

1 **The genetic architecture of pain intensity in a sample of 598,339 U.S. veterans**

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27 **Abstract**

28 Chronic pain is a common problem, with more than one-fifth of adult Americans reporting pain daily or
29 on most days. It adversely affects quality of life and imposes substantial personal and economic costs.
30 Efforts to treat chronic pain using opioids played a central role in precipitating the opioid crisis. Despite
31 an estimated heritability of 25-50%, the genetic architecture of chronic pain is not well characterized, in
32 part because studies have largely been limited to samples of European ancestry. To help address this
33 knowledge gap, we conducted a cross-ancestry meta-analysis of pain intensity in 598,339 participants in
34 the Million Veteran Program, which identified 125 independent genetic loci, 68 of which are novel. Pain
35 intensity was genetically correlated with other pain phenotypes, level of substance use and substance
36 use disorders, other psychiatric traits, education level, and cognitive traits. Integration of the GWAS
37 findings with functional genomics data shows enrichment for putatively causal genes (n = 142) and
38 proteins (n = 14) expressed in brain tissues, specifically in GABAergic neurons. Drug repurposing analysis
39 identified anticonvulsants, beta-blockers, and calcium-channel blockers, among other drug groups, as
40 having potential analgesic effects. Our results provide insights into key molecular contributors to the
41 experience of pain and highlight attractive drug targets.

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54 **Introduction**

55 Pain is an unpleasant sensory and emotional experience associated with, or resembling that
56 associated with, actual or potential tissue damage¹. Pain is often classified as either acute, which
57 typically lasts less than four weeks, or chronic, lasting more than three months and potentially
58 maladaptive². An individual's experience of pain is influenced by biological, psychological, and social
59 factors^{1,3}.

60 In a national survey, 50.2 million US adults (20.5%) reported experiencing pain on most days or
61 every day⁴, making pain the most common reason for seeking medical treatment⁵ and resulting in total
62 healthcare costs of 560 to 635 billion dollars in 2010⁶. Chronic pain is also associated with a poor quality
63 of life⁷. In the late 1980's many medical and pain organizations adopted policies to increase patients'
64 access to pain management, including opioids. These policies included efforts to ensure the adequate
65 assessment of pain, which was designated as "the fifth vital sign"². The resulting dramatic increase in
66 prescriptions for opioid analgesics contributed to the opioid epidemic and a doubling of opioid-related
67 deaths in the 1990s^{8,9}.

68 Success rates for treating chronic pain with currently available medications are estimated to be
69 as low as 10%¹⁰. Opioids are not efficacious in managing chronic non-cancer pain¹¹ and their long-term
70 use is associated with adverse effects such as addiction, sleep disturbance, opioid-induced hyperalgesia,
71 endocrine changes, and cardiac and cognitive effects^{12,13}. Other medications used to treat chronic non-
72 cancer pain, such as non-steroidal anti-inflammatory medications and antiepileptic drugs, are effective
73 for only some types of pain and may be associated with significant adverse effects¹⁴. Because non-
74 pharmacologic interventions are not accessible to most patients with pain, safe and efficacious
75 medications are needed to address this highly prevalent condition. Thus, novel therapeutic targets for
76 chronic pain are needed to facilitate the discovery or repurposing of safe, effective analgesics.

77 Notably, drug development efforts informed by genetics can double the rate of success¹⁵⁻¹⁷.
78 Although the heritability (h^2) of individual differences in the susceptibility to develop chronic pain is
79 estimated in twin and family studies to be 25-50%^{18,19}, the mechanisms that underlie it are poorly
80 understood²⁰. To date, genome-wide association studies (GWAS) of chronic pain in large samples,
81 including the UK Biobank (UKBB) and 23andMe cohorts, have focused on specific bodily sites²¹⁻²⁴ or
82 aspects of an individual's sensitivity to experiencing and reporting pain²⁵⁻²⁸. Although in samples of
83 150,000 to nearly 500,000 individuals GWAS have identified genome-wide significant (GWS) loci for
84 headache²⁹, osteoarthritis^{30,31}, low back pain^{23,24}, knee pain²¹, neuropathic pain³², and multisite chronic

85 pain^{25,26}, loci replication across pain phenotypes has been challenging²⁷. This may be due to the different
86 pain phenotypes employed, despite their having high genetic correlations among them^{27,33}.

87 There are also significant genetic correlations between pain phenotypes and psychiatric,
88 substance use, cognitive, anthropometric, and circadian traits^{21,23–25,29,34}. This shared genetic
89 predisposition suggests that a common genetic susceptibility underlies a broad range of diverse chronic
90 pain conditions³⁴ and common co-occurring conditions. For example, Mendelian randomization (MR)
91 and latent causal variable analyses have shown positive causal effects of specific bodily site pain on
92 depression^{35,36} and bi-directional casual associations between multisite chronic pain and major
93 depressive disorder (MDD)^{25,35}.

94 Despite a growing literature on pain GWAS, most studies have been conducted in predominantly
95 European ancestry cohorts recruited from non-clinical biobanks. However, biobanks linked to electronic
96 health records (EHRs) with large, well-characterized, multi-ancestry samples are now available for use in
97 identifying genetic risk factors and therapeutic targets for chronic pain³⁷. The Million Veteran Program
98 (MVP)³⁸, an observational cohort study and mega-biobank implemented in the U.S. Department of
99 Veterans Affairs (VA) health care system, includes data on routine pain screening. Pain ratings in the
100 MVP use an 11-point ordinal Numeric Rating Scale (NRS), which has been a standard practice in VA
101 primary care for more than a decade³⁹. The NRS has been shown to be a consistent, valid measure of
102 reported pain^{40–42} and is particularly informative for a GWAS of pain, as over 50% of VA patients
103 experience chronic pain⁴³.

104 We conducted a cross-ancestry meta-analysis of the NRS in samples of African American (AA),
105 European American (EA) and Hispanic American (HA) ancestries from the MVP (N = 598,339). Because of
106 the frequency with which the NRS is administered to patients in the VA, for each individual we
107 calculated the median annual score and then the median across years. Thus, although the NRS is a
108 report of pain intensity experienced at a specific point in time, the median of medians provided a proxy
109 for chronic pain. We also conducted a secondary analysis in a subsample of 566,959 individuals that
110 excluded participants with a lifetime opioid use disorder (OUD) diagnosis to assess potential
111 confounding by OUD.

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113 **Methods**

114 **Overview of analyses**

115 We conducted ancestry-specific GWASs of pain scores using an 11-point ordinal NRS in a) all
116 AAs, EAs, and HAs with pain ratings from the MVP, b) a subset of these participants that excluded those
117 with a lifetime OUD diagnosis, c) a subset of participants that excluded those with zero pain ratings and
118 d) a sex-stratified manner, each followed by a cross-ancestry meta-analysis. Details on phenotyping are
119 provided below. Downstream analyses are based principally on the GWAS of pain scores in the full
120 sample, complemented by the estimated heritability and genetic correlations (r_g s) for the sample
121 exclusive of participants with OUD and stratified by sex. An overview of the analyses is provided in
122 Supplementary Fig. 1.

123 **Million Veteran Program cohort**

124 The MVP³⁸ is an EHR-based cohort comprising >900,000 veterans recruited at 63 VA medical
125 centers nationwide. All participants provided written informed consent, a blood sample for DNA
126 extraction and genotyping, and approval to securely access their EHR for research purposes. The
127 protocol and consent were approved by the Central Veterans Affairs Institutional Review Board (IRB)
128 and all site-specific IRBs. All relevant guidelines for work with human participants were followed in the
129 conduct of the study.

131 **Phenotype description**

132 As early as 2000, the VA recommended using the NRS to routinely measure pain in clinical
133 practice as a “fifth vital sign”⁴⁴. Since that time, veterans have been asked to rate their pain severity in
134 response to the question: “Are you in pain?” They then rated their current pain on a scale of 0-10 where
135 “0 is no pain and 10 is the worst pain imaginable”. Participants had at least one inpatient or outpatient
136 pain rating in the EHR. We included 598,339 individuals with 76,798,104 NRS scores (median number of
137 scores = 109, IQR = 28 – 351) in the primary GWAS. To reduce the large number of pain observations, we
138 calculated the median pain score by year for each participant and the median of the annual median pain
139 scores. In a supplementary GWAS we excluded individuals with a documented ICD-9/10 diagnosis code
140 for OUD in the EHR, yielding a total of 566,959 study participants. Demographic characteristics for the
141 secondary analysis sample are presented in Supplementary Table 1.

143 **Genotyping and imputation**

144 DNA samples were genotyped on the Affymetrix Axiom Biobank Array (MVP Release 4). For
145 genotyped SNPs, standard quality control (QC) and subsequent imputation were implemented. Full

146 details about SNP and sample QC by the MVP Genomics Working Group are published⁴⁵. Briefly, DNA
147 samples were removed for sex mismatch, having seven or more relatives in MVP (kinship > 0.08),
148 excessive heterozygosity, or genotype call rate < 98.5%. Variants were removed if they were
149 monomorphic, had a high degree of missingness (call rate < 0.8) or a Hardy–Weinberg equilibrium
150 (HWE) threshold of $P < 1 \times 10^{-6}$ both in the entire sample using a principal-component analysis (PCA)-
151 adjusted method and within one of the three major ancestral groups (AA, EA and HA).

152 Genotype phasing and imputation were performed using SHAPEIT4 (v.4.1.3)⁴⁶ and Minimac4
153 software⁴⁷, respectively. Biallelic SNPs were imputed using the African Genome Resources reference
154 panel by the Sanger Institute (comprising all samples from the 1000 Genomes Project phase 3, version 5
155 reference panel⁴⁸, and 1,500 unrelated pan-African samples). Non-biallelic SNPs and indels were
156 imputed in a secondary imputation step using the 1000 Genomes Project phase 3, version 5 reference
157 panel⁴⁸, with indels and complex variants from the second imputation merged into the African Genome
158 Resources imputation.

159 We removed one individual from each pair of related individuals (kinship > 0.08, $N = 31,010$) at
160 random. The HARE method⁴⁹ was used to classify subjects into major ancestral groups (AA = 112,968, EA
161 = 436,683, HA = 48,688) and QC of imputed variants was performed within each ancestral group. SNPs
162 with imputation quality (INFO) score < 0.7; minor allele frequency (MAF) in AAs < 0.005, EAs < 0.001, and
163 HAs < 0.01; a genotype call rate < 0.95; or an HWE $P < 1 \times 10^{-6}$ were excluded.

164 **Association analyses and risk locus definition**

165 Genome-wide association testing was based on a linear regression model using PLINK (v.2.0)⁵⁰
166 and was adjusted for sex, mean age of assessment, and the first 10 within-ancestry genetic principal
167 components (PCs). Due to substantial differences in sample size across ancestral groups, meta-analyses
168 were performed using a sample-size weighted method in METAL⁵¹. Variants with $P < 5 \times 10^{-8}$ were
169 considered genome-wide significant (GWS). Because the LD intercept (1.1, se = 0.01) and attenuation
170 ratio (0.13, se = 0.01) of the LDSC showed minimal evidence of inflation or confounding, suggesting that
171 none of the GWS lead SNPs showed evidence of heterogeneity across ancestries we did not select the
172 genomic control option in METAL.

173 To identify risk loci and their lead variants, we performed LD clumping in FUMA⁵² at a range of
174 3,000 kb, $r^2 > 0.1$, and the respective ancestry 1000 Genomes reference panel⁴⁸. Following clumping,

175 genomic risk loci within 1 Mb of one another were incorporated into the same locus. We used GCTA
176 COJO⁵³ to define independent variants by conditioning them on the most significant variant within the
177 locus. After conditioning, significant variants ($P < 5 \times 10^{-8}$) were considered independently associated.
178 We performed a sign test to compare the direction of SNP effects across individual ancestral datasets.
179 Independent lead variants in EAs were examined in AAs and HAs and a binomial test used to evaluate
180 the null hypothesis that 50% of variants have the same effect direction across ancestries. For lead SNPs
181 in EAs that were absent in AAs and HAs, we considered proxy GWS SNPs ($p < 5 \times 10^{-8}$) in high LD with the
182 EA lead variant ($r^2 \geq 0.8$).

183 To prioritize credible sets of variants driving our GWAS results, we used FINEMAP⁵⁴ to fine-map
184 regions defined by LD clumps ($r^2 > 0.1$). Because fine-mapping requires data from all markers in the
185 region of interest⁵⁵, we merged LD clumps that physically overlapped (within a 1-MB window of the lead
186 variant) and excluded SNPs in the major histocompatibility complex (MHC) region due to its complexity.
187 FINEMAP credible set reports the likelihood of causality using the marginal posterior probability (PP),
188 which ranges from 0 to 1, with values closer to 1 being most likely causal.

189 **SNP-based heritability and functional enrichment**

190 We used the linkage disequilibrium score (LDSC) regression⁵⁶ method to estimate the SNP-based
191 heritability (h^2_{SNP}) of pain intensity (in both the full and the supplementary samples) in all ancestry
192 groups based on common SNPs in HapMap3⁵⁷. To ensure matching of population LD structure, pre-
193 calculated LD scores for EAs were derived from the 1000 Genomes European reference population
194 (version 3)⁴⁹ using LDSC⁵⁶. In-sample LD scores for AAs and HAs were calculated from MVP AA and HA
195 genotype data using cov-LDSC⁵⁸.

196 We used S-LDSC to partition the SNP heritability for pain intensity among EAs and explored the
197 enrichment of the partitioned heritability by functional genomic categories^{59,60} using three models: (a) a
198 baseline-LD model that contains 75 overlapping annotations, including coding and regulatory regions of
199 the genome and epigenomic features⁵⁹ (b) a specific tissue model that examines 10 overlapping cell-
200 type groups derived from 220 cell-type-specific histone marks, including methylated histone H3 Lys4
201 (H3K4me1), trimethylated histone H3 Lys4 (H3K4me3), acetylated histones H3 Lys4 (H3K4ac) and
202 H3K27ac⁵⁹ and (c) a multi-tissue model based on gene expression and chromatin datasets generated by
203 GTEx⁶¹ and the Roadmap Epigenomics Mapping Consortium⁶². For each model, we excluded multi-allelic

204 and MHC region variants. Functional categories within each model were considered significantly
205 enriched based on a Bonferroni-corrected P value.

206 **Gene-set functional characterization**

207 We applied multi-marker analysis of genomic annotation (MAGMA) v.1.08⁶³ in FUMA (v1.3.6a)⁵²
208 to identify genes and gene sets associated with the findings from the pain intensity GWAS and meta-
209 analysis. Using the default setting in MAGMA, we mapped GWS SNPs to 18,702 protein-coding genes
210 according to their physical position in NCBI build 37. We also used chromatin interaction (Hi-C) coupled
211 MAGMA (H-MAGMA)⁶⁴ to assign non-coding (intergenic and intronic) SNPs to genes based on their
212 chromatin interactions. H-MAGMA uses six Hi-C datasets derived from fetal brain, adult brain ($N = 3$),
213 induced pluripotent stem cell (iPSC)-derived neurons and iPSC-derived astrocytes⁶⁵. We applied a
214 Bonferroni correction (MAGMA, $\alpha = 0.05/18,702$; H-MAGMA, $\alpha = 0.05/293,157/6$) to identify genes
215 significantly associated with pain intensity, correcting for all genes tested in each analysis (see
216 Supplementary Tables 15 and 21 for full lists).

217 To determine the plausible tissue enrichment of mapped genes, we integrated our cross-
218 ancestry and EA GWAS results with gene expression data from 54 tissues (GTEx v8) in FUMA⁵². Next, we
219 used FUMA to curate gene sets and Gene Ontology terms (from the Molecular Signature Database
220 v.7.0⁶⁶). We corrected for gene size, density of variants, and LD pattern between genes in each tissue
221 (Bonferroni-corrected $\alpha = 0.05/54$).

222 Enrichment for cell-type specific (CTS) transcriptomic profiles was performed in FUMA⁶⁷ using 13
223 human single-cell RNA-sequencing (sc-RNAseq) datasets derived from brain (see Supplementary Table
224 14 for a detailed list). FUMA estimates CTS transcriptomic enrichment from the sc-RNAseq in three
225 ways: (1) per selected dataset, (2) within datasets using a conditionally independent analysis (based on
226 stepwise conditional testing of P values for each cell type that passes Bonferroni correction within the
227 same dataset), and (3) across datasets (testing for proportional significance across the results from step
228 2). Proportional significance (PS) reports the confidence level for observed cell type enrichment as low
229 significance: < 0.5 , jointly significant: $0.5 - 0.8$; and independently significant: > 0.8 . We considered CTS
230 enrichments with conditional independent signals ($P < 0.05$) and PS > 0.5 to be driven by
231 joint/independent genetic signals in our pain intensity GWAS results.

232 **Transcriptomic and proteomic regulation**

233 To identify genes and proteins whose expression is associated with pain intensity, we integrated
234 EA GWAS results with human brain transcriptomic (eQTL, N = 452; and sQTL, N = 452)^{68,69} and proteomic
235 (N = 722)⁶² data. We also obtained pretrained models of gene expression from GTEx v.8 for five brain
236 tissues significantly enriched in MAGMA analyses – cerebellum, cerebellar hemisphere, cortex, frontal
237 cortex, and anterior cingulate cortex^{61,71}. Human brain transcriptomic and proteomic data for
238 dorsolateral prefrontal cortex were derived from the study by Wingo et al⁷⁰. Transcriptome-wide
239 association study (TWAS) and proteome-wide association study (PWAS) analyses were performed using
240 the FUSION pipeline⁷¹ with Bonferroni correction ($\alpha = 0.05/N$ genes tested) to account for multiple
241 testing.

242 We used the colocalization (coloc R package⁷² in FUSION⁷¹) as our primary method to identify
243 SNPs that mediate association with pain intensity through effects on gene and protein expression and a
244 posterior colocalization probability (PP) of 80% to denote a shared causal signal. To test the robustness
245 of the colocalized signals, we also performed summary-based Mendelian randomization (SMR)
246 analyses⁷³. We applied the HEIDI test⁷³ to filter out SMR signals ($P_{\text{HEIDI}} < 0.05$) due to linkage
247 disequilibrium between pain-associated variants and eQTLs/sQTLs. Human brain cis-eQTL and cis-sQTL
248 summary data were obtained from Qi et al⁷⁴ and GTEx⁶¹. For genomic regions containing multiple genes
249 with significant SMR associations, we selected the top-associated cis-eQTL. We used Bonferroni
250 correction to correct for multiple testing ($\alpha = 0.05/N$ genes tested).

251 To explore the enrichment of causal genes and proteins in the dorsal root ganglia (DRG), we
252 accessed human and mouse RNA-seq data from 13 tissues (6 neural and 7 non-neural) from the DRG
253 sensoryomics repository⁷⁵. The data contain relative gene abundances in standardized transcripts per
254 million mapped reads and have been normalized to allow comparison across genes. The proportions of
255 gene expression in the CNS (neural proportion score) and DRG (DRG enrichment score) in the context of
256 profiled tissues were calculated, as described in Ray et al⁷⁵. Scores ranging from 0 to 1 were used to
257 denote the strength of tissue enrichment.

258 **Drug repurposing**

259 We examined the drug repurposing status of genes in EAs (N = 156) with high causal probability
260 from fine mapping and transcriptomic and proteomic analyses, using the Druggable Genome database⁷⁶.
261 For completeness, we also included the significantly associated genes mapped to GWS variants and
262 MAGMA results in AAs (N = 7) and HAs (N = 2). The Druggable Genome database contains 4,479 coding

263 gene sets with the potential to be modulated by a drug-like small molecule based on their nucleotide
264 sequence and structural similarity to targets of existing drugs⁷⁶. This druggable genome was divided into
265 three tiers. Tier 1 (N = 1,427) contains targets of licensed small molecules and biotherapeutic drugs
266 (curated from the ChEMBL database⁷⁷) and drugs in clinical development. Tier 2 (N = 682) includes
267 targets with verified bioactive drug-like small molecule binding partners and > 50% identity with
268 approved drug targets based on their nucleotide sequence. Tier 3 (N = 2,370) comprises targets or
269 secreted proteins with more distant similarity with an approved drug and members of active protein
270 complexes not included in Tiers 1 and 2. All causal genes and those reported in any of the three tiers of
271 the Druggable Genome were also examined for interaction with prescription drug targets in clinical
272 development using the Drug-Gene Interaction database (DGIdb)⁷⁸, which compiles clinical trial
273 information from the FDA, PharmGKB, Therapeutic Target Database, and DrugBank databases, among
274 others. We categorized each prescription drug identified using the Anatomical Therapeutic Chemical
275 classification system, retrieved from the Kyoto Encyclopedia of Genes and Genomics
276 (<https://www.genome.jp/kegg/drug/>).

277 **Genetic correlation**

278 We used LDSC⁵⁶ to calculate the r_g of pain intensity with (a) 89 other published pain, substance
279 use, medication use, psychiatric, and anthropometric traits from EA datasets selected using prior
280 epidemiological evidence and (b) 12 psychiatric, substance use, and anthropometric traits based on
281 available AA GWAS summary data (see Supplementary Tables 24 and 26 for detailed lists). In EAs, all
282 traits were tested using pre-computed LD scores for HapMap3⁵⁷, while in AAs, LD scores derived using
283 cov-LDSC⁵⁸ from MVP AA genotype data were used. In a hypothesis-neutral manner, we also calculated
284 r_g s of pain intensity with 1344 published and unpublished traits from the UKBB using the Complex Trait
285 Virtual Lab (CTG-VL) (<https://genoma.io/>). CTG-VL is a free open-source platform that incorporates
286 publicly available GWAS data that allow for the calculation of r_g for complex traits using LDSC⁷⁹. Each set
287 of r_g analyses was Bonferroni corrected to control for multiple comparisons ($\alpha = 0.05/\text{number of traits}$
288 tested).

289 We also estimated the cross-ancestry r_g s for pain intensity between AAs, EAs and HAs using
290 Popcorn⁸⁰, a computational method that determines the correlation of causal-variant effect sizes at
291 SNPs common across population groups using GWAS summary-level data and LD information. Ancestry-
292 specific LD scores were derived from the 1000 Genomes reference population⁴⁸.

293 **Polygenic risk score-based phenome-wide association studies**

294 We calculated polygenic risk scores (PRS) for pain intensity and performed a PheWAS analysis in
295 two samples – the Yale-Penn sample and the Penn Medicine Biobank (PMBB). The Yale-Penn sample⁸¹
296 was deeply phenotyped using the Semi-Structured Assessment for Drug Dependence and Alcoholism
297 (SSADDA), a comprehensive psychiatric instrument that assesses physical, psychosocial, and psychiatric
298 aspects of SUDs and comorbid psychiatric traits^{82,83}. As described in detail previously⁸¹, genotyping was
299 performed using the Illumina HumanOmni1-Quad microarray, the Illumina HumanCoreExome array, or
300 the Illumina Multi-Ethnic Global array, followed by imputation using Minimac3⁸⁴ and the 1000 Genomes
301 Project phase3 reference panel⁴⁸ implemented on the Michigan imputation server
302 (<https://imputationserver.sph.umich.edu>). SNPs with imputation quality (INFO) score < 0.7, MAF < 0.01,
303 missingness > 0.01, or an allele frequency difference between batches > 0.04; and individuals with
304 genotype call rate < 0.95, or related individuals with pi-hat > 0.25 were excluded. PCs were used to
305 determine genetic ancestry based on the 1000 Genomes Project phase3⁴⁸. The resulting dataset
306 included 4,922 AAs and 5,709 EAs.

307 The PMBB⁸⁵ is linked to EHR phenotypes. PMBB samples were genotyped with the GSA
308 genotyping array. Genotype phasing was done using EAGLE⁸⁴ and imputation was performed using
309 Minimac3⁸⁴ on the TOPMed Imputation server⁴⁷. Following QC (INFO < 0.3, missingness > 0.95, MAF > 0.5,
310 sample call rate > 0.9), PLINK 1.90 was used to identify and remove related individuals based on identity
311 by descent (Pi-hat > 0.25). To estimate genetic ancestry, PCs were calculated using SNPs common to the
312 PMBB and the 1000 Genomes Project phase3⁴⁸ and the smartpca module of the Eigensoft package
313 (<https://github.com/DReichLab/EIG>). Participants were assigned to an ancestral group based on the
314 distance of 10 PCs from the 1000 Genomes reference populations. The resulting dataset included 10,383
315 AAs and 29,355 EAs.

316 PRSs for pain intensity were calculated in the Yale-Penn and the PMBB datasets using PRS-
317 Continuous shrinkage software (PRS-CS)⁸⁶, with the default setting used to estimate the shrinkage
318 parameters and the random seed fixed to 1 for reproducibility. To identify associations between the
319 pain intensity PRSs and phenotypes, we performed a PheWAS in each dataset by fitting logistic
320 regression models for binary traits and linear regression models for continuous traits. Analyses were
321 conducted using the PheWAS v0.12 R package⁸⁷ with adjustment for sex, age at enrollment (in PMBB) or
322 at interview (in Yale-Penn) and the first 10 PCs within each genetic ancestry. We Bonferroni corrected

323 each ancestry-specific analysis (Yale-Penn EAs and AAs: $P < 7.87 \times 10^{-5}$, PMBB EAs and AAs: $P < 3.65 \times 10^{-5}$).

325 **Mendelian Randomization**

326 We used two-sample Mendelian randomization⁸⁸ to evaluate causal associations between
327 genetically correlated traits and pain intensity among EAs only because the two other population groups
328 provided inadequate statistical power for the analysis. Of the 56 traits that showed significant r_g , we
329 removed traits with phenotypic similarity across each of the tested r_g categories (Supplementary Table
330 31), selected traits with higher r_g and excluded traits without known biopsychosocial associations with
331 pain. This left 16 traits for MR analysis. Instrumental variants (IVs) were SNPs associated with the
332 exposure at $P < 1 \times 10^{-5}$ and a clumping threshold of $r^2 = 0.01$.

333 To quantify the strength of IVs, we calculated the F-statistics of all genetic instruments using the
334 per-allele effect size of SNP association with the phenotype (β) and standard error (SE) using the
335 following formula^{89,90}: $F\text{-statistic} = (\beta/SE)^2$. IVs with F-statistic estimates < 10 were considered weak
336 instruments that could bias results⁹¹. We used Steiger's test⁹² to determine whether the SNP-outcome
337 correlation is greater than the SNP-exposure correlation. SNPs that fail Steiger's test may not be
338 primarily associated with the exposure (Steiger $P > 0.05$) and were filtered out before MR analysis.
339 Because pleiotropy can bias MR findings⁹³, we investigated its possible presence by assessing
340 heterogeneity in the MR estimates across SNPs, using the I^2 index and the Cochran's Q heterogeneity
341 test⁹⁴. Finally, MR-Egger intercepts were used to assess the bias due to weak IVs and the possibility of
342 horizontal pleiotropy. Potential causal effects were those for which at least two MR tests were
343 significant after multiple correction ($P = 3.13 \times 10^{-3}$, 0.05/16) and did not violate the assumption of
344 horizontal pleiotropy (MR-Egger intercept $P > 0.05$).

345

346 **Results**

347 **Description of the sample**

348 The study sample comprised 598,339 individuals (AA = 112,968, EA = 436,683, HA = 48,688), of
349 whom 91.2% were male (Supplementary Table 1). The secondary analyses from which individuals with a
350 lifetime OUD diagnosis were excluded were reduced by 5% across population groups (AA = 104,050, EA
351 = 415,740, HA = 46,169) (Supplementary Table 1). The median ages were 61.4 (s.d = 14.0) and 61.7 (s.d =

352 14.1) in the full and non-ODU samples, respectively. About half of individuals in both the full sample
353 (51.2%) and the non-ODU sample (52.7%) reported a median NRS of 0, i.e., no pain. Mild (NRS 1-3),
354 moderate (NRS 4-6) and severe pain (NRS 7-10) were reported by 24.4%, 19.2%, and 4.5%, respectively
355 in the full sample, and 24.6%, 18.2%, and 4.0%, respectively in the non-ODU sample.

356 **Identification of pain intensity risk loci**

357 In our cross-ancestry meta-analysis of 16,254,110 imputed SNPs among the AA, EA, and HA
358 samples, we identified 4,416 GWS variants represented by 158 LD-clumped index variants ($r^2 > 0.1$)
359 (Figure 1). None of the lead SNPs showed evidence of heterogeneity across ancestries, based on the I2
360 index (Supplementary Figure 2). Analyses conditioned on the lead SNP left 125 independent association
361 signals (Supplementary Table 2), 57 of which have previously been reported as pain-related loci^{23,25} and
362 68 of which are novel (Figure 1, Supplementary Table 2). Eight independent variants are exonic, 84
363 reside within a gene transcript, and 33 are intergenic. Of the 8 exonic variants, 2 have likely damaging
364 (PolyPhen > 0.5 , CADD > 15) effects (*SLC39A8*-rs13107325 and *WSCD2*-rs3764002) and 5 are potentially
365 deleterious (CADD > 15 ; *ANAPC4*-rs34811474, *MIER*-rs2034244, *NUCB2*-rs757081, *AKAP10*-rs203462 and
366 *APOE*-rs429358) (Supplementary Table 2).

367 [Insert Figure 1 here]

368 For the 125 independent variants associated with pain intensity, we looked up the associations
369 in a recent meta-analysis of 17 UKBB pain-related traits²⁷, a common genetic pain factor consisting of 24
370 chronic pain conditions in the UKBB⁹⁵, and the human pain genes database (HPGD)⁹⁶. Two variants
371 (*TCF4*-rs618869 and *APOE*-rs429358) were GWS in the meta-analyses of pain traits (Supplementary
372 Table 2). Of the 68 novel pain associations in our study none were GWS in any of these published
373 studies^{27,95} or the HPGD⁹⁶, confirming the novelty of our findings.

374 Inflammation appears to play a role in pain susceptibility²⁷. We explored the 125 independent
375 pain intensity loci (within a 1-Mb buffer) for pleiotropy with immune traits in the GWAS catalog⁹⁷. Of the
376 125 loci, 25 (9 novel) showed pleiotropic association with immune/hematopoietic traits, such as C-
377 reactive protein levels, erythrocytes, leukocytes, and platelet counts (Supplementary Table 3).

378 The GWAS using 7,069,962 imputed SNPs in EAs yielded 103 LD clumps ($r^2 > 0.1$) across 86
379 independent loci (Supplementary Figure 3, Supplementary Table 4). Of these, 15 were not GWS in the
380 cross-ancestry meta-analysis (Supplementary Table 4). We also identified 2 GWS variants in 1 locus
381 (nearest gene *PPARD*; chr 6) in AAs (11,183,154 imputed SNPs), and 15 GWS variants in 2 loci (nearest

382 genes *RNU6-461P*; chr 3 and *RNU6-741P*; chr 15) in HAs (5,859,313 imputed SNPs; Supplementary Table
383 5). We used a sign test to examine the 86 independent EA index variants in AAs and HAs, of which 57
384 and 74, respectively, were directly analyzed or had proxy SNPs in these populations (Supplementary
385 Table 6). Most variants had the same direction of effect in both populations (N_{SNPs} AAs = 41, HAs = 61;
386 sign test AAs $P = .0013$, HAs $P = 1.39 \times 10^{-8}$). Only 15 variants (N_{SNPs} AAs = 2, HAs = 13) were nominally
387 associated ($P < 0.05$) and none survived multiple test correction (Supplementary Table 6). The cross-
388 ancestry genetic-effect correlation (ρ_{pe}) was 0.71 (SE = 0.13, $P = 2.12 \times 10^{-2}$) between EAs and AAs and
389 0.74 (SE = 0.08, $P = 6.81 \times 10^{-4}$) between EAs and HAs. The cross-ancestry heritability estimates between
390 AAs and HAs were too low to calculate ρ_{pe} between those ancestries.

391 **Identification of loci related to non-ODU diagnosis, non-zero pain ratings and sex differences.**

392 To identify genetic association for pain intensity independent of OUD, a secondary analysis that
393 excluded participants with a lifetime OUD diagnosis identified 3,400 SNPs in 101 LD-independent risk
394 loci (Supplementary Table 7). Of these, 87 were GWS, 13 were $p < 10^{-6}$ in the primary GWAS, of which,
395 10 represent novel associations (Supplementary Table 7). We also identified 18 were ancestry specific
396 loci (17 in EAs and 1 in AAs) (Supplementary Tables 8 & 9).

397 The cross-ancestry meta-analysis that excluded individuals with NRS=0 identified 461 SNPs in 12
398 independent risk loci (Supplementary Table 10). Of these, 8 were associated with pain intensity in the
399 primary GWAS, whereas 4 loci were not, 3 of which (*TNFK- rs189788533* , *RP11-99C10.1- rs7124028* ,
400 *FAM81A- rs149493877*) are novel pain loci (Supplementary Table 10). In EAs and AAs, we identified 11
401 and 1 independent risk loci, respectively, of which 3 (EA, *TNFK- rs189788533* and *RP11-404L6.2- rs6884145* ;
402 AA, *FAM81A- rs149493877*) were additional associations and novel for each ancestry
403 (Supplementary Table 11).

404 In a cross-ancestry meta-analysis that examined genetic associations among males only, we
405 identified 96 independent risk loci, of which 8 were not GWS in the primary GWAS, 7 of which were
406 novel associations for pain (*NASP- rs2991977* , *PDE11A- rs16865764* , *RP11-138I17.1- rs1726312995* , *CD14- rs2569190* ,
407 *RP11-572H4.1- rs1122665* , *SLITRK1- rs1331928* , and *SDK2- rs150636180*) (Supplementary
408 Table 12). We also identified 74 independent risk loci in EAs – six of which are novel for pain -
409 (Supplementary Table 13) and one novel locus each for AAs and HIS (Supplementary Table 14). No
410 variant was GWS among females. However, 28 LD-clumped variants ($r^2 > 0.1$) showed a suggestive level
411 of association with pain intensity ($P < 5 \times 10^{-6}$, Supplementary Table 15). The direction of allele effect
412 sizes between males and females was significantly highly correlated ($r = 0.68$, $P = 2.2 \times 10^{-16}$)

413 (Supplementary Figure 4). SNP heritability was moderate for both females (EAs = 0.12 and AAs = 0.05)
414 and males (EAs = 0.08 and AAs = 0.06). Pain intensity was significantly genetically correlated between
415 males and females (EAs, $r_g = 0.87$, $P = 1.41 \times 10^{-35}$ and AAs, $r_g = 1$, $P = 6.8 \times 10^{-3}$).

416 Overall, the per-allele effect sizes of lead risk variants between the primary and secondary
417 GWASs were high, ranging from 0.88 to unity ($P < 2.2 \times 10^{-16}$; Supplementary Figure 5). The genomic
418 inflation factor (λ_{GC}) of the fixed-effect meta-analysis across all GWASs ranges from 1.03 to 1.23
419 (Supplementary Figure 6), consistent with highly-powered meta-analyses ($n > 100,000$)⁹⁸⁻¹⁰⁰ and as
420 expected for a polygenic trait^{101,102}. Across all GWASs, the univariate LDSC intercept ranges from 0.99 to
421 1.2 (s.e. 0.01), which, being close to 1.0, suggests that most of the genome-wide elevation of the
422 association statistics comes from true additive polygenic effects rather than from a confounder such as
423 population stratification. LDSC genetic correlations [r_g] between the primary and secondary GWASs were
424 positive and high, ranging from 0.89 to unity, with overlapping confidence intervals (Supplementary
425 Figure 7). In the primary GWAS, the LDSC ratio between the intercept and mean χ^2 statistics (1.90) was
426 0.13, suggesting that 87% of the observed inflation in χ^2 -statistics is due to the polygenicity of the pain
427 trait.

428 **Single-nucleotide polymorphism heritability and enrichment**

429 The proportion of variation in pain intensity explained by common genetic variants (h^2_{SNP}) was
430 similar both for the primary (AAs: 0.06 ± 0.009 , EAs: 0.08 ± 0.003 and HAs: 0.07 ± 0.011) and the non-
431 OUD GWAS (AAs: 0.07 ± 0.009 , EAs: 0.08 ± 0.003 and HAs: 0.07 ± 0.011) (Supplementary Table 16).

432 Partitioning the SNP heritability for pain intensity revealed significant tissue-group enrichment
433 in central nervous system (CNS) ($P = 1.47 \times 10^{-12}$), adrenal ($P = 8.97 \times 10^{-5}$), liver ($P = 3.15 \times 10^{-4}$), skeletal
434 ($P = 8.50 \times 10^{-4}$), cardiovascular ($P = .001$), and immune/hematopoietic ($P = .004$) tissues (Figure 2A & B,
435 Supplementary Table 17). In gene expression datasets derived from multiple tissues, we observed
436 predominant h^2_{SNP} effects in brain ($P = 2.87 \times 10^{-5}$), including hippocampus ($P = 1.00 \times 10^{-4}$) and limbic
437 system ($P = 1.15 \times 10^{-4}$) (Figures 2C & D, Supplementary Table 18). SNP-based heritability in histone
438 modification data also showed robust enhancer (H3K27ac and H3K4me1) and active promoter
439 (H3K4me3 and H3K9ac) enrichments in brain tissues, including the dorsolateral prefrontal cortex
440 ($P < 1.32 \times 10^{-4}$), inferior temporal lobe ($P < 3.09 \times 10^{-4}$), angular gyrus ($P = 8.42 \times 10^{-5}$), and anterior
441 caudate ($P = 1.12 \times 10^{-4}$) (Figure 2E, Supplementary Table 19). Similar results were obtained for the
442 partitioned heritability analysis of the supplementary GWAS (Supplementary Tables 17 & 18), though it
443 also included significant expression effects in the cortex and cerebellum.

444 Although the SNP-based heritability and enrichment for the primary and non-OUO GWASs were
445 similar, because the primary GWAS using the full sample yielded more risk loci, we based all
446 downstream analyses (except r_g analyses) on the GWAS results from that sample.

447 [Insert Figure 2 here]

448 **Gene-set enrichment in tissue and cell types**

449 To clarify the potential transcriptomic mechanism of each GWS pain locus, we mapped GWAS
450 variants to genes via expression quantitative trait locus (eQTL) association in GTEx⁶¹ and assessed the
451 tissue enrichment of mapped genes in FUMA⁵². After correcting for multiple testing ($P = 9.25 \times 10^{-4}$) in
452 the cross-ancestry and EA-specific GWASs, we uncovered significant transcriptomic enrichment only in
453 brain tissues (Supplementary Figure 8). Consistent with previous findings of brain tissue enrichment
454 across different pain phenotypes in EAs^{22,25,27}, both our EA and cross-ancestry analyses showed notable
455 enrichment in the cerebellum (cross-ancestry, $P = 2.48 \times 10^{-7}$; EA, $P = 2.90 \times 10^{-6}$), cerebellar hemisphere
456 (cross-ancestry, $P = 4 \times 10^{-7}$; EA, $P = 6.23 \times 10^{-6}$), cortex (cross-ancestry, $P = 2.79 \times 10^{-6}$; EA, $P = 3 \times 10^{-4}$),
457 and frontal cortex (cross-ancestry, $P = 2.82 \times 10^{-6}$; EA, $P = 4.17 \times 10^{-4}$) (Supplementary Figure 8). Among
458 AAs there were no significantly enriched tissues (Supplementary Table 20).

459 To investigate enrichment at the level of the cell type in the EA GWAS results, we conducted
460 FUMA cell-type specific analysis⁶⁷ in a collection of cell types in 13 human brain sc-RNAseq datasets.
461 After adjusting for possible confounding due to correlated expression within datasets using a stepwise
462 conditional analysis, we detected jointly significant cell-type enrichments (proportional significance, $PS >$
463 0.5) for GABAergic neurons largely in the human adult mid-brain ($P = 0.003$, $\beta = 0.206$, s.e. = 0.075, $PS >$
464 0.56) and to a lesser extent in the prefrontal cortex ($P = 0.044$, $\beta = 0.045$, s.e. = 0.016, $PS >$
465 0.39) (Supplementary Table 21).

466 **Prioritization of candidate genes**

467 To facilitate the biological interpretation and identification of druggable targets, we used a
468 combination of MAGMA and fine-mapping, transcriptomic, proteomic, and chromatin interaction
469 models to prioritize high-confidence variants and genes that most likely drive GWAS associations.
470 Assigning SNPs to genes using physical proximity, MAGMA gene-based analyses⁶³ identified 6 GWS
471 genes in AAs, 203 in EAs, and 125 in the cross-ancestry results (Supplementary Figure 9, Supplementary
472 Table 22), but none in HAs. MAGMA gene-set analysis⁶³ using cross-ancestry GWAS results identified
473 significantly enriched biological processes in catecholamine uptake (GO:0051944; Bonferroni $P = 0.019$)

474 and startle response (GO:0001964; Bonferroni $P = 0.024$). Negative regulation of synaptic transmission
475 (GO:0050805; Bonferroni $P = 0.016$) was related to pain intensity in EAs (Supplementary Table 23).

476 For consistency with available reference data, we based the fine mapping procedure on EA
477 GWAS results using 78 genomic regions (spanning 103 index variants) (Supplementary Table 24) defined
478 by the maximum physical distance between the LD block of independent lead SNPs (Methods).
479 Functional genomic prediction models used the full EA GWAS results (Supplementary Figure 1).

480 We fine-mapped the 78 regions using the Bayesian method implemented in FINEMAP⁵⁴
481 (Methods). For each region with independent causal signals (Supplementary Table 24), credible sets of
482 variants ($PP > 0.5$) were constructed to capture 95% of the regional posterior probability ($k \leq 5$,
483 Supplementary Table 25). Of these regions, 4 harbored 1 SNP (potentially indicating the causal variant),
484 20 regions 2 SNPs and 44 regions 3 or more SNPs (Supplementary Table 25). In total, FINEMAP
485 prioritized 76 unique credible variants ($N = 108$, Figure 3A), including 26 independent lead SNPs and 18
486 novel pain loci (Figure 3B). Most (50/76) of the credible variants map to protein-coding genes and are
487 mostly eQTLs (Supplementary Table 25), and five harbor missense variants, of which three (*ANAPC4*,
488 *APOE*, and *SLC39A8*) are known pain loci^{25,31} and two (*RYR2* and *AKAP10*) are novel (Figure 3B). This
489 small proportion of missense variants and high eQTL enrichment are consistent with an increased
490 probability that the credible variants influence liability to pain intensity through gene expression
491 modulation.

492 We performed TWAS and PWAS analyses to determine whether risk variants exert their effects
493 via gene and/or protein expression. After correction for multiple testing, 196 unique genes (TWAS eQTL
494 – 294, TWAS sQTL – 67 and PWAS – 32) were associated with pain intensity (Supplementary Tables 26 &
495 27). Of these, 69 represent novel associations (based on a window from the index GWAS locus > 1 MB).
496 PWAS showed significant associations in the dorsolateral prefrontal cortex (dlPFC) that overlapped for
497 22 unique genes across multiple brain tissues in the TWAS (eQTL – 16, sQTL – 8) (Figure 3C).

498 [Insert Figure 3 here]

499 Chromatin interaction mapping using Hi-C data in adult and fetal brain identified 512 unique
500 significantly interacting genes ($P = 2.84 \times 10^{-8}$) (Supplementary Table 28), of which 60 are associated
501 with all six chromatin annotations (Supplementary Figure 10) and 20 overlap with TWAS and/or PWAS
502 findings, including *DPYSL5*, *KHK*, *MAPRE3*, *MST1R*, *NEK4*, *GNL3*, *GRK4*, *UHRF1BP1* and *VKORC1* (Figure
503 3C, Supplementary Tables 26, 27 & 28).

504 Based on concordant evidence from colocalization analyses in TWAS and PWAS (COLOC PP4 >
505 0.80), 104 unique genes (TWAS eQTL – 139, TWAS sQTL – 20 and PWAS – 14) were putatively causal for
506 pain intensity (Supplementary Tables 26 & 27), of which 10 (including *DPYSL5*, *GRK4*, *KHK* and *MST1R*)
507 were validated by SMR analysis ($P_{\text{HEIDI}} > 0.05$) (Figure 3D, Supplementary Table 29). Among the 104
508 genes, 6 (*CHMP1A*, *GRIA1*, *GRK4*, *MST1R*, *STMN3* and *TRAF3*) captured 50% or more of the FINEMAP
509 posterior probability (Supplementary Table 25). Notably, the *MST1R* intronic locus (rs9815930), which is
510 in a credible set that harbors four other variants in high LD with the novel index variant rs2247036
511 (nearest gene – *TRAIIP*) (Supplementary Figure 11), displayed the most robust causal effects from COLOC
512 and SMR in more than one brain tissue (Figure 3D).

513 We also explored enrichment of causal genes and proteins in the dorsal root ganglia (DRG),
514 which are important for transduction of nociceptive signals from the periphery to the CNS. None of the
515 causal genes or proteins (N = 104) were enriched in human or mouse DRG (DRG enrichment score > 0.5)
516 (Supplementary Figure 12A). Supporting results from TWAS and PWAS, 63 unique genes (human – 38
517 and mouse – 49) were primarily enriched in the CNS, of which 22 (including *GRK4*, *GRIA1*, *MAPRE3*,
518 *NEK4*, *STMN3* and *TRAF3*) showed common enrichment patterns across species (Supplementary Figure
519 12B).

520 Integrating FINEMAP, colocalization and SMR prioritized 156 high-confidence genes underlying
521 the pain intensity GWAS association, of which 5 are exonic and missense (Supplementary Table 30), and
522 151 exert their effect via gene or protein expression.

523 **Phenotypic correlates of pain intensity**

524 As expected, the strongest positive genetic correlations of pain intensity were with other pain
525 phenotypes (e.g., multisite chronic pain $r_g=0.789$, osteoarthritis $r_g=0.710$, neck/shoulder pain $r_g=0.669$,
526 back pain $r_g=0.697$, hip pain $r_g=0.729$, knee pain $r_g=0.637$; Figure 4A). Of 72 medical, anthropometric, or
527 psychiatric traits associated epidemiologically with pain severity and mortality, 56 were significantly
528 genetically correlated with pain intensity in EAs (Bonferroni $P < 5.62 \times 10^{-4}$) (Figure 4A, Supplementary
529 Table 31).

530 [Insert Figure 4 here]

531 Notably, the liability to pain intensity was significantly positively genetically correlated with
532 neuroticism, depression, insomnia, a variety of smoking-related measures, cannabis use disorder (CUD),

533 alcohol dependence, OUD, and being overweight or obese (Figure 4A). As in prior studies of other pain-
534 related phenotypes^{24,29,103}, pain intensity was significantly negatively correlated with educational
535 attainment, cognitive performance, intelligence, and age of smoking initiation (Figure 4A). Relevant to
536 drug repurposing, pain intensity was also positively correlated with the use of a variety of analgesic and
537 anti-inflammatory drugs (Figure 4A). We also found significant r_g s with pain intensity for several medical
538 conditions and health outcomes in the UKBB (including genitourinary disease, chronic bronchitis, angina,
539 etc., Bonferroni $P < 3.72 \times 10^{-5}$, Supplementary Table 32). In AAs, pain intensity was positively
540 genetically correlated with PTSD-related features (e.g., re-experiencing, hyperarousal) and nominally
541 associated ($p < 0.05$) with substance use traits (e.g., maximum alcohol intake and smoking trajectory,
542 Supplementary Table 33).

543 In the Yale-Penn sample, we calculated PRS for 4,922 AAs and 5,709 EAs. Among AAs, none of
544 the associations survived Bonferroni correction, likely due to the smaller discovery sample than for EAs
545 (Supplementary Figure 13, Supplementary Table 34). In EAs, PheWAS identified 147 phenotypes,
546 including 107 in the substance-related domain (40 opioid-related, 30 cocaine-related, 20 tobacco-
547 related, 12 alcohol-related, and 6 cannabis-related) and 39 in other domains (9 medical, 18 psychiatric
548 [9 PTSD, 5 ADHD, 2 conduct disorder, and 2 antisocial], 7 early childhood environmental, and 5
549 demographic phenotypes) that were significantly associated with the pain PRS (Supplementary Figure
550 14, Supplementary Table 34). The most significant findings were a negative association of the pain
551 severity PRS with educational attainment ($P = 2.39 \times 10^{-26}$) and a positive association with the
552 Fagerström Test for Nicotine Dependence ($P = 4.71 \times 10^{-25}$). Opioid dependence was also positively
553 associated with the pain PRS ($P = 3.87 \times 10^{-12}$), and remained significant when using a PRS based on the
554 supplementary GWAS that excluded individuals with an OUD diagnosis (OR = 1.27, $P = 1.35 \times 10^{-6}$).

555 In PMBB, we calculated PRS for 10,383 AAs and 29,355 EAs. In AAs, no association with the pain
556 PRS survived Bonferroni correction (Supplementary Figure 15, Supplementary Table 35). In EAs, the pain
557 severity PRS was associated with 63 phenotypes, including 7 pain phenotypes and 6 psychiatric
558 disorders (i.e., substance-, depression-, and anxiety-related traits). Other phenotypic categories with
559 associations with the pain severity PRS were circulatory system (n=11), infectious diseases (n=4),
560 endocrine/metabolic (n=8), genitourinary (n=2), musculoskeletal (n=3), and neoplasms (n=4). The most
561 significant findings were positive correlations with obesity ($P = 1.97 \times 10^{-45}$) and tobacco use disorder
562 ($P = 1.55 \times 10^{-24}$) and a negative association with benign neoplasm of skin ($P = 2.67 \times 10^{-26}$)
563 (Supplementary Figure 16, Supplementary Table 35). In females, pain PRS was positively associated with

564 sleep apnea and obstructive sleep apnea, and negatively associated with disorders of refraction,
565 degenerative skin conditions and astigmatism ($P < 3.65 \times 10^{-5}$) (Supplementary Table 35). Pain PRS was
566 negatively associated with elevated prostate specific antigen in males ($P = 1.03 \times 10^{-6}$) (Supplementary
567 Table 35).

568 Two-sample MR between genetically correlated traits ($N = 16$) and pain intensity yielded 9 traits
569 with evidence of heterogeneity (Cochran $P < 0.05$) and no horizontal pleiotropy (MR-Egger interval $P >$
570 0.05), , 3 of which were bidirectional (Supplementary Table 36). Genetically predicted higher depressed
571 affect subcluster, neuroticism, and smoking initiation had a significant positive bidirectional causal effect
572 with pain intensity (Supplementary Table 36). Further, increased opioid use (N02A) positively predicted
573 pain intensity.

574 **Genetically inferred drug repurposing**

575 Of the 156 genes in EAs with evidence supporting causality from fine-mapping and functional
576 genomic prediction, 20 were present in the druggable genome database⁷⁶ (Supplementary Table 37). Of
577 these druggable candidate genes, 11 (including *GRIA1*, *GRK4* and *MST1R*) are tier-1 candidates, which
578 includes targets of licensed drugs and drugs in clinical trial, 4 genes (e.g., *NEK4* and *RYR2*) are in tier 2,
579 and 4 are in tier 3 (Supplementary Table 30). Within tier 1, drugs that interact with *GRK4* (a credible pain
580 gene locus in moderate LD with the novel index variant *NOP14**rs71597204 – Supplementary Figure 17)
581 are beta-blockers (atenolol and metoprolol) and a calcium-channel blocking agent (verapamil) (Figure
582 4B), which have analgesic effects in osteoarthritis^{104,105} and migraine¹⁰⁶. Another tier-1 candidate gene –
583 *GRIA1* – is targeted by anesthetics (sevoflurane, isoflurane, desflurane), antiepileptics (topiramate,
584 perampanel), analgesics (methoxyflurane), psychoanaleptics (piracetam, aniracetam), and a diuretic
585 (cyclothiazide) (Figure 4B). Drug classes for pain intensity also included anti-hemorrhagic agents (e.g.,
586 fostamatinib [tier 1: *MST1R* and *FYN*; tier 2: *NEK4*] and menadione [*VKORC1*]) (Figure 4B, Supplementary
587 Table 37).

588 Of the 7 genes associated with pain intensity in AAs, *PPARD*, which harbors the new genetic
589 signal discovered in this study, is a tier-1 druggable candidate with 30 interacting drug classes
590 (Supplementary Table 37). The *PPARD* negative modulator sulindac is an approved non-steroidal anti-
591 inflammatory and antirheumatic drug used to treat osteoarthritis.

592 **Discussion**

593 We conducted the largest multi-ancestry, single-sample GWAS of pain intensity to date,
594 comprising 112,968 AA, 436,683 EA, and 48,688 HA individuals. Cross-ancestry analyses identified 125
595 independent risk loci, of which 68 represent novel pain associations. Although prior GWASs for chronic
596 pain phenotypes have identified 99 loci^{23–27,32}, the study samples have largely been limited to EA
597 individuals. The diversity of the MVP sample enabled us to identify novel association signals in both AAs
598 (*PPARD**rs9470000) and HAs (nearest genes *RNU6-461P**rs146862033, *RNU6-741P**rs1019597899).

599 Findings from gene set analysis, tissue enrichment, and cell-type specificity highlight novel
600 biological pathways linking genetic variation to the etiopathology of pain. These functional analyses all
601 implicate the brain, providing genetic support to the current understanding of the pathophysiology of
602 pain severity¹⁰⁷. Genes predominantly expressed in the CNS, particularly in the cerebellum, cerebellar
603 hemisphere, and cortex region, rather than in the DRG, appear to play a salient role in modulating the
604 intensity of pain, consistent with prior associations of sustained chronic pain intensity with increased
605 activity in these brain regions^{108–110}. Our findings are also consistent with prior reports^{24,25,111,112} of
606 enriched gene expression in brain that contribute to pain intensity in a dose- and time-dependent
607 manner and may involve specific neuronal processes in brain regions implicated in emotional
608 processing¹⁰⁷. Evidence that GABAergic neurons are cells of specific interest is a key novel finding. GABA
609 has long been implicated in the modulation and perception of pain^{113–115} and previous work has
610 implicated specific GABAergic activity in the midbrain as a modulator of pain and anxiety¹¹⁶. Altered
611 GABA levels have been reported in individuals with various types of pain^{117,118}, and have been associated
612 with greater self-reported pain¹¹⁹. Targeting GABA functioning (e.g.,¹²⁰), particularly in the brain regions
613 enriched for pain intensity, may represent a novel therapeutic strategy.

614 Eleven of 156 prioritized genes encode druggable small molecules that are targets of licensed
615 drugs or those in clinical trials, representing drug repurposing opportunities for treating chronic pain.
616 We highlight *MST1R*, *GRK4* and *GRIA1*, each with at least three lines of evidence supporting their
617 involvement in chronic pain. *MST1R* encodes a cell-surface receptor with tyrosine kinase activity that
618 mediates the inflammatory response. The *MST1R* inhibitor fostamatinib – prioritized by our drug
619 repurposing analyses – is a possible therapeutic target for rheumatoid arthritis¹²¹. Increased connectivity
620 between frontal mid-brain regions implicated in affective pain processing has been reported in patients
621 with rheumatoid arthritis¹²². Here, we demonstrated that *MST1R* is highly expressed in the adult brain
622 cortex, cerebellum, and cerebellar hemisphere, which suggests that *MST1R* inhibitors may be effective
623 in treating patients with inflammation-related pain.

624 *GRK4* encodes G protein-coupled receptor kinase 4 and has been linked with hypertension¹²³,
625 which is associated with chronic pain at the population level^{124,125}. Of note, *GRK4* showed significant
626 upregulation in the cerebellar hemisphere, fine maps to an intronic variant with > 95% PP, and is a
627 target of beta-blockers. The use of beta-blockers has been associated with reduced osteoarthritis pain
628 scores, prescription analgesic use¹⁰⁴ and consultations for knee osteoarthritis, knee pain, and hip pain¹⁰⁵.
629 *GRIA1* encodes an ionotropic glutamate receptor subunit, an excitatory neurotransmitter receptor at
630 many synapses in the CNS. Loss-of-function mutations in *GRIA1* are linked to neurodevelopmental
631 impairments^{126,127}. The *GRIA1* antagonist sevoflurane reduced pain in patients suffering from chronic
632 venous ulcer¹²⁸. However, clinical trials of topiramate (another drug target for *GRIA1*) for treating
633 neuropathic chronic pain are inconclusive¹²⁹. Research on the mechanisms that underlie the biology of
634 these potential drug targets for *GRK4* and *GRIA1* and their effects on the onset and severity of chronic
635 pain are warranted. Pain intensity was strongly genetically correlated with other chronic pain
636 phenotypes. Corroborating existing epidemiological studies on the comorbid nature of different pain
637 conditions³³, the strongest genetic correlations of pain intensity were with multisite chronic pain,
638 followed by pain in specific bodily locations. In line with previous observations in GWASs of other pain-
639 related phenotypes^{24,25,27,28,103}, there were also positive genetic correlations of pain intensity with
640 psychiatric disorders, substance use and use disorders, and anthropometric traits.

641 PheWAS findings in both the Yale-Penn sample – enriched for individuals with substance-related
642 traits – and the PMBB – comprising a medical population – were prominent in EAs. These findings
643 underscore the important influence of co-occurring substance-related, psychiatric, and medical
644 pathology and educational achievement on the intensity of the pain experience. In contrast, the PRS
645 generated from the pain intensity discovery sample in AAs yielded few associations in either of the
646 target samples, which underscores the need for larger non-European samples to elucidate the genetic
647 architecture of pain intensity.

648 Two-sample MR analysis supported causal associations between pain and multiple traits.
649 Smoking has previously been associated with greater pain intensity, but studies can be confounded by
650 socioeconomic factors, and a bi-directional relationship has been proposed¹³⁰. Here, we show evidence
651 for a causal relationship of pain on smoking initiation. In line with previous findings^{25,33,35,36}, pain
652 intensity had a bidirectional causal effect on the risk of both depressed affect sub-cluster and
653 neuroticism, suggesting that greater pain could predispose individuals to increased risk for these

654 psychiatric disorders and vice versa. Supporting the positive genetic correlation between opioid use and
655 pain intensity, MR showed evidence of a causal effect between pain intensity and opioid use.

656 Our findings underscore the complex nature of pain intensity, with the hundreds of genetic loci
657 contributing to the experience of pain identified here and in prior studies reflecting a substantial genetic
658 contribution to pain-related traits. The evidence adduced here of pleiotropy of pain intensity with
659 psychiatric traits such as neuroticism and depression reflects the contribution of non-physical factors to
660 the experience of pain intensity. This is consistent with the observed significant tissue-group enrichment
661 in CNS, the predominant gene expression findings in brain (including the hippocampus and limbic
662 system), and the SNP-based enhancer enrichments in histone modification in brain tissues (including the
663 dorsolateral prefrontal cortex, inferior temporal lobe, angular gyrus, and anterior caudate).

664 A limitation of the present study concerns the NRS phenotype. Although such a quantitative trait
665 is more informative than a binary one (e.g., the presence of a specific pain diagnosis), it is based on
666 subjective report. However, because the subjective experience of pain is a key defining feature of the
667 clinical phenomenon^{1,131} the phenotype has high public health significance. Pain scores recorded by
668 clerks and nurses in a clinical setting may consistently under report the patient's response. In earlier
669 work that compared self-reported pain from a direct patient survey to scores recorded in a VA clinical
670 setting¹¹⁷, it was determined that, despite lower scores recorded in the clinic the two reports correlated
671 well. Nonetheless, the imprecise measurement of pain intensity likely yields lower power for gene
672 discovery. Related to the use of the NRS, we did not stratify the analyses using different types of pain
673 (e.g., secondary to osteoarthritis vs. lower back pain), to maximize statistical power. We plan in future
674 analyses to examine different sources of pain. The routine assessment of pain severity provided a very
675 large number of pain scores, which we reduced by taking each individual's median of medians NRS score
676 as a trait for GWAS. In subsequent analyses, we plan to evaluate other methods for characterizing pain
677 severity (e.g., pain trajectories). Another limitation is that our sample comprises predominantly male
678 veterans, which in view of well demonstrated sex differences in the experience and frequency of pain²⁶,
679 limits the application of the findings to the general population. Studies that examine pain intensity in
680 large samples with more even sex distributions are needed. Although our sample was more diverse than
681 prior GWAS of pain traits, analyses in the AA and HA samples were underpowered. Finally, because of
682 the lack of a suitable replication sample, we are unable to identify potential spurious findings, so efforts
683 are needed to replicate the findings reported here.

684 Despite these limitations, the large MVP sample and informative quantitative trait measured
685 repeatedly within subjects enabled us to generate a proxy for chronic pain and identify many novel loci
686 contributing to the trait. Downstream analyses localize the genetic effects largely to four CNS regions
687 and using available single-cell RNAseq data specifically to GABAergic neurons. Combined with drug
688 repurposing findings that implicate 20 druggable targets, the study provides a basis for studies of novel,
689 non-opioid medications for use in alleviating chronic pain.

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708 Figure Legends

709 **Figure 1. Manhattan plot for the pain intensity cross-ancestry GWAS meta-analysis.** This identified 125
710 independent index variants. SNPs above the red line are GWS after correction for multiple testing
711 ($P < 5 \times 10^{-8}$)

712

713 **Figure 2. Enrichment of pain intensity in the brain.** **A**, Partitioning heritability enrichment analyses using
714 LDSC showing enrichment for pain intensity in the CNS, adrenal, liver, cardiovascular, and skeletal
715 tissues. The dashed black lines indicate Bonferroni-corrected significance ($P < 0.005$). **B**, Proportion of
716 heritability shows robust enrichment for SNPs in brain and immune-related tissues. Heritability
717 enrichment analyses for gene expression (**C & D**) and chromatin interaction (top 35 annotations are
718 shown in **E**, see supplementary Table 12 for full details) using GTEx data show enrichment for pain
719 intensity in brain regions previously associated with chronic pain. Bonferroni correction was applied
720 within each tissue conditioned on the number of genes tested.

721

722 **Figure 3. Gene prioritization for pain intensity.** **A**, Genomic annotation of credible sets using FINEMAP
723 shows enrichment largely in non-coding regions and to a lesser extent in exons. **B**, Annotation of known
724 and novel credible genes. Dashed lines indicate posterior probability > 0.5 . **C**, Number of overlapping
725 genes across functional prediction models. **D**, Tissue enrichment of prioritized genes using SMR and
726 GTEx data show enrichment in brain regions. Size of circle reflects $-\log_{10}P$. Bonferroni correction was
727 applied within each tissue conditioned on the number of genes tested.

728

729 **Figure 4. Genetic correlation and drug repurposing.** **A**, Genetic correlation for pain intensity using LDSC.
730 All points passing Bonferroni correction (Bonferroni correction threshold = 5.62×10^{-4} [0.05/89]) are
731 plotted. The color of the circle indicates the phenotypic category. **B**, Druggable targets and drug
732 interactions for 8 credible genes associated with pain intensity. For a full list of credible drug targets see
733 Supplementary Table 30.

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739 **Data Availability.** The full summary statistics from the meta-analyses will be available through dbGaP
740 upon publication.

741

742 **Code Availability.** Imputation was performed using Minimac3
743 (<https://genome.sph.umich.edu/wiki/Minimac3>). GWAS was performed using PLINK2 ([https://www.cog-
744 genomics.org/plink2](https://www.cog-
744 genomics.org/plink2)). Meta-analyses were performed using METAL
745 (https://genome.sph.umich.edu/wiki/METAL_Documentation). GCTA-COJO
746 (<https://cnsgenomics.com/software/gcta/#Overview>) was used for identification of independent loci.
747 FUMA (<https://fuma.ctglab.nl/>) was used for gene association, functional enrichment and gene-set
748 enrichment analyses. Transcriptomic and proteomic analyses were performed using FUSION
749 (https://github.com/gusevlab/fusion_twas). Chromatin accessibility analyses were performed using H-
750 MAGMA (<https://github.com/thewonlab/H-MAGMA>). LDSC (<https://github.com/bulik/ldsc>) was used for
751 heritability estimation, genetic correlation analysis (also using the CTG-VL; <https://genoma.io>) and
752 heritability enrichment analyses. Trans-ancestry genetic correlation was estimated using Popcorn
753 (<https://github.com/brielin/Popcorn>). PRS analyses were performed using PRS-CS
754 (<https://github.com/getian107/PRScs>). PheWAS analyses were run using the PheWAS R package
755 (<https://github.com/PheWAS/PheWAS>). The MendelianRandomization R package ([https://cran.r-
756 project.org/web/packages/MendelianRandomization/index.html](https://cran.r-
756 project.org/web/packages/MendelianRandomization/index.html)) was used for MR analyses.

757

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779 **Contributions**

780 S.T conducted the main analyses and drafted the manuscript. R.V.S conducted phenotype-related
781 analyses. Z.J and H.X conducted downstream analyses. D.S annotated gene findings. M.P.V and K.S
782 helped conduct analyses. R.V.S, Z.J, H.X, D.S, E.H, M.P.V, K.S, K.X, J.G, D.A.J, C.T.R, M.C, E.S, and S.G.W
783 helped to write the manuscript. A.C.J obtained funding to support the project and helped to write the
784 manuscript. R.L.K supervised the analyses and helped to write the manuscript. H.R.K conceived the
785 project, obtained funding to support it, and helped to supervise the analyses and write the manuscript.
786 All authors reviewed and approved the final version of the manuscript

787 **Ethics declarations**

788 HRK is a member of advisory boards for Dicerna Pharmaceuticals, Sophrosyne Pharmaceuticals, Enthion
789 Pharmaceuticals, and Clearmind Medicine; a consultant to Sobrera Pharmaceuticals; the recipient of
790 research funding and medication supplies from Alkermes for an investigator-initiated study; and a
791 member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which
792 was supported in the last three years by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, and
793 Otsuka. HRK and JG are named as inventors on PCT patent application #15/878,640 entitled: "Genotype-

794 guided dosing of opioid agonists," filed January 24, 2018. ES is a full-time employee of Regeneron
795 Pharmaceuticals. The other authors have no disclosures to make.

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