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TITLE: Genetic, lifestyle and environmental risk factors for chronic pain revealed through GWAS

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ABSTRACT:

Chronic pain is a leading cause of disability worldwide with complex aetiologies that remain elusive. Here we explore the genetic architecture of chronic pain by performing a genome-wide association study on 188,352 cases and 69,627 controls from the UK Biobank. We identified two independent genome-wide significant loci ($P<5\times10^{-8}$) associated with chronic pain near *ADAMTS6* (rs113313884) and *LEMD2* (rs10660361). Using gene-based association tests, we identified genetic variants associated with chronic pain (associated genes: *DCAKD*, *NMT1*, *MLN*, *IP6K3*; $P<2\times10^{-6}$). Furthermore, genetic correlation (r_G) analyses revealed largely similar genetic influences between male and female patients ($r_G=1$), suggesting individual differences in the presentation of chronic pain may emerge due to environmental exposures and lifestyle factors. Using linkage disequilibrium score-regression applied to 1,328 complex traits, 548 (41%) were found to be genetically correlated with chronic pain (FDR<5%), of which 175 (13%) showed genetic causal relationships using the latent causal variable model and Generalised Summary-data-based Mendelian Randomisation. In particular, major depressive disorder, anxiety, smoking, body fat, BMI and musculoskeletal diseases were found to increase the risk of chronic pain, whereas diet, walking for pleasure and higher educational attainment were associated with a reduced risk. In conclusion, this data-driven hypothesis-free approach has uncovered several specific risk factors that warrant further examination to help deliver effective early screening and management strategies for chronic pain.

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