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Multi-ancestral genome-wide association study of chronic pain reveals widespread genetic correlations with substance use and substance use disorders

Chronic pain (CP) is a debilitating condition that impacts an individual's physical and mental health. CP is common, affecting around 12-40% of individuals worldwide. We conducted a genome-wide association study (GWAS) of CP in the All of Us Research Program v.8 across six genetic ancestries in the United States (Ntotal = 313 931, Ncase = 64 894, Ncontrol = 249 037). In the cross-ancestral meta-analysis, one locus on chromosome 3 reached genome-wide significance (lead SNP: rs3849410, p = 2.64E-08, p < 5E-08). This same lead SNP, rs3849410, reached genome-wide significance after adjusting for multiple comparisons in the European subsample (p = 7.45E-10, p < 8.33E-09). Two additional loci, with lead SNPs rs7652179 and rs4760489, reached traditional genome-wide significance (p = 8.57E-09, and 3.07E-08, respectively; p < 5E-08) in the European subsample. A variant on chromosome 5, chr5:70496454:ACAC:A (no rsID available, p = 2.47E-08), also reached traditional genome-wide significance threshold in the African subsample. Sex-stratified analyses revealed 2 loci in females and 1 in males, 1 of which overlapped with loci identified in the cross-sex analyses.
CP was genetically correlated with multiple substance use behaviors and disorders, including cigarettes per day (rg = 0.32, p = 1.36E-12), generalized addiction risk (rg = 0.38, p = 2.08E-17), and opioid use disorder (rg = 0.46, p = 2.08E-17). Genomic Structural Equation Modeling models revealed a significant genetic correlation between a CP factor and a generalized addiction risk factor (rg = 0.45, SE = 0.020); problematic alcohol use (PAU) and tobacco use disorder (TUD) had independent significant genetic correlations with the CP factor (rg = -0.13, SE = 0.025; rg = 0.11, SE = 0.025; respectively). This study represents one of the largest cross-ancestral genetic investigations of CP to date and demonstrates shared genetic effects between chronic pain and substance use behaviors and disorders.

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