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Genetically Regulated Gene Expression in the Brain Associated With Chronic Pain: Relationships With Clinical Traits and Potential for Drug Repurposing

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Abstract

BACKGROUND: Chronic pain is a common, poorly understood condition. Genetic studies including genome-wide association studies have identified many relevant variants, which have yet to be translated into full understanding of chronic pain. Transcriptome-wide association studies using transcriptomic imputation methods such as S-PrediXcan can help bridge this genotype-phenotype gap.

METHODS: We carried out transcriptomic imputation using S-PrediXcan to identify genetically regulated gene expression associated with multisite chronic pain in 13 brain tissues and whole blood. Then, we imputed genetically regulated gene expression for over 31,000 Mount Sinai Bio*Me* participants and performed a phenome-wide association study to investigate clinical relationships in chronic pain–associated gene expression changes.

RESULTS: We identified 95 experiment-wide significant gene-tissue associations ($p < 7.97 \times 10^{-7}$), including 36 unique genes and an additional 134 gene-tissue associations reaching within-tissue significance, including 53 additional unique genes. Of the 89 unique genes in total, 59 were novel for multisite chronic pain and 18 are established drug targets. Chronic

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DISCLOSURES

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pain genetically regulated gene expression for 10 unique genes was significantly associated with cardiac dysrhythmia, metabolic syndrome, disc disorders/dorsopathies, joint/ligament sprain, anemias, and neurologic disorder phecodes. Phenome-wide association study analyses adjusting for mean pain score showed that associations were not driven by mean pain score.

CONCLUSIONS: We carried out the largest transcriptomic imputation study of any chronic pain trait to date. Results highlight potential causal genes in chronic pain development and tissue and direction of effect. Several gene results were also drug targets. Phenome-wide association study results showed significant associations for phecodes including cardiac dysrhythmia and metabolic syndrome, thereby indicating potential shared mechanisms.

Chronic pain is a common, debilitating condition (1–3). Risk factors for and mechanisms of chronic pain development are not fully understood. Treating chronic pain successfully is a complex process, and many treatments, including pharmacological treatments, are suboptimal [reviewed by (4)].

Genetic studies of chronic pain (5–7) and conditions associated with chronic pain [e.g., rheumatoid arthritis (8), endometriosis (9), and migraine (10)] [see also (11) for a recent review of genetic studies in chronic pain] have revealed hundreds of genetic loci, but these results have not been translated into actionable treatment. In the pathway from genotype to phenotype, transcription and gene expression represent intermediate steps. Understanding expression changes that are associated with chronic pain could aid in increasing understanding of the mechanisms and best pharmaceutical treatments for chronic pain.

Transcriptomic imputation (TI) approaches combine expression quantitative trait loci and genome-wide association study (GWAS) association statistics to identify trait-associated genetically regulated gene expression (GREX), thereby providing directional and tissue-specific context (12–15). This approach is especially useful because changes to the brain and spinal cord, including regional brain activity (functional) changes as measured by functional magnetic resonance imaging, structural plasticity in central nervous system cells and synapses, morphological changes in neurons, changes to cell population sizes, changes in volume, and decreased gray matter, have been widely implicated in the development of chronic pain (16–20), and brain tissue is relatively inaccessible and impossible to assay in living study participants. Furthermore, genes that are involved in axonal guidance and enriched for expression in the brain have also been found to be associated with chronic overlapping pain conditions (21). TI studies have been carried out in a range of conditions (22–24), including complex traits that are commonly associated with chronic pain (10,24–27), but no direct TI analyses of chronic pain have been undertaken. Here, we applied a TI method, S-PrediXcan (13), to impute GREX in 13 brain regions and test for associations with multisite chronic pain (MCP) (5).

There is an unmet need to interrogate consequences of genetic variants in clinical data (28,29). Phenome-wide association studies (PheWASs) test for significant associations between exposures (e.g., genetic variants or other risk factors) and large sets of phenotypes, such as ICD-10 or other electronic health record traits (30). Previous PheWAS analyses have shown a relationship between seronegative rheumatoid arthritis and fibromyalgia (31) and

between genetic risk for problematic opioid use and pain-related phenotypes (32). Here, we tested for associations between chronic pain–associated GREX and a phenome of over 1000 phecodes in an ancestrally diverse hospital biobank.

This study involves GWAS summary statistics from one of the largest studies of chronic pain to date, in which chronic pain was examined as a complex disease trait (5). This may represent a more powerful way to uncover genetic variation specific to chronic pain development compared to genetic study of chronic pain–associated conditions. We have highlighted genes of interest through their GREX, in specific tissues, relevant to mechanisms of chronic pain development. We also present the first PheWAS of GREX for chronic pain.

METHODS AND MATERIALS

GWAS Output and Phenotype: MCP

MCP was found to be a complex, polygenic trait genetically correlated with psychiatric and other disorders in a 2019 GWAS (5). Recent changes to ICD-11 coding for chronic pain and International Association for the Study of Pain definitions of chronic pain (33–35) support the study of chronic pain as a disease. Genes involved in central nervous system and immune function were found to be associated with MCP using MAGMA (36), and gene expression of MCP-related genes was enriched in the brain. Summary statistics were used for transcriptome-wide association study analysis through the TI approach S-PrediXcan (13).

Discovery of GREX in Chronic Pain

GREX was imputed using MCP GWAS output and TI models from the GTEx (Genotype-Tissue Expression Project) (37) in 13 brain tissues (Table S1) using S-PrediXcan. Multiple testing correction (Bonferroni) was applied and resulted in 2 thresholds for significance: 1) a per-tissue threshold correcting for all genes tested in each tissue (Table S1), and 2) an experiment-wide threshold correcting for all genes across all tissues ($p = 7.9 \times 10^{-7}$). Then, we sought to replicate our findings using a different TI method, summary–transcriptome-wide association study (38) (see the Supplement).

Replication of Significant TI Gene-Tissue Associations

A recent genetic study of pain intensity was carried out in 598,339 Million Veterans Program participants (39) and included FUSION transcriptome-wide association analysis and prediction models for 6 brain tissues (anterior cingulate cortex, cerebellar hemisphere cortex, frontal cortex, cerebellum, and dorsolateral prefrontal cortex). Pain intensity was significantly genetically correlated with MCP ($r_g = 0.79$) (39). We downloaded the 361 significant gene-tissue results [Supplementary Table 20 in Toikumo *et al.* (39)] and carried out a Fisher's exact test to ascertain whether results overlap represented significant replication.

Downstream Analysis: FUMA

Pathway analyses were carried out using FUMA GENE2FUNC (40) including all per-tissue significant gene results ($n = 89$). We tested for enrichment of all gene sets available in

FUMA GENE2FUNC with all genes that had at least one S-PrediXcan prediction model available and were included in FUMA as background (n = 15,588). Significant gene results were also investigated using the FUMA DrugBank (see the Supplement).

Connectivity Map Analysis

We queried Connectivity Map (CMap), a large database of perturbation signatures maintained by the Broad Institute (41,42), using genes up- and downregulated in MCP (Table S2). We filtered results to retain compounds (drugs) passing CMap quality control with significant connectivity scores ($-\log_{10}$(FDR [false discovery rate]–corrected p) > 1.3, FDR–corrected $p < .05$).

Phenome-wide Association Analysis in Mount Sinai Bio*Me*

To probe relationships between MCP-associated GREX and clinical phenotypes, we performed a series of PheWASs (see the Supplement) in the Mount Sinai Bio*Me* biobank.

Bio*Me* is a large, diverse, hospital-based biobank that includes electronic health record and genotype data for 31,704 participants in the first data freeze. A total of 1236 phecodes for Bio*Me* participants were included in analyses presented in this paper. Phecodes are a high-throughput method that reduce electronic health record dimension and complexity in which ICD-10 codes are manually grouped according to clinical similarity (43). Here, we used previously curated phecodes (44). A full list of phecodes can be searched at https://phewascatalog.org/phecodes_icd10 or through download of the “PheCode Definitions v1.2 ICD-10-CM map” available at https://phewascatalog.org/phecodes_icd10cm.

First, we imputed MCP-GREX (chronic pain–related genetically regulated gene expression) for 31,704 Bio*Me* freeze 1 participants, split across 6 genotype-derived ancestry groups (Table S3).

Specifically, we imputed GREX in all 13 brain regions and in whole blood for all 89 unique genes previously identified as significant MCP-GREX. We tested for associations between these GREX values and Bio*Me* phecodes with at least 10 available cases in at least one ancestry [total phecodes = 1236 (44)]. Results were meta-analyzed using inverse variance-weighted meta-analysis in METAL (45). Multiple testing correction (within-gene FDR) was then applied.

To validate our MCP associations, we tested whether MCP-associated genes were associated with pain. A numeric rating scale (NRS) ranging from 0 to 10, where 10 is the worst pain possible and 0 is no pain, was recorded for Bio*Me* participants and aggregated into a mean pain score across instances in which the pain NRS was recorded. Associations were tested between significant MCP-GREX results and mean pain scores, and results were meta-analyzed across ancestry groups using inverse variance-weighted meta-analysis in METAL. FDR correction was performed as previously described.

RESULTS

Novel Brain-Specific Genes and Pathways Associated With Chronic Pain Identified With TI

We applied S-PrediXcan to the largest available summary statistics for MCP (n = 387,649). We identified 95 experiment-wide significant gene-tissue associations ($p < 7.97 \times 10^{-7}$), including 36 unique genes (Table 1). An experiment-wide threshold is likely overly conservative because many expression quantitative trait loci are shared between tissues; therefore, we also applied a within-tissue Bonferroni threshold (Table S1; Figure 1A, B). We identified an additional 134 gene-tissue associations that reached within-tissue significance, including 53 additional unique genes.

Of these 89 genes, 59 were not previously associated with MCP (5) (Table S4; Figure S2). We also found significant levels of replication of our gene-tissue findings in summary–transcriptome-wide association study (Supplement; Tables S5, S6). We also found significant replication of S-PrediXcan findings within significant TI findings for pain intensity. Six significant gene-tissue associations for MCP (Tables S7, S8) were also significant in analyses of pain intensity, representing significant replication ($p = 4 \times 10^{-9}$). To test whether significant associations were enriched in specific brain regions, we compared the proportion of experiment-wide significant associations per region with the proportion of genes tested in that region (binomial enrichment tests). We found significantly more experiment-wide significant associations in the nucleus accumbens basal ganglia than would be expected by chance (14.7% vs. 7.6%, $p_{\text{Binomial}} = .0075$) and significantly fewer in the cerebellar hemisphere (4.2% vs. 9.0%, $p_{\text{Binomial}} = .038$). Repeating this test for nominally associated genes, 3 brain regions showed fewer associations than would be expected by chance: the hippocampus (5.3% vs. 5.8%, $p_{\text{Binomial}} = .033$), spinal cord cervical C1 (4.4% vs. 5.1%, $p_{\text{Binomial}} = .0014$), and substantia nigra (3.4% vs. 4.0%, $p_{\text{Binomial}} = .0035$).

Downstream Analyses Indicate Potential Chronic Pain Drug Targets

To identify functional patterns of MCP-GREX associations, we conducted a gene set enrichment analysis using FUMA (see the Supplement). Genes associated with MCP-GREX were significantly enriched in the positional gene set chr3p21 ($p = 5.27 \times 10^{-19}$) (Figure 2A), which was also implicated in anorexia nervosa (46). MCP-GREX genes were significantly enriched for genes associated with 8 GWASs (Figure 2B). This included a previous GWAS of MCP ($p = 5.54 \times 10^{-6}$) (5), sleep duration (short sleep) ($p = 2.27 \times 10^{-11}$), extremely high intelligence ($p = 6.66 \times 10^{-8}$), regular attendance at gyms and sports clubs ($p = 6.66 \times 10^{-8}$), and religious group attendance ($p = 7.66 \times 10^{-6}$), as well as inflammatory conditions (ulcerative colitis, $p = 1.95 \times 10^{-5}$, inflammatory bowel disease, $p = 5.9 \times 10^{-3}$) and age at first birth ($p = 1.57 \times 10^{-3}$). FUMA DrugBank lookups (Table S9) identified 19 genes as drug targets. CMap analyses identified 23 compounds with significant connectivity scores (Table 2).

Clinical Associations With Chronic Pain GREX Revealed Through PheWAS

To probe clinical consequences of our MCP-associated genes, we performed a PheWAS in the Mount Sinai Bio*Me* biobank. First, we imputed MCP-GREX for 89 significant

MCP-GREX gene-tissue associations for 18,806 biobank participants who had available mean pain score data and tested for association between GREX and mean pain score. We identified 37 associations including 10 unique genes between MCP-GREX and mean pain score (Table 3). Next, we tested for phenome-wide associations, imputing MCP-GREX for 89 significant MCP-GREX gene-tissue associations for 31,704 Bio*Me* participants across 6 ancestry groups. Then, we meta-analyzed across ancestry using METAL and applied multiple testing correction (FDR). We identified 16 significant GREX-phecode associations across 9 brain regions, including 10 unique gene-phecode associations (Table 3; Figure 3). Associated phecodes included cardiac dysrhythmia, metabolic syndrome, disc disorders/dorsopathies, joint/ligament sprain, anemias, and neurological disorders.

Because pain and chronic pain are core symptoms of many of these diagnoses, and some genes with significant MCP-GREX were significantly associated with pain NRS, it is difficult to discern whether our MCP genes are associated with pain experience or directly with the trait itself. Therefore, we repeated our PheWAS on a subset of Bio*Me* participants and included mean pain scores derived from pain NRS information as covariates. We also carried out a PheWAS with adjustment identical to our main analyses (no adjustment for mean pain score) on the same subset of participants. We found the results to be significantly different from the main PheWAS results, but after comparison with the unadjusted-subset PheWAS, this appears to have been driven by a reduction in sample size rather than by mean pain score (Tables S10, S11). Sample size is significantly reduced when adjusting for pain score because many Bio*Me* participants do not have pain NRS information available.

DISCUSSION

These results reveal novel genes, theoretically enriched for causal effect, that are relevant to chronic pain development, thus providing new insight into mechanisms of chronic pain. By applying TI using S-PrediXcan, we were able to perform a well-powered study of gene expression in brain tissue and whole blood, which is currently not feasible with existing cohorts in which chronic pain phenotyping, genotype, and expression data are available together due to limited sample sizes. In the following section, we contextualize our findings with a focus on MCP-GREX genes found to be significantly associated with clinical traits (phecodes) in our Bio*Me* PheWAS analysis.

Gene Findings Give Insight Into Shared Pathways Between Chronic Pain and Other Medical Conditions

GREX of *ILRUN*, involved in innate immune response and highly expressed in B cells (47), was significantly associated with MCP in the basal ganglia of the nucleus accumbens, hypothalamus, amygdala, and cortex in the original S-PrediXcan analysis and with primary thrombocytopenia across all 4 tissues in our PheWAS (Table 4). Primary thrombocytopenia is an autoimmune platelet disorder that causes low peripheral plate counts and symptoms including joint and abdominal pain, bleeding, and bruising. *ILRUN* has also been linked to the renin-angiotensin-aldosterone system (involved in blood volume, sodium reabsorption, and vascular tone among other processes) in a study of SARS-CoV-2 infection (48). Peripheral small Ad and C fibers that transmit pain signals contain

cells expressing renin-angiotensin-aldosterone system components, and renin-angiotensin-aldosterone system modulators have been shown to affect pain relief (49). Our results suggest a role for *ILRUN* in the brain in chronic pain development, in addition to in pain perception in the periphery.

MCP-GREX of *MON1B* in both the amygdala and cervical spinal cord C1 was found to be significantly associated with anemias (Table 4); this phecode includes sickle cell anemia, thalassemia, and hemolytic anemias, all of which have often been associated with significant pain (50). Iron deficiency and iron-deficiency anemia are also generally associated with chronic inflammatory disease and chronic pain (51). Dysregulation of iron metabolism can play a key role in immune cell homeostasis and inflammation (52,53). *MON1B* also encodes a protein for which defects are associated with autoimmune pathology (54), a process that plays a significant role in chronic pain (55). This protein is also a key regulator of endocytic sorting by Numb, and so is linked to cell migration, asymmetrical cell division, and differentiation (56).

DCAKD encodes a protein linked to neurodevelopment (57) that is expressed widely in the brain (58), and MCP-GREX of this gene in the caudate basal ganglia was negatively associated with cardiac dysrhythmia (Table 4). Previous studies indicate a relationship between magnetic resonance imaging markers of cerebral small vessel disease and *DCAKD* (59) and Friedrich's ataxia (60), a disease of progressive neurodegeneration, heart, and spinal problems (61,62). Heart rate variability is thought to represent hyperarousal and has been linked to emotion regulation and chronic pain (63,64). In addition, certain nerve blocks can treat both cardiac and chronic pain conditions (65).

ECM1 encodes a protein involved in type 2 helper T cell migration (66) and skin development (67). In PheWAS analyses, *ECM1* MCP-GREX was associated with dysmetabolic syndrome X (aka metabolic syndrome) in 3 different brain tissues (68,69) (Table 4). This syndrome has been associated with increased risk of cardiovascular disease and type 2 diabetes (68,70). T cells have been associated with insulin resistance development in obesity (71); having metabolic syndrome can affect T cell development [reviewed by (72)]; and the amount of memory T cells has been associated with a proinflammatory state (73). These cell types could be therapeutic targets in chronic pain treatment (74–77) and could represent a sex-dimorphic mediator of pain hypersensitivity [reviewed by (78,79)].

PACSIN3 encodes a protein involved in the actin cytoskeleton and formation of vesicles (80). This protein also binds TRPV4; channelopathy mutations in the *TRPV4* gene lead to skeletal dysplasias, Charcot-Marie-Tooth disease subtype 2C, premature osteoarthritis, and neurological disorders (81). *TRPV4* channels are also important in skin function (82) and are involved in the itch-scratch cycle (83,84). TRP channels have also been implicated in chronic low back pain (85) and investigated as a therapeutic target in fibromyalgia (86,87). *PACSIN3* MCP-GREX in the basal ganglia of the nucleus accumbens was significantly associated with bullous dermatoses in PheWAS analyses (Table 4). Bullous dermatoses are autoimmune skin conditions of painful blistering (88–91). Although itch and pain are considered to be distinct (84), they share many similarities (92). Results here suggest that

TRPV4 ion channels and their interaction with PACSIN3 could be a point of overlap between chronic pain and itch.

RAD51 is involved in DNA repair (93,94). *RAD51* mutations have been linked to congenital mirror movement disorder (95) and cancers (96). MCP-GREX at this gene in the substantia nigra was significantly associated with disturbances of sulfur-bearing amino acid metabolism (Table 4). This phecode includes homocystinuria (the body is unable to process methionine) and methylenetetrahydrofolate reductase (MTHFR) deficiency (homocysteine levels are elevated) (97). Both processes are part of DNA metabolism (98), and elevated homocysteine levels are associated with a range of illnesses and neurotoxicity (99). RAD51 foci (indicators of cellular replication stress) (100) were increased in experiments examining folate deficiency (101). Previous studies in rodents showed that elevated homocysteine caused mechanical allodynia (102), and PheWAS results indicate a role for this mechanism of sensitization in human chronic pain.

SCAI encodes a transcriptional cofactor that regulates invasive cell migration (103), including in gliomas (104). MCP-GREX of this gene in the cortex was associated with toxic/inflammatory neuropathy in PheWAS analyses, and this gene was differentially expressed in rat models of diabetic neuropathy in the spinal cord (105). Our findings suggest a similar role for human *SCAI* in neuropathy.

SLC38A3 encodes a glutamine transporter (106) involved in cell energy metabolism. Glutamine is the preferred energy source for rapidly proliferating cell populations in the nervous system, immune system, and cancer cells (107–111). *SLC38A3* is also expressed in muscles, and significant MCP-GREX in the caudate basal ganglia was found to be associated with joint and muscle sprain (Table 4), suggesting that the glutamine transporter encoded by *SLC38A3* has a central as well as a peripheral role. *SLC38A3* MCP-GREX in the same brain area was also significantly associated with neurological disorders (Table 4), consistent with research showing relationships between glutamine metabolism in the brain and neurological conditions (112–115). GABAergic (gamma-aminobutyric acidergic) gene regulatory elements have also been implicated in neurological and psychiatric diseases (116–120), glutamate receptors in neurological dysfunction (121), and treating neurodegeneration through targeting glutamate transporters (122). Activity-dependent synaptic plasticity also involves glutamate and glutamine metabolism (123). Glutamine has also been investigated as a chronic pain biomarker because concentrations vary in individuals with chronic pain compared with control participants (124,125), and glutamine supplementation may be helpful in vaso-occlusive crisis in sickle cell disease (126). Glutamine levels have also been associated with individual pain sensitivity differences (127) and migraine (128). Finally, glutamine supplementation was associated with reduced opioid use in sickle cell disease in a small study, highlighting potential as a harm- and pain-reducing compound in chronic pain treatment (129). Finally, *ERICH2* MCP-GREX in the amygdala was significantly associated with dorsopathies (Table 4).

Comparison With Genetic Correlation Results

Psychiatric disorder–related phecodes and phecodes assigned to chronic pain conditions, e.g., rheumatoid arthritis or endometriosis, were not significantly associated with MCP-

GREX. In contrast, significant genetic correlations between MCP and, e.g., major depressive disorder and MCP and rheumatoid arthritis were found in a previous study (5). Genetic correlations are calculated using all single nucleotide polymorphism associations genome wide rather than at a gene level, which may explain these differences. In addition, in theory, S-PrediXcan results represent gene expression changes that occur before chronic pain development (whereas GWAS summary statistics used in linkage disequilibrium score regression represent genetic associations more generally). This suggests that the gene expression changes that contribute to chronic pain development do not directly contribute to psychiatric conditions (e.g., major depressive disorder), which is consistent with previous studies that have suggested that chronic pain can have a causal effect on major depression development but not vice versa (5). Another possibility is that tissues that were not examined in this study are associated with MCP-GREX and would show associations with psychiatric disorder or other expected phecodes in a PheWAS. However, it is difficult to explain why these nonbrain tissues, and not brain tissue, would show this result. We chose to examine brain and whole blood because chronic pain involves significant changes in the brain and spinal cord (16–19), and whole blood represents a tissue of interest due to immune components and ease of testing for, e.g., potential chronic pain biomarkers. Finally, phecodes generally represent a broad category of diagnoses; for example, the phecode for mood disorder (296) encompasses depression associated with major depressive disorder, bipolar disorder, and schizophrenia, and this heterogeneity could affect PheWAS results.

Changes to PheWAS Findings When Adjusting for Mean Pain Score

After adjusting our PheWAS association testing for mean pain score, results were significantly different compared with the main PheWAS analyses. However, these changes appear to be driven by reduction in sample size because unadjusted and adjusted analyses in the same subset of individuals showed similar results. Although NRS is a widely used pain reporting measure in clinical and research settings (130), it can change in unpredictable ways over time in chronic pain (131,132), may not accurately reflect treatment outcome when used alone (133), and may not be the most useful measure for identifying clinically important pain (134) or changes in pain (135). Pain NRS may not represent an ideal assessment tool in nonacute pain at the population or group level despite some studies demonstrating stability when an NRS was used to assess improvement in individuals over time (136) because perception of pain, which influences NRS ratings, is likely to be significantly different between individuals with and without chronic pain (137). People with chronic pain may rate moderate to high levels of pain as tolerable (138); conversely, depression or depressive symptoms that are commonly comorbid with chronic pain could lead to the reporting of higher NRS scores (139–141).

Drug Targets in Chronic Pain

Chronic pain is complex and difficult to treat successfully. The results shown here could inform treatment development; genes where MCP-GREX is associated with upregulation may present better targets in genomic medicine (downregulation of a gene can be easier to induce than upregulation), and genes where significant MCP-GREX is shown in a singular tissue may present a better target for potential animal modeling of chronic pain compared with genes where MCP-GREX is widespread. DrugBank lookups provide suggestions for

drug repurposing, and several drugs highlighted are already used experimentally in chronic pain treatment, e.g., monoclonal antibodies in migraine (142–144) and drugs that increase inhibitory glycinergic neurotransmission in the spinal cord (145,146). Several compounds identified in CMap analysis also show potential in chronic pain treatment; PX-12 showed anti-allodynia effects in a rodent model of chronic pain (147); physostigmine showed an antihyperalgesic effect in clinical trials (148); and SR-2640 activates TREK-1 channels that are associated with nociceptive hypersensitivity in rodent models (149). Arcyriaflavin-a is a potential therapeutic compound in endometriosis (150), as sorbinil (151) and fenoterol (152) are in diabetic neuropathy. Ursolic acid has demonstrated antinociceptive properties in animal models (153), and analgesic properties of palmitoylethanolamide (154) and luteolin (155) have been shown in multiple studies. Other findings are established pain treatments, e.g., aspirin and nimesulide. Other compounds, e.g., epidermal growth factor receptor (EGFR) inhibitor PD-153035, affect cancer-related pathways, which are also implicated in chronic pain (156), thus presenting novel treatment targets.

Conclusions

We carried out the largest TI study of a chronic pain trait to date, making important progress in translating GWAS findings into insights into chronic pain development and beginning to bridge the gap between genotype (GWAS output) and phenotype (MCP). Specific brain tissues and the direction of effect of MCP-GREX are also given; pathways of interest and potential mechanistic overlap with other medical conditions are indicated; and several genes showing significant MCP-GREX are also potential drug targets. We also identified several compounds with opposite expression perturbation signatures to MCP (i.e., potentially therapeutic compounds in chronic pain). Results of our PheWAS in which we adjusted for mean pain score indicate that associations tend not to be driven solely by pain perception. PheWAS results indicate potential shared causal pathways between chronic pain and conditions such as metabolic syndrome, anemias, and cardiac dysrhythmia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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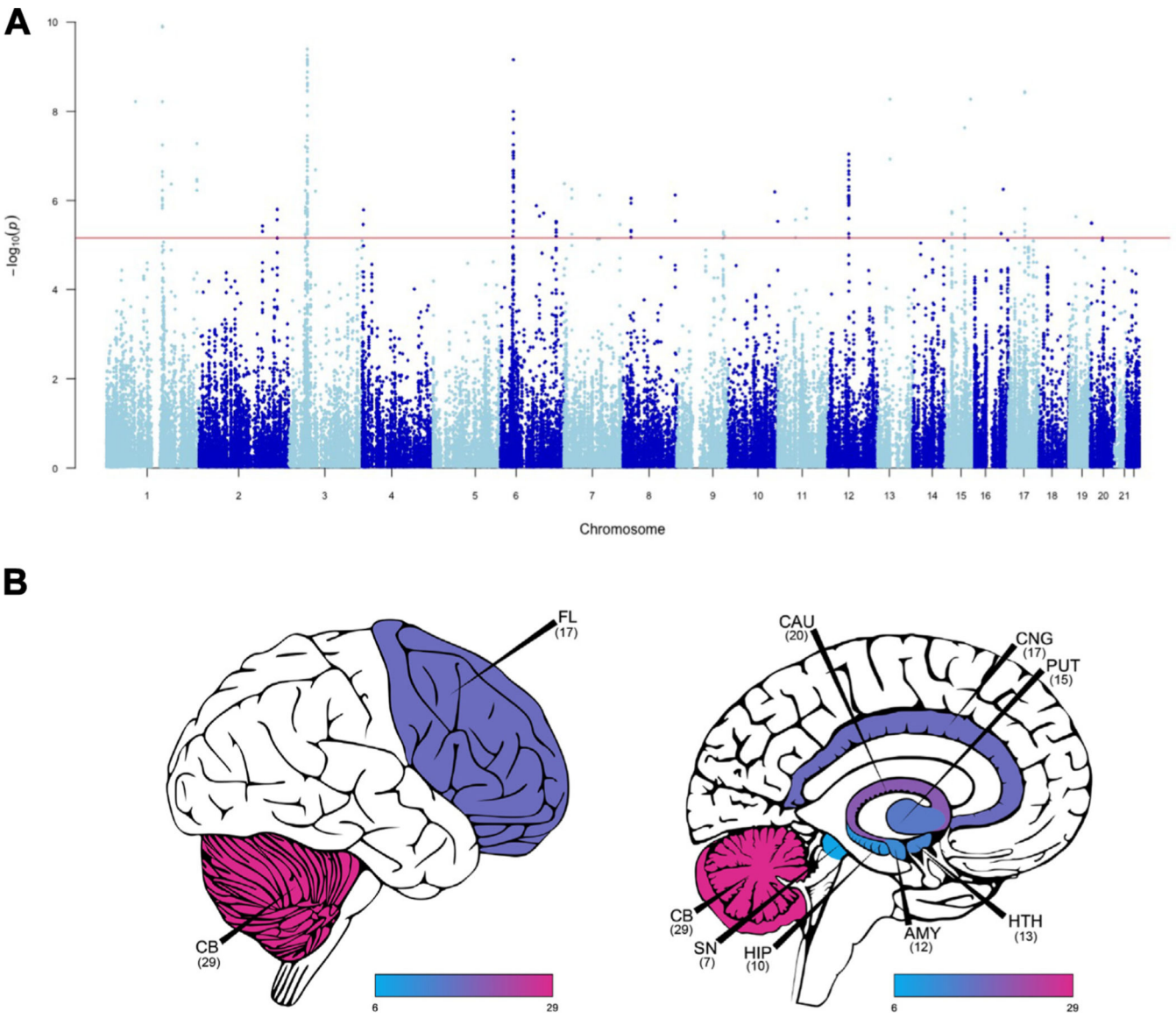

Figure 1.

S-PrediXcan analysis identifies 89 unique genes associated with chronic pain. **(A)** S-PrediXcan analyses identified 89 unique significant gene associations across 14 tissues. Red line indicates most conservative per-tissue significance threshold. **(B)** Number of significant multisite chronic pain–genetically regulated gene expression genes per brain region. Created using cerebroViz (157). AMY, amygdala; CAU, caudate; CB, cerebellum; CNG, anterior cingulate cortex; FL, frontal lobe; HIP, hippocampus; HTH, hypothalamus; PUT, putamen; SN, substantia nigra.

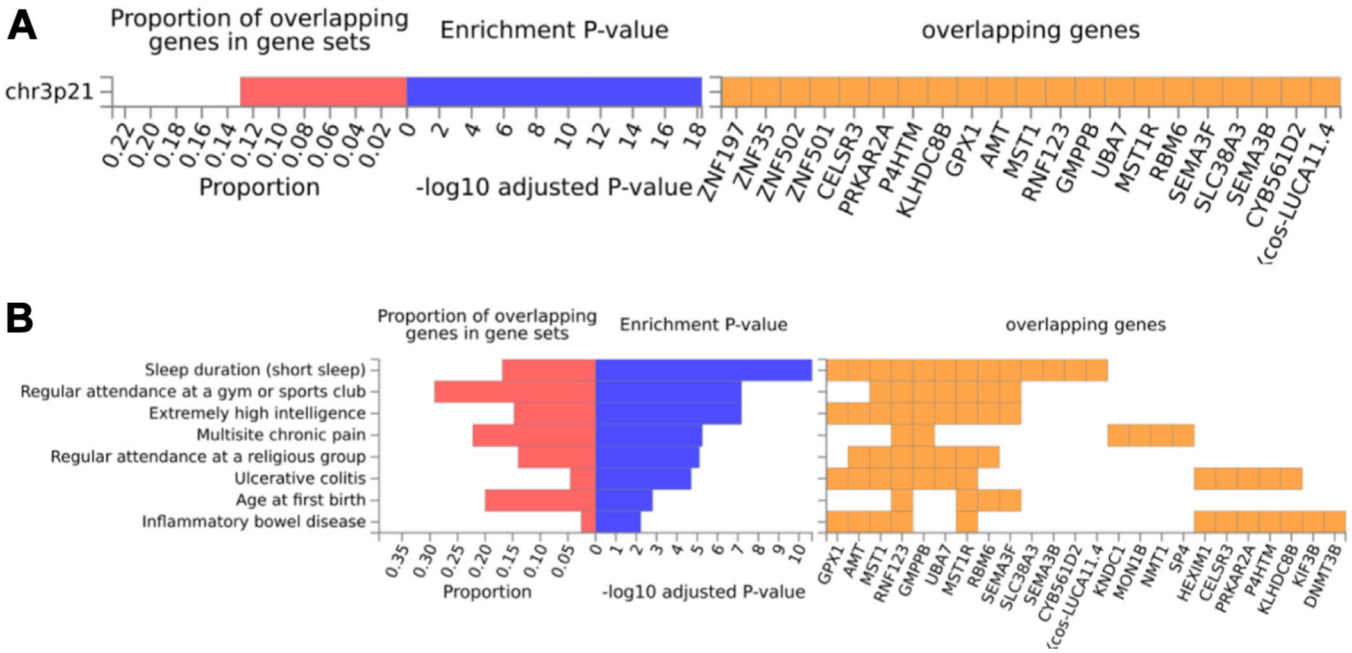

Figure 2.

Gene set enrichment analysis identifies positional and genome-wide association study enrichments. **(A)** FUMA gene set enrichment identified one positional gene set (chr3p21) enriched for multisite chronic pain–genetically regulated gene expression genes. **(B)** Enrichment analyses showed 9 genome-wide association study catalog traits significantly enriched for multisite chronic pain–genetically regulated gene expression genes.

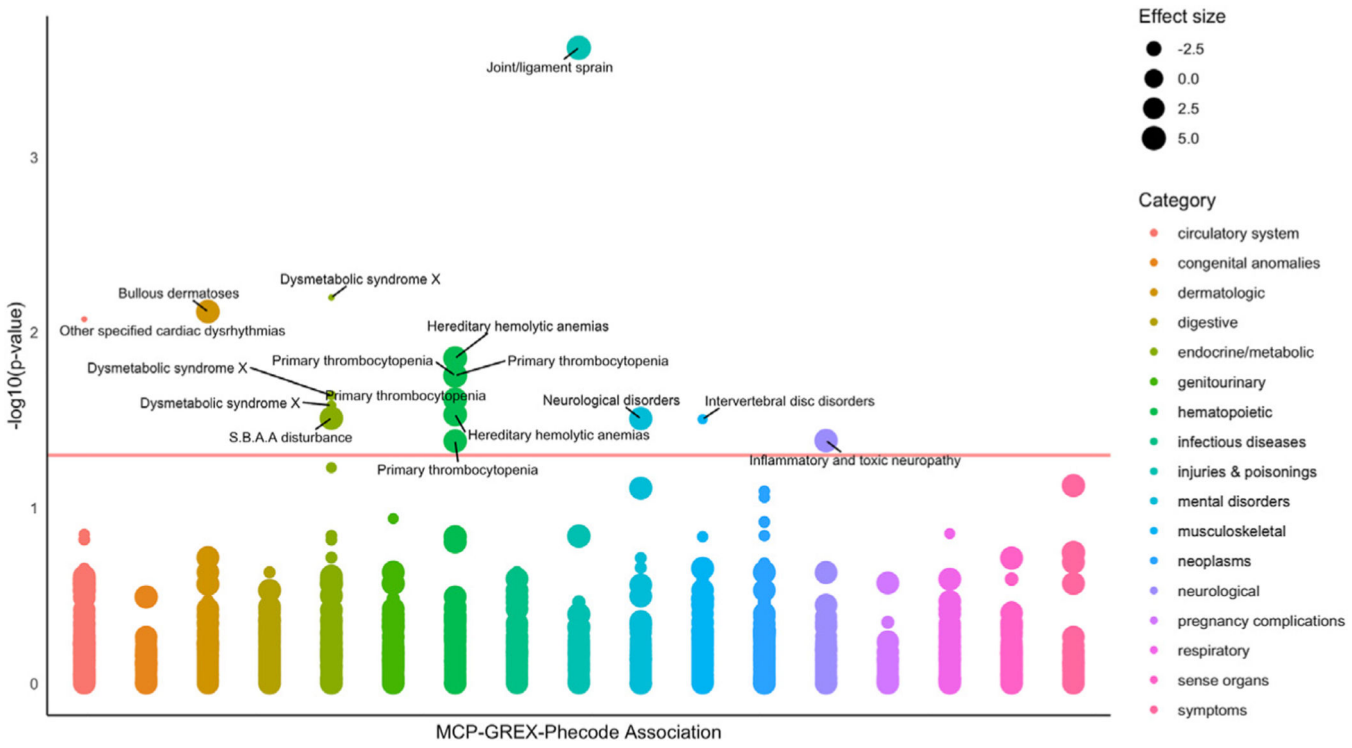

Figure 3.

Phenome-wide associations with chronic pain–associated genes. Effect size = *z* score value for the association between MCP-GREX and phecode. Red horizontal line indicates *p* value significance threshold ($-\log_{10}(0.05) = 1.3$); phecodes are color-coded according to wider phecode category [using mapping tables made available at https://phewascatalog.org/phecodes_icd10 and associated with Wu *et al.* (44)]. GREX, genetically regulated gene expression; MCP, multisite chronic pain; S.B.A.A, sulfur-bearing amino acid.

Table 1.

Eighty-nine Unique Genes Associated With Multisite Chronic Pain

Gene Symbol	Tissue	*z* Score	Effect Size	*p* (Unadjusted)
ECM1	Hippocampus	6.43	0.182	$1.24 \times 10{-}10^{a}$
TARS2	Cerebellum	6.43	0.157	$1.29 \times 10{-}10^{a}$
GPX1	Frontal cortex, BA 9	6.25	0.083	$4.03 \times 10{-}10^{a}$
GPX1	Cerebellar hemisphere	6.20	0.113	$5.54 \times 10{-}10^{a}$
GMPPB	Anterior cingulate cortex, BA 24	−6.17	0.051	$6.77 \times 10{-}10^{a}$
SNRPC	Anterior cingulate cortex, BA 24	−6.17	−0.082	$6.95 \times 10{-}10^{a}$
GMPPB	Hypothalamus	6.17	0.046	$6.96 \times 10{-}10^{a}$
GMPPB	Caudate, basal ganglia	6.15	0.041	$7.77 \times 10{-}10^{a}$
GMPPB	Cerebellum	6.14	0.032	$8.38 \times 10{-}10^{a}$
GMPPB	Nucleus accumbens, basal ganglia	6.12	0.037	$9.08 \times 10{-}10^{a}$
GMPPB	Cerebellar hemisphere	6.07	0.039	$1.30 \times 10{-}9^{a}$
CELSR3	Amygdala	6.02	0.218	$1.77 \times 10{-}9^{a}$
SEMA3B	Nucleus accumbens, basal ganglia	−5.97	−0.267	$2.32 \times 10{-}9^{a}$
GMPPB	Spinal cord cervical C1	−5.97	0.038	$2.40 \times 10{-}9^{a}$
GMPPB	Whole blood	5.95	0.120	$2.70 \times 10{-}9^{a}$
AMT	Hypothalamus	−5.91	−0.110	$3.44 \times 10{-}9^{a}$
GMPPB	Cortex	5.90	0.032	$3.53 \times 10{-}9^{a}$
NMT1	Putamen, basal ganglia	5.90	0.075	$3.63 \times 10{-}9^{a}$
NMT1	Anterior cingulate cortex, BA 24	5.89	0.120	$3.83 \times 10{-}9^{a}$
VPS33B	Whole blood	−5.84	−0.069	$5.35 \times 10{-}9^{a}$
RP11–24H2.3	Amygdala	−5.84	−0.059	$5.36 \times 10{-}9^{a}$
FUBP1	Cerebellum	−5.81	−0.227	$6.06 \times 10{-}9^{a}$
RPRD2	Nucleus accumbens, basal ganglia	5.81	0.290	$6.10 \times 10{-}9^{a}$

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Gene Symbol	Tissue	*z* Score	Effect Size	*p* (Unadjusted)
AMT	Substantia nigra	−5.23	−0.077	1.68×10^{-7a}
GPX1	Cerebellum	5.23	0.060	1.69×10^{-7a}
GPR27	Cortex	5.19	0.183	2.06×10^{-7a}
C6orf106 (ILRUN)	Nucleus accumbens, basal ganglia	5.19	0.079	2.10×10^{-7a}
SNRPC	Hippocampus	−5.19	−0.086	2.13×10^{-7a}
AMT	Anterior cingulate cortex, BA 24	−5.19	−0.075	2.13×10^{-7a}
SUOX	Nucleus accumbens, basal ganglia	5.18	0.054	2.18×10^{-7a}
UHRF1BP1	Cerebellar hemisphere	5.18	0.068	2.18×10^{-7a}
MRPS21	Frontal cortex, BA 9	−5.18	−0.182	2.27×10^{-7a}
SNRPC	Putamen, basal ganglia	−5.16	−0.054	2.50×10^{-7a}
RPS26	Cerebellum	−5.15	−0.015	2.58×10^{-7a}
RPRD2	Whole blood	5.13	0.250	2.87×10^{-7a}
SNRPC	Whole blood	−5.13	−0.486	2.91×10^{-7a}
GPX1	Caudate, basal ganglia	5.12	0.078	2.98×10^{-7a}
UHRF1BP1	Cortex	5.12	0.044	3.07×10^{-7a}
CEP170	Whole blood	5.10	0.159	3.34×10^{-7a}
SUOX	Putamen, basal ganglia	5.10	0.079	3.40×10^{-7a}
GMPPB	Amygdala	5.09	0.027	3.55×10^{-7a}
AMT	Nucleus accumbens, basal ganglia	−5.09	−0.049	3.65×10^{-7a}
SDCCAG8	Caudate, basal ganglia	5.08	0.114	3.70×10^{-7a}
P4HTM	Cerebellum	−5.08	−0.072	3.83×10^{-7a}
RBM6	Caudate, basal ganglia	−5.06	−0.050	4.14×10^{-7a}
INTS1	Spinal cord cervical C1	−5.06	−0.025	4.19×10^{-7a}
RBM6	Cortex	−5.06	−0.031	4.27×10^{-7a}
RP11–160H22.5	Whole blood	−5.06	−0.059	4.28×10^{-7a}

Gene Symbol	Tissue	z Score	Effect Size	p (Unadjusted)
UHRF1BP1	Caudate, basal ganglia	5.04	0.062	4.59×10^{-7} [a]
UHRF1BP1	Whole blood	5.04	0.029	4.71×10^{-7} [a]
SUOX	Cerebellum	5.03	0.027	4.88×10^{-7} [a]
SUOX	Cerebellar hemisphere	5.03	0.044	4.90×10^{-7} [a]
UHRF1BP1	Frontal cortex, BA 9	5.02	0.157	5.17×10^{-7} [a]
SP4	Nucleus accumbens, basal ganglia	5.00	0.243	5.61×10^{-7} [a]
MON1B	Whole blood	5.00	0.105	5.63×10^{-7} [a]
SUOX	Caudate, basal ganglia	5.00	0.075	5.82×10^{-7} [a]
SDCCAG8	Putamen, basal ganglia	4.99	0.087	5.89×10^{-7} [a]
RPRD2	Substantia nigra	4.99	0.102	5.91×10^{-7} [a]
ZNF197	Whole blood	−4.99	−0.037	5.98×10^{-7} [a]
GPR27	Frontal cortex, BA 9	4.98	0.137	6.21×10^{-7} [a]
UHRF1BP1	Cerebellum	4.98	0.080	6.28×10^{-7} [a]
CTBP2	Cerebellum	−4.98	−0.080	6.40×10^{-7} [a]
GPX1	Nucleus accumbens, basal ganglia	4.96	0.055	7.03×10^{-7} [a]
PTK2	Nucleus accumbens, basal ganglia	4.95	0.079	7.56×10^{-7} [a]
SLC25A13	Whole blood	4.94	0.070	7.66×10^{-7} [a]
RPS26	Caudate, basal ganglia	−4.94	−0.016	7.80×10^{-7} [a]
SEMA3F	Anterior cingulate cortex, BA 24	−4.94	−0.205	7.80×10^{-7} [a]
RPS26	Nucleus accumbens, basal ganglia	−4.94	−0.014	7.89×10^{-7} [a]
RNF123	Cerebellum	4.94	0.042	7.94×10^{-7} [a]
SUOX	Cortex	4.94	0.071	7.94×10^{-7} [a]
SUOX	Amygdala	4.94	0.081	7.99×10^{-7}
SUOX	Hypothalamus	4.93	0.073	8.10×10^{-7}
RBM6	Cerebellar hemisphere	−4.92	−0.044	8.50×10^{-7}

Gene Symbol	Tissue	*z* Score	Effect Size	*p* (Unadjusted)
TSKU	Cerebellar hemisphere	4.80	0.038	1.55×10^{-6}
UBA7	Caudate, basal ganglia	−4.80	−0.240	1.56×10^{-6}
LANCL1	Cortex	4.80	0.102	1.59×10^{-6}
GRK4	Anterior cingulate cortex, BA 24	4.80	0.060	1.62×10^{-6}
ZNF501	Cerebellum	−4.79	−0.046	1.71×10^{-6}
UHRF1BP1	Nucleus accumbens, basal ganglia	4.78	0.149	1.73×10^{-6}
SNRPC	Caudate, basal ganglia	−4.78	−0.059	1.77×10^{-6}
C15orf57	Cortex	−4.78	−0.035	1.79×10^{-6}
UHRF1BP1	Anterior cingulate cortex, BA 24	4.78	0.058	1.79×10^{-6}
RBM6	Anterior cingulate cortex, BA 24	−4.77	−0.035	1.80×10^{-6}
MST1R	Caudate, basal ganglia	4.77	0.068	1.82×10^{-6}
KLHDC8B	Cerebellum	4.77	0.113	1.86×10^{-6}
TSPYL4	Cerebellum	4.76	0.099	1.93×10^{-6}
C15orf57	Nucleus accumbens, basal ganglia	−4.76	−0.040	1.93×10^{-6}
ZNF35	Whole blood	−4.76	−0.127	1.93×10^{-6}
RBM6	Spinal cord cervical C1	−4.75	−0.043	2.07×10^{-6}
LIN28B-AS1	Putamen, basal ganglia	4.73	0.120	2.24×10^{-6}
AMT	Caudate, basal ganglia	−4.73	−0.031	2.29×10^{-6}
MAU2	Cerebellum	−4.72	−0.124	2.31×10^{-6}
TSKU	Cerebellum	4.71	0.044	2.48×10^{-6}
RPS26	Amygdala	−4.71	−0.015	2.53×10^{-6}
SNRPC	Amygdala	−4.69	−0.045	2.68×10^{-6}
ACADL	Frontal cortex, BA 9	−4.69	−0.208	2.71×10^{-6}
PACSIN3	Cortex	−4.69	−0.095	2.72×10^{-6}
C6orf106 (ILRUN)	Amygdala	4.68	0.089	2.80×10^{-6}
MPI	Putamen, basal ganglia	4.68	0.058	2.81×10^{-6}
PTK2	Caudate, basal ganglia	4.68	0.097	2.85×10^{-6}
NUP43	Cerebellum	−4.68	−0.033	2.93×10^{-6}

Gene Symbol	Tissue	z Score	Effect Size	p (Unadjusted)
KNDC1	Cerebellum	4.68	0.035	2.94×10^{-6}
NUP43	Cerebellar hemisphere	−4.67	−0.037	3.04×10^{-6}
RBM6	Hippocampus	−4.67	−0.071	3.08×10^{-6}
SNRPC	Cortex	−4.66	−0.036	3.15×10^{-6}
GINM1	Whole blood	4.66	0.054	3.17×10^{-6}
FASTKD5	Cortex	4.66	0.108	3.20×10^{-6}
UBOX5	Nucleus accumbens, basal ganglia	−4.65	−0.080	3.27×10^{-6}
AMT	Hippocampus	−4.65	−0.049	3.36×10^{-6}
HEXIM1	Frontal cortex, BA 9	−4.65	−0.129	3.37×10^{-6}
KCNH2	Cerebellar hemisphere	−4.64	−0.057	3.46×10^{-6}
NELFA	Cerebellum	4.64	0.097	3.47×10^{-6}
P4HTM	Cerebellar hemisphere	−4.64	−0.065	3.50×10^{-6}
ERICH2	Amygdala	−4.63	−0.072	3.74×10^{-6}
RNF123	Cerebellar hemisphere	4.60	0.055	4.30×10^{-6}
LATS1	Cerebellum	−4.59	−0.067	4.51×10^{-6}
RNF123	Amygdala	4.58	0.106	4.65×10^{-6}
DCAKD	Frontal cortex, BA 9	−4.58	−0.052	4.68×10^{-6}
NUDT18	Amygdala	−4.58	−0.186	4.69×10^{-6}
DCAKD	Whole blood	−4.58	−0.044	4.75×10^{-6}
RBM6	Cerebellum	−4.57	−0.022	4.80×10^{-6}
C6orf106 (ILRUN)	Cerebellar hemisphere	4.57	0.115	4.85×10^{-6}
RNF123	Anterior cingulate cortex, BA 24	4.57	0.102	4.87×10^{-6}
AC007405.6	Caudate, basal ganglia	−4.57	−0.080	4.93×10^{-6}
NUDT18	Nucleus accumbens, basal ganglia	−4.57	−0.033	4.98×10^{-6}
PPP6C	Anterior cingulate cortex, BA 24	4.56	0.109	5.04×10^{-6}
LLGL1	Anterior cingulate cortex, BA 24	−4.56	−0.222	5.07×10^{-6}
NUP43	Whole blood	4.56	0.043	5.19×10^{-6}
C15orf57	Cerebellum	−4.55	−0.028	5.42×10^{-6}

Gene Symbol	Tissue	*z* Score	Effect Size	*p* (Unadjusted)
RP11–147L13.11	Spinal cord cervical C1	−4.46	−0.146	8.16×10^{-6}
RNF123	Hypothalamus	4.46	0.106	8.30×10^{-6}
MST1R	Nucleus accumbens, basal ganglia	4.46	0.041	8.34×10^{-6}
LINC01671	Nucleus accumbens, basal ganglia	−4.45	−0.090	8.42×10^{-6}
CYB561D2	Cortex	−4.45	−0.172	8.44×10^{-6}
S100A1	Cortex	4.45	0.163	8.58×10^{-6}
RBM6	Hypothalamus	−4.44	−0.043	8.96×10^{-6}
RBM6	Substantia nigra	−4.41	−0.035	1.01×10^{-5}
DNAH11	Putamen, basal ganglia	4.41	0.045	1.03×10^{-5}
C15orf57	Hypothalamus	−4.40	−0.032	1.06×10^{-5}
ZNF502	Frontal cortex, BA 9	−4.40	−0.041	1.10×10^{-5}
COX11	Anterior cingulate cortex, BA 24	−4.39	−0.049	1.11×10^{-5}
NMT1	Hippocampus	4.39	0.085	1.13×10^{-5}
BAK1	Hippocampus	4.39	0.070	1.15×10^{-5}
SHMT1	Hypothalamus	4.38	0.044	1.18×10^{-5}
COX11	Amygdala	−4.37	−0.059	1.22×10^{-5}
COX11	Hippocampus	−4.37	−0.069	1.27×10^{-5}
RP11–147L13.11	Anterior cingulate cortex, BA 24	−4.36	−0.102	1.30×10^{-5}
GINM1	Substantia nigra	4.36	0.076	1.31×10^{-5}

All entries are tissue-wide significant. A positive sign indicates increased genetically regulated gene expression in these genes is associated with increased trait value (number of chronic pain sites).

BA, Brodmann area.

[a] *p* Values reaching experiment-wide significance.

Table 2.

CMap Compounds With Significant Connectivity Scores With MCP-GREX

Compound Name	Mechanism of Action	CS (Normalized)
PX-12	Thioredoxin inhibitor	−1.62
Physostigmine	Cholinesterase inhibitor, acetylcholinesterase inhibitor	−1.62
Ibrutinib	BTK inhibitor	−1.62
SR-2640	Leucotriene receptor antagonist	−1.62
Aspirin	Cyclooxygenase inhibitor	−1.63
Fenoterol	Adrenergic receptor agonist	−1.64
Nimesulide	Cyclooxygenase inhibitor	−1.64
Arcyriaflavin-a	CDK inhibitor	−1.65
BRD-A04553218	Histamine receptor antagonist	−1.67
Ponatinib	Bcr-abl inhibitor, FLT3 inhibitor, PDGFR inhibitor	−1.67
SB-525334	TGF-β receptor inhibitor	−1.67
Sorbinil	Aldose reductase inhibitor	−1.68
L-689560	Glutamate receptor antagonist	−1.68
Entecavir	DNA inhibitor, reverse transcriptase inhibitor	−1.68
Ursolic acid	11-beta-HSD1 inhibitor, acetylcholinesterase inhibitor, caspase inhibitor, HIV protease inhibitor, lipid peroxidase inhibitor, quorum sensing signaling modulator, stearyl sulfatase inhibitor, tyrosine phosphatase inhibitor, ATPase inhibitor, NF-κB inhibitor, STAT inhibitor	−1.68
Palmitoylethanolamide	Cannabinoid receptor agonist	−1.68
Luteolin	Glucosidase inhibitor	−1.69
Resiquimod	TLR agonist	−1.69
Tiabendazole	Angiogenesis inhibitor	−1.72
BRD-K18059238	Cyclooxygenase inhibitor, prostanoid receptor agonist	−1.74
KO-143	Breast cancer resistance protein inhibitor	−1.75
PD-153035	EGFR inhibitor	−1.76
Dutasteride	5-alpha reductase inhibitor	−1.85

CMap, Connectivity Map; CS, connectivity score; GREX, genetically regulated gene expression; MCP, multisite chronic pain.

Table 3.

Associations Between Mean Pain Score and MCP-GREX

Gene	Tissue	*z* Score	*p*FDR	*p*Raw
SDCCAG8	Brain: cerebellar hemisphere	−2.25	.049	.025
	Brain: putamen, basal ganglia	−2.65	.043	.008
	Whole blood	−2.45	.043	.014
UHRF1BP1	Brain: amygdala	−3.58	.002	.000
	Brain: anterior cingulate cortex, BA 24	−2.78	.011	.005
	Brain: caudate, basal ganglia	−2.72	.011	.006
	Brain: cerebellar hemisphere	−2.68	.011	.007
	Brain: cerebellum	−2.63	.011	.009
	Brain: cortex	−3.56	.002	.000
	Brain: frontal cortex, BA 9	−2.67	.011	.008
	Brain: hypothalamus	−2.71	.011	.007
	Brain: nucleus accumbens, basal ganglia	−2.90	.011	.004
	Brain: putamen, basal ganglia	−2.35	.020	.019
	Brain, spinal cord cervical C1	−3.03	.011	.002
	Whole blood	−2.52	.014	.012
DNMT3B	Brain: anterior cingulate cortex, BA 24	−2.91	.011	.004
ACADL	Brain: frontal cortex, BA 9	2.42	.031	.015
SNRPC	Brain: amygdala	2.95	.017	.003
	Brain: caudate, basal ganglia	2.13	.046	.033
	Brain: cerebellum	2.69	.017	.007
	Brain: cortex	2.67	.017	.008
	Brain: hippocampus	2.69	.017	.007
	Brain: nucleus accumbens, basal ganglia	2.50	.021	.012
	Brain: putamen, basal ganglia	2.48	.021	.013
	Whole blood	3.02	.017	.003
TARS2	Brain: anterior cingulate cortex, BA 24	3.26	.006	.001
	Brain: cerebellar hemisphere	2.39	.028	.017

Gene	Tissue	*z* Score	*p*FDR	*p*Raw
	Brain: cerebellum	2.98	.007	.003
CEP170	Whole blood	−2.52	.023	.012
HEXIM1	Brain: cortex	2.60	.028	.009
ILRUN	Brain: hippocampus	−3.07	.024	.002
MRPS21	Brain: caudate, basal ganglia	2.48	.025	.013
	Brain: cerebellum	−3.15	.015	.002
	Brain: cortex	−2.45	.025	.014
	Brain: frontal cortex, BA 9	−2.53	.025	.011
	Brain: hypothalamus	−2.37	.027	.018
	Brain: nucleus accumbens, basal ganglia	2.71	.025	.007

BA, Brodmann area; FDR, false discovery rate; GREX, genetically regulated gene expression; MCP, multisite chronic pain.

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Table 4.

Significant GREX-Phecode Associations

Gene	Phecode Description	Tissue	Full Analysis			Correcting for Pain Scores		
			z Score	p_{FDR}	p_{Raw}	z Score	p_{FDR}	p_{Raw}
DCAKD	Cardiac dysrhythmias	Caudate, basal ganglia	−4.98	.0084	6.18×10^{-7}	−5.52	.0046	3.47×10^{-8}
ECM1	Dysmetabolic syndrome X	Cerebellar hemisphere	4.58	.0063	6.39×10^{-7}	–	–	–
		Cerebellum	−4.99	.0228	4.61×10^{-6}	–	–	–
		Nucleus accumbens, basal ganglia	5.33	.026	7.89×10^{-6}	–	–	–
ERICH2	Disc disorders/dorsopathies	Amygdala	4.7	.0312	8.4×10^{-6}	−4.42	.033	9.83×10^{-6}
ILRUN (C6orf106)	Primary thrombocytopenia	Amygdala	−4.47	.0176	1.98×10^{-6}	–	–	–
		Hypothalamus	4.81	.0176	2.59×10^{-6}	–	–	–
		Nucleus accumbens, basal ganglia	4.46	.024	5.3×10^{-6}	–	–	–
		Cortex	−4.45	.0415	1.22×10^{-5}	–	–	–
MON1B	Anemias	Spinal cord cervical C1	−4.58	.014	1.14×10^{-6}	–	–	–
		Amygdala	4.21	.0293	4.74×10^{-6}	–	–	–
PACSIN3	Bullous dermatoses	Nucleus accumbens, basal ganglia	4.87	.0076	1.54×10^{-6}	–	–	–
RAD51	Disturbances of sulfur-bearing amino acid metabolism	Substantia nigra	4.76	.0307	1.24×10^{-5}	–	–	–
SCAI	Inflammatory and toxic neuropathy	Cortex	4.55	.0412	8.34×10^{-6}	–	–	–
SLC38A3	Joint/ligament sprain	Caudate, basal ganglia	4.37	.0002	9.62×10^{-8}	6.00	4.34×10^{-06}	1.92×10^{-9}
	Neurological disorders	Caudate, basal ganglia	4.37	.0309	2.5×10^{-5}	–	–	–
ZNF197	Hand/finger injuries and lacerations	Substantia nigra	–	–	–	4.45	.048	8.45×10^{-6}
ENSG00000278730 (Novel Transcript, *lncRNA*, a.k.a. *RP11–147L13.11*)	Spondylosis with myelopathy	Anterior cingulate cortex, BA 24	–	–	–	4.93	.0046	8.21×10^{-7}
		Cerebellum	–	–	–	4.59	.017	4.41×10^{-6}
		Cortex	–	–	–	5.05	.0046	4.46×10^{-7}
		Hypothalamus	–	–	–	4.37	.035	1.25×10^{-5}

FDR correction carried out within gene; *z* score presents PheWAS *z* score value; tissue represents GREX tissue; p_{FDR} presents GREX-phecode phenome-wide association study *p* value (FDR corrected); and p_{Raw} presents uncorrected *p* value.

a.k.a., also known as; FDR, false discovery rate; GREX, genetically regulated gene expression; lncRNA, long noncoding RNA.

KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Antibody				
Bacterial or Viral Strain				
Biological Sample				
Cell Line				
Chemical Compound or Drug				
Commercial Assay Or Kit				
Deposited Data; Public Database	GTEx	https://doi.org/10.1038/ng.2653		https://gtexportal.org/home/
Deposited Data; Public Database	CMap	https://doi.org/10.1016/j.cell.2017.10.049		https://www.broadinstitute.org/connectivity-map-cmap
Deposited Data; Public Database	Phewas Catalog	https://doi.org/10.2196/14325		https://phewascatalog.org/
Deposited Data; Public Database	Multisite Chronic Pain GWAS summary statistics	https://doi.org/10.1371/journal.pgen.1008164		https://researchdata.gla.ac.uk/822/
Genetic Reagent				
Organism/Strain				
Peptide, Recombinant Protein				
Recombinant DNA				
Sequence-Based Reagent				
Software; Algorithm	S-PrediXcan	https://doi.org/10.1038/s41467–018-03621–1		
Software; Algorithm	FUSION	https://doi.org/10.1038/ng.3506		http://gusevlab.org/projects/fusion/
Software; Algorithm	PheWAS	https://doi.org/10.1093/bioinformatics/btu197		https://github.com/PheWAS/PheWAS
Software; Algorithm	FUMA	https://doi.org/10.1038/s41467–017-01261–5		https://fuma.ctglab.nl/
Transfected Construct				
Other				