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Genetic risk shared across 24 chronic pain conditions: identification and characterization with genomic structural equation modeling

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Abstract

Chronic pain conditions frequently co-occur, suggesting common risks and paths to prevention and treatment. Previous studies have reported genetic correlations among specific groups of pain conditions and reported genetic risk for within-individual multisite pain counts (≤7). Here, we identified genetic risk for multiple distinct pain disorders across individuals using 24 chronic pain conditions and genomic structural equation modeling (Genomic SEM). First, we ran individual genome-wide association studies (GWASs) on all 24 conditions in the UK Biobank ($N \leq 436{,}000$) and estimated their pairwise genetic correlations. Then we used these correlations to model their genetic factor structure in Genomic SEM, using both hypothesis- and data-driven exploratory approaches. A complementary network analysis enabled us to visualize these genetic relationships in an unstructured manner. Genomic SEM analysis revealed a general factor explaining most of the shared genetic variance across all pain conditions and a second, more specific factor explaining genetic covariance across musculoskeletal pain conditions. Network analysis revealed a large cluster of conditions and identified arthropathic, back, and neck pain as potential hubs for cross-condition chronic pain. Additionally, we ran GWASs on both factors extracted in Genomic SEM and annotated them functionally. Annotation identified pathways associated with organogenesis, metabolism, transcription, and DNA repair, with overrepresentation of strongly associated genes exclusively in brain tissues. Cross-reference with previous GWASs showed genetic overlap with cognition, mood, and brain structure. These results identify common genetic risks and suggest neurobiological and psychosocial mechanisms that should be targeted to prevent and treat cross-condition chronic pain.

Keywords: GWAS, UK Biobank, Genomic SEM, Pain genetics, Genetic correlations, Chronic pain

1. Introduction

Chronic pain is a well-documented burden on the patient[1,25,43,66,83,109] and the healthcare system.[94] The costs of pain management are driven by an incomplete understanding of pain chronification mechanisms, which impedes effective prevention and treatment. It is now widely understood that chronic pain is complex and involves changes in brain pathways as well as peripheral mechanisms.[79,86,93] This understanding has led to the introduction of chronic primary pain disease codes in version 11 of the International Classification of Diseases (ICD-11).[101] Nonetheless, with few exceptions,[109] pain conditions are still classified largely based on the body site affected and either treated in the primary care setting[91] or referred to specialists by body site (back pain to orthopedists, irritable bowel syndrome [IBS] to gastroenterologists, etc). Unfortunately, the processes that drive chronic pain across conditions remain insufficiently understood, and most current treatments do not work for most patients.[30,107] There is an urgent need for a fundamentally different approach.

Recent work in mental health epidemiology has revealed extensive co-occurrence across disorders, leading to identification of common factors underlying multiple conditions.[13,48,75] Co-occurrence across pain conditions with different pathologies (eg, migraine with IBS) has also been documented.[3,56,61,88,95] Furthermore, chronic pain conditions are heritable (with estimates up to 45%),[44] and genetic risks for pain are shared across conditions.[70] Two recent genome-wide association studies (GWASs) in the UK Biobank (UKBB) identified genetic variants related to multisite pain.[50,52] These important studies, however, focused on pain widespreadness (quantitative 0-7[50] or binarized: 1 vs 2 or more affected body sites[52]), without tracking whether genetic risks were shared across conditions. Widespreadness may either arise from co-occurring pain conditions or itself be a pain condition that

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affects a number of musculoskeletal body sites.[19] Given that 5 of the 7 body sites used in both studies are musculoskeletal, including the most prevalent site, back pain, the genetic associations they assessed are likely driven by the genetic risk for widespread musculoskeletal pain and may not identify genes that cut across distinct disorders.

Here, we examine shared genetic risks across 24 distinct pain conditions in over 400,000 individuals in the UKBB.[12] We use genomic structural equation modeling (SEM)[40] to identify common genetic factors across conditions. Genomic SEM applies the traditional techniques of SEM, a widely used method for latent factor modeling,[53] to genetic correlations estimated from genome-wide association statistics. Then we annotate the factors with associated biological pathways.

Figure 1 provides a graphical overview of the study. The specific questions we address are as follows: (1) Is there a general, condition-agnostic genetic risk factor for chronic pain? (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? Addressing these questions may shed light on transdiagnostic causes of chronic pain and potential targets for prevention and treatment.

2. Methods

The main steps in the analysis included: (1) GWAS, yielding association effect sizes for genetic variants (single-nucleotide polymorphisms, SNPs) with chronic pain conditions; (2) genetic correlations, which use the GWAS association effect sizes to estimate shared genetic risk across pain conditions; (3) Genomic SEM to identify common factors and compare factor models; (4) factor GWAS to identify SNPs associated with common factors; and (5) functional annotation of factor-associated SNPs in likeliest implicated genes, pathways, and tissues.

2.1. Cohort

Participants in the UKBB were aged 40 to 69 years and 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 population stratification.[98] We analyzed data from White Europeans, identified using UKBB-provided genomic principal components 1 to 4,[12] given that no other group had a sufficient sample size for our analyses (see Supplementary Table S2 for descriptive statistics of South Asians, the next highest sample size, available at http://links.lww.com/PAIN/B817). 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. Up to 435,971 people (54% female) were included in the analysis, with sample size varying by phenotype (**Table 1**).

2.2. 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. We drew an initial list of 91 phenotypes from 5 UKBB categories: medical conditions (100,074), health outcomes (713), self-reported medical conditions (1003), health and medical history (100,036), and first occurrences (1712), downloaded in May 2021. We were able to greatly expand the number of pain conditions included in this study compared with previous studies[50,51,52,100] because of the First Occurrences dataset. This dataset gave researchers access to primary care and death register records to supplement self-reports and ICD-10 diagnoses that had been earlier available exclusively from hospital intake records. This updated UKKB dataset thus had, for the first time, more accurate case prevalences for a large number of conditions. We recoded these conditions into binary phenotypes (Supplementary Table S1, available at http://links.lww.com/PAIN/B817) and pruned them to remove those that fell into one of the following categories: (1) heterogeneous

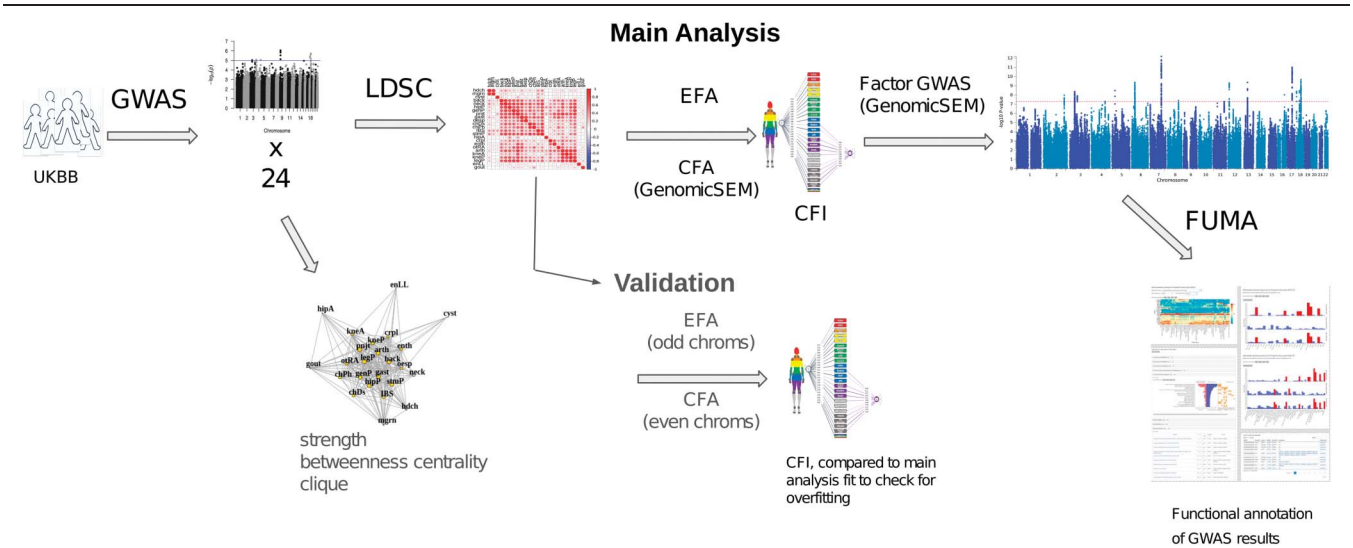

Figure 1. Scheme of study methods and analyses. CFA, confirmatory factor analysis; CFI, comparative fit index; EFA, exploratory factor analysis; FUMA, functional mapping and annotation; Genomic SEM, genomic structural equation modeling; GWAS, genome-wide association study; LDSC, linkage-disequilibrium score regression; UKBB, United Kingdom Biobank.

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Table 1

Pain condition descriptive statistics.

Condition	Full name	Cases	Controls	Prevalence	h^2_{SNP} (SE)	Reported h^2_{SNP}	Citations
*aCMC	Arthropathy of carpometacarpal joint	1837	201,439	0.009	0.09 (0.036)	NA	NA
arth	Arthropathies (nonspecific, incl. osteoarthritis)	80,737	157,458	0.339	0.09 (0.005)	NA	NA
back	Back pain	119,216	132,641	0.473	0.09 (0.005)	0.11/0.12/0.076	33,69,94
chDs	Chest pain/discomfort	72,156	359,415	0.167	0.08 (0.004)		
chPh	Chest pain during physical activity	2938	61,044	0.046	0.13 (0.032)		
*Crhn	Crohn's disease	1826	201,030	0.009	0.13 (0.038)	0.47	99
crpl	Carpal tunnel	11,912	424,059	0.027	0.16 (0.011)	0.02/0.01	86,110
CWP	Chronic widespread pain	6021	427,884	0.014	0.14 (0.014)	0.10	49
cyst	Cystitis	15,371	189,253	0.075	0.03 (0.008)		
*dbNr	Diabetic neuropathy	772	435,199	0.002	0.13 (0.051)	0.11	71
enLL	Enthesopathies of lower limb	7000	195,713	0.035	0.06 (0.014)		
enth	Enthesopathies	28,754	175,077	0.141	0.06 (0.007)		
*FM	Fibromyalgia	2149	433,822	0.005	0.10 (0.025)	0.14	24
gast	Gastritis	41,746	179,970	0.188	0.07 (0.006)		
gout	Gout	15,069	192,253	0.073	0.20 (0.029)		
hdch	Headache	40,222	345,292	0.104	0.13 (0.008)	0.21	67
hipA	Hip arthrosis	17,676	193,048	0.084	0.14 (0.012)		
hipP	Hip pain	41,907	381,055	0.099	0.08 (0.005)	0.12	69
IBS	Irritable bowel syndrome	28,419	182,876	0.134	0.07 (0.008)		
kneA	Knee arthrosis	31,267	184,763	0.145	0.14 (0.009)		
kneP	Knee pain	78,507	334,812	0.190	0.10 (0.005)	0.08	68
legP	Leg pain	41,484	108,241	0.277	0.10 (0.008)		
mgrn	Migraine	21,586	189,874	0.102	0.12 (0.009)	0.15	37
nksh	Neck/shoulder pain	72,952	329,192	0.181	0.08 (0.004)	0.11	70
oesp	Oesophagitis	13,003	195,329	0.062	0.06 (0.010)		
rhAt	Rheumatoid arthritis	8685	198,125	0.042	0.08 (0.014)		
†plrh	Polymyalgia rheumatica	2460	433,511	0.006	0.09 (0.023)		
pnjt	Pain in joint	12,016	423,955	0.028	0.05 (0.008)		
*prst	Prostatitis	3604	199,950	0.018	0.06 (0.020)		
*seRA	Seropositive rheumatoid arthritis	839	201,957	0.004	0.15 (0.064)		
stmP	Stomach pain	21,417	396,116	0.051	0.08 (0.006)	0.14	69
†ulcC	Ulcerative colitis	4211	199,773	0.021	0.12 (0.022)		
*urCl	Urinary colic	4743	198,679	0.023	0.06 (0.016)		

h^2_{SNP} is SNP heritability, variance in the phenotype explained by variance in genotypes (SNPs). Reported h^2_{SNP} is provided where available.

* Phenotypes that did not have a significant h^2_{SNP} in either the odd or the even autosome set.

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

CFA, confirmatory factor analysis; EFA, exploratory factor analysis.

disorders or groups of other conditions already included, 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 as the branching question for pain experienced for more than 3 months); (3) disorders with case count <500; (4) disorders that were not sufficiently related to genetics, with SNP heritability (see Section 2.4.1 below) ≤2 SEs above zero ($h^2_{SNP} - 2 \times SE \leq 0$) (see Supplementary Note, available at http://links.lww.com/PAIN/B816). Genomic SEM models genetic covariances and traits with low heritability cannot show significant genetic covariance with other traits; hence, they were not included here. This pruning left 33 heritable chronic pain conditions (**Table 1**), which were further reduced to 24 during factor analysis (see Section 2.4.2 below).

2.3. Genome-wide association study

To prepare the data for GWAS, we used Plink,[16] a commonly used, open-source toolset for genetic analyses (details in Supplementary Note, available at http://links.lww.com/PAIN/B816). For the next step, GWAS, we estimated associations between each SNP and each chronic pain condition (phenotype)

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of interest using logistic regression, with the SNP variant as the predictor and the pain condition as the outcome. For these analyses, we used Regenie (details in Supplementary Note, available at http://links.lww.com/PAIN/B816).

2.4. Factor analysis and structural equation model

2.4.1. Heritability and genetic correlations

We used linkage disequilibrium score regression (LDSC) software[11] to determine SNP heritability, h^2_{SNP}, and to estimate genetic correlations between every pair of pain conditions. For heritability, LDSC uses the pattern of SNP effects to estimate the variance in the phenotype that is attributable to all measured SNPs in aggregate (details in Supplementary Note, available at http://links.lww.com/PAIN/B816). **Table 1** reports the h^2_{SNP} for each condition on a liability scale (Supplementary Note, available at http://links.lww.com/PAIN/B816). For genetic correlations, LDSC determines the extent to which the pattern of genetic associations for one phenotype is correlated with the pattern of genetic associations for another phenotype. The resulting matrix of pairwise genetic correlations across pairs of chronic pain conditions is in **Figure 2A**. These genetic correlations provide the basis for factor analysis in Genomic SEM.

2.4.2. Factor analysis and genomic structural equation modeling

We used Genomic SEM to test for evidence of shared genetic risk. Structural equation modeling analyses test whether a hypothesized factor structure can adequately capture the observed correlations across a set of observed phenotypes (indicators). Genomic SEM applies the same method but to genetic correlations instead of phenotypic correlations; thus, the indicators are chronic pain conditions, but the data constitute correlations of genetic effects on phenotypes rather than phenotypic scores themselves. In confirmatory factor analysis (CFA), one specifies a series of hypothesis-driven models and compares their ability to accurately reproduce the pattern of correlations across conditions. Each model comprises a specification of which conditions load on which factors and whether the factors are themselves correlated. In exploratory factor analysis (EFA), one allows for the factor loadings to be determined in a data-driven fashion, identifying which groupings of conditions are best supported.

Our main analysis goal was to test for common factors without rigidly specifying groupings a priori. Thus, our main strategy combined EFA and CFA, using EFA to select the number of factors and their loadings and then evaluate the goodness of fit and compare with alternative models (see below for details). Exploratory factor analysis–confirmatory factor analysis, evaluated in 36 and recently used in Refs. 18,23,55, is a partially data-driven approach that captures observed groupings in the data while still permitting structure and inferences based on theory.

Confirmatory factor analysis can also be used to compare alternative theories about which types of common factors best explain observed correlations across chronic pain conditions. Here, we compared our EFA-guided model with 2 hypothesis-based CFA models: one based on shared genetic risks across conditions with similar body sites ("anatomic") and one based on shared risk for inflammatory conditions ("etiologic"). The anatomic model included one general factor (on which all disorders load) 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 models, the goal was to test a bifactor structure, which consisted of a general factor with loadings for all conditions and specific factors that are orthogonal to the general factor and have loadings for specific subsets of conditions. This type of model allowed us to test whether a common genetic factor underlay all tested pain conditions while still allowing for shared variance for particular groups of conditions. Similar approaches have been used to model other multidimensional constructs, including personality[17] and psychopathology.[8]

For the EFA portion of the EFA–CFA approach, we used the fa function in the "psych" R package; a scree plot (Supplementary Figure S1, available at http://links.lww.com/PAIN/B816) suggested 3 factors, allowing for correlations among factors using oblique rotation. The factor loadings were thresholded to define a CFA model for subsequent validation in Genomic SEM. The final model structure is shown in **Figure 2C**.

The use of EFA to guide model development requires validating the model's fit on independent data to avoid overfitting.[31] For this validation, we used a split-genome approach.[32,39] We developed a model using the EFA–CFA procedure described above in odd autosomes (1, 3, … 21) and assessed the fit of the final CFA in even autosomes (2, 4, … 22). This split created 2 independent sets, given that SNPs are not correlated across chromosomes (Mendel's law of independent assortment).

Using an odd–even autosome split assumes that traits are polygenic (many genes contribute) and that relevant genes are distributed across autosomes, so that an estimate of genetic correlations from odd autosomes can be replicated in even ones. The polygenic nature of pain conditions, like other complex traits, was evident in this dataset (Supplementary Figure S2, available at http://links.lww.com/PAIN/B816). However, to be conservative, we excluded conditions whose genetic associations were not heritable in both odd and even autosomes (Supplementary Note, available at http://links.lww.com/PAIN/B816). 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 final 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 quantifies the extent to which the model fits better than a baseline model (one in which the variables are uncorrelated), and SRMR (standardized root mean residual), which quantifies the mean absolute difference between the observed correlations and the correlations predicted by the model.[45] A well-fitting model should generally have a CFI $\geq$0.95 and an SRMR $\leq$0.08.[45] The models were additionally compared using the Akaike information criterion (AIC), which is a goodness-of-fit index favoring more parsimonious models (lower values indicate better fit).[53]

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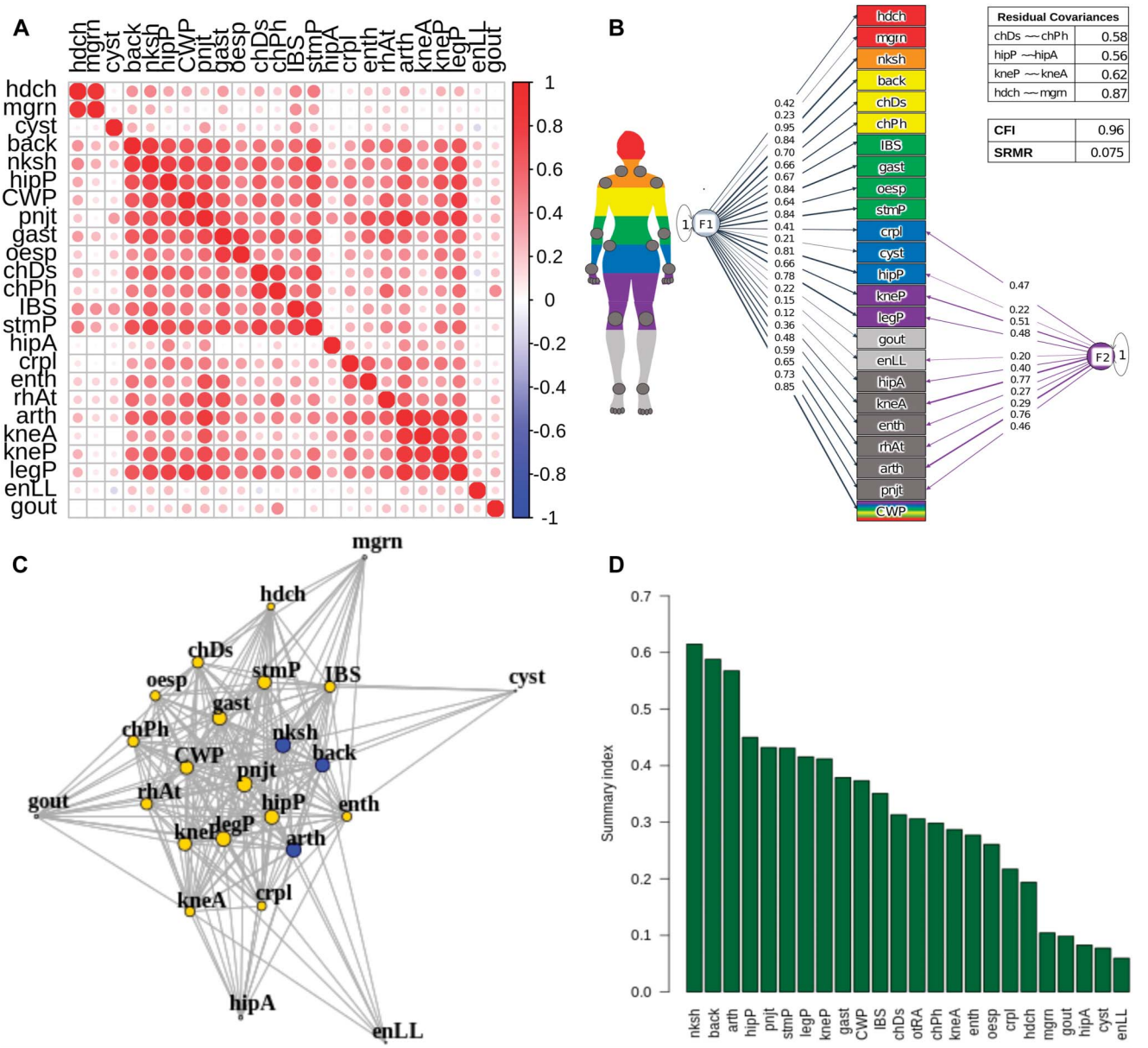

Figure 2. Genetic correlations, network, and Genomic SEM model. (A) Genetic correlations for 24 pain conditions estimated using LDSC implemented in Genomic SEM. (B) Network of genetic correlations for 24 pain conditions, pruned for significance at FDR 0.01. The 19 conditions in yellow form a clique, complete subgraph. The 3 conditions in blue 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 (table in top left): hip arthrosis and pain; knee arthrosis 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. All loadings shown are significant at $\alpha = 0.05$. (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 are provided in Supplementary Table 1 (available at http://links.lww.com/PAIN/B817). arth, arthroses; back, back pain; CFA, confirmatory factor analysis; CFI, comparative fit index; chDs, chest pain/discomfort; chPh, chest pain during physical activity; crpl, carpal tunnel; CWP, chronic widespread pain; cyst, cystitis; EFA, exploratory factor analysis; enLL, enthesopathies in lower limbs; enth, enthesopathies; FDR, false discovery rate; gast, gastritis; Genomic SEM, genomic structural equation modeling; hdch, headache; hipA, hip arthrosis; hipP, hip pain; IBS, inflammatory bowel syndrome; kneA, knee arthrosis; kneP, knee pain; legP, leg pain; mgrn, migraine; nksh, neck/shoulder pain; oesp, oesphagitis; pnjt, joint pain; rhAt, rheumatoid arthritis; SRMR, standardized root mean squared residual; stmP, stomach pain.

2.5. Factor genome-wide association study

Common factors may have associations with genetic variants that are not detectable in analysis with individual conditions. To identify the SNPs with the largest associations with common chronic pain factors, we ran a factor GWAS in Genomic SEM (userGWAS function; Supplementary Figure S3, available at http://links.lww.com/PAIN/B816).

One issue to address when calculating GWAS on common factors is whether SNPs are associated primarily with the common factor or instead are more strongly associated with individual conditions that contribute to it. To assess each SNP for disproportionately strong or directionally opposing effects on a subset of conditions, we conducted a heterogeneity Q test[40,46] and discarded SNPs with heterogeneous effects as

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Table 2

Single-nucleotide polymorphism heritability in whole genome and odd and even chromosomes.

Condition	Whole genome h^2_{SNP} (SE)	Odd chroms. h^2_{SNP} (SE)	Even chroms. h^2_{SNP} (SE)
*aCMC	0.09 (0.036)	0.09 (0.026)	0.00 (0.023)
arth	0.09 (0.005)	0.05 (0.004)	0.04 (0.004)
back	0.09 (0.005)	0.04 (0.003)	0.05 (0.003)
chDs	0.08 (0.004)	0.04 (0.003)	0.04 (0.002)
chPh	0.13 (0.032)	0.09 (0.025)	0.05 (0.023)
*Crhn	0.13 (0.038)	0.08 (0.029)	0.05 (0.025)
crpl	0.16 (0.011)	0.07 (0.008)	0.08 (0.009)
cyst	0.03 (0.008)	0.01 (0.006)	0.02 (0.006)
*dbNr	0.13 (0.051)	0.02 (0.033)	0.11 (0.038)
enLL	0.06 (0.014)	0.03 (0.010)	0.03 (0.009)
enth	0.06 (0.007)	0.03 (0.005)	0.03 (0.005)
*FM	0.10 (0.025)	0.06 (0.017)	0.04 (0.019)
gast	0.07 (0.006)	0.03 (0.004)	0.04 (0.004)
CWP	0.14 (0.014)	0.07 (0.010)	0.07 (0.010)
gout	0.20 (0.029)	0.08 (0.013)	0.12 (0.024)
hdch	0.13 (0.008)	0.06 (0.004)	0.07 (0.007)
hipA	0.14 (0.012)	0.07 (0.009)	0.07 (0.008)
hipP	0.08 (0.005)	0.04 (0.003)	0.04 (0.003)
IBS	0.07 (0.008)	0.04 (0.005)	0.03 (0.004)
kneA	0.14 (0.009)	0.07 (0.005)	0.08 (0.007)
kneP	0.10 (0.005)	0.05 (0.003)	0.05 (0.003)
legP	0.10 (0.008)	0.05 (0.005)	0.05 (0.005)
mgrn	0.12 (0.009)	0.06 (0.006)	0.06 (0.007)
neck	0.08 (0.004)	0.04 (0.003)	0.04 (0.003)
oesp	0.06 (0.010)	0.03 (0.007)	0.03 (0.006)
rhAt	0.08 (0.014)	0.05 (0.010)	0.04 (0.010)
†plrh	0.09 (0.023)	0.05 (0.016)	0.03 (0.015)
pnjt	0.05 (0.008)	0.03 (0.006)	0.02 (0.005)
*prst	0.06 (0.020)	0.03 (0.014)	0.04 (0.013)
*seRA	0.15 (0.064)	0.17 (0.043)	−0.02 (0.047)
stmP	0.08 (0.006)	0.04 (0.004)	0.04 (0.005)
†ulcC	0.12 (0.022)	0.07 (0.016)	0.05 (0.015)
*urCl	0.06 (0.016)	0.02 (0.012)	0.03 (0.012)

h^2_{SNP} is SNP heritability, variance in the phenotype explained by variance in genotypes (SNPs).
* 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 Table 1, and details are in Supplementary Table S1, available at http://links.lww.com/PAIN/B817.
CFA, confirmatory factor analysis; EFA, exploratory factor analysis; SNPs, single-nucleotide polymorphisms.

well as those correlated with them (Supplementary Note, available at http://links.lww.com/PAIN/B816).

2.5.1. Genome-wide association study annotation

Genome-wide association study yields a list of SNPs significantly associated with a trait. Follow-up analyses are then needed to characterize those SNPs in genes and pathways. Functional mapping and annotation (FUMA) of GWAS[112] is a platform developed to facilitate a number of standard GWAS follow-up analyses. To functionally characterize the genetic contributors to both individual phenotypes and the 2 factors, we submitted all GWAS results to FUMA for gene prioritization and functional annotation, using several integrated databases.[112] 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 using FUMA-implemented MAGMA (https://ctg.cncr.nl/software/magma) for gene analysis and gene property analyses; (4) gene set analysis for enrichment in known biological pathways; and (5) gene property analysis or testing for preferential expression of associated genes with 53 Gene-Tissue Expression repository (GTEx), version 8, tissues. We used FUMA's default and standard significance thresholds and parameters, including $P < 5 \times 10^{-8}$ for lead SNPs (independent at $r^2 < 0.1$) and $P < 0.05$ for all other SNPs; r^2 threshold for independent significant SNPs used for further annotations, including gene mapping: 0.6; reference panel population = UKBB 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 (general and musculoskeletal) identified in the final EFA–CFA model were 422,752 and 468,929, respectively, calculated using the method described in 63. Variants from the reference panel that were in LD with GWAS lead SNPs were included to increase the chance of including causal variants.

Mappings of independent significant (as defined in FUMA, $P < 5 \times x\, 10^{-8}$ 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). Only protein-coding genes were included, and the major histocompatibility region was excluded from annotation. MAGMA analysis for gene-based (vs SNP-based) associations[22] was conducted with SNP assignment within windows of 10 kilobases of gene start and stop coordinates, and GTEx, version 8,[60] was used for gene expression analysis in 53 tissues. Given that the highest association statistic is not necessarily correlated with its relative importance (see this recent publication discussing negative selection as a mechanism for purging high-effect variants in critical gene loci[80]), our approach was to prioritize genes based on (1) an a priori association P cut-off to ensure statistical rigor; and (2) convergent lines of evidence for functional importance, ie, overlap in the 3 mapping approaches. In the resulting set, we interpret our findings in their entirety, without deference to the top association.

The gene-tissue expression analysis tested for association between highly expressed genes in 53 GTEx tissues and GWAS effect sizes for the same genes, which tests the relationship between the genes highly associated with the pain factors and highly expressed in different tissues (details in Supplementary Note, available at http://links.lww.com/PAIN/B816). The parameters are summarized in Supplementary Table S3, available at http://links.lww.com/PAIN/B817.

We used REVIGO[93] to assign, prune, and summarize biological pathways to the 25 genes with overlapping mappings

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(details in Supplementary Note, available at http://links.lww.com/PAIN/B816).

2.6. Network analysis

Although 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.[106] We made no strong claims about the underlying causal structure and complemented the factor-analytic models with a network-based approach to characterize genetic relationships among conditions in terms of multiple local causes instead of a few latent causes. Network characterization and visualization was done in igraph in R.[21] Genetic correlations of the final 24 pain conditions were filtered for positive significant correlations, using a threshold of 0.01 false discovery rate-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 pain condition in question.[10] *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,[28] which identifies a group of genetically interrelated conditions that may together serve as indicators of multi-disorder susceptibility.

2.7. Summary score

To summarize the evidence for which conditions are the most consistent key indicators of multi-disorder vulnerability, we combined results from Genomic SEM and network analysis, obtaining an overall measure of interconnectedness for each pain condition. Thus, we derived summary scores for all pain conditions using general factor loadings from EFA–CFA, network strength, and betweenness centrality, which are intercorrelated, $r = 0.935$ (general factor and strength), $r = 0.614$ (general factor and betweenness), $r = 0.693$ (strength and betweenness). We calculated a geometric mean of these 3 measures, after vector-normalizing them using the norm function in R.

3. Results

The work reported here is part of a project pre-registered on Open Science Foundation (Identifying and characterizing genetic susceptibility and its overlap with psychosocial traits, https://osf.io/4p5e3).

3.1. Univariate pain condition genome-wide association study curation and annotation

We considered 91 potentially relevant pain phenotypes in the UKBB and selected 24 that (1) were indicative of chronic pain conditions, (2) had sufficient case counts (>500), and (3) were significantly heritable (see Methods; **Table 1** and Supplementary Table S1, available at http://links.lww.com/PAIN/B817). 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). Single-nucleotide polymorphism 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 S2 and S4 (available at http://links.lww.com/PAIN/B816) for Manhattan and quantile-quantile (QQ)-plots, and in Supplementary Table S14 for numbers of significant SNPs and genes, available at http://links.lww.com/PAIN/B817.

3.2. Pain condition genetic correlations

Pairwise genetic correlations for the 24 pain conditions, **Figure 2A**, show a large cluster of interconnected vertices. This main cluster includes 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 form a tight mini-cluster (top left), and cystitis, hip arthrosis, enthesopathies of the lower limb, and gout show weaker correlations, suggesting more specific genetic risks for each of these 4 conditions.

A natural question is whether genetic correlations are potentially inflated when estimated in individuals with comorbid conditions. The answer is no. Conditions are primarily comorbid because of shared genetic risks or shared environmental risks. However, conditions with shared environmental risks would not correlate genetically because alleles of different genes segregate independently from each other (Mendel's law of independent assortment). Thus, given distinct genetic profiles for 2 conditions, the risk alleles for one condition would not correlate with the risk alleles for another. A similar genetic profile in many individuals with comorbid conditions indicates a true common predisposition.

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. Both the anatomic model, based on body site (Supplementary Figure S5, CFI = 0.875 and SRMR = 0.087), and the etiologic model, based on a grouping of inflammatory disorders (Supplementary Figure S6, CFI = 0.905, SRMR = 0.095, available at http://links.lww.com/PAIN/B816), had suboptimal fit (CFI $\leq$ 0.95 and SRMR $\geq$ 0.08), 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. The specific factor had substantial positive loadings for arthropathies (which include 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 the specific factor as musculoskeletal. This factor is 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

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systems.[110] The EFA–CFA was superior (AIC = 4849.164) to both the anatomic (AIC = 13,184.43) and the etiologic (AIC = 10,024.93) models. In addition, the latter models had nonsignificant loadings on their specific factors (leg/foot, pelvic, and torso for the anatomic, Supplementary Figure S5, and inflammatory for the etiologic, Supplementary Figure S6, suggesting that shared variance for those indicators was mainly explained by the general factor [details in the Supplementary Note, available at http://links.lww.com/PAIN/B816]). We validated this model by using the same approach, EFA on odd (CFI = 0.884 and SRMR = 0.123) and CFA testing on even (CFI = 0.903 and SRMR = 0.129) autosomes (details in the Supplementary Note, available at http://links.lww.com/PAIN/B816). These comparable metrics in the odd/even and whole-genome datasets suggest 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. Graph-theoretical properties of the network (**Fig. 2B**) indicate shared genetic susceptibility, and node size corresponds to strength (magnitude-weighted number of connections). There is 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 arthrosis, 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 noninflammatory as well as musculoskeletal and nonmusculoskeletal forms of pain. Gout, hip arthrosis, enthesopathies of the lower limb, cystitis, and migraine lie outside the large cluster, but they still have >10 connections each. Overall, the network reveals 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 (the highest number of shortest paths between node pairs that go through the index node), indicating that genetic associations between many conditions share genetic vulnerability with at least 1 of these 3.

The summary score derived from the general factor, network node strength, and betweenness centrality, **Figure 2D**, reflects 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 genome-wide association study and annotation

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

3.5.1. General factor

The general factor GWAS yielded 33 genome-wide independent significant SNPs, Supplementary Table S4 (available at http://links.lww.com/PAIN/B817), **Figure 3**. Functional mapping and annotation 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 (available at http://links.lww.com/PAIN/B817): 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, available at http://links.lww.com/PAIN/B817.

REVIGO pathway analysis suggested that the pathways represented by these genes cover 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, available at http://links.lww.com/PAIN/B817). Functional mapping and annotation gene set annotation showed a significant enrichment for a pathway involved in learned vocalization behavior or vocal learning ($P = 8.93 \times 10^{-07}$, Bonferroni-corrected $P = 0.0138$). Additionally, this analysis showed a trend towards significance in several other pathways involved in mechanosensory behavior, several neuronal development processes, and several biosynthesis and calcium channel regulation processes (Supplementary Table S7, available at http://links.lww.com/PAIN/B817). Although these pathways did not reach corrected significance, we note them because they are supported by previous findings[51,52,69,96] and may be useful for hypothesis generation purposes. We note, additionally, that biological pathways have roles in multiple functions, and our results do not imply a direct link between pain and the functions, such as vocal learning, associated with these pathways.

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 (Supplementary Note, available at http://links.lww.com/PAIN/B816). 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 is the overlap in SNPs (Supplementary Table S8, available at http://links.lww.com/PAIN/B817), and significant enrichment for genes reported to be associated with chronic pain conditions (back pain, Crohn disease, IBS, and multisite chronic pain), brain structural traits, anthropometric traits, cognition and intelligence-related phenotypes, sleep-related phenotypes, neuroticism, and mood phenotypes (Supplementary Figure S7, available at http://links.lww.com/PAIN/B816). Genetic overlap with nonpain conditions is suggestive of the complexity of factors contributing to chronic pain and suggests potential pathways of susceptibility to pain chronification. Furthermore, colorectal cancer suppressor (*DCC*), the top gene associated with the general factor, is also the top gene reported in a recent study of chronic overlapping pain conditions, which used pain for >3 months in different body sites from the UKBB (head, face, neck/shoulder, back, stomach, hip, knee, and all over the body).[52] Of the 241 genes mapped to independent significant SNPs from the general factor GWAS, *FKBP5* is the only one previously targeted in a candidate gene study (as opposed to GWAS) for posttraumatic musculoskeletal pain.[9,59,119].

3.5.2. Musculoskeletal factor

The musculoskeletal factor GWAS yielded 7 genome-wide significant lead SNPs (Supplementary Table S9, available at http://links.lww.com/PAIN/B817, and Supplementary Figure S8, available at http://links.lww.com/PAIN/B816). Positional

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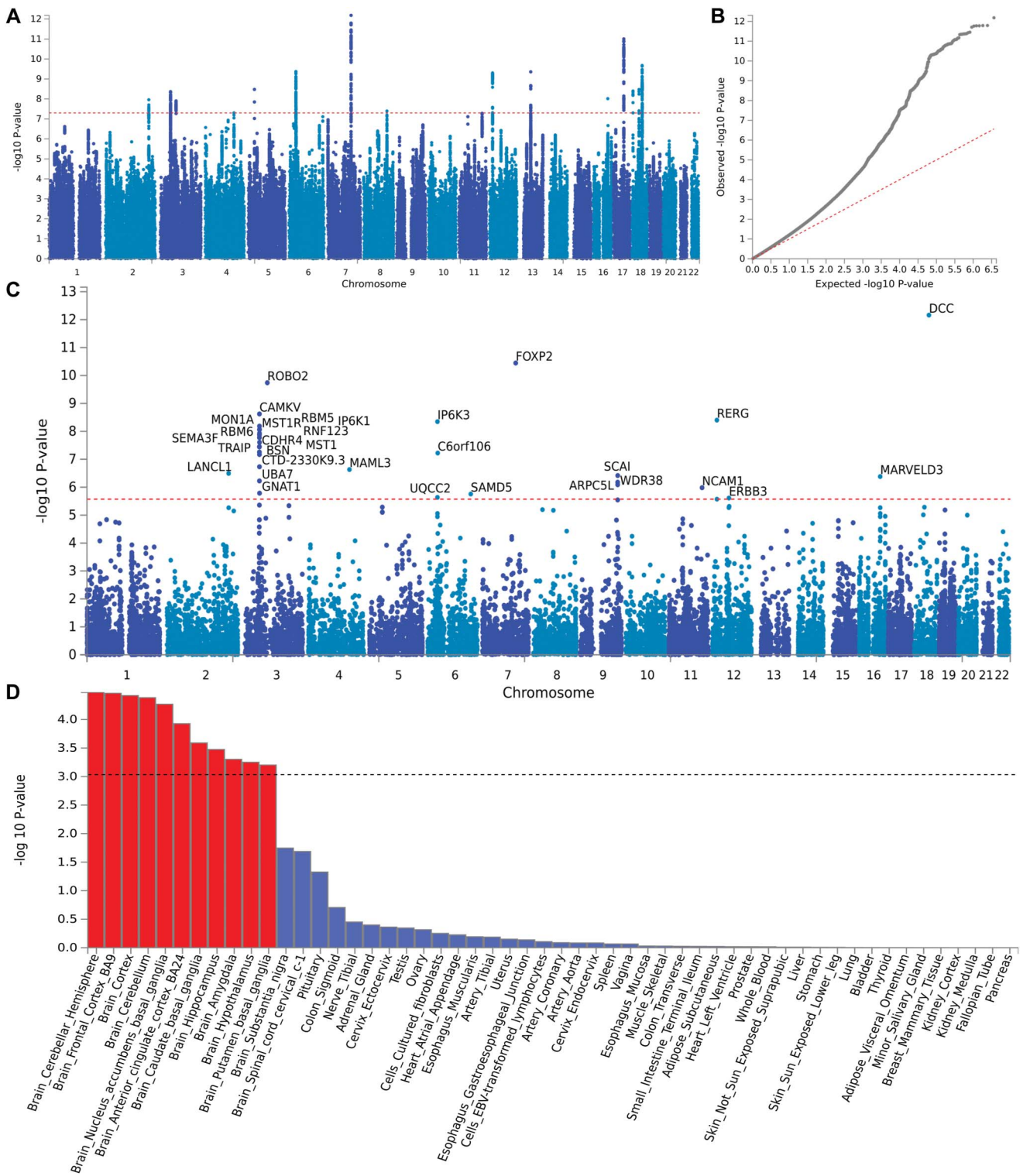

Figure 3. F1 factor GWAS output. Genome-wide association study (GWAS) results for general pain factor (F1). Single-nucleotide polymorphism Manhattan (A) and quantile–quantile, QQ (B), plots for F1 GWAS. (C) Gene-based genome-wide association Manhattan plot, with the top 31 associated genes labeled. Full gene names taken from the NCBI gene database, https://www.ncbi.nlm.nih.gov/gene/: ARPC5L, actin-related protein 2/3 complex subunit 5-like protein; BSN, Bassoon presynaptic cytomatrix protein; C6orf106, inflammation and lipid regulator with UBA-like and NBR1-like domains; CAMKV, CaM kinase like vesicle associated; CDHR4, cadherin-related family member 4; CTD-2330K9.3, Coats disease; DCC, colorectal cancer suppressor; ERBB3, Erb-B2 receptor tyrosine kinase 3; FOXP2, forkhead box P2; GNAT1, G protein subunit alpha transducin 1; IP6K1, inositol hexakisphosphate kinase 1; IP6K3, inositol hexakisphosphate kinase 3; LANCL1, LanC like glutathione S-transferase 1; MAML3, mastermind like transcriptional coactivator 3; MARVELD3, MARVEL (membrane-associating) domain containing 3; MON1A, MON1 homolog A, secretory trafficking associated; MST1, macrophage stimulating 1; MST1R, macrophage stimulating 1 receptor; NCAM1, neural cell adhesion molecule 1; RBM5, RNA-binding motif protein 5; RBM6, RNA-binding motif protein 6; RERG, RAS-like estrogen-regulated growth inhibitor; RNF123, ring finger protein 123; ROBO2, roundabout guidance receptor 2; SAMD5, sterile alpha motif domain containing 5; SCAI, suppressor of cancer cell invasion; SEMA3F, semaphorin 3F; TRAIP, TRAF interacting protein; UBA7, ubiquitin-like modifier activating enzyme 7; UQCC2, ubiquinol–cytochrome c reductase complex assembly factor 2; WDR38, WD repeat domain 38. (D) Gene property analysis for association between factor GWAS gene effects and gene expression levels in 53 specific tissues from GTEx, version 8. GTEx, gene-tissue expression.

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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 *SLC44A2* (Supplementary Table S10, available at http://links.lww.com/PAIN/B817).

REVIGO pathway analysis showed associations with genes involved in bone and neuronal development, cell cycle, transcription regulation, and signal transduction, Supplementary Table S11, available at http://links.lww.com/PAIN/B817. 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, available at http://links.lww.com/PAIN/B817). MAGMA tissue expression analysis found no significant association between gene expression and GWAS effect sizes for 53 tissues (Supplementary Figure S8D, available at http://links.lww.com/PAIN/B816).

Cross-referencing with other GWAS reports identified previously reported SNP associations with anthropometric traits (height, hip circumference, and offspring birth weight), hip or knee osteoarthritis, sleep-related phenotypes, and type 2 diabetes (Supplementary Table S13, available at http://links.lww.com/PAIN/B817), and significant overlap with genes reported to be associated with inflammatory skin disease, palmitic, and stearic acid levels (Supplementary Figure S9, available at http://links.lww.com/PAIN/B816). None of the genes previously targeted in candidate gene studies for pain[117] mapped to independent significant SNPs for the musculoskeletal factor.

4. Discussion

We ran Genomic SEM on 24 pain conditions in the UKBB to examine the structure of their shared genetic risk and characterize the genetic variants common to them. Our results identify a general factor that explains substantial genetic variance in pain conditions with different suspected etiologies and anatomic presentations and points to their shared systemic pathophysiology. Additionally, a second factor explains some of the shared genetic variance across musculoskeletal conditions. The 2-factor model explains the pattern of genetic associations among disorders better than either the anatomic or the etiologic grouping of known inflammatory disorders. The shared genetic burden is also apparent in our network analyses.

We identified 184 novel targets for cross-condition chronic pain (Supplementary Table S5, available at http://links.lww.com/PAIN/B817). Two lines of evidence suggest that genes associated with our general pain factor have an important role in the central nervous system (CNS). First, the genes most associated with the general factor for pain also have the highest expression in brain tissues. Second, the pathways of these genes include CNS development and maintenance. Our study further adds to existing evidence for the role of *DCC*,[52,87,97] an axonal guidance mediator,[116] in chronic pain. Beyond CNS, the pathways of genes associated with the general pain factor also 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 new molecular targets we identify can be cross-referenced with animal models in "reverse-translation" approaches to better understand the pathophysiology of chronic pain and develop novel treatments.

We note overlap between the genetic variants associated with our general factor and those previously reported in GWAS for cognitive, structural, mood, sleep, and personality traits, regulation of inflammation and neuroplasticity, and psychiatric disorders. This overlap underscores the highly multifaceted nature of pain as a biopsychosocial condition while elucidating the key genes and systems involved.[14,19,20,64,104,105] This pleiotropy, or the association of genes with multiple conditions, together with the polygenic nature of the general factor we identified, exemplifies the frequently observed many-to-many mapping between genes and traits.[111] Identifying links between polygenic risk profiles of different disorders can provide important information on susceptibility and treatment.

As might be expected, the genes associated with the musculoskeletal factor are fewer, and their pathways are less diverse. They implicate skeletal development, choline transport, signalling, and transcription machinery. Notably, they do not implicate the nervous system. Overlap with previous GWAS results suggests involvement of variants affecting anthropometric traits and thereby body-structural mechanisms. Similar associations have been shown for musculoskeletal pain conditions before: genetic overlap in osteoarthritis with height and BMI,[27] back pain,[33] and multisite musculoskeletal pain[102] with structural–anatomic genes.

Our work builds on earlier genetic analyses of combinations of pain conditions selected based on anatomic proximity or hypothesized etiology.[42,62,84,108,113] Although most studies have been conducted in twins, several large-scale chronic pain GWAS, with strengths complementary to twin studies,[34] have been published on pain in the past 3 years.[33,68,69,71–73,96] These reports, which used earlier releases of the UKBB before primary care data availability, include 3 on multisite pain.[50,51,52] Most recently, another study reported a polygenic risk score for pain spreading that was associated with a phenotypic profile dominated by mood, sleep, and neuroticism.[97]

Studies of multisite pain differ from our study in a critical way. They may show genes associated with only one of the constituent conditions to be associated with the average count of pain sites (widespreadness), if that condition is present in several combinations of comorbid pain sites. Thus, given a genetic variant associated with hip pain and 2 three-site combinations—hip, knee, and back pain and hip, neck, and stomach pain—this variant will appear to be associated with a widespreadness score of 3 without having associations with any of the other constituent conditions in this example. Analyses of association with multisite pain are thus not designed to identify the genetic variants shared among multiple distinct conditions. However, Genomic SEM is designed to identify genetic variants that are truly common to different conditions, and it enabled us to capture genetic risk for chronic pain, regardless of etiology or symptomatology.

The existence of cross-condition genetic risk factors challenges the current clinical practice of grouping and treating chronic pain conditions based on location of symptoms on the body or suspected etiology.[29] Evidence for central processes beyond local pathophysiology has been accumulating. Biopsychosocial factors,[19,20,64,104,105] neuroinflammation and neuroplasticity,[5,6,26,35,53,74,77,82,103,118], and neuroimaging traits,[2,4,15,44,47,54,57,58,65,76,81,85,89,115] have all been reported to modulate pain experience and chronic pain risk. This work has culminated in a new classification system for chronic pain in ICD-11, which shifts pain category assignment to a

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hierarchical approach: etiology, then pathophysiology, and then body site.[100] It also includes chronic primary pain as a diagnosis "agnostic with regard to etiology."[78] These changes are important steps toward aligning diagnosis with pathophysiology, and genetics is an important piece of the puzzle. Our Genomic SEM model suggests that, in addition to condition-specific genetic susceptibility, there is a genetically encoded pathophysiology common to different chronic pain conditions and supports the view of chronic pain as a disorder involving systemic pathology.[114] This study further identifies genetic risk markers that are shared across distinct pain conditions contributing to a new, biologically grounded way of conceptualizing chronic pain conditions. The strong association between expression of chronic pain risk genes in the brain and cross-condition chronic pain provides additional evidence that the common genetic risk markers we identified may be associated with central sensitization and chronic primary pain, which have both been linked to alterations in the brain and spinal cord.[110,114]

4.1. Limitations

There are several notable limitations of this study. First, although the annotated genetic associations for the general factor suggest a combination of systemic biological and psychological predispositions, the precise mechanisms underlying these predispositions need to be elucidated in future studies before they can be translated to clinical applications. In service of this goal, the pathways implicated by the SNPs and genes we have identified can be targeted in follow-up studies to further elucidate the systemic mechanisms that lead to chronic pain.

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, evidence for their role in pain is abundant[38,49,92] and should be investigated further.

Third, we do not expect the genetic patterns we identified to be either selective or sufficient to explain cross-condition chronic pain. This is because of both pleiotropy (the effects of one gene on several different conditions) and environmental effects, which are certain to play a large part in the development of chronic pain.

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

Fifth, given sample size limitations in the UKBB for non-European individuals, we were not able to test our model for generalizability across ancestral populations, which we attempted to do in the next largest sample: South Asians (Supplementary Table 2, available at http://links.lww.com/PAIN/B817).

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 study aims to establish risk factors for postsurgical pain from genetic, multi-omics, psychosocial, and neuroimaging measures in another large sample (2800 patients; a2cps.org). Our factor scores could be tested alongside previously identified genetic patterns for multisite pain and compared with them as prognostic risk factors for chronic postsurgical pain.

5. Conclusion

In summary, our findings confirm that there is a genetic susceptibility common to a broad range of diverse chronic pain conditions. The shared pathophysiology for the conditions examined here seems 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 genetic factor. Our study calls for 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 by the clinician specializing in it, but is seen as a manifestation of an underlying shared pathology with concurrent risk for other pain conditions and previously unexplored centralized treatment targets. Future work will go beyond pain conditions and explore genetic links with psychological and physical traits to help identify patients who would benefit most from specific interventions.

Conflict of interest statement

The authors have no conflict of interest to declare.

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References

[1] Apkarian VA, Sosa Y, Krauss BR, Thomas SP, Fredrickson BE, Levy RE, Harden NR, Chialvo DR. Chronic pain patients are impaired on an emotional decision-making task. PAIN 2004;108:129–36.
[2] Ayoub LJ, Seminowicz DA, Moayedi M. A meta-analytic study of experimental and chronic orofacial pain excluding headache disorders. Neuroimage Clin 2018;20:901–12.
[3] Bair E, Gaynor S, Slade GD, Ohrbach R, Fillingim RB, Greenspan JD, Dubner R, Smith SB, Diatchenko L, Maixner W. Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study. PAIN 2016;157:1266–78.
[4] Baliki MN, Baria AT, Apkarian AV. The cortical rhythms of chronic back pain. J Neurosci 2011;31:13981–90.
[5] Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. PLoS One 2014;9:e106133.
[6] Bannister K, Dickenson A. The plasticity of descending controls in pain: translational probing. J Physiol 2017;595:4159–66.
[7] Barrat A, Barthelemy M, Pastor-Satorras R, Vespignani A. The architecture of complex weighted networks. Proc Natl Acad Sci USA 2004;101:3747–52.
[8] Bornovalova MA, Choate AM, Fatimah H, Petersen KJ, Wiernik BM. Appropriate use of bifactor analysis in psychopathology research: appreciating benefits and limitations. Biol Psychiatry 2020;88:18–27.
[9] Bortsov AV, Smith JE, Diatchenko L, Soward AC, Ulirsch JC, Rossi C, Swor RA, Hauda WE, Peak DA, Jones JS, Holbrook D, Rathlev NK, Foley

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KA, Lee DC, Collette R, Domeier RM, Hendry PL, McLean SA. Polymorphisms in the glucocorticoid receptor co-chaperone FKBP5 predict persistent musculoskeletal pain after traumatic stress exposure. PAIN 2013;154:1419–26.
[10] Brandes U. A faster algorithm for betweenness centrality. J Math Sociol 2001;25:163–77.
[11] Bulik-Sullivan BK, Loh P-R, Finucane HK, Ripke S, Yang J, Patterson N, Daly MJ, Price AL, Neale BM. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 2015;47:291–5.
[12] Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, Cortes A, Welsh S, Young A, Effingham M, McVean G, Leslie S, Allen N, Donnelly P, Marchini J. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562:203–9.
[13] Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, Meier MH, Ramrakha S, Shalev I, Poulton R, Moffitt TE. The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci 2014;2:119–37.
[14] Cay M, Gonzalez-Heydrich J, Teicher MH, van der Heijden H, Ongur D, Shinn AK, Upadhyay J. Childhood maltreatment and its role in the development of pain and psychopathology. Lancet Child Adolesc Health 2022;6:195–206.
[15] Čeko M, Shir Y, Ouellet JA, Ware MA, Stone LS, Seminowicz DA. Partial recovery of abnormal insula and dorsolateral prefrontal connectivity to cognitive networks in chronic low back pain after treatment. Hum Brain Mapp 2015;36:2075–92.
[16] Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation plink: rising to the challenge of larger and richer datasets. Gigascience 2015;4:7.
[17] Chen FF, Hayes A, Carver CS, Laurenceau J-P, Zhang Z. Modeling general and specific variance in multifaceted constructs: a comparison of the bifactor model to other approaches. J Personal 2012;80:219–51.
[18] Chen P-Y, Yang C-M, Morin CM. Validating the cross-cultural factor structure and invariance property of the insomnia severity index: evidence based on ordinal EFA and CFA. Sleep Med 2015;16:598–603.
[19] Clauw DJ. Fibromyalgia and related conditions. In: Mayo clinic proceedings. Vol. 90. Elsevier, 2015. p. 680–92.
[20] Clauw DJ, Essex MN, Pitman V, Jones KD. Reframing chronic pain as a disease, not a symptom: rationale and implications for pain management. Postgrad Med 2019;131:185–98.
[21] Csardi G, Nepusz T. The igraph software package for complex network research. Inter J Comp Syst 2006;1695:1–9.
[22] de Leeuw CA, Mooij JM, Heskes T, Posthuma D. Magma: generalized gene-set analysis of GWAS data. PLoS Comput Biol 2015;11:e1004219.
[23] Din HM, Minhatb HS. Psychometric properties of anxiety about aging scale among Malaysian youths. J Appl Struct Equ Model 2021;5:9–18.
[24] Dutta D, Brummett CM, Moser SE, Fritsche LG, Tsodikov A, Lee S, Clauw DJ, Scott LJ. Heritability of the fibromyalgia phenotype varies by age. Arthritis Rheumatol 2020;72:815–23.
[25] Eccleston C, Wastell S, Crombez G, Jordan A. Adolescent social development and chronic pain. Eur J Pain 2008;12:765–74.
[26] Edelmayer RM, Vanderah TW, Majuta L, Zhang E-T, Fioravanti B, De Felice M, Chichorro JG, Ossipov MH, King T, Lai J, Kori SH, Nelsen AC, Cannon KE, Heinricher MM, Porreca F. Medullary pain facilitating neurons mediate allodynia in headache-related pain. Ann Neurol 2009;65:184–93.
[27] Elliott KS, Chapman K, Day-Williams A, Panoutsopoulou K, Southam L, Lindgren CM, Arden N, Aslam N, Birrell F, Carluke I, Carr A, Deloukas P, Doherty M, Loughlin J, McCaskie A, Ollier WER, Rai A, Ralston S, Reed MR, Spector TD, Valdes AM, Wallis GA, Wilkinson M, Zeggini E. Evaluation of the genetic overlap between osteoarthritis with body mass index and height using genome-wide association scan data. Ann Rheum Dis 2013;72:935–41.
[28] Eppstein D, Löffler M, Strash D. Listing all maximal cliques in sparse graphs in near-optimal time. arXiv preprint. arXiv preprint arXiv:1006.5440. 2010 Jun 28.
[29] Fillingim RB, Loeser JD, Baron R, Edwards RR. Assessment of chronic pain: domains, methods, and mechanisms. J Pain 2016;17:T10–20.
[30] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice ASC, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73.
[31] Fokkema M, Greiff S. How performing PCA and CFA on the same data equals trouble: overfitting in the assessment of internal structure and some editorial thoughts on it [Editorial]. Eur J Psychol Assess 2017;33:399–402.
[32] Foote IF, Jacobs BM, Mathlin G, Watson CJ, Bothongo PL, Waters S, Dobson R, Noyce AJ, Bhui KS, Korszun A, Marshall CR. The genetic architecture of Alzheimer's disease risk: a genomic structural equation modelling study. medRxiv 2021, doi: 10.1101/2021.02.23.21252211.
[33] Freidin MB, Freidin MB, Tsepilov YA, Tsepilov YA, Palmere M, Palmere M, Karssen LC, Karssen LC, Suri P, Suri P, Aulchenko YS, Aulchenko YS, Williams FM, Williams FM. Insight into the genetic architecture of back pain and its risk factors from a study of 509,000 individuals. PAIN 2019;160:1361–73.
[34] Friedman NP, Banich MT, Keller MC. Twin studies to GWAS: there and back again. Trends Cogn Sci 2021;25:855–69.
[35] Geha P, Waxman SG. Pain perception: multiple matrices or one? JAMA Neurol 2016;73:628–30.
[36] Gerbing DW, Hamilton JG. Viability of exploratory factor analysis as a precursor to confirmatory factor analysis. Struct Equ Modeling 1996;3:62–72.
[37] Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH, Farh K-H, Cuenca-Leon E, Muona M, Furlotte NA, Kurth T, Ingason A, McMahon G, Ligthart L, Terwindt GM, Kallela M, Freilinger TM, Ran C, Gordon SG, Stam AH, Steinberg S, Borck G, Koiranen M, Quaye L, Adams HHH, Lehtimäki T, Sarin AP, Wedenoja J, Hinds DA, Buring JE, Schürks M, Ridker PM, Hrafnsdottir MG, Stefansson H, Ring SM, Hottenga JJ, Penninx BWJH, Färkkilä M, Artto V, Kaunisto M, Vepsäläinen S, Malik R, Heath AC, Madden PAF, Martin NG, Montgomery GW, Kurki MI, Kals M, Mägi R, Pärn K, Hämäläinen E, Huang H, Byrnes AE, Franke L, Huang J, Stergiakouli E, Lee PH, Sandor C, Webber C, Cader Z, Muller-Myhsok B, Schreiber S, Meitinger T, Eriksson JG, Salomaa V, Heikkilä K, Loehrer E, Uitterlinden AG, Hofman A, van Duijn CM, Cherkas L, Pedersen LM, Stubhaug A, Nielsen CS, Männikkö M, Mihailov E, Milani L, Göbel H, Esserlind AL, Christensen AF, Hansen TF, Werge T, Kaprio J, Aromaa AJ, Raitakari O, Ikram MA, Spector T, Järvelin MR, Metspalu A, Kubisch C, Strachan DP, Ferrari MD, Belin AC, Dichgans M, Wessman M, van den Maagdenberg AMJM, Zwart JA, Boomsma DI, Smith GD, Stefansson K, Eriksson N, Daly MJ, Neale BM, Olesen J, Chasman DI, Nyholt DR, Palotie A. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet 2016;48:856–66.
[38] Gregory NS, Harris AL, Robinson CR, Dougherty PM, Fuchs PN, Sluka KA. An overview of animal models of pain: disease models and outcome measures. J Pain 2013;14:1255–69.
[39] Grotzinger AD, Mallard TT, Akingbuwa WA, Ip HF, Adams MJ, Lewis CM, McIntosh AM, Grove J, Dalsgaard S, Peter-Lesch K, Strom N, Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic and molecular genetic levels of analysis. Nature Genetics 2022;54:548–59.
[40] Grotzinger AD, Rhemtulla M, de Vlaming R, Ritchie SJ, Mallard TT, Hill WD, Ip HF, Marioni RE, McIntosh AM, Deary IJ, Koellinger PD, Harden KP, Nivard MG, Tucker-Drob EM. Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. Nat Hum Behav 2019;3:513–25.
[41] Han X, Ashar YK, Kragel P, Petre B, Schelkun V, Atlas LY, Chang LJ, Jepma M, Koban L, Losin EAR, Roy M, Woo CW, Wager TD. Effect sizes and test-retest reliability of the fMRI-based neurologic pain signature. Neuroimage 2022;247:118844.
[42] Hartvigsen J, Nielsen J, Kyvik KO, Fejer R, Vach W, Iachine I, Leboeuf-Yde C. Heritability of spinal pain and consequences of spinal pain: a comprehensive genetic epidemiologic analysis using a population-based sample of 15,328 twins ages 20–71 years. Arthritis Rheum 2009;61:1343–51.
[43] Hengstebeck E, Roskos S, Breejen K, Arnetz B, Arnetz J. Chronic pain disrupts ability to work by interfering with social function: a cross-sectional study. Scand J Pain 2017;17:397–402.
[44] Hocking L, Morris A, Dominiczak A, Porteous D, Smith B, Smith B. Heritability of chronic pain in 2195 extended families. Eur J Pain 2012;16:1053–63.
[45] Hu L-T, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Model 1999;6:1–55.
[46] Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006;11:193–206.
[47] Jefferson T, Kelly CJ, Martina M. Differential rearrangement of excitatory inputs to the medial prefrontal cortex in chronic pain models. Front Neural Circuits 2021;15:791043.

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[48] Jensen AR. The g factor: psychometrics and biology. In The Nature of Intelligence: Novartis Foundation Symposium 233 2000 Oct 11 (Vol. 233, pp. 37-57). Chichester, UK: John Wiley & Sons, Ltd.

[49] Ji R-R, Xu Z-Z, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. Nat Rev Drug Discov 2014;13:533–48.

[50] Johnston KJ, Adams MJ, Nicholl BI, Ward J, Strawbridge RJ, Ferguson A, McIntosh AM, Bailey ME, Smith DJ. Genome-wide association study of multisite chronic pain in UK Biobank. PLoS Genet 2019;15:e1008164.

[51] Johnston KJ, Ward J, Ray PR, Adams MJ, McIntosh AM, Smith BH, Strawbridge RJ, Price TJ, Smith DJ, Nicholl BI, Bailey MES. Sex-stratified genome-wide association study of multisite chronic pain in UK Biobank. PLoS Genet 2021;17:e1009428.

[52] Khoury S, Parisien M, Thompson SJ, Vachon-Presseau E, Roy M, Martinsen AE, Winsvold BS, Skogholt AH, Brumpton B, Willer CJ, Fors EA, Heuch I, Nielsen JB, Storheim K, Hagen K, Nilsen KB, Hveem K, Fritsche L, Thomas LF, Pedersen LM, Gabrielsen ME, Johnsen MB, Lie MU, Holmen O, Børte S, Stensland SØ, Zhou W, Mundal IP, Zwart JA, Kania A, Mogil JS, Diatchenko L. Genome-wide analysis identifies impaired axonogenesis in chronic overlapping pain conditions. Brain 2021;145:1111–23.

[53] Kline RB. Principles and practice of structural equation modeling. New York: Guilford Publications, 2015.

[54] Kong J, Spaeth B, Wey H-Y, Cheetham A, Cook AH, Jensen K, Tan Y, Liu H, Wang D, Loggia ML, Napadow V, Smoller JW, Wasan AD, Gollub RL. S1 is associated with chronic low back pain: a functional and structural MRI study. Mol Pain 2013;9:43.

[55] Kyriazos TA. Applied psychometrics: sample size and sample power considerations in factor analysis (EFA, CFA) and SEM in general. Psychology 2018;9:2207–30.

[56] Lau C-I, Lin C-C, Chen W-H, Wang H-C, Kao CH. Association between migraine and irritable bowel syndrome: a population-based retrospective cohort study. Eur J Neurol 2014;21:1198–204.

[57] Lee J-J, Kim HJ, Čeko M, Park B-y, Lee SA, Park H, Roy M, Kim S-G, Wager TD, Woo CW. A neuroimaging biomarker for sustained experimental and clinical pain. Nat Med 2021;27:174–82.

[58] Lee J, Protsenko E, Lazaridou A, Franceschelli O, Ellingsen D-M, Mawla I, Isenburg K, Berry MP, Galenkamp L, Loggia ML, Wasan AD, Edwards RR, Napadow V. Encoding of self-referential pain catastrophizing in the posterior cingulate cortex in fibromyalgia. Arthritis Rheumatol 2018;70:1308–18.

[59] Lobo JJ, Ayoub LJ, Moayedi M, Linnstaedt SD. Hippocampal volume, FKBP5 genetic risk alleles, and childhood trauma interact to increase vulnerability to chronic multisite musculoskeletal pain. Sci Rep 2022;12:6511–10.

[60] Lonsdale J, Thomas J, Salvatore M, Phillips R, Lo E, Shad S, Hasz R, Walters G, Garcia F, Young N, Foster B, Moser M, Karasik E, Gillard B, Ramsey K, Sullivan S, Bridge J, Magazine H, Syron J, Fleming J, Siminoff L, Traino H, Mosavel M, Barker L, Jewell S, Rohrer D, Maxim D, Filkins D, Harbach P, Cortadillo E, Berghuis B, Turner L, Hudson E, Feenstra K, Sobin L, Robb J, Branton P, Korzeniewski G, Shive C, Tabor D, Qi L, Groch K, Nampally S, Buia S, Zimmerman A, Smith A, Burges R, Robinson K, Valentino K, Bradbury D, Cosentino M, Diaz-Mayoral N, Kennedy M, Engel T, Williams P, Erickson K, Ardlie K, Winckler W, Getz G, DeLuca D, MacArthur D, Kellis M, Thomson A, Young T, Gelfand E, Donovan M, Meng Y, Grant G, Mash D, Marcus Y, Basile M, Liu J, Zhu J, Tu Z, Cox NJ, Nicolae DL, Gamazon ER, Im HK, Konkashbaev A, Pritchard J, Stevens M, Flutre T, Wen X, Dermitzakis ET, Lappalainen T, Guigo R, Monlong J, Sammeth M, Koller D, Battle A, Mostafavi S, McCarthy M, Rivas M, Maller J, Rusyn I, Nobel A, Wright F, Shabalin A, Feolo M, Sharopova N, Sturcke A, Paschal J, Anderson JM, Wilder EL, Derr LK, Green ED, Struewing JP, Temple G, Volpi S, Boyer JT, Thomson EJ, Guyer MS, Ng C, Abdallah A, Colantuoni D, Insel TR, Koester SE, Little AR, Bender PK, Lehner T, Yao Y, Compton CC, Vaught JB, Sawyer S, Lockhart NC, Demchok J, Moore HF. The genotype-tissue expression (GTEx) project. Nat Genet 2013;45:580–5.

[61] Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping chronic pain conditions: implications for diagnosis and classification. J Pain 2016;17:T93–107.

[62] Malkin I, Williams FM, LaChance G, Spector T, MacGregor AJ, Livshits G. Low back and common widespread pain share common genetic determinants. Ann Hum Genet 2014;78:357–66.

[63] Mallard TT, Linn´er RK, Grotzinger AD, Sanchez-Roige S, Seidlitz J, Okbay A, de Vlaming R, Meddens SF, Palmer AA, Davis LK. Tucker-Drob EM. Multivariate GWAS of psychiatric disorders and their cardinal symptoms reveal two dimensions of cross-cutting genetic liabilities. Cell Genomics 2022;2:100140.

[64] Mansour A, Farmer M, Baliki M, Apkarian AV. Chronic pain: the role of learning and brain plasticity. Restor Neurol Neurosci 2014;32:129–39.

[65] Martins D, Dipasquale O, Veronese M, Turkheimer F, Loggia ML, McMahon S, Howard MA, Williams SC. Transcriptional and cellular signatures of cortical morphometric remodelling in chronic pain, PAIN 2021;163:e759–73.

[66] Mayer S, Spickschen J, Stein KV, Crevenna R, Dorner TE, Simon J. The societal costs of chronic pain and its determinants: the case of Austria. PLoS One 2019;14:e0213889.

[67] Meints SM, Mawla I, Napadow V, Kong J, Gerber J, Chan S-T, Wasan AD, Kaptchuk TJ, McDonnell C, Carriere J, Rosen B, Gollub RL, Edwards RR. The relationship between catastrophizing and altered pain sensitivity in patients with chronic low back pain. PAIN 2019;160:833–43.

[68] Meng W, Adams MJ, Hebert HL, Deary IJ, McIntosh AM, Smith BH. A genome-wide association study finds genetic associations with broadly-defined headache in UK Biobank (n = 223,773). EBioMedicine 2018;28:180–6.

[69] Meng W, Adams MJ, Palmer CN, Agee M, Alipanahi B, Bell RK, Bryc K, Elson SL, Fontanillas P, Furlotte NA, Hicks B, Hinds DA, Huber KE, Jewett EM, Jiang Y, Kleinman A, Lin KH, Litterman NK, McCreight JC, McIntyre MH, McManus KF, Mountain JL, Noblin ES, Northover CAM, Pitts SJ, Poznik GD, Sathirapongsasuti JF, Shelton JF, Shringarpure S, Tian C, Tung JY, Vacic V, Wang X, Wilson CH, Shi J, Auton A, Ryan KA, Jordan JM, Mitchell BD, Jackson RD, Yau MS, McIntosh AM, Smith BH. Genome-wide association study of knee pain identifies associations with GDF5 and COL27A1 in UK Biobank. Commun Biol 2019;2:321–8.

[70] Meng W, Adams MJ, Reel P, Rajendrakumar A, Huang Y, Deary IJ, Palmer CN, McIntosh AM, Smith BH. Genetic correlations between pain phenotypes and depression and neuroticism. Eur J Hum Genet 2020;28:358–66.

[71] Meng W, Chan BW, Harris C, Freidin MB, Hebert HL, Adams MJ, Zheng H, Lu HZ, Ray D, Colvin LA. Meta-Analysis of the Genome-Wide Association Studies on Two Genetically Correlated Phenotypes Suggests Four New Risk Loci for Headaches. Phenomics 2023;3:64–76.

[72] Meng W, Deshmukh H, Zuydam N, Liu Y, Donnelly L, Zhou K; Wellcome Trust Case Control Consortium 2 (WTCCC2), Surrogate Markers for Micro- and Macro-Vascular Hard Endpoints for Innovative Diabetes Tools (SUMMIT) Study Group, Morris AD, Colhoun H, Palmer C, Smith B. A genome-wide association study suggests an association of Chr8p21.3 (GFRA2) with diabetic neuropathic pain. Eur J Pain 2015;19:392–9.

[73] Meng W, Reel PS, Nangia C, Rajendrakumar AL, Hebert HL, Guo Q, Adams MJ, Zheng H, Lu ZH, Ray D, Colvin LA. A Meta-Analysis of the Genome-Wide Association Studies on Two Genetically Correlated Phenotypes Suggests Four New Risk Loci for Headaches. Phenomics 2023;3:64–76.

[74] Miller Neilan R, Majetic G, Gil-Silva M, Adke AP, Carrasquillo Y, Kolber BJ. Agent-based modeling of the central amygdala and pain using cell-type specific physiological parameters. PLoS Comput Biol 2021;17:e1009097.

[75] Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex frontal lobe tasks: a latent variable analysis. Cogn Psychol 2000;41:49–100.

[76] Napadow V, Harris RE. What has functional connectivity and chemical neuroimaging in fibromyalgia taught us about the mechanisms and management of centralized pain? Arthritis Res Ther 2014;16:425.

[77] Navratilova E, Porreca F. Reward and motivation in pain and pain relief. Nat Neurosci 2014;17:1304–12.

[78] Nicholas M, Vlaeyen JW, Rief W, Barke A, Aziz Q, Benoliel R, Cohen M, Evers S, Gi- amberardino MA, Goebel A, Korwisi B, Perrot S, Svensson P, Wang SJ, Treede RD. The IASP classification of chronic pain for ICD-11: chronic primary pain. PAIN 2019;160:28–37.

[79] Niv D, Devor M. Chronic pain as a disease in its own right. Pain Practice. 2004;4:179–81.

[80] O'Connor LJ, Schoech AP, Hormozdiari F, Gazal S, Patterson N, Price AL. Extreme polygenicity of complex traits is explained by negative selection. Am J Hum Genet 2019;105:456–76.

[81] Osborne NR, Anastakis DJ, Davis KD. Peripheral nerve injuries, pain, and neuro- plasticity. J Hand Ther 2018;31:184–94.

[82] Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care 2014;8:143–51.

[83] Phillips CJ. Economic burden of chronic pain. Expert Rev Pharmacoecon Outcomes Res 2006;6:591–601.

[84] Plesh O, Noonan C, Buchwald DS, Goldberg J, Afari N. Temporomandibular disorder-type pain and migraine headache in women: a preliminary twin study. J Orofac Pain 2012;26:91–8.

[85] Quesada C, Kostenko A, Ho I, Leone C, Nochi Z, Stouffs A, Wittayer M, Caspani O, Brix Finnerup N, Mouraux A, Pickering G, Tracey I, Truini A,

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Treede R, Garcia-Larrea L. Human surrogate models of central sensitization: a critical review and practical guide. Eur J Pain 2021;25:1389–428.
[86] Raffaeli W, Arnaudo E. Pain as a disease: an overview. J Pain Res 2017; 10:2003–8.
[87] Schubert A-L, Held M, Sommer C, Üçeyler N. Reduced gene expression of netrin family members in skin and sural nerve specimens of patients with painful peripheral neuropathies. J Neurol 2019;266:2812–20.
[88] Schur EA, Afari N, Furberg H, Olarte M, Goldberg J, Sullivan PF, Buchwald D. Feeling bad in more ways than one: comorbidity patterns of medically unexplained and psychiatric conditions. J Gen Intern Med 2007;22:818–21.
[89] Seminowicz DA, Labus JS, Bueller JA, Tillisch K, Naliboff BD, Bushnell MC, Mayer EA. Regional gray matter density changes in brains of patients with irritable bowel syndrome. Gastroenterology 2010;139: 48–57.e2.
[90] Simon LS. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. J Pain Palliat Care Pharmacother 2012;26:197–8.
[91] Smith BH, Torrance N. Management of chronic pain in primary care. Curr Opin Support Palliat Care 2011;5:137–42.
[92] Sommer C, Leinders M, Üçeyler N. Inflammation in the pathophysiology of neuropathic pain. PAIN 2018;159:595–602.
[93] Stanos S, Brodsky M, Argoff C, Clauw DJ, DArcy Y, Donevan S, Gebke KB, Jensen MP, Lewis&Clark E, McCarberg B, Park PW, Turk DC, Watt S. Rethinking chronic pain in a primary care setting. Postgrad Med 2016; 128:502–15.
[94] Steglitz J, Buscemi J, Ferguson MJ. The future of pain research, education, and treatment: a summary of the IOM report relieving pain in America: a blueprint for transforming prevention, care, education, and research. Transl Behav Med 2012;2:6–8.
[95] Suri P, Morgenroth DC, Kwoh CK, Bean JF, Kalichman L, Hunter DJ. Low back pain and other musculoskeletal pain comorbidities in individuals with symptomatic osteoarthritis of the knee: data from the osteoarthritis initiative. Arthritis Care Res 2010;62:1715–23.
[96] Suri P, Palmer MR, Tsepilov YA, Freidin MB, Boer CG, Yau MS, Evans DS, Gelemanovic A, Bartz TM, Nethander M, Arbeeva L, Karssen L, Neogi T, Campbell A, Mellstrom D, Ohlsson C, Marshall LM, Orwoll E, Uitterlinden A, Rotter JI, Lauc G, Psaty BM, Karlsson MK, Lane NE, Jarvik GP, Polasek O, Hochberg M, Jordan JM, Van Meurs JBJ, Jackson R, Nielson CM, Mitchell BD, Smith BH, Hayward C, Smith NL, Aulchenko YS, Williams FMK. Genome-wide meta-analysis of 158,000 individuals of european ancestry identifies three loci associated with chronic back pain. PLoS Genet 2018;14:e1007601.
[97] Tanguay-Sabourin C, Fillingim M, Parisien M, Guglietti GV, Zare A, Norman J, Da-ano R, Perez J, Thompson SJ, Martel MO, Roy M, Diatchenko L, Vachon-Presseau E. A data-driven biopsychosocial framework determining the spreading of chronic pain. medRxiv 2022. doi: 10.1101/2022.07.22.22277850.
[98] Tian C, Gregersen PK, Seldin MF. Accounting for ancestry: population substructure and genome-wide association studies. Hum Mol Genet 2008;17:R143–50.
[99] Treede R-D, Kenshalo DR, Gracely RH, Jones AK. The cortical representation of pain. PAIN 1999;79:105–11.
[100] Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JW, Wang SJ. A classification of chronic pain for ICD-11. PAIN 2015;156:1003–7.
[101] Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JW, Wang SJ. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). PAIN 2019;160:19–27.
[102] Tsepilov YA, Freidin MB, Shadrina AS, Sharapov SZ, Elgaeva EE, Zundert Jv, Karssen L, Suri P, Williams FM, Aulchenko YS. Analysis of genetically independent phenotypes identifies shared genetic factors associated with chronic musculoskeletal pain conditions. Commun Biol 2020;3:329.
[103] Tylee DS, Sun J, Hess JL, Tahir MA, Sharma E, Malik R, Worrall BB, Levine AJ, Martinson JJ, Nejentsev S, Speed D, Fischer A, Mick E, Walker BR, Crawford A, Grant SFA, Polychronakos C, Bradfield JP, Sleiman PMA, Hakonarson H, Ellinghaus E, Elder JT, Tsoi LC, Trembath RC, Barker JN, Franke A, Dehghan A, Faraone SV, Glatt SJ. Genetic correlations among psychiatric and immune-related phenotypes based on genome-wide association data. Am J Med Genet B Neuropsychiatr Genet 2018;177:641–57.
[104] Vachon-Presseau E, Centeno M, Ren W, Berger S, Tétreault P, Ghantous M, Baria A, Farmer M, Baliki M, Schnitzer T, Apkarian A. The emotional brain as a predictor and amplifier of chronic pain. J Dent Res 2016;95:605–12.
[105] Vachon-Presseau E, Roy M, Martel M-O, Caron E, Marin M-F, Chen J, Albouy G, Plante I, Sullivan MJ, Lupien SJ, Rainville P. The stress model of chronic pain: evidence from basal cortisol and hippocampal structure and function in humans. Brain 2013;136:815–27.
[106] van Bork R, Epskamp S, Rhemtulla M, Borsboom D, van der Maas HL. What is the p-factor of psychopathology? Some risks of general factor modeling. Theor Psychol 2017;27:759–73.
[107] van der Gaag WH, Roelofs PD, Enthoven WT, van Tulder MW, Koes BW. Non- steroidal anti-inflammatory drugs for acute low back pain. Cochrane Database Syst Rev 2020;2:CD012087.
[108] Vehof J, Zavos HM, Lachance G, Hammond CJ, Williams FM. Shared genetic factors underlie chronic pain syndromes. PAIN 2014;155:1562–8.
[109] Walitt B, Ceko M, L Gracely J, H Gracely R. Neuroimaging of central sensitivity syndromes: key insights from the scientific literature. Curr Rheumatol Rev 2016;12:55–87.
[110] Wang Z, Tang Q, Liu B, Zhang W, Chen Y, Ji N, Peng Y, Yang X, Cui D, Kong W, Tang X, Yang T, Zhang M, Chang X, Zhu J, Huang M, Feng Z. Gray matter abnormalities in patients with chronic primary pain: a coordinate-based meta-analysis. J Biomed Res 2022;25:1–13.
[111] Watanabe K, Stringer S, Frei O, Umićević Mirkov M, de Leeuw C, Polderman TJ, van der Sluis S, Andreassen OA, Neale BM, Posthuma D. A global overview of pleiotropy and genetic architecture in complex traits. Nat Genet 2019;51:1339–48.
[112] Watanabe K, Taskesen E, Van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun 2017;8:1826.
[113] Williams FM, Spector TD, MacGregor AJ. Pain reporting at different body sites is explained by a single underlying genetic factor. Rheumatology 2010;49:1753–5.
[114] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. PAIN 2011;152:S2–15.
[115] Wrigley PJ, Press SR, Gustin SM, Macefield VG, Gandevia SC, Cousins MJ, Middleton JW, Henderson LA, Siddall P. Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. PAIN 2009;141:52–9.
[116] Wu C-H, Yuan X-C, Gao F, Li H-P, Cao J, Liu Y-S, Yu W, Tian B, Meng X-F, Shi J, Pan HL, Li M. Netrin-1 contributes to myelinated afferent fiber sprouting and neuropathic pain. Mol Neurobiol 2016;53:5640–51.
[117] Zaitlen N, Kraft P. Heritability in the genome-wide association era. Hum Genet 2012;131:1655–64.
[118] Zhou H, Zhang Q, Martinez E, Dale J, Hu S, Zhang E, Liu K, Huang D, Yang G, Chen Z, Wang J. Ketamine reduces aversion in rodent pain models by suppressing hyperactivity of the anterior cingulate cortex. Nat Commun 2018;9:3751.
[119] Zorina-Lichtenwalter K, Meloto CB, Khoury S, Diatchenko L. Genetic predictors of human chronic pain conditions. Neuroscience 2016;338: 36–62.

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