General Section
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Brain-specific genes contribute to chronic but not to acute back pain

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Abstract

Introduction: Back pain is the leading cause of disability worldwide. Although most back pain cases are acute, 20% of acute pain patients experience chronic back pain symptoms. It is unclear whether acute pain and chronic pain have similar or distinct underlying genetic mechanisms.

Objectives: To characterize the molecular and cellular pathways contributing to acute and chronic pain states.

Methods: Cross-sectional observational genome-wide association study.

Results: A total of 375,158 individuals from the UK Biobank cohort were included in the discovery of genome-wide association study. Of those, 70,633 (19%) and 32,209 (9%) individuals met the definition of chronic and acute back pain, respectively. A total of 355 single nucleotide polymorphism grouped into 13 loci reached the genome-wide significance threshold ($5x10^{-8}$) for chronic back pain, but none for acute. Of these, 7 loci were replicated in the Nord-Trøndelag Health Study (HUNT) cohort (19,760 chronic low back pain cases and 28,674 pain-free controls). Single nucleotide polymorphism heritability was 4.6% ($P=1.4x10^{-78}$) for chronic back pain and 0.81% (P=1.4x10-8) for acute back pain. Similar differences in heritability estimates between acute and chronic back pain were found in the HUNT cohort: 3.4% (P=0.0011) and 0.6% (P=0.851), respectively. Pathway analyses, tissue-specific heritability enrichment analyses, and epigenetic characterization suggest a substantial genetic contribution to chronic but not acute back pain from the loci predominantly expressed in the central nervous system.

Conclusion: Chronic back pain is substantially more heritable than acute back pain. This heritability is mostly attributed to genes expressed in the brain.

Keywords: Back pain, Genomics, Brain

1. Introduction

Back pain is the world's leading cause of disability, reducing quality of life, and imposing significant health care costs.[10,12,27,51] According to the International Association for the Study of Pain criteria, a back pain episode lasting less than 3 months is defined as acute back pain, whereas pain lasting for 3 months or longer is defined as chronic.[14] Although most individuals with acute back pain experience resolution of their pain,[9,21] a substantial proportion of these cases transition to chronic back pain. As a result, chronic back pain is the most common painful condition which

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affects 10% to 15% of the adult population.[10,27,51] Mechanisms involved in the development of chronic back pain remain largely unknown and seem to be different from causes leading to the onset of acute back pain.

Heritability estimates for back pain from twin studies range from 30% to 68%.[5,24,29,35] Twin studies also show shared heritability between chronic back pain and lumbar disc degeneration,[5] depression,[36] anxiety,[36] education,[52] obesity,[13] and chronic widespread musculoskeletal pain.[31] Recent genome-wide association studies (GWAS) using the UK Biobank cohort have identified a number of genes associated with chronic back pain, including *SPOCK2*, *SOX5*, and *DCC*.[18,19,47] These studies confirm genetic involvement both in the etiology of chronic back pain and its related comorbidities.

Despite the mounting evidence that acute and chronic back pain are distinct states with different pathologies, there is a gap in knowledge about the genetic risk factors and molecular pathophysiology associated with acute vs chronic back pain. Previous genetic studies have looked either at back pain in general[18] or only at the chronic pain.[47] One important question is whether acute pain and chronic pain have similar underlying genetic pathways. Here, we performed GWAS for both acute and chronic back pain groups in 2 large human cohorts to characterize the corresponding molecular and cellular pathways contributing to these pain states.

2. Methods

2.1. The UK Biobank cohort

The UK Biobank cohort was used as a discovery cohort. This cohort is a high-powered prospective study of 500,000 people recruited in the United Kingdom.[1,44] It is mainly comprised of individuals of Anglo-American ancestry whose ages range between 37 and 73 years, with a female-to-male participant ratio of about 1.2:1. Chronic cases were defined as those answering "yes" to the question "Have you had back pains for more than 3 months?" (field 3571). This question was asked to participants if they answered "yes" for the "Back Pain" option at this question: "In the last month, have you experienced any of the following that interfered with your usual activities?" (field 6159). Participants were discarded based on the following criteria: answering "no," "do not know," or "prefer not to answer" (field 3571); not "White British"; failed genotyping quality control or sex mismatch; and voluntary withdrawal from the study. Acute back pain cases were identified as those answering "no" at field 3571. All other participants (ie, those who did not meet the criteria for acute or chronic back pain) were qualified as controls. Therefore, control individuals might have experienced acute or chronic pain at other bodily sites than in the back. Genotyping, quality control, and genomic imputation in the UK Biobank cohort were previously described.[8]

2.2. The HUNT cohort

The Nord-Trøndelag Health Study (HUNT) cohort was used for replication of results. The HUNT study has been conducted in Nord-Trøndelag County, Norway, in 3 consecutive waves: HUNT in 1984 to 1986, HUNT2 in 1995 to 1997, and HUNT3 in 2006 to 2008.[26] This work combines baseline data from the second survey, HUNT2,[22] and the third survey, HUNT3.[26] All residents of Norway aged 20 years and older were invited to take part in the HUNT2 survey. They were requested to complete a questionnaire on health status and invited to a clinical consultation that included measuring height and weight. In the HUNT3 survey 11 years later, similar information was collected using a questionnaire and a clinical examination. Each participant in the HUNT2 and HUNT3 surveys signed a written informed consent regarding the collection and use of data for research purposes.

One question in the HUNT2 and HUNT3 questionnaires was expressed: "During the last year, have you suffered from pain and/or stiffness in your muscles and joints that has lasted for at least 3 consecutive months?" Each participant answering yes was given the following question: "Where did you have these complaints?" Several body regions were listed. Individuals answering yes to the first question and including the lower back as a relevant region were regarded as having chronic lower back pain.[7] Acute low back pain cases (n = 4,379) were defined as those who had lumbar pain in the last month (at HUNT2), but not had musculoskeletal pain for more than 3 of the past 12 months (at HUNT2). Controls (n = 11,309) were defined as those participants without musculoskeletal pain in the last month or musculoskeletal pain for more than 3 of the past 12 months (at HUNT2) and if they did not have musculoskeletal pain for more than 3 of the past 12 months (at HUNT3). Chronic low back pain cases (n = 19,760) were defined as those who had lumbar pain for more than 3 of the past 12 months. Controls (n = 28,674) had no musculoskeletal pain for more than 3 of the past 12 months at either HUNT2 or HUNT3. Genotyping of study subjects was performed in 3 batches using the Illumina HumanCoreExome (Illumina Inc, San Diego, CA).

2.3. Statistical analyses

Genome-wide association tests in the UK Biobank cohort were performed using a linear mixed model as implemented in BOLT-LMM software, version 2.3.[28] Covariates were sex, age^2, genotyping platform, first 40 genetic principal components, and recruitment centers. Kinship was considered by BOLT-LMM using genotyped position data. Retained single nucleotide polymorphisms (SNPs) had minor allele frequencies of at least one-in-a-thousand, departed from Hardy–Weinberg equilibrium with *P*-values greater or equal to 10^{-12} and were part of the Haplotype Reference Consortium panel.[32] Association analyses in the HUNT cohort were performed using a mixed logistic regression, adjusted for sex, genotyping batch, and 5 principal components.

Epigenetic data for functional characterization of GWAS significant SNPs was taken from the NIH Roadmap Epigenomics Consortium.[41] At each significant locus, the list of SNPs in high linkage disequilibrium (LD) ($r^2 \geq 0.5$) with the locus' lead SNP was retrieved from LDlink[30] using the Great Britain population as the reference. We used the "intersect" option of the bedtools[38] to retrieve high-LD SNPs that overlapped with epigenetic features. Two analyses of epigenetic markers were performed: the first one in relation to the overlap of high-LD SNPs with known epigenetic activation marker peaks and the second one in relation to the overlap with NIH Roadmap's 15 states chromatin model built from peaks of activation or repression markers, focusing on transcription start sites (state 1), transcription enhancers (states 6 or 7) indicating active transcription, and bivalent or poised transcription start site (state 10) indicating the absence of active transcription. For analyses of activation peaks, retained broad peaks had experimental ChIP-Seq evidence *P*-values $\leq (0.05/[13 \times 19 \times 3])$, correcting for 13 genome-wide significant loci in 19 pain-relevant tissues for 3 epigenetic activation markers (H3K4me3, H3K4me1, and H3K36me3). For chromatin states,

we only considered the presence of an overlap with one of these states (because no *P*-values were available), prioritized as follows: state 1, states 6 and 7, and state 10. All data files were downloaded from the following URLs:

https://egg2.wustl.edu/roadmap/data/byFileType/peaks/consolidated/gappedPeak/, https://egg2.wustl.edu/roadmap/data/byFileType/chromhmmSegmentations/ChmmModels/coreMarks/jointModel/final/.

Partitioned heritability analyses were performed to determine heritability enrichment in annotated SNP sets using an LD Score regression.[17] Functional genomic annotations (tissue-specific and cell-specific gene expression) were retrieved from an online source database comprised of 152 different human tissues.[16]

For pathway analyses, the summary GWAS data were first analyzed using MAGMA,[2] which aggregated GWAS SNP *P*-values into gene-level ones, while considering linkage disequilibrium between the SNPs. MAGMA was also used to deduce pathway-level *P*-values from gene-level ones. Pathways were sourced from Gene Ontology's biological processes,[3,20] obtained from the Bader lab at the following URL: http://download.baderlab.org/EM_Genesets/December_01_2019/. Pathways in the discovery cohort (the UK Biobank) at the FDR 20% level were ascertained for replication in the replication cohort (HUNT) with *P*-value of replication smaller or equal to 0.05.

3. Results

In our genome-wide exploration of genetic factors contributing to acute vs chronic back pain, we used data on individuals of white British ancestry from the UK Biobank cohort (**Fig. 1**). A genome-wide association analysis of chronic back pain (n = 375,158; 70,633 cases; 304,525 controls) revealed 355 SNPs that reached the genome-wide significance threshold (5×10^{-8}), grouped into 13 loci (**Fig. 1A**; Supplementary table 1, available at http://links.lww.com/PR9/A164). Most of the significant loci (8 of 13) have already been reported as significantly associated with back pain in the UK Biobank cohort by other groups (loci 1, 4, 5, 6, 8, 9, 10, and 12 in **Table 1**), and 5 loci were new (loci 2, 3, 7, 11, and 13).[18,47] The estimated narrow-sense SNP heritability (h^2) for chronic back pain was 4.6% ($P = 1.4 \times 10^{-78}$, **Fig. 1A**).

The GWAS of acute back pain (n = 336,734; 32,209 cases and 304,525 controls) revealed no statistically significant genetic variants (**Fig. 1C**). The estimated narrow-sense SNP heritability ($h^2 = 0.81\%$) for acute back pain was lower than for chronic back pain; however, the heritability was significantly different from zero ($P = 1.4 \times 10^{-8}$, **Fig. 1C**). Of note, among the 13 statistically significant loci in chronic back pain, only one locus on chromosome 8 was associated with both acute and chronic back pain (Supplementary table 2, available at http://links.lww.com/PR9/A164).

In the HUNT replication cohort, we found similar differences in heritability estimates between acute and chronic back pain. Heritability of chronic back pain was 3.4% ($P = 0.0011$), whereas heritability of acute back pain was 0.6% ($P = 0.851$). A total of 7 of 13 statistically significant loci were replicated in the HUNT cohort for chronic pain cases (**Table 1**) at the $P < 0.05$ level using sets of SNPs at high LD ($r > 0.8$).

At the pathway level, a total of 21 Gene Ontology (GO) pathways were significantly enriched (FDR 20%) in chronic back pain and 10 pathways were enriched (FDR 20%) in acute back pain in the UK Biobank discovery cohort (**Table 2**). Neurogenesis and synaptic plasticity were significant in chronic back pain,

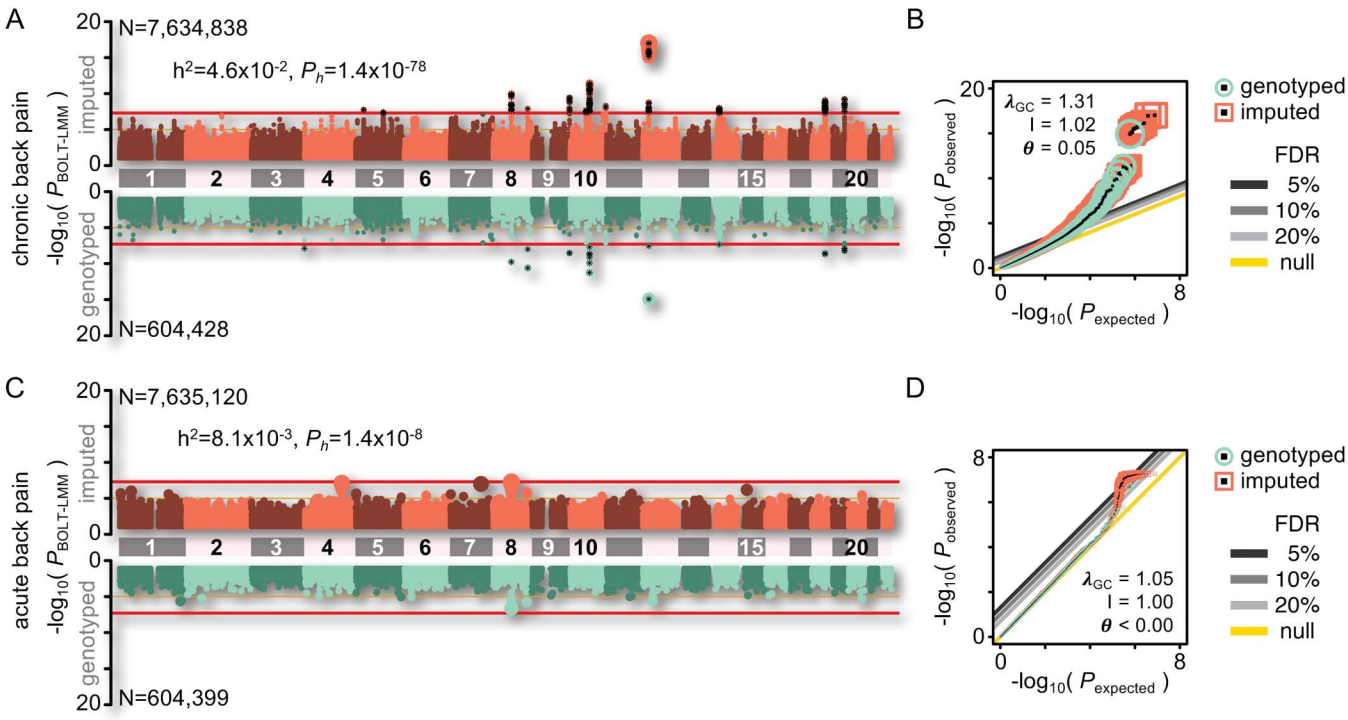

Figure 1. Genome-wide association analysis of chronic back pain (A and B) and acute back pain (C and D) in 375,158 participants from the UK Biobank cohort. (A and C) Miami plots show –log10 *P*-values for imputed (top, orange) and genotyped (bottom, green) SNPs (N, number of analyzed subjects). Horizontal red lines indicate genome-wide statistical significance at 5×10^{-8}. Genetic heritability estimate (h^2) shown with corresponding *P*-value (P_h). (B and D) QQ plots show observed –log10 *P*-values ($P_{observed}$) as a function of expected –log10 *P*-values ($P_{expected}$), for both genotyped (green) and imputed (orange) SNPs. Genomic control parameter (λ_{GC}), LD Score regression intercept (I), and their ratios (θ) are shown.

Table 1

Single nucleotide polymorphism (SNP)-level discovery and replication results of chronic back pain GWAS.

Loc	Chr	Genes cluster	Discovery, top hit (UK Biobank)			Replication (HUNT)				
			SNP	BP	*P*	SNP	BP	*P*	I^2	Direction
1	4	LOC105374344•TMED11P•SPON2	rs6826705	1122634	1.30E-08	rs4368552	1128054	0.067	0.97	↑↑
2	5	LOC105374704•CDH6	rs2066928	30843787	1.80E-08	rs2066928	30843787	0.034	1	↑↑
3	5	NUDT12•RAB9BP1	rs325485	103995368	3.90E-08	rs325528	104048590	0.0065	0.88	↑↑
4	8	C8orf34-AS1•C8orf34•LINC01592	rs1865442	69574165	1.10E-10	rs72666774	69587018	0.0042	0.96	↑↑
5	8	CCDC26•GSDMC	rs12056383	130711839	1.00E-08	rs77753889	130711599	0.631	0.85	↑↓
6	9	NRARP•EXD3•NOXA1	rs28458909	140257189	2.90E-09	—	—	—	—	—
7	10	LINC00844•CCEPR	rs12415581	60899641	2.10E-08	rs7084967	60945358	0.356	0.80	↑↑
8	10	PSAP•CHST3•SPOCK2•ASCC1	rs1668172	73823019	4.10E-12	rs1245561	73837350	0.0046	0.98	↑↑
9	10	BNIP3•JAKMIP3•DPYSL4	rs10870267	133968063	5.00E-09	rs34588848	134005567	0.480	0.83	↑↑
10	12	LOC101928441•SOX5•SOX5-AS1	rs12310519	23975219	9.50E-18	rs56290807	23972014	0.035	0.97	↑↑
11	14	SLC25A21-AS1•MIPOL1•FOXA1	rs8018823	37718177	9.70E-09	rs8018493	37644792	0.012	0.82	↑↑
12	18	LINC01630•DCC•LINC01919	rs10502966	50748499	8.40E-10	rs17410557	50776391	2.33E-05	0.83	↑↑
13	19	BCAM•NECTIN2•TOMM40•APOE•APOC1•APOC1P1	rs12972970	45387596	2.50E-09	rs34342646	45388130	0.363	1	↑↑

Replication of the top hit within each locus was performed using SNP sets in high LD ($r^2 > 0.8$). SNPs with lowest replication *P*-values for each locus in the discovery and replication cohort are shown.
BP, base pair; Chr, chromosome; Loc, locus.

whereas odontogenesis, cardiac muscle depolarization, and immune response through Th2-helpers were significant in acute back pain. Of note, the significance of the odontogenesis pathway was driven by genes linked to connective tissue disorders (*RSP O 2*) and bone remodeling (*TNFRSF11B*).[34,40,49] Three pathways for chronic pain were replicated ($P < 0.05$) in the HUNT cohort: spinal cord ventral commissure morphogenesis (GO:0021965), positive regulation of the kinase activity (GO: 0033674), and positive regulation of transferase activity (GO: 0051347). None of the acute pain pathways were replicated in the HUNT cohort.

We next investigated how the genetic heritabilities of chronic and acute back pain were distributed across different tissues. We measured the enrichment for the genes corresponding to identified genomic loci expressed in various human tissues. A total of 152 cell types and tissues from Fehtmann et al.,[16] grouped into 8 categories (adipose, blood and immune, cardiovascular, central nervous system (CNS), digestive, endocrine, musculoskeletal and connective, and other tissues) were included in the analyses (**Fig. 2**). For chronic back pain, estimates for heritability that exhibited the smallest *P*-values were attributed to genomic regions expressed only in brain regions or brain as a whole (**Fig. 2A**). Specific parts of the brain that reached the significance threshold (FDR 10%) were the limbic system, parietal lobe, brain stem, cerebral cortex, entorhinal cortex, cerebellum, hippocampus, and metencephalon (**Fig. 2B**). By contrast, for acute back pain, none of the cell types or tissues reached the statistical significance threshold (**Fig. 2C**), likely because of low overall heritability of acute back pain. Furthermore, the pattern of tissue-specific partitioned heritabilities for acute back pain appeared to be different from those for chronic back pain, with notable absence of significant signals from brain regions (**Figs. 2A and C**).

Next, we estimated genetic correlations between acute and chronic back pain and several selected phenotypes known to be correlated with chronic back pain at the phenotypic level, including body mass index (BMI), insomnia, neuroticism, and depression (**Fig. 2D**). All of these phenotypes were moderately genetically correlated with chronic back pain, and some of them (BMI, insomnia, and neuroticism) appeared to have significant partitioned heritability in brain tissues, similar to that of chronic back pain (**Fig. 2D**). To compare the heritability patterns in brain tissues between chronic back pain and the other phenotypes, we performed a correlation analysis of the heritability estimate coefficients in brain regions (**Fig. 2E**). A positive correlation would suggest that partitioned heritability is similarly distributed in brain regions between chronic back pain and another phenotype. Interestingly, chronic back pain and acute back pain had strong overall genetic correlation ($R_g = 0.97$, $P < 10^{-194}$), suggesting that genetic heritability for acute pain, although small, largely overlaps with genetic heritability for chronic back pain. However, when considering only brain tissues, no correlation was found between acute and chronic back pain ($P = 0.53$, **Fig. 2E**). Positive correlations of partitioned heritability coefficients in chronic back pain were found for BMI, depression, insomnia, and neuroticism, suggesting that heritability estimates are distributed similarly across brain tissues for these conditions. By contrast, partitioned heritability estimates for brain tissues were not statistically significant in standing height and did not correlate with heritability estimates for chronic back pain (**Figs. 2D and E**).

We then hypothesized that epigenetic markers of the 13 genomic loci that reached genome-wide significance (**Table 1**) in our chronic back pain analyses would be enriched in brain tissues (**Fig. 3**). To test this hypothesis, we first mapped the significant SNPs onto corresponding genes and defined 13 gene clusters (**Fig. 3A**). Then, we looked at the intersection of SNPs in LD with the lead SNP in each cluster with NIH Roadmap Epigenetics activation markers for statistically significant enrichment in 396 different tissues[6] (**Fig. 3B**). Our results again aligned with the partitioned heritability findings: 7 of 13 loci colocalized with epigenetic markers in multiple brain tissues (Bonferroni-corrected $P < 0.05$, **Fig. 3B**). These results suggest that these regions are transcriptionally active in the CNS. Using a different chromatin epigenome mapping (NIH Roadmap Epigenetic chromatin 15-state model),[41] we found that 9 of 13 loci had significant enrichment in multiple brain tissues (**Fig. 3C**). Thus, our epigenetic characterization of the chronic back pain–related variants suggests that expression of the genes in the CNS plays a significant role in the chronic back pain phenotype, followed by genes expressed in the musculoskeletal system (osteoblasts, chondrocytes, and muscles).

Table 2

Pathway analysis in the discovery (UK Biobank) and replication (HUNT) cohorts.

GO term	GO term definition	Leading edge genes	Discovery FDR	Replicated at $P < 0.05$?
Chronic back pain				
GO:0021965	Spinal cord ventral commissure morphogenesis	DCC, ADARB1, and GLI2	9.06E-05	Yes
GO:0099560	Synaptic membrane adhesion	NRXN1, EFNA5, LRFN5, LRRC4C, IGSF9B, NLGN1, CDH9, NTNG1, PCDH17, and LRRC4B	1.85E-02	No
GO:0021955	Central nervous system neuron axonogenesis	DCC, PTK2, TSKU, ADARB1, HSP90AB1, ARHGAP35, NDEL1, DCLK1, SLIT2, and ZEB2	1.85E-02	No
GO:0051347	Positive regulation of transferase activity	FGFR1, F2, AMBRA1, ATG13, PTK2, EFNA5, DGKZ, FYN, STOX1, and FGF18	1.30E-01	Yes
GO:1990074	Polyuridylation-dependent mRNA catabolic process	ZCCHC11, DIS3L2, and ZCCHC6	1.30E-01	No
GO:0060684	Epithelial–mesenchymal cell signaling	FOXA1, BMP4, PDGFA, SHH, WNT6, and SMO	1.30E-01	No
GO:0033674	Positive regulation of the kinase activity	FGFR1, F2, AMBRA1, ATG13, PTK2, EFNA5, DGKZ, FYN, STOX1, and FGF18	1.34E-01	Yes
GO:0021952	Central nervous system projection neuron axonogenesis	DCC, TSKU, ADARB1, DCLK1, SLIT2, ZEB2, NR2E1, CDH11, NFIB, and GLI2	1.45E-01	No
GO:0098742	Cell–cell adhesion by plasma membrane adhesion molecules	SDK1, ADGRL3, NRXN1, EFNA5, ROBO2, LRFN5, PCDHB12, CDHR4, REG3A, and PLXNB2	1.51E-01	No
GO:0021670	Lateral ventricle development	TSKU, NUMB, ATP1B2, MYH10, DPCD, KDM2B, CDK6, PAX5, DNAH5, and NUMBL	1.51E-01	No
GO:0060255	Regulation of macromolecule metabolic process	SPOCK2, FNIP2, MAML3, BBX, FGFR1, EFNB2, FAM172A, F2, PHF21A, and SP4	1.51E-01	No
GO:0051963	Regulation of synapse assembly	ADGRL3, NRXN1, PTK2, EFNA5, ROBO2, LRFN5, NTRK1, NLGN2, MUSK, and AMIGO3	1.51E-01	No
GO:0031325	Positive regulation of the cellular metabolic process	FNIP2, MAML3, FGFR1, F2, SP4, AMBRA1, ATG13, APOC1, PTK2, and EFNA5	1.51E-01	No
GO:0019222	Regulation of the metabolic process	SPOCK2, FNIP2, MAML3, BBX, FGFR1, EFNB2, FAM172A, F2, PHF21A, and SP4	1.51E-01	No
GO:1902841	Regulation of the netrin-activated signaling pathway	DCC, SIAH2, SIAH1, and NTN1	1.51E-01	No
GO:1902842	Negative regulation of the netrin-activated signaling pathway	DCC, SIAH2, SIAH1, and NTN1	1.51E-01	No
GO:0098609	Cell–cell adhesion	SDK1, ADGRL3, NRXN1, EFNA5, CYFIP2, THBS4, ROBO2, LRFN5, NLGN2, and PCDHB12	1.53E-01	No
GO:0051128	Regulation of cellular component organization	DCC, SDK1, FNIP2, ADGRL3, FGFR1, CKAP5, NRXN1, EFNB2, F2, and ATG13	1.53E-01	No
GO:0097116	Gephyrin clustering involved in postsynaptic density assembly	NRXN1, NLGN2, and NRXN2	1.53E-01	No
GO:0030702	Chromatin silencing at centromere	HIRA and ZNFX1	1.53E-01	No
GO:0010604	Positive regulation of the macromolecule metabolic process	FNIP2, MAML3, FGFR1, F2, SP4, ATG13, PTK2, EFNA5, SPON1, and FYN	1.82E-01	No
Acute back pain				
GO:0042483	Negative regulation of odontogenesis	RSPO2, TNFRSF11B, and ASPN	3.05E-02	No
GO:1904381	Golgi apparatus mannose trimming	MAN1A1, MAN1A2, and MAN1C1	1.24E-01	No
GO:0072033	Renal vesicle formation	WNT4, FMN1, KIF26B, SMO, CTNNB1, and SALL1	1.30E-01	No
GO:0042481	Regulation of odontogenesis	RSPO2, TNFRSF11B, WNT10A, DMP1, ASPN, ENAM, C4orf26, MMP20, SP6, and PAX9	1.30E-01	No
GO:0098914	Membrane repolarization during atrial cardiac muscle cell action potential	KCNJ5, KCNJ3, KCNN2, KCNQ1, and KCNA5	1.30E-01	No
GO:0099624	Atrial cardiac muscle cell membrane repolarization	KCNJ5, KCNJ3, KCNN2, KCNQ1, and KCNA5	1.30E-01	No
GO:0015838	Aminoacid betaine transport	PDZK1, SLC38A2, SLC25A29, SLC22A4, SLC22A5, and SLC22A16	1.30E-01	No
GO:0042489	Negative regulation of odontogenesis of dentin-containing tooth	RSPO2 andTNFRSF11B	1.30E-01	No
GO:0051409	Response to nitrosative stress	ATG5, STOX1, GCLC, GCLM, DUSP6, ADH5, DDIT3, and ATM	1.51E-01	No
GO:0045630	Positive regulation of T-helper 2 cell differentiation	CD86, NLRP3, IL4R, PRKCZ, IL18, TNFSF4, and RARA	1.65E-01	No

Pathways that pass the significance threshold FDR 20% in the discovery cohort are shown.
FDR, false discovery rate; GO, gene ontology.

4. Discussion

Our results from 2 large cohorts indicate the genetic contribution to chronic back pain is greater than to acute back pain, and much of the heritability of chronic back pain can be traced to genes predominantly expressed in the CNS. At the pathway level, we found the enrichment for genes in the spinal cord ventral commissure morphogenesis pathway in both cohorts. Our observation that acute back pain is significantly less heritable than chronic back pain (0.8% for acute vs 4.6% for chronic, narrow-sense SNP heritability) may be due to a greater role of environmental (eg, tissue injury) factors in acute pain. In turn, transition to chronic back pain, or development of chronic back pain per se, appears to require predisposing genetic or epigenetic risk factors. It was observed that epigenetic regulation was still occurring in the forebrains of mice that underwent peripheral nerve injuries long after the injury.[48]

Although we found a high genetic correlation between chronic and acute back pain, this observation does not contradict our

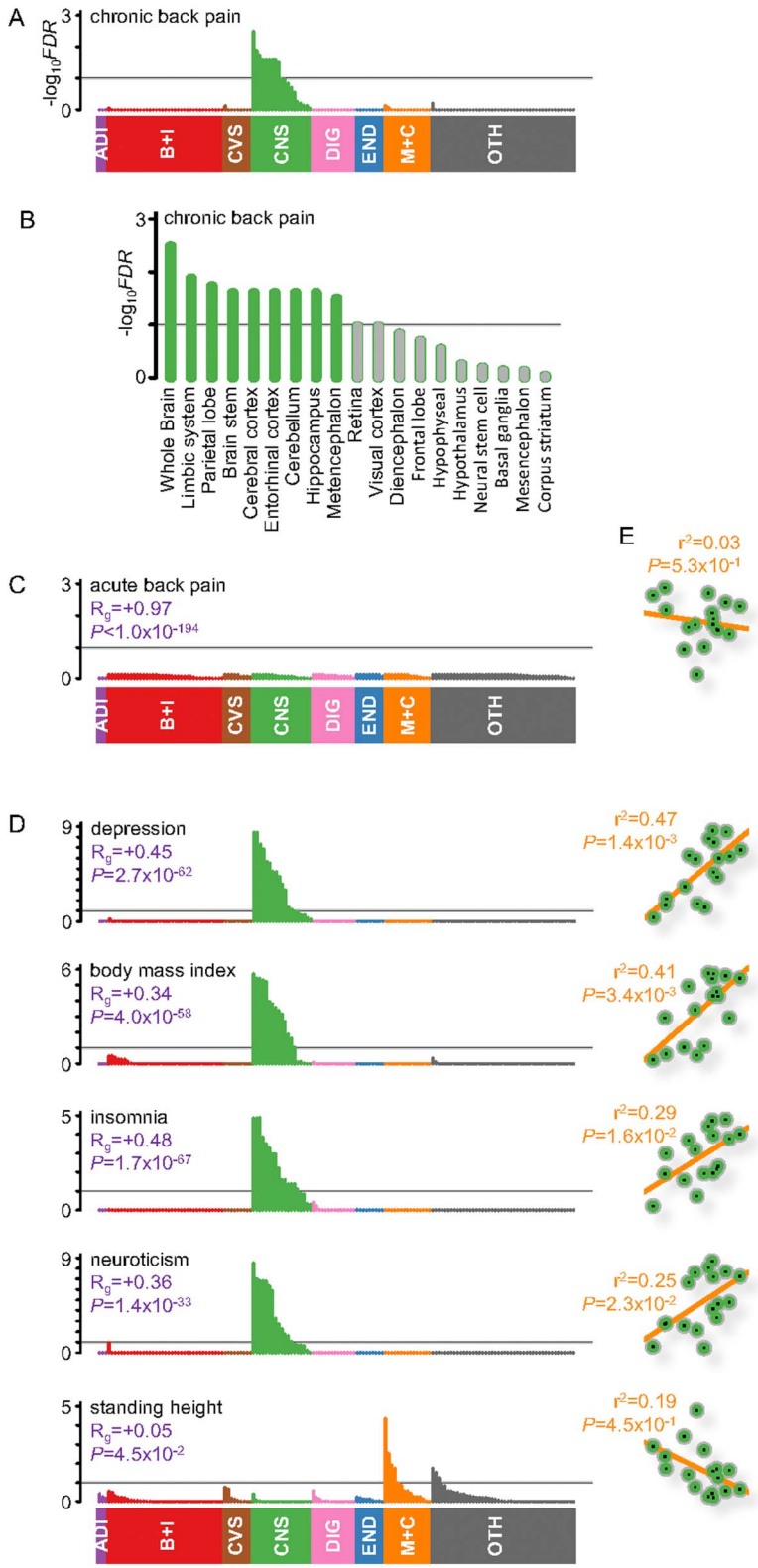

Figure 2. Tissue-specific heritability enrichment for chronic back pain, acute back pain, and other related phenotypes. Genomic tissue–specific annotations for 152 tissues were grouped into 8 categories: adipose, ADI (n = 3, purple); blood + immune, B + I (n = 37, red); cardiovascular, CVS (n = 9, brown); central nervous system, CNS (n = 19, green); digestive, DIG (n = 14, pink); endocrine, END (n = 9, blue); musculoskeletal + connective, M + C (n = 15, orange); and others, OTH (n = 46, grey). Vertical bars in each plot denote $-\log_{10}$(FDR) values for enrichment of each tissue. FDR 10% threshold is denoted by a horizontal grey line. (A and B) Tissue-specific partitioned heritability for chronic back pain. (C) Tissue-specific partitioned heritability for acute back pain, genetic correlation (R_g) with chronic back pain, and genetic correlation *P*-value. (D) Tissue-specific partitioned heritability for depression, body mass index, insomnia, neuroticism and standing height, genetic correlation (R_g) with chronic back pain, and genetic correlation *P*-value. (E) Brain regions partitioned heritability enrichment correlation between chronic back pain (horizontal axis, not shown) and acute back pain, depression, body mass index, insomnia, neuroticism, and standing height (vertical axis, not shown). Squared correlation coefficient (r^2) and associated *P*-value (*P*) are shown in orange.

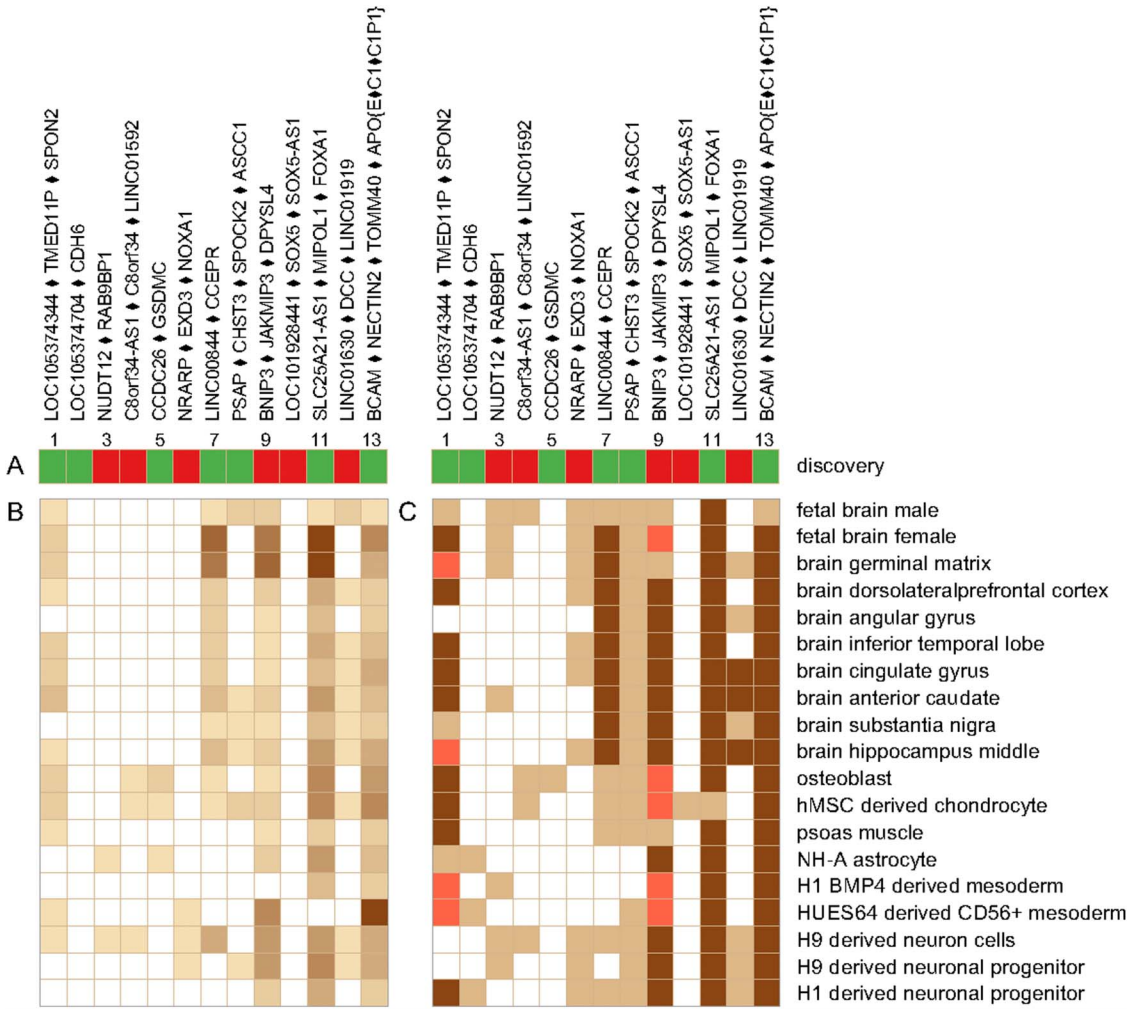

Figure 3. Epigenetic characterization of the GWAS significant 13 chronic back pain loci. (A) Gene clusters. Lead SNP effect of minor allele in the discovery cohort: protective (green) or risk (red). (B) Intersection of SNPs in LD with lead SNP ($r^2 \geq 0.5$) with NIH Epigenetics Roadmap activation markers in selected tissues. Markers are H3K4me3, H3K4me1, and H3K36me3. Darker hues for increased signal. (C) Intersection of SNPs in LD with lead SNP ($r^2 \geq 0.5$) with NIH Epigenetics Roadmap 15 states chromatin model in selected tissues. States are transcription start site (state 1: dark brown) and enhancer (states 6 or 7: light brown) indicating active transcription and bivalent or poised transcription start site (state 10: orange) indicating absence of active transcription. Statistical significance for ChIP-Seq signal established at $P \leq 0.05/(3 \text{ markers} \times 13 \text{ loci} \times 19 \text{ tissues})$. Cells are colored white otherwise. SNP, single nucleotide polymorphism.

finding that acute back pain is considerably less heritable than chronic back pain. Indeed, genetic correlation is the genetic covariance divided by the square root of h_1^2 and h_2^2. This genetic correlation can be large if total heritability of one of the traits (h_1) because of a set of SNPs is relatively small compared with total heritability of the second trait (h_2) and when h_1 constitutes a subset of h_2 for individual SNP contributions. Indeed, some of the patients included in the acute back pain group will go on to transition to chronic pain. These patients will have enrichment for genotypes predisposing them to chronic back pain, thus contributing to the genetic correlation between acute and chronic back pain groups. Genetic correlations between chronic back pain and other phenotypes (BMI, insomnia, neuroticism, and depression) were of moderate strength and are in line with previous reports showing genetic similarities between these phenotypes.[18,42,46]

The main finding in our study is that heritability of chronic back pain, but not acute back pain, is largely attributed to genes expressed in brain tissues. Previous genetic[23,25,39] and imaging[15,25,45] studies have reported a CNS component contributing to multisite chronic pain. Our results together with others[18] imply that a central component may be important for localized chronic back pain as well, but not for acute back pain. Involvement of the CNS in chronic back pain is an area of active research,[43] supported by a significant comorbidity between chronic back pain and psychological disorders.[50] Indeed, we found genetic overlap of chronic back pain with sleep disorders, neuroticism, and BMI. While this overlap has been previously described in several genetic studies,[18,36,37] here, we show that the overlap is localized in genes predominantly expressed in the CNS: limbic system, parietal lobe, brain stem, cerebral cortex, entorhinal cortex, cerebellum, hippocampus, and metencephalon. Moreover, the distribution of heritability across brain regions was similar for chronic back pain, insomnia, neuroticism, and BMI, suggesting shared genetic and pathophysiological mechanisms between these phenotypes. Our finding of predominant involvement of brain-expressed genes in chronic back pain, but not acute back pain, corroborates previous studies' findings, suggesting that spontaneous pain in chronic pain patients involves specific spatiotemporal neuronal mechanisms implicating a salient role for the emotional brain, distinct from mechanisms observed for acute experimental pain.[4]

Interestingly, we found only limited evidence of the involvement of musculoskeletal tissues in chronic back pain.

Using the UK Biobank cohort for discovery allowed the use of a larger sample size than in previous GWAS studies[18,47] and enabled us to identify 13 loci that exceeded a genome-wide significance threshold for chronic back pain. We have replicated 7 loci in the HUNT cohort. Of those, 3 loci are novel (Chr5: LOC105374704•CDH6, Chr5:NUDT12•RAB9BP1, and Chr14: SLC25A21-AS1•MIPOL1•FOXA1). Another locus (Chr18: LINC01630•DCC•LINC01919) has never previously been replicated in an independent cohort.

Pathway analyses of chronic back pain GWAS revealed enrichment for genes involved in the spinal cord ventral commissure morphogenesis pathway in both the UK Biobank and HUNT cohorts. The ventral white commissure is comprised of A delta and C fibers, which are known to be involved in pain signal transduction. This suggests that molecular mechanisms of nerve fiber growth might be involved in the pathophysiology of chronic back pain.[11] Interestingly, the most significant pathway in acute back pain, GO:00042483, contains 2 genes linked to connective tissue disorders (RSPO2) and bone remodeling (TNFRSF11B).[34,40,49] It is possible, therefore, that different gene subsets drive the bulk of the onset and persistence of back pain, with most of the pathways contributing to acute back pain not necessarily contributing to pain becoming chronic, in addition to a strong environmental component in acute back pain.

A limitation of our study is in the extent to which the phenotypes of interest, acute and chronic back pain, are ascertained in the UK Biobank cohort. Pain intensity, frequency of episodes, and pain medication use were not available for analyses. Participants that were chosen as controls could have had acute or chronic pain at other body sites. Moreover, there is evidence of considerable genetic overlap between chronic pain phenotypes in the UK Biobank,[33] which complicates the interpretation of our results. In addition, phenotype definitions varied slightly between the UK Biobank and the HUNT cohorts (back pain in the UK Biobank and low back pain in the HUNT). However, we concluded that these differences did not affect the validity of our findings given the high replication success rate of our findings between the 2 cohorts.

In conclusion, our analyses show that chronic back pain is substantially more heritable than acute back pain, and this heritability is mostly attributed to genes expressed in the brain. Molecular pathophysiology of acute back pain is largely contributed by connective and bone tissue remodeling pathways, whereas chronic back pain is contributed by neuronal development processes. These results provide insight into physiological systems and pathways responsible for acute and chronic back pain and should be expanded on to develop targeted treatments.

Disclosures

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A164.

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