Identification and characterization of genetic risk shared across 24 chronic pain conditions in the UK Biobank.

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Abstract

Chronic pain is attributable to both local and systemic pathology. To investigate the latter, we focused on genetic risk shared among 24 chronic pain conditions in the UK Biobank. We conducted genome-wide association studies (GWAS) on all conditions and estimated genetic correlations among them, using these to model a factor structure in Genomic SEM. This revealed a general factor explaining most of the shared genetic variance in all conditions and an additional musculoskeletal pain-selective factor. Network analyses revealed a large cluster of highly genetically inter-connected conditions, with arthropathic, back, and neck pain showing the highest centrality. Functional annotation (FUMA) showed organogenesis, metabolism, transcription, and DNA repair as associated pathways, with enrichment for associated genes exclusively in brain tissues. Cross-reference with previous GWAS showed genetic overlap with cognition, mood, and brain structure. In sum, our results identify common genetic risks and suggest neurobiological and psychosocial mechanisms of vulnerability to chronic pain.

1. Introduction

Chronic pain is a well-documented individual and societal burden, with large costs in suffering [108] as well as cognitive [1], social [26, 46], and economic well-being [97, 77]. These costs are driven by an incomplete understanding of pain chronification mechanisms, which impedes effective prevention and treatment. Chronic pain is often conceptualized as a symptom of a specific, localized pathology. With few exceptions [131], pain conditions are classified based on suspected etiology and/or affected anatomic sites. However, this approach has had limited success. As evidenced by reviews showing that pain treatments fail to reduce pain (e.g. NSAIDs for low back pain [128] and gabapentinoids for neuropathic pain [31]), there is an urgent need for a fundamentally different approach.

A re-conceptualization of chronic pain as a primary disease has been evolving in the pain scholarship community for over 2 decades [93, 111, 101] and recently culminated in the introduction of chronic primary pain disease codes in version 11 of the International Classification of Diseases (ICD-11) [119]. Nevertheless, clinical support for pain sufferers continues to be divided among medical disciplines based on symptoms: back pain is treated by orthopedists, irritable bowel syndrome by gastroenterologists, and so on.

Recent work in the epidemiology of mental health has revealed extensive patterns of co-occurrence across disorders, leading to identification of common factors underlying multiple conditions [88, 53], including the ‘p factor’ [15], which captures general psychopathology. Similar approaches have emerged in pain research, informed by studies of the co-occurrence of pain conditions in large samples [105, 113, 66, 72, 3] and the recognition that different forms of pain are related to similar alterations in the nervous system [65, 76, 54, 63]. Some studies have examined genetic correlations among pain syndromes [129] and genetic risks of having pain in more than 1
of 7 locations on the body [56, 59]. However, a systematic assessment of shared susceptibility across a broad spectrum of pain conditions is lacking, and common factors underlying general pain susceptibility have not yet been characterized.

Most chronic pain conditions are the result of a complex interaction between genetic, environmental, lifestyle, and experiential contributors [80]. However, assessing the genetic component gives insight into commonalities across conditions that can be linked to measurable and potentially targetable biological pathways. In addition, genetic predispositions can be measured cost-effectively using genome-wide association studies (GWASs) and used to characterize and predict risk for chronic pain (e.g., after surgery), predict treatment response, and identify new targets.

We applied this approach here, using the U.K. Biobank (UKBB) [14] and recently developed Genomic Structural Equation Modeling (SEM) software [43]. Genomic SEM enabled us to model the underlying factor structure while accounting for the complex correlations within genetic segments and run a GWAS on the extracted factors. Genomic SEM also produces a Q heterogeneity statistic (QSNP) that indexes single nucleotide polymorphisms (SNPs) unlikely to operate through the genomic factors, such as variants that have a disproportionately strong effect on 1 condition or directionally opposing effects on a subset of traits. Collectively, this allowed for distilling SNPs associated with general pain etiology from trait-specific, genetic pathways. Lastly, we performed functional characterization of common-factor SNPs in FUMA [133].

The questions we aimed to answer in this study were: (1) Is there a general, condition-agnostic genetic risk factor? (2) Are there additional genetic factors underlying subsets of pain conditions? (3) Does the genetic structure correspond to organization of pain by symptom location or hypothesized etiology? (4) What biological pathways and tissues are associated with these genetic factors? Figure 1 provides a graphical overview of the study.

2. Methods

2.1 Individual pain conditions

2.1.1 Cohort

Analyses were conducted in the UKBB cohort of participants aged 40-69, who were recruited between 2006 and 2010 (UKBB data-request application 16651). The current standard in genetics is to limit analyses to samples of homogeneous ancestral background to avoid introducing confounds from ethnically mixed samples [115]. We analyzed data from White Europeans (UKBB data field 22006), given that no other group had a sufficient sample size (see Supplementary Table S2 for descriptive statistics of South Asians, the next highest sample size), though analyses in different ancestral groups will be a high priority when more data become available. Individuals who withdrew from the study by August 2020 were removed. A maximum of
435,971 people were included in the analysis, with sample size varying by phenotype, Table 1.

2.1.2 Phenotypes
The selected phenotypes were either chronic pain conditions, such as migraine or back pain lasting longer than 3 months, or conditions with persistent pain as a prevalent symptom, such as osteoarthritis. An initial list of 92 phenotypes was drawn from 4 UKBB categories: Medical conditions (100074), Health outcomes (713), Self-reported medical conditions (1003), Health and medical history (100036), and First occurrences (1712), downloaded in May 2020. These conditions were recoded into binary phenotypes for analysis (Supplementary Table S1) and subsequently pruned to remove conditions in the following categories: 1. heterogeneous disorders or groupings thereof, such as “Other diabetic polyneuropathies”; 2. branching traits (answers to questions dependent on endorsement of a previous question, with the exception of DF6159: “Pain type(s) experienced in last month”, which was included); 3. disorders with case count < 500; 4. disorders that were not sufficiently related to genetics, with SNP heritability less than or equal to 2 standard errors above zero $h^2_{SNP} - 2*SE \leq 0$, as described below. This pruning left 33 conditions (Table 1), further reduced to 24 during the factor analysis step (see section “Factor analysis and Genomic SEM” below).

2.1.3 GWAS
We used genotypes (EGAD00010001474 downloaded using ukbgene imp), imputed from the UK10K reference panel [50]. SNP quality control filters consisted of heterozygosity rate ($|F_{het}| > 0.2$) (determined using the --het option in Plink), final call rate > 0.95 (--geno option in Plink), Hardy-Weinberg equilibrium (1.0x10^{-8}), and minor allele frequency > 0.01. The sample quality control filter removed mismatches between reported and genotyped sex (Category 100313). We ran GWAS analyses in Regenie [78], using Firth approximation-corrected logistic regression [32]. Briefly, the analysis was run in 2 steps: 1. a model-fitting step, in which genotyped SNPs were split into chunks and 2 levels of ridge regression were run to obtain a per-chromosome genetic predictor of the phenotype; 2. a test of association for all available (imputed) SNPs, also split into chunks, with covariates (described below) regressed out and predictors from the first step removed from phenotypes, using a leave-one-chromosome-out (LOCO) scheme. We used 339,444 genotyped SNPs in 100-SNP chunks in the first step and 11,359,143 imputed SNPs in 200-SNP chunks in the second step, with age, sex, and 10 PCs from genetic PCA (principal component analysis) as covariates [99].
2.2 Factor analysis and structural equation model

2.2.1 Heritability and genetic correlations

Using the Genomic SEM R package, summary association statistics from GWAS were converted to z-scores with the `munge` function, and genetic covariances [12] and SNP heritabilities [142] were estimated with the `ldsc` function [13], modified by the authors of Genomic SEM to include a sampling matrix that corrects for sample overlap [43]. We estimated SNP heritability on a continuous liability scale [69] for each pain condition. Genetic covariances were converted to correlations using the `cov2cor` function in R and ordered using hierarchical clustering, which produced a matrix of genetic correlations across pairs of pain conditions (Figure 2A).

2.2.2 Factor analysis and Genomic SEM

For the factor analytic step, we pursued 3 primary genomic SEM models: one using a confirmatory factor analysis (CFA) informed by an exploratory factor analysis (EFA), and 2 using hypothesis-based CFA. EFA-CFA, is a partially data-driven approach that captures observed groupings in the data, while still permitting structure and inferences based on theory. This approach aligned with our main goal: to test for common factors without rigidly specifying the groupings *a priori*. The 2 hypothesis-based CFAs were used to test whether the observed correlations were well described by pre-specified anatomic and etiological groupings. The anatomic model included the general factor (on which all disorders loaded) and 6 specific factors that group conditions based on body site: Cranial, Gastrointestinal, Joint, Leg/Foot, Pelvic, and Torso. The etiologic model included the general factor and a specific factor for inflammatory conditions, which was the only putative etiology with a substantial number of representative conditions. We discussed a variety of other groupings, but as biological etiology is often unknown – a central problem in pain research – we did not reach clear consensus on additional etiological factors.

For all 3 approaches, the goal was to test a bifactor model, which consisted of a general factor with loadings for all conditions and specific factors that were orthogonal to the general factor and had loadings for specific subsets of conditions. This type of model aligned well with our aim to test whether a common genetic factor underlay all tested conditions, while still allowing for additional shared variance for certain groups of conditions, such as joint-related pain. Similar approaches have been used to model other multidimensional constructs, including personality [18] and psychopathology [9]. EFA as a precursor to CFA has been evaluated in [38] and recently used in [19, 64, 24].

For the EFA portion of the EFA-CFA approach, a scree plot (Supplementary Figure S3) suggested 3 factors. We specified oblique rotation to estimate expected factor covariances. The resulting factor loadings were used to specify a correlated-factors CFA model, first, for testing in Genomic SEM. A condition loaded on a factor in the CFA model if it had positive standardized EFA loadings > 0.2, with the highest loading dictating the factor onto which
the indicator would load in CFA. If an indicator had 2 loadings within 0.1, both were included in the CFA model. We further specified residual covariances for conditions that were very similar conceptually and had definitional overlap (knee arthrosis and knee pain, hip arthrosis and hip pain, general chest pain/discomfort and chest pain during physical activity, headache and migraine). This obviated one of the 3 factors (a headache-migraine factor), leaving a 2-factor model. Polymyalgia rheumatica and ulcerative colitis were excluded at this step due to lack of positive loadings > 0.2 onto any factor in the EFA model. This correlated factors CFA served as the interim step between EFA and bifactor CFA, in which we specified all conditions to load onto one general factor and the prior model’s correlated factors as uncorrelated additional specific factors.

As the EFA-CFA model is more flexible, we tested for overfitting [33] by repeating the analysis originally conducted on the whole dataset, using a split-genome approach [42, 34]. In step 1, we applied the EFA-CFA procedure described above in odd autosomes (1,3,...,21), and in step 2, we assessed the fit of the CFA from step 1 in even autosomes (2,4,...,22). This validation step led to a further exclusion of 7 conditions (arthropathy of carpometacarpal joint, diabetic neuropathy, Crohn’s disease, fibromyalgia, prostatitis, seropositive rheumatoid arthritis, and urinary colitis), whose heritability estimates were not significantly above 0 in at least one holdout set, Table 2. This does not imply that these conditions are not heritable or are genetically unrelated to the common factors, as some conditions may be selectively related to genes on odd or even autosomes (limiting replicability here). However, the exclusions helped ensure that the conditions included in the factor model had broad polygenic representation across odd and even autosomes independently. The exclusion left 24 pain conditions for the validation step, which we also used in the main analysis and in the 2 hypothesis-driven approaches for consistency and comparability.

Models were evaluated using CFI (comparative fit index), which compares the model fit to one with entirely independent variables, and SRMR (standardized root mean residual), a measure of variance unexplained by the model [49]. A well-fitting model should generally have a CFI≥ .95 and an SRMR≤ .08 [49]. The models were additionally compared using AIC (Akaike information criterion), a goodness-of-fit index favoring more parsimonious models [60].

2.2.3 Factor GWAS
To estimate the genetic effects of genome-wide variants on the EFA-CFA model factors, we ran a factor GWAS in Genomic SEM (userGWAS function). SNP effects on the common factor and one specific factor were calculated by adding the genotypic score for each SNP to the genetic correlation matrix output by ldsc for 24 conditions, estimating a new matrix of correlations, and fitting the model with additional paths from the SNP to each of the factors (Supplementary Figure S6).
To conduct a heterogeneity Q test [51, 43], we specified a less restrictive model, in which for every SNP, path coefficients were estimated from the SNP to the individual phenotypes (independent pathways model). We formally assessed the difference between the 2 models – common and independent pathways – using the chi-square difference test. If significant, the SNP’s effects on the individual pain conditions were interpreted to be inadequately modelled by the factor approach. Because this test was calculated for every imputed SNP, we used the standard whole-genome correction for multiple testing, \( p < 5 \times 10^{-8} \), as the threshold for Q significance. The resulting QSNPs were considered to be associated with pain conditions independent of common factors.

Additionally, we tested for SNPs in linkage disequilibrium (LD), i.e. correlated with QSNPs, using Plink, version 1.9, --indep-pairwise 500 50 0.6, corresponding to 500 kilobases, 50 SNPs, 0.6 \( r^2 \) threshold. We removed QSNPs, and SNPs in LD with them, which were liable to capture the contribution of QSNPs, before annotating the GWAS results.

2.3 Network analysis
While CFA has many strengths in permitting model comparison, some groups have emphasized that relationships among clinical conditions can have a complex causal structure that can be characterized in terms of networks of interacting variables [127]. We make no strong claims about the underlying causal structure and complement the factor-analytic models with a network-based approach to characterize genetic relationships among conditions. Network characterization and visualization was done in igraph in R [22]. Genetic correlations of the final 24 pain conditions were filtered for positive significant correlations, using a threshold of 0.01 false discovery rate (FDR)-corrected, calculated with fdrtool in R. We calculated 2 graph-theoretic properties for each pain condition: (1) strength, calculated as the number of edges (genetic correlations with other pain conditions) weighted by their magnitude [7]; and (2) betweenness-centrality, the number of shortest paths between pairs of pain conditions that go through the condition in question) [11]. Strength identifies ‘hub’ conditions that are robustly genetically related to many other conditions and may thus be prominent indicators of multi-disorder susceptibility. Betweenness-centrality identifies ‘connector hubs’, conditions that are genetically related to multiple other conditions that are themselves less interrelated. ‘Connector hubs’ are thus key indicators of shared genetic vulnerability. These measures may themselves be correlated, and if so, combined into an overall index, as we did here (described below). At the network level, we estimated the largest clique, complete subgraph of intercorrelated pain conditions [29], which identifies a group of genetically linked conditions that may together serve as indicators of multi-disorder susceptibility.
2.4 Summary score
To summarize the evidence on which conditions were the most consistent key indicators of multi-disorder vulnerability, we combined results from Genomic SEM and network analysis, obtaining an overall measure of interconnectedness. We derived a summary score for each pain condition using F1 loadings from EFA-CFA, network strength, and betweenness centrality, which are intercorrelated: $r = .935$ for F1 and strength, $r = .614$ for F1 and betweenness, and $r = .693$ for strength and betweenness. We calculated a geometric mean of these 3 measures, after vector-normalizing them using the \texttt{norm} function in R.

2.5 GWAS annotation
To functionally characterize the genetic contributors to both individual phenotypes and the 2 factors, we submitted all GWAS results to FUMA for prioritization and annotation, using several integrated databases [133]. These analyses consisted of: 1. prioritizing SNPs based on their effect sizes and independence from each other; 2. mapping significant SNPs to genes as described below; 3. conducting a genome-wide gene-based association analysis with FUMA-implemented MAGMA (only used for FUMA’s gene analysis and gene property analyses; 4. gene set analysis for enrichment in known biological pathways; and 5. gene property analysis (testing for preferential expression of associated genes with 53 Gene-Tissue Expression repository (GTEx) tissues). We used standard significance thresholds and parameters, including $p < 5\times 10^{-8}$ for lead SNPs (independent at $r^2 < 0.1$); $p < 0.05$ for all other SNPs; $r^2$ threshold for independent significant SNPs used for further annotations, including gene mapping: 0.6; reference panel population = UKB release 2b 10K European; minimum minor allele frequency = 0.01; maximum distance between LD blocks to merge into a locus = 250 kilobases. The $r^2$ threshold represents a squared pairwise correlation for SNP variant alleles. The sample sizes for the 2 factors (common and musculoskeletal) identified in the final EFA-CFA model were 422,752 and 468,929, respectively, calculated using the method described in [74]. Variants from the reference panel that were in LD with GWAS lead SNPs were included to increase the chance of capturing causal variants.

Mappings of independent significant (as defined in FUMA, $p < 5\times 10^{-8}$ and $r^2 < 0.6$) SNPs onto genes was based on (1) positional distance (within 10 kilobases of gene start and stop coordinates); (2) statistical associations with transcription levels (expression quantitative trait locus, eQTL); and (3) chromatin interaction mapping, physical interactions with gene chromatin states (indicative of transcriptional accessibility). We included protein-coding genes and excluded the major histocompatibility (MHC) region from annotation. MAGMA analysis for gene-based associations [23] was conducted with SNP assignment within windows of 10 kilobases of gene start and stop coordinates, and GTEx, version 8, [71] was used for gene expression analysis in 53 tissues. FUMA parameters are summarized in Supplementary Table S3.
3. Results
The work reported here is part of a project preregistered on Open Science Foundation, OSF (Identifying and Characterizing Genetic Susceptibility and Its Overlap with Psychosocial Traits, https://osf.io/4p5e3).

3.1 Univariate pain condition GWAS curation and annotation
We considered 24 pain phenotypes in the UK Biobank that (a) were indicative of chronic pain conditions, (b) had sufficient case counts (> 500), and (c) were sufficiently heritable (see Methods; Table 1 and Supplementary Table S1). The sample size available for case assessment varied by condition and ranged from 63,982 (chest pain during physical activity) to 435,971 (several conditions). Prevalence ranged from 0.002 (772 cases, diabetic neuropathy) to 0.473 (119,216 cases, back pain). SNP heritability (variance in the phenotype explained by variance in the genotype) ranged from 0.03 (SE 0.008) for cystitis to 0.20 (SE 0.029) for gout. Summaries of results from univariate GWAS are reported in Table 1 (SNP heritabilities), in Supplementary Figures S1 and S2 for Manhattan and quantile-quantile (QQ)-plots, and in Supplementary Table S14 (numbers of significant SNPs and genes).

3.2 Pain condition genetic correlations
Pairwise genetic correlations for the 24 pain conditions, Figure 2A, showed a large cluster of interconnected vertices. This main cluster included etiologically and anatomically diverse conditions, such as back pain, oesophagitis, IBS, and carpal tunnel, suggesting shared genetic susceptibility among these disparate syndromes. Headache and migraine formed a tight mini-cluster (top left), and cystitis, hip arthrosis, enthesopathies of the lower limb and gout showed weaker correlations, suggesting more specific genetic risks for each of these 4 conditions.

3.3 Structural equation modeling
Using 3 approaches – hypothesis-driven anatomic (1) and etiologic (2), and largely data-driven exploratory-then-confirmatory (3) factor analyses (EFA-CFA) – we fit a bifactor model to test the loadings of all conditions onto a general factor, with differences in specific factor groupings in each approach. The anatomic model based on body site (Supplementary Figure S4, CFI= .875 and SRMR = .087) and the etiologic model, based on a grouping of inflammatory disorders (Supplementary Figure S5, CFI= .905, SRMR= .095) both had suboptimal fit (CFI≤ 0.95 and SRMR≥ .08), see Methods. The EFA-CFA model, shown in Figure 2C, produced an adequate overall fit (CFI= 0.956, SRMR = 0.075). All pain conditions loaded positively and significantly onto the general factor (F1). The specific factor (F2) had substantial positive loadings for arthropathies (which included osteoarthritis), carpal tunnel, enthesopathies of lower limb, other enthesopathies, hip arthrosis, hip pain, knee arthrosis, knee pain, leg pain, pain in joint, and rheumatoid arthritis.
Given the pronounced musculoskeletal component among these indicators, we interpreted F2 as a musculoskeletal factor. This model was superior (AIC=4849.164) to both the anatomic (AIC=13184.43) and the etiologic (AIC=10024.93) models (see Methods). In addition, the latter models had non-significant loadings on their specific factors (Leg/Foot, Pelvic, and Torso for the anatomic, Supplementary Figure S4, and Inflammatory for the etiologic, Supplementary Figure S5, suggesting that shared variance for those indicators was mainly explained by the general factor (details in Supplementary Note). We validated this model by training on odd (CFI= .884 and SRMR= .123) and testing on even (CFI= 0.903 and SRMR= .129) autosomes (details in Supplementary Note). These comparable metrics in the training, validation, and whole genome datasets suggested that using EFA and CFA on the same dataset did not result in substantial overfitting.

3.4 Network analysis and central conditions
Network analysis provided additional evidence for substantial genetic overlap across pain conditions with a different theoretical model (Figure 2B). There was a complete subgraph of 19 interconnected conditions, highlighted in yellow: arthropathies, back pain, neck/shoulder pain, hip pain, knee pain, leg pain, chest pain (baseline and during physical activity), rheumatoid arthritis, knee arthropathy, joint pain, carpal tunnel, enthesopathies, widespread pain, gastritis, oesophagitis, stomach pain, headache, and IBS. Consistent with the CFA model, these conditions affect diverse body sites and span inflammatory and non-inflammatory as well as musculoskeletal and non-musculoskeletal forms of pain. Gout, hip arthropathy, enthesopathies of the lower limb, cystitis, and migraine lay outside the large cluster, but they still had more than 10 connections each. Overall, the network revealed a large core of pain syndromes with shared genetic vulnerability.

Some conditions were particularly central in the network, in several ways. Arthropathies, back, and neck/shoulder pain had the highest betweenness centrality, indicating that genetic associations between many conditions shared genetic vulnerability with at least 1 of these 3.

The summary score derived from F1, network node strength, and betweenness centrality, Figure 2d, reflected the highest degree of genetic overlap with other conditions. Once again, the top highest scorers were neck/shoulder pain, back pain, and arthropathies.

3.5 Factor GWAS and annotation
After running factor GWASs, we excluded QSNPs, which showed evidence of effects specific to certain pain conditions (not through the common factors), and we conducted functional annotation of the GWAS output for each of these factors.

3.5.1 General Factor (F1)
The F1 GWAS yielded 33 genome-wide independent significant SNPs, Supplementary Table S4, Figure 3. FUMA mapped these to a total of 241
genes, using at least 1 of 3 methods (positional, eQTL, and chromatin interactions, see Methods), Supplementary Table S5: 26 by positional, 52 by eQTL, and 57 by chromatin interaction mappings. All 3 annotations were identified for 25 genes, highlighted in green in Supplementary Table S5.

We used REVIGO [112] to assign, prune, and summarize biological pathways to the 25 genes with overlapping mappings (details in Supplementary Note). The resulting pathways represented by these genes covered a broad range of biological processes, including organ development (gut, heart, muscle and brain), metabolism, catabolism, signaling, immunity, neuronal development, transcription, and DNA repair (Supplementary Table S6).

Additionally, FUMA gene set annotation showed a suggestive significant enrichment ($p = 1.64 \times 10^{-5}$, Bonferroni-corrected $p = .253$) for mechanosensory behavior, several neuronal development processes, and several biosynthesis and calcium channel regulation processes, Supplementary Table S7.

MAGMA-based tissue expression analysis, as implemented in FUMA, tested for association between highly expressed genes in 53 GTEx tissues and GWAS effect sizes for the same genes (details in Supplementary Note). Associations were significant only in brain tissues: cortical regions (the cerebral cortex, dorsomedial prefrontal cortex BA9, and anterior cingulate cortex BA24), nucleus accumbens, basal ganglia, amygdala, hippocampus, hypothalamus, and cerebellum, Figure 3D.

Additionally, we used FUMA to cross-reference SNPs and genes with other GWAS reports. Of note was the overlap in SNPs (Supplementary Table S8), and significant enrichment for genes reported to be associated with chronic pain conditions (back pain, Crohn’s disease, IBS, and multi-site chronic pain), brain structural traits, anthropometric traits, cognition and intelligence-related phenotypes, sleep-related phenotypes, neuroticism, and mood phenotypes (Supplementary Figure S9). Genetic overlap with non-pain conditions was suggestive of the complexity of factors contributing to chronic pain. Furthermore, DCC, the top gene associated with F1, was also the top gene reported in a recent study of chronic overlapping pain conditions (COPCs), which used pain for more than 3 months in different body sites from the UKBB (head, face, neck/shoulder, back, stomach, hip, knee, all over the body) [59]. Of the 241 genes mapped to independent significant SNPs from the F1 GWAS, FKBPS was the only one previously targeted in a candidate gene study (as opposed to GWAS) for posttraumatic musculoskeletal pain [144, 10].

### 3.5.2 Musculoskeletal Factor (F2)

The F2 GWAS yielded 7 genome-wide significant lead SNPs, Supplementary Table S9. Positional mapping yielded 5 unique genes; eQTL mapping yielded 18 genes; and chromatin interaction mapping yielded 19 genes, with 5 genes mapped using all 3 methods, green: DPYD, MAPK6, GLIS3, COL27A1, and SLC4A2, Supplementary Table S10.
REVIGO pathway analysis showed associations with genes involved in bone and neuronal development, cell cycle, transcription regulation and signal transduction, Supplementary Table S11. Gene set annotation showed a Bonferroni-corrected significant enrichment for regulation of RNA biosynthetic process and nominally significant ($p < 0.05$) enrichment for several other regulatory processes, chromatin organization, cell migration involved in heart development, and DNA damage response, Supplementary Table S12. MAGMA tissue expression analysis found no significant association between gene expression and GWAS effect sizes for 53 tissues, Supplementary Figure S7D.

Cross-referencing with other GWAS reports identified previously reported SNP associations with anthropometric traits (height, hip circumference, offspring birth weight), hip or knee osteoarthritis, sleep-related phenotypes, and type 2 diabetes (Supplementary Table S13), and significant overlap with genes reported to be associated with inflammatory skin disease, palmitic and stearic acid levels, (Supplementary Figure S9). None of the genes previously targeted in candidate gene studies for pain [144] mapped to independent significant SNPs for F2.

4. Discussion
The UKBB is a large and extensively phenotyped cohort, which recently added First Occurrences data (category 1712), giving researchers access to primary care and death register records to supplement self-reports and ICD-10 diagnoses, earlier available exclusively from hospital intake records. This growing trove of genotypic and phenotypic data has enabled us to examine a much larger number of pain conditions than reported in prior genetic studies of multi-site pain [58, 56, 59, 120]. Our work builds on earlier studies, which included smaller numbers of conditions, often selected a priori based on anatomic proximity or hypothesized etiology. Most of these have been conducted in twins. They include reports of genetic correlations of musculoskeletal pain in different body sites [136]; spinal pain syndromes [45]; chronic pain syndromes (chronic widespread musculoskeletal pain, chronic pelvic pain, migraine, and IBS), which estimated 66% heritability using a common pathway model [130]; low back pain with common widespread pain [73]; and TMD with migraine [98].

Several large-scale chronic pain GWAS, with strengths complementary to twin studies [36], have been published on pain in the past 3 years [114, 81, 35, 82, 84, 86]. These reports, which used earlier releases of the UKBB, include 3 on multi-site pain [56, 57, 59]. However, a significant caveat to earlier GWAS on multi-site pain as a single phenotype is the potential for gene variants that selectively act on one of the conditions included in the multi-site definition to be interpreted as cross-condition variants. The Genomic SEM approach has allowed us to extract genetic variance that is truly common to different conditions, rather than detecting associations with
an averaged phenotype. In other words, it enabled us to capture genetic risk for chronic pain, regardless of etiology or symptomatology.

Our results identified a single common genetic factor that explained substantial genotypic variance in pain conditions with different suspected etiologies and anatomic presentations, as evidenced by significant loadings onto this factor for all 24 conditions tested. This common factor implied shared genetic risk for a range of conditions, some as clinically distinct as migraine and cystitis, and pointed to their shared systemic pathophysiology. Additionally, a second factor explained some of the shared genetic variance across diverse musculoskeletal conditions: arthropathies, carpal tunnel, enthesopathies (general and lower limb), hip arthrosis, hip pain, knee arthrosis, knee pain, leg pain, and joint pain. This musculoskeletal factor was in line with the World Health Organization’s grouping of pain diseases of the musculoskeletal system, which groups conditions that affect joints, bones, muscles, the spine, and multiple body areas or systems [134]. The 2-factor model explained the pattern of genetic associations among disorders better than either the anatomic or etiologic grouping of known inflammatory disorders. The shared genetic burden was also apparent in network-based analyses, which complemented factor analyses by conceptualizing common risk in terms of multiple local causes instead of a few latent causes.

The existence of widespread shared genetic risk factors – and the existence of a general factor in particular – challenges the current clinical practice of grouping chronic pain conditions based on location of symptoms on the body or suspected etiology [30]. Evidence for central processes beyond local pathophysiology has been accumulating, including recent studies demonstrating that chronic pain is best conceptualized as a combination of biopsychosocial factors that may lead to a variety of pain conditions [21, 125, 75, 20, 124, 16]. Studies in rodents have identified neuroinflammation- and neuroplasticity-related changes in brain pathways that mediate persistent pain behavior in animal models of different pain modalities [143, 96, 91, 27, 6, 122, 52, 5, 37, 87]. Neuroimaging studies have identified common brain systems involved in musculoskeletal pain [79, 68, 17, 44, 67, 61, 90], IBS [106, 4], orofacial pain [2], neuropathic pain [95, 100, 139], and postsurgical pain [47]. These different lines of evidence have led to a new classification system for chronic pain in ICD-11.

The new system shifts pain category assignment from “perceived location”, “etiology”, or “primarily affected anatomical system” to a hierarchical approach, which assigns based on etiology first, then pathophysiology, then body site, and allows for “multiple parenting”, i.e. assignment of a diagnosis to multiple categories [118]. Furthermore, chronic primary pain was included in the ICD-11 as a diagnosis “agnostic with regard to etiology” [92]. These changes are important steps toward a more comprehensive characterization of chronic pain that considers the complex and multifaceted nature of its experience.

In service of this goal, our model suggests that, in addition to condition-specific genetic susceptibility, there is a genetically encoded
pathophysiology common to different chronic pain conditions. This supports the view of chronic pain as a disorder involving systemic pathology and of localized peripheral pain as a possible symptom of non-local vulnerabilities and central pathophysiology [137].

Beyond identifying shared genetic risk components, the functional annotation of these components offers insight into possible molecular mechanisms involved in their pathophysiology. Our study adds to existing evidence for the role of DCC, which is involved in axonal guidance [140], in chronic pain [114, 103, 59]. However, the presence of other statistically significantly associated genes and the myriad different pathways they tag suggests that focus exclusively on the top association - however tempting it may be to uphold this representative of the nervous system in a pain study - may be detrimental to obtaining a more comprehensive picture of pain susceptibility. Primary chronic pain, like many other complex traits, is very likely a highly polygenic trait [138]. Nor is the highest association statistic necessarily correlated with its relative importance (see this recent publication discussing negative selection as a mechanism for purging high-effect variants in critical genetic loci [94]). Therefore, our approach is to prioritize genes based on: 1. an a priori association p value cut-off to ensure statistical rigor; and 2. convergent lines of evidence for functional importance, i.e. overlap in mapping approaches. In the resulting set, we interpret our findings in their entirety, without deference to the top association.

Gene mapping of the common factor (F1) implicates a large number of genes. Gene set analysis highlights genes with regulatory function and likely pleiotropy, i.e., roles in other complex traits [132]. There is converging evidence for the involvement of the nervous system: gene expression data shows an enrichment exclusively for brain tissues, and FUMA gene set analysis implicates biological processes specific to the nervous system. Echoing a recent report of heritability enrichment for chronic overlapping pain conditions exclusive to the CNS [59], these findings provide a genetic line of evidence for the reported alterations in brain circuitry shared by chronic pain conditions [116, 5, 62, 52]. In addition to CNS activity, however, the pathways mapped in FUMA implicate a broad range of other functions, such as gut development, locomotion, and protein secretion, suggesting that susceptibility to chronic pain may involve other systemic biological changes. The overlap with genetic variants previously reported in GWAS for cognitive, structural, mood, and personality traits, regulation of inflammation and neuroplasticity, and psychiatric disorders underscores the highly multifaceted nature of pain as a biopsychosocial condition, while providing new clues about the key genes and systems involved [21, 125, 75, 20, 124, 16].

As might be expected, the genes associated with the specific musculoskeletal factor are fewer, and their pathways are less diverse. They implicate skeletal development, choline transport, signaling, and transcription machinery. Notably, they do not implicate the nervous system.
Overlap with previous GWAS results suggests involvement of variants affecting anthropometric traits, thus implicating body-structural mechanisms. Similar associations have been shown for musculoskeletal pain conditions before: genetic overlap in osteoarthritis with height and BMI [28], back pain [35] and multi-site musculoskeletal pain [120] with structural-anatomic genes.

4.1 Limitations
There are several notable limitations of this study. First, the precise biological and psychological traits that may underlie the common genetic pain factors remain to be elucidated in future studies. The annotated genetic profile of the general factor (F1) suggests a combination of systemic biological and psychological predispositions, including the tendency to evaluate somatic experience in a more negative way (genetic association overlap with traits such as neuroticism and moodiness). Prior studies of psychosocial [48], biological [107], as well as structural and functional brain [126, 63] correlates for pain should be extended to assess the specific roles of each of these contributors to general pain risk, as was recently done for chronic back pain [123].

The second limitation lies in the reliance of annotations obtained from FUMA on the information available in existing data repositories, which may be restricted by insufficient resolution or small sample sizes. Thus, although we did not find associations with inflammatory cytokines, a wealth of evidence links inflammation with multiple forms of chronic pain [110, 55, 40] and should be investigated further.

Third, the genetic scores of our common factors should be validated for association with chronic pain or intermediate phenotypes using either association analysis in an independent sample or cross-validation methods. This would require obtaining a polygenic score and is the aim of a follow-up study.

Fourth, given sample size limitations in the UKBB for non-European individuals, we were not able to test our model for generalizability across ancestral populations. On a related note, it would be of interest to examine the common factors for sex differences, given a larger sample.

By establishing genetic risk factors in a large sample, this study paves the way for more detailed assessments of pain prognosis and treatment response in targeted studies. For example, the ongoing Acute to Chronic Pain Signatures (A2CPS) study aims to establish risk factors for post-surgical pain from genetic, multi-omics, psychosocial, and neuroimaging measures in another large sample (3,000 patients; a2cps.org). Our factor scores could be tested as prognostic risk factors for chronic post-surgical pain, combined with psychosocial [104, 89] and quantitative sensory testing (QST) measures [30, 119, 109].
4.2 Conclusions
In summary, our findings support the hypothesis that there is a genetic susceptibility common to a broad range of diverse chronic pain conditions. The shared pathophysiology for the conditions examined here appears to lie partly in the CNS and partly scattered across many different systems and functional processes. Additionally, there is a body-wide, suggestively musculoskeletal system-specific shared genetic factor. These findings are consistent with emerging views that chronic pain is a disease in its own right [116, 92, 124], meaning that one systemic pathology underlies disparate types of pain. Our results help identify and characterize the genetic components of this pathology and suggest that brain prefrontal and affective/motivational circuits may play a key role, supporting converging evidence from animal [117, 54, 141, 41, 52] and human [8, 91, 62, 70] studies. Together, this evidence underscores the importance of new ways to diagnose and treat chronic pain, whereby a given chronic pain condition is not considered as only a symptom of a localized somatic disease but is seen as a manifestation of an underlying shared pathology with concurrent risk for other pain conditions and previously unexplored centralized treatment targets.

Acknowledgements
This work is supported by R01DA046064, "Brain and Genetic Predictors of Individual Differences in Pain and Placebo Analgesia"; PIs are Naomi Friedman and Tor Wager. The authors declare no conflict of interest.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Full name</th>
<th>Cases</th>
<th>Controls</th>
<th>Prevalence</th>
<th>$h_{SNP}^2\text{(SE)}$</th>
<th>Reported $h_{SNP}^2$</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
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<td>*aCMC</td>
<td>Arthropathy of carpometacarpal joint</td>
<td>1837</td>
<td>201439</td>
<td>0.009</td>
<td>0.09 (0.036)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>arth</td>
<td>Arthropathies (non-specific, incl. osteoarthritis)</td>
<td>80737</td>
<td>157458</td>
<td>0.339</td>
<td>0.09 (0.005)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
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<td>Back pain</td>
<td>119216</td>
<td>132641</td>
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<td>0.11/0.12/0.076</td>
<td>[83, 35, 114]</td>
</tr>
<tr>
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<td>Chest pain/discomfort</td>
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<td>0.08 (0.004)</td>
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<td></td>
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<tr>
<td>chPh</td>
<td>Chest pain during physical activity</td>
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<td>61044</td>
<td>0.046</td>
<td>0.13 (0.032)</td>
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<tr>
<td>*Crhn</td>
<td>Crohn’s Disease</td>
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<td>201030</td>
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<td>0.13 (0.038)</td>
<td>0.47</td>
<td>[121]</td>
</tr>
<tr>
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<td>Condition</td>
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<td>CRP</td>
<td>p-Value</td>
<td>E-value</td>
<td>Ce</td>
<td>Reference</td>
</tr>
<tr>
<td>------</td>
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<td>------</td>
<td>---------</td>
<td>---------</td>
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<td>-----------</td>
</tr>
<tr>
<td>crpl</td>
<td>Carpal tunnel</td>
<td>11912</td>
<td>424059</td>
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<td>0.02/0.01</td>
<td>[135, 102]</td>
</tr>
<tr>
<td>CWP</td>
<td>Chronic widespread pain</td>
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<td>[56]</td>
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<td>Cystitis</td>
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<td>189253</td>
<td>0.075</td>
<td>0.03 (0.008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*dbNr</td>
<td>Diabetic Neuropathy</td>
<td>772</td>
<td>435199</td>
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<td>0.13 (0.051)</td>
<td>0.11</td>
<td>[85]</td>
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<td>0.06 (0.014)</td>
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<tr>
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<td>Enthesopathies</td>
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<td>0.141</td>
<td>0.06 (0.007)</td>
<td></td>
<td></td>
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<tr>
<td>*FM</td>
<td>Fibromyalgia</td>
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<td>433822</td>
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<td>0.14</td>
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</tr>
<tr>
<td>gast</td>
<td>Gastritis</td>
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<td>179970</td>
<td>0.188</td>
<td>0.07 (0.006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gout</td>
<td>Gout</td>
<td>15069</td>
<td>192253</td>
<td>0.073</td>
<td>0.20 (0.029)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hdch</td>
<td>Headache</td>
<td>40222</td>
<td>345292</td>
<td>0.104</td>
<td>0.13 (0.008)</td>
<td>0.21</td>
<td>[81]</td>
</tr>
<tr>
<td>hipA</td>
<td>Hip arthrosis</td>
<td>17676</td>
<td>193048</td>
<td>0.084</td>
<td>0.14 (0.012)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hipP</td>
<td>Hip pain</td>
<td>41907</td>
<td>381055</td>
<td>0.099</td>
<td>0.08 (0.005)</td>
<td>0.12</td>
<td>[83]</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td>Count</td>
<td>Control</td>
<td>p-value</td>
<td>SE (p-value)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>------------------------------------</td>
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<td>---------</td>
<td>---------</td>
<td>-------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>IBS</td>
<td>Irritable bowel syndrome</td>
<td>28419</td>
<td>182876</td>
<td>0.134</td>
<td>0.07 (0.008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kneA</td>
<td>Knee arthrosis</td>
<td>31267</td>
<td>184763</td>
<td>0.145</td>
<td>0.14 (0.009)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kneP</td>
<td>Knee pain</td>
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<td>334812</td>
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<td>0.10 (0.005)</td>
<td>0.08 [82]</td>
<td></td>
</tr>
<tr>
<td>legP</td>
<td>Leg pain</td>
<td>41484</td>
<td>108241</td>
<td>0.277</td>
<td>0.10 (0.008)</td>
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<td></td>
</tr>
<tr>
<td>mgrn</td>
<td>Migraine</td>
<td>21586</td>
<td>189874</td>
<td>0.102</td>
<td>0.12 (0.009)</td>
<td>0.15 [39]</td>
<td></td>
</tr>
<tr>
<td>nksh</td>
<td>Neck/Shoulder pain</td>
<td>72952</td>
<td>329192</td>
<td>0.181</td>
<td>0.08 (0.004)</td>
<td>0.11 [84]</td>
<td></td>
</tr>
<tr>
<td>oesp</td>
<td>Oesophagitis</td>
<td>13003</td>
<td>195329</td>
<td>0.062</td>
<td>0.06 (0.010)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rhAt</td>
<td>Rheumatoid arthritis</td>
<td>8685</td>
<td>198125</td>
<td>0.042</td>
<td>0.08 (0.014)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>**plrh</td>
<td>Polymyalgia rheumatica</td>
<td>2460</td>
<td>433511</td>
<td>0.006</td>
<td>0.09 (0.023)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pnjt</td>
<td>Pain in joint</td>
<td>12016</td>
<td>423955</td>
<td>0.028</td>
<td>0.05 (0.008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*prst</td>
<td>Prostatitis</td>
<td>3604</td>
<td>199950</td>
<td>0.018</td>
<td>0.06 (0.020)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*seRA</td>
<td>Seropositive rheumatoid arthritis</td>
<td>839</td>
<td>201957</td>
<td>0.004</td>
<td>0.15 (0.064)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stmP</td>
<td>Stomach pain</td>
<td>21417</td>
<td>396116</td>
<td>0.051</td>
<td>0.08 (0.006)</td>
<td>0.14 [83]</td>
<td></td>
</tr>
</tbody>
</table>
**ulcC** | Ulcerative colitis | 4211 | 199773 | 0.021 | 0.12 (0.022) |
---|---|---|---|---|---|
*urCl* | Urinary colic | 4743 | 198679 | 0.023 | 0.06 (0.016) |

\(h^2_{SNP}\) is SNP heritability, variance in the phenotype explained by variance in genotypes (SNPs). S.E. is standard error. Reported \(h^2_{SNP}\) is provided where available. *phenotypes that did not have a significant \(h^2_{SNP}\) in either the odd or even autosome set.

**phenotypes that did not load significantly onto either the common or specific factor in the EFA-informed CFA.

Table 2: SNP heritability in whole genome, odd and even chromosomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Whole genome (h^2_{SNP}) (SE)</th>
<th>Odd chroms. (h^2_{SNP}) (SE)</th>
<th>Even chroms. (h^2_{SNP}) (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*aCMC</td>
<td>0.09 (0.036)</td>
<td>0.09 (0.026)</td>
<td>0.00 (0.023)</td>
</tr>
<tr>
<td>arth</td>
<td>0.09 (0.005)</td>
<td>0.05 (0.004)</td>
<td>0.04 (0.004)</td>
</tr>
<tr>
<td>back</td>
<td>0.09 (0.005)</td>
<td>0.04 (0.003)</td>
<td>0.05 (0.003)</td>
</tr>
<tr>
<td>chDs</td>
<td>0.08 (0.004)</td>
<td>0.04 (0.003)</td>
<td>0.04 (0.002)</td>
</tr>
<tr>
<td>chPh</td>
<td>0.13 (0.032)</td>
<td>0.09 (0.025)</td>
<td>0.05 (0.023)</td>
</tr>
<tr>
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<td>0.13 (0.038)</td>
<td>0.08 (0.029)</td>
<td>0.05 (0.025)</td>
</tr>
<tr>
<td>crpl</td>
<td>0.16 (0.011)</td>
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<td>0.08 (0.009)</td>
</tr>
<tr>
<td>Term</td>
<td>Mean (Std Dev)</td>
<td>Mean (Std Dev)</td>
<td>Mean (Std Dev)</td>
</tr>
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<td>-------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>cyst</td>
<td>0.03 (0.008)</td>
<td>0.01 (0.006)</td>
<td>0.02 (0.006)</td>
</tr>
<tr>
<td>*dbNr</td>
<td>0.13 (0.051)</td>
<td>0.02 (0.033)</td>
<td>0.11 (0.038)</td>
</tr>
<tr>
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<td>0.06 (0.014)</td>
<td>0.03 (0.010)</td>
<td>0.03 (0.009)</td>
</tr>
<tr>
<td>enth</td>
<td>0.06 (0.007)</td>
<td>0.03 (0.005)</td>
<td>0.03 (0.005)</td>
</tr>
<tr>
<td>*FM</td>
<td>0.10 (0.025)</td>
<td>0.06 (0.017)</td>
<td>0.04 (0.019)</td>
</tr>
<tr>
<td>gast</td>
<td>0.07 (0.006)</td>
<td>0.03 (0.004)</td>
<td>0.04 (0.004)</td>
</tr>
<tr>
<td>CWP</td>
<td>0.14 (0.014)</td>
<td>0.07 (0.010)</td>
<td>0.07 (0.010)</td>
</tr>
<tr>
<td>gout</td>
<td>0.20 (0.029)</td>
<td>0.08 (0.013)</td>
<td>0.12 (0.024)</td>
</tr>
<tr>
<td>hdch</td>
<td>0.13 (0.008)</td>
<td>0.06 (0.004)</td>
<td>0.07 (0.007)</td>
</tr>
<tr>
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<td>0.07 (0.008)</td>
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<td>0.04 (0.003)</td>
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<tr>
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<td>0.03 (0.004)</td>
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<td>0.07 (0.005)</td>
<td>0.08 (0.007)</td>
</tr>
<tr>
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<td>0.05 (0.003)</td>
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<td></td>
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<td>----</td>
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<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
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<td>0.12 (0.009)</td>
<td>0.06 (0.006)</td>
<td>0.06 (0.007)</td>
</tr>
<tr>
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<td>0.04 (0.003)</td>
<td>0.04 (0.003)</td>
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<td>0.03 (0.006)</td>
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<tr>
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<td>0.08 (0.014)</td>
<td>0.05 (0.010)</td>
<td>0.04 (0.010)</td>
</tr>
<tr>
<td>**plrh</td>
<td>0.09 (0.023)</td>
<td>0.05 (0.016)</td>
<td>0.03 (0.015)</td>
</tr>
<tr>
<td>pnjt</td>
<td>0.05 (0.008)</td>
<td>0.03 (0.006)</td>
<td>0.02 (0.005)</td>
</tr>
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<td>*prst</td>
<td>0.06 (0.020)</td>
<td>0.03 (0.014)</td>
<td>0.04 (0.013)</td>
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<td>stmP</td>
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<td>0.04 (0.004)</td>
<td>0.04 (0.005)</td>
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<td>0.12 (0.022)</td>
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<tr>
<td>*urCl</td>
<td>0.06 (0.016)</td>
<td>0.02 (0.012)</td>
<td>0.03 (0.012)</td>
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</table>

$h^2_{SNP}$ is SNP heritability, variance in the phenotype explained by variance in genotypes (SNPs). S.E. is standard error. *phenotypes that did not have a significant $h^2_{SNP}$ in either the odd or even autosome set. **phenotypes that did not load significantly onto either the common or specific factor in the EFA-informed CFA. Condition definitions are in 1, and details are in Supplementary Table S1.
Figure Legends

Figure 1 Scheme of study methods and analyses. Abbreviations: GWAS, genome-wide association study; LDSC, linkage-disequilibrium score regression; EFA, exploratory factor analysis; CFA, confirmatory factor analysis; Genomic SEM, genomic structural equation modeling; CFI, comparative fit index.

Figure 2 Genetic correlations, network, and Genomic SEM model. (a) Genetic correlations for 24 pain conditions estimated using linkage disequilibrium score regression (LDSC) implemented in Genomic SEM. (b) Network of genetic correlations for 24 pain conditions, pruned for significance at FDR 0.01. The 19 conditions in yellow (arthropathies, back pain, neck/shoulder pain, hip pain, knee pain, leg pain, chest pain (baseline and during physical activity), rheumatoid arthritis, knee arthropathy, joint pain, carpal tunnel, enthesopathies, widespread pain, gastritis, oesophagitis, stomach pain, headache, and IBS) form a clique, complete subgraph. The 3 conditions in blue (neck/shoulder pain, back pain, and arthropathic pain) have the highest betweenness centrality, shortest path between 2 other nodes. Node size corresponds to strength, magnitude-weighted number of connections with other nodes. (c) EFA-CFA model for 24 pain conditions with residual covariances (~~) estimated for same body-site conditions: hip arthropathy and pain; knee arthropathy and pain; headache and migraine; chest pain at baseline and during physical activity. F1 is the general factor with positive loadings from all conditions, and F2 is the musculoskeletal factor with positive loadings from carpal tunnel, hip pain, knee pain, leg pain, enthesopathies, rheumatoid arthritis, arthropathies, and pain in joint. CFI, comparative fit index; SRMR, standardized root mean squared residual. All loadings shown are significant at α=0.05. (d) Summary scores (overall measure of interconnectedness for each pain condition) obtained using F1 loadings from EFA-CFA and network strength and betweenness centrality, vector-normalized geometric means (y-axis). (More information on all conditions in Supplementary Table 1 [https://docs.google.com/spreadsheets/d/1S-vFvnwkD5iCP16La_iyjRDTxIqBoMRqAOV6SXpKhN8/edit\#gid=0].

Figure 3 F1 factor GWAS output. Genome-wide association study (GWAS) results for general pain factor (F1). SNP Manhattan (a) and quantile-quantile, QQ, (b) plots for F1 GWAS. (c) Gene-based genome-wide association Manhattan plot, with the top 31 associated genes labelled. (d) Gene property analysis for association between factor GWAS gene effects and gene expression levels in 53 specific tissues from GTEx, version 8.
Figure 1

Main Analysis

GWAS

LDSC

EFA

CFA (GenomicSEM)

Factor GWAS (GenomicSEM)

CFI

FUMA

Validation

Strength betweenness centrality clique

EFA (odd chroms)

CFA (even chroms)

CFI, compared to main analysis fit to check for overfitting

Functional annotation of GWAS results
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