±10.2	20.0 [11, 68]

Table 2 Key: FPQ = Fear of Pain Questionnaire; PCS = Pain Catastrophizing Scale; PHQ = Patient Health Questionnaire; STAI = State Trait Anxiety Inventory; TSK-11 = Tampa Scale of Kinesiophobia; BPI = Brief Pain Inventory; DASH = Disability of Arm, Shoulder, and Hand questionnaire

Table 3

Regression analyses for prediction of clinical outcomes by pain modulatory genes and psychological factors

Dependent Variable	Genetic and Psychological Predictors	Demographics Only		Add Baseline Variable		Add Genotype		Add Psychological Factor		Add Interaction		P-Value of Full Model	R² of Full Model
		R²	P-value	R²	P-value	R² Increment	P-value	R² Increment	P-value	R² Increment	P-value		
Pre-Operative Status													
Average Pain Intensity	*KCNS1*(rs734784) + TSK-11	0.246	<.0001			0.000	0.957	0.039	0.007	0.055	0.004	<.0001	0.341
Worst Pain Intensity	*KCNS1*(rs734784) + **TSK-11**	**0.163**	**<.0001**			**0.009**	**0.480**	**0.081**	**0.000**	**0.071**	**0.001**	**<.0001**	**0.324**
12 Month Post-Operative Course (AUC)													
Average Pain Intensity	*ADRB2*(rs1042713) + PHQ	0.188	<.0001	0.160	<.0001	0.001	0.863	0.044	0.002	0.048	0.0036	<.0001	0.442
	AVPR1A(rs1042615) + TSK-11	0.188	<.0001	0.160	<.0001	0.010	0.338	0.005	0.304	0.036	0.0197	<.0001	0.399
Quick-DASH Average	*ADRB2*(rs1042713)+ **PHQ**	**0.102**	**0.004**	**0.110**	**<.0001**	**0.018**	**0.193**	**0.028**	**0.024**	**0.091**	**0.0001**	**<.0001**	**0.349**
Quick-DASH Peak	*ADRB2*(rs1042713) + PHQ	0.136	0.001	0.021	0.077	0.029	0.109	0.002	0.543	0.058	0.0106	<.0001	0.246
12 Month Post-Operative Status													
Average Pain Intensity	*GCH1*(rs3783641) + **STAI**	**0.097**	**0.020**	**0.039**	**0.026**	**0.032**	**0.122**	**0.012**	**0.199**	**0.086**	**0.0025**	**0.000**	**0.267**

Table 3 Key: *Bolded variables met our criterion for strong statistical evidence for an interaction (p < 0.0027 for addition of interaction term); AUC = area under curve; DASH = Disability of Arm, Shoulder, and Hand questionnaire; FPQ = Fear of Pain Questionnaire; PCS = Pain Catastrophizing Scale; PHQ = Patient Health Questionnaire; STAI = State Trait Anxiety Inventory; TSK-11 = Tampa Scale of Kinesiophobia

Table 4

Regression analyses for prediction of clinical outcomes by inflammatory genes and psychological factors

Dependent Variable	Genetic and Psychological Predictors	Demographics Only		Add Baseline Variable		Add Genotype		Add Psychological Factor		Add Interaction		P-Value of Full Model	R² of Full Model
		R²	P-value	R²	P-value	R² Increment	P-value	R² Increment	P-value	R² Increment	P-value		
Pre-Operative Status (none)													
12 Month Post-Operative Course (AUC)													
Average Pain Intensity	TNF/LTA(rs2229094) + FPQ	0.197	<.0001	0.158	<.0001	0.009	0.368	0.002	0.496	0.032	0.0312	<.0001	0.399
	IL6(rs1800797) + PCS	0.197	<.0001	0.158	<.0001	0.002	0.793	0.015	0.076	0.036	0.0190	<.0001	0.408
	IL6(rs2069840) + FPQ	0.197	<.0001	0.158	<.0001	0.001	0.867	0.003	0.467	0.036	0.0215	<.0001	0.395
	IL6(rs2069840) + PCS	**0.197**	**<.0001**	**0.158**	**<.0001**	**0.001**	**0.867**	**0.014**	**0.081**	**0.077**	**0.0002**	**<.0001**	**0.448**
	IL6(rs2069840) + PHQ	0.197	<.0001	0.158	<.0001	0.001	0.867	0.036	0.005	0.051	0.0027	<.0001	0.444
Quick-DASH Average	IL1B(rs1143627) + PHQ	0.109	0.003	0.105	<.0001	0.008	0.516	0.023	0.045	0.058	0.0048	<.0001	0.303
	IL6(rs1800797) + PCS	0.109	0.003	0.105	<.0001	0.001	0.931	0.043	0.006	0.045	0.0162	<.0001	0.303
	IL6(rs2069840) + FPQ	0.109	0.003	0.105	<.0001	0.012	0.354	0.006	0.291	0.054	0.0075	<.0001	0.287
	IL6(rs2069840) + PCS	**0.109**	**0.003**	**0.105**	**<.0001**	**0.012**	**0.354**	**0.040**	**0.008**	**0.081**	**0.0004**	**<.0001**	**0.347**
	IL6(rs2069840) + PHQ	**0.109**	**0.003**	**0.105**	**<.0001**	**0.012**	**0.354**	**0.024**	**0.041**	**0.067**	**0.0019**	**<.0001**	**0.317**
Quick DASH Peak	IL6(rs2069840) + FPQ	0.132	0.001	0.023	0.066	0.001	0.945	0.003	0.498	0.059	0.0117	0.001	0.218
12 Month Post-Operative Status													
Quick-DASH Average	TNF/LTA(rs2229094) + STAI	0.104	0.014	0.019	0.122	0.031	0.141	0.022	0.089	0.054	0.027	0.001	0.229
	IL6(rs2069840) + FPQ	0.104	0.014	0.019	0.122	0.003	0.839	0.009	0.302	0.073	0.009	0.004	0.207

Table 4 Key: *Bolded variables met our criterion for strong statistical evidence for an interaction (p < 0.0027 for addition of interaction term); AUC = area under curve; DASH = Disability of Arm, Shoulder, and Hand questionnaire; FPQ = Fear of Pain Questionnaire; PCS = Pain Catastrophizing Scale; PHQ = Patient Health Questionnaire; STAI = State Trait Anxiety Inventory; TSK-11 = Tampa Scale of Kinesiophobia