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Common Threads: Uncovering Convergent Pathways for Cannabis Use Disorder Across Diverse Populations

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Large disparities in the prevalence of cannabis use disorder (CUD) exist across ethnic groups in the U.S. Despite large GWAS meta-analyses identifying numerous genome-wide significant loci for CUD in European descents, little is known about other ethnic groups. While most GWAS and SNP-heritability studies focus on common genomic variants, rare and low-frequency variants, particularly those altering proteins, are enriched for the heritability of complex traits and may contribute to disease in different way across populations, either through converging or alternative pathways. In this study, we examined three populations including two understudied: American Indians (AI), European Americans (EA), and Mexican Americans (MA), using whole genome (AI, EA) and exome data (MA). We focused on rare and low frequency functional variants in genes and pathways, specifically nonsynonymous and splicing variants, and performed association analysis with CUD severity. We identified three significant pathways in MA and one in EA associated with CUD severity. Notably, pathways related to arylsulfatases activation and heparan sulfate degradation were supported by both EA and MA, with additional evidence from AI. The integrin beta-1 cell surface interaction pathway, involved in cell adhesion, was uniquely significant in MA. Several immune-related pathways were also found, including an autoimmune condition in MA, and a p38-gamma/delta mediated signaling pathway supported across all three cohorts. Although each population displayed distinct pathways linked to CUD, overlapping genes in top pathways suggested shared genetic factors, further highlighting the importance of considering diverse populations in genetic research on CUD.