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Exploring the genetic contribution to chronic pain conditions

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Abstract

Chronic pain (CP) presents a significant challenge in clinical management, profoundly affecting patients' quality of life. Understanding the genetic underpinnings of CP is important to enhance our comprehension of its pathophysiology and for elucidating the heritability of this complex condition.

This study aims to identify genetic factors influencing disease risk, highlight genes enriched with rare variants, and assess the importance of deep phenotyping to stratify patients into distinct clinical subgroups, to achieve stronger significance in genetic correlations.

We investigated a cohort of 640 CP patients and 216 healthy controls (HC). Patients underwent a comprehensive neurological work-up, including nerve conduction studies, intra-epidermal nerve fibre density assessments, pain questionnaires, and clinical evaluations. All samples were analysed using Next-Generation Sequencing to detect rare coding variants in pain-related genes. These variants were aggregated through Gene-Wise Aggregation Analysis. The Sequence Kernel Association Test-Optimal (SKAT-O) was employed to explore any excess of rare variants in CP patients compared to HC.

Based on anamnestic and instrumental data, patients were categorized into "neuropathic" or "nociplastic" pain subgroups. The gene-wise aggregation test revealed two genes as suggestively enriched with rare coding variants in CP patients compared to HC, namely TRPA1 (p-value=6.05E-03, ρ=1) and PTPRZ1 (p-value=4.77E-02, ρ=1). The significance of these findings increased when considering the phenotypic subgroups of patients, with TRPA1 surviving Bonferroni correction, showing significant enrichment of rare variants in nociplastic pain patients compared to healthy controls (P=6.7×10−4, ρ=1), with a 4.8-fold higher risk based on the simple burden test.

Our study unveils novel genes contributing to chronic pain (CP) and demonstrates the effectiveness of SKAT-O in identifying genes that collectively influence disease risk. These findings provide essential insights into CP pathophysiology and inter-individual variability, revealing new potential drug targets. Deep phenotyping has proven to be a valuable strategy for patient stratification, enhancing statistical significance in the analysis of complex traits. Close collaboration among experts in medical science, electrophysiology, biology, genetics, and data science is crucial to advancing our understanding of complex conditions like chronic pain.