***Supplemental Information. Candidate Gene Description***

*Neuronal* *Signaling (HTR2A, DRD3, NPY, BDNF)*

The 5-hydroxytryptamine receptor 2A gene (*HTR2A*) codes for a serotonin receptor (1). SNPs in *HTR2A* have been associated with risk of schizophrenia, obsessive compulsive disorder, and response to citalopram (1).The serotonin 2A receptor also alters expression of *BDNF* in several limbic neurocircuits (2). *HTR2A* is the target of many drugs in clinical trials for the treatment of GAD, social anxiety disorder, PTSD, and obsessive compulsive disorder (3). The SNP rs731245 associated with constant-severe pain in CP and RAP+CP has two eQTLs in *HTR2A* in the testis and aorta (See Table S5, Supplemental Digital Content 3, which reports eQTLs) (4).

Dopamine receptor D3 (*DRD3*) codes the high affinity D3 subtype of the five dopamine receptors and is regulated by G proteins (1). *DRD3* is expressed mainly in the areas of the brain (limbic) associated with emotional, cognitive, reward sensitivity, impulsivity, and endocrine functions (1, 5, 6). The *DRD3* receptor is involved in several signaling pathways, including inhibiting the formation of cAMP via G protein coupling (7). Many anti-Parkinsonian and antipsychotic drugs target *DRD3* and *DRD2* (7). Levodopa, which targets *DRD3*, has been through clinical trials for the treatment of PTSD (3). Individuals with low stress resilience appear to have overexpression of dopamine receptor genes, including *DRD3*, and lower levels of dopamine degradation resulting in higher levels of dopamine in their brains (8). Variants in *DRD3* in combination with variants in *BDNF* (below) are associated with anxiety that is comorbid with bipolar disorder (9).

Pro-neuropeptide Y gene (*NPY*) is expressed in the central nervous system, is a target for anxiolytic drugs, and is associated with decreased endogenous μ-opioid response to pain (1, 10). *NPY* is involved with food motivation response in mesolimbic dopamine circuits (11). *NPY* also shows some environmental interactions and is associated with stress resilience (8, 10).

Low levels of brain-derived neurotropic factor (*BDNF*), a nerve growth factor, are strongly associated with major depressive disorder, possibly through disturbed neuronal plasticity and impaired neurogenesis (12). *BDNF* has several alternative splice sites; one of these proteins increases survival of neurons in the brain (1). *BDNF* is involved in the stress response and mood disorders, and is associated with “anticipatory worry”, depression, and anxiety (1, 8-10). BDNF can be produced by anti-inflammatory M2 microglia (6). The protein is a target of dopamine and serotonin, and regulates expression of *DRD3* (8, 13). Our SNP associated with constant pain in CP, rs1491851, has eQTLs in both *LIN7C* and *BDNF-AS* in multiple tissue types (See Table S5, Supplemental Digital Content 3, which reports eQTLs) (4).

*Prepulse Inhibition (SLC6A3, SHMT1)*

The solute carrier family 6 member 3 (*SLC6A3*) gene encodes a dopamine transporter that removes dopamine from the synapse (1, 14). A variable number tandem repeat in the 3’ untranslated region has been associated with attention deficit hyperactivity disorder, epilepsy, alcohol and cocaine dependence, Parkinson disease, prepulse inhibition, and reduced nicotine dependence (1, 15). *SLC6A3* has been the target of a clinical trial treating PTSD with methylphenidate (3). It is suggested that variation in *SLC6A3* is associated with response to antidepressants; however, more studies are needed (14).

Serine hydroxymethyltransferase 1 (*SHMT1*) codes for the cytosolic version of serine hydroxymethyltransferase, which is mainly expressed in the kidney and liver (1). However, SHMT1 has higher expression in schizophrenic human brains (16). SHMT1 converts glycine (a NMDA receptor co-chaperone) to L-serine; a process implicated in abnormal prepulse inhibition, which is involved in many psychiatric disorders (15, 16). *SHMT1* is a predictor for emergency department visits associated with female PTSD (17).

*HPA Axis (NR3C1, FKBP5)*

The nuclear receptor subfamily 3 group C member 1 (*NR3C1*) gene codes for a glucocorticoid receptor that acts as a transcription factor, and is a part of inflammation (1). Glucocorticoids are stress hormones involved in the HPA axis; dysregulation of this axis is often associated with stress related disorders (18). Clinical trials have tested whether variants in the *NR3C1* locus affect PTSD response to Mifepristone, Dexamethasone, Prednisone, and Hydrocortisone and suggest some predictive value (3). The SNP associated with constant pain in CP and both constant and constant-severe pain in RAP+CP patients (rs72802806) also has an eQTL associated with *NR3C1* measured in the esophagus (See Table S5, Supplemental Digital Content 3, which reports eQTLs) (4).

The FKBP prolyl isomerase 5 gene (*FKBP5*) codes for a protein in the immunophilin family that is involved in immunoregulation, protein folding and trafficking expressed mainly in fat (1). The SNP rs56977771 associated with constant-severe pain in CP presently also has eQTLs in *ZNF76* and *TEAD3* (See Table S5, Supplemental Digital Content 3, which reports eQTLs)(4). *FKBP5* shows a gene-by-environmental association with childhood trauma and increased risk of the stress disorders PTSD and depression (19, 20). Some variants in *FKBP5* affect HPA axis activity, as the FKBP5 protein is a co-chaperone of the glucocorticoid receptor (18, 20). Previous research found an association between lower response to psychotherapy in PTSD and DNA methylation in the promoter region of this gene (20).

*G Protein-Coupled Receptor Signaling* (*CAMKMT, PDE1A, NPSR1*)

Calmodulin-lysine N-methyltransferase (*CAMKMT*) codes for a class I protein methyltransferase that is involved in trimethylation of lysine 115 in calmodulin (1) and influences the activator properties of calmodulin with target enzymes (21). High expression of *CAMKMT* is seen in the testis, thyroid, and brain (1) and is required for somatosensory development and brain function (22). The lead SNP (rs62132337) associated with constant-severe pain in CP patients in our study contains an eQTL in *LRPPRC*, a gene linked to mitochondrial function (See Table S5, Supplemental Digital Content 3, which reports eQTLs)(4). *CAMKMT* has been associated with overall latent anxiety disorder factor scores (10). Phosphodiesterase 1A (*PDE1A*) is a cyclic nucleotide phosphodiesterase involved in signal transduction and is activated by calmodulin when Ca2+ is present (1). *PDE1A* is associated with response to antidepressants in individuals with GAD (10) but we are not aware of studies linking beneficial clinical responses of patients with variants in the *CAMKMT* locus and leading SNPs in our study.

Neuropeptide S receptor 1 (*NPSR1*) codes for a vasopression/oxytocin subfamily of G protein-coupled receptors, a membrane protein that binds neuropeptide S (NPS) (1). The NPS/NPSR system affects anxiety, food intake, memory, arousal, locomotion, and drug addiction (23). SNPs in *NPSR1* are associated with rheumatoid arthritis, asthma, inflammatory bowel disease, panic disorders, PTSD and a gene-by-environment interaction with childhood trauma highlighted an association with anxiety within the functional neuropeptide S receptor (1, 10, 24). In one small 8-week case-control study from China of patients with GAD, the *NPSR1* rs324981 genotypes appeared to predict response to escitalopram, a selective serotonin reuptake inhibitor (SSRI) and to a lesser degree venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), further studies are needed to verify the observation (25).

*Cell-Cell Interaction (CTNND2, THBS2)*

Catenin delta 2 (*CTNND2*) codes for an adhesive junction protein in the armadillo/β-catenin family, which promotes cell spreading (1). δ-catenin interacts with glutamate receptors in neurons and is implicated in brain processes involving synaptic regulation such as emotion and learning (26) δ-catenin is also involved in maintaining neurons in the mature cortex and the developing hippocampus (26). *CTNND2* has been associated with anxiety (19, 27).

Thrombospondin 2 (*THBS2*) is expressed mainly in the gallbladder and endometrium (1). This protein is part of the thrombospondin family and regulates cell-to-cell and cell-to-matrix interactions. Additionally, the protein is a tumor growth inhibitor (1). Previously, a SNP within the *THBS2* gene was associated with anxiety in individuals of Hispanic and Latin American ancestry; although, a meta-analysis failed to replicate the association (10). However, we did find an association between a different SNP in *THBS2* and constant-severe and constant pain in RAP+CP patients. This SNP, rs9294969, has an eQTL associated with *RP11-417E7.2* and *LINC01615* (See Table S5, Supplemental Digital Content 3, which reports eQTLs) (4).

SNPs in *DRD3*, *NR3C1, and PDE1A* have previously been associated with treatment of anxiety with duloxetine (10). Additionally, SNPs in *NR3C1* and *FKBP5* are associated with response to treatment in patients with depression (28). Although SNPs in *BDNF* and *SLC6A3* show associations with response to venlafaxine for treating depression, they do not show a response for anxiety (10). SNPs in *HTR2A* respond well to treatment of anxiety with venlafaxine (10). Drug targets of *DRD3*, *HTR2A*, *NR3C1*, and *SLC6A3* have been investigated in clinical trials for the treatment of PTSD, social anxiety, and GAD (3). The SNPs associated with treatment in candidate genes are not the same individual SNPs associated with pancreatitis pain in this study; however, there remains potential for locus-based therapies that should be investigated further.

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