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Pleiotropic Loci for Cannabis use Disorder Severity in Multi-Ancestry High-Risk Populations

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Cannabis use disorder (CUD) has been found to be comorbid and genetically correlated with other disorders. If two or more traits are affected by the same genetic locus, they are said to be pleiotropic. This study aimed to identify specific pleiotropic loci for the severity level of CUD in three high-risk population cohorts: American Indians (AI), Mexican Americans (MA), and European Americans (EA). Using a previously developed computational method based on a machine learning technique, we leveraged the entire GWAS catalog and identified 114, 119, and 165 potentially pleiotropic variants for CUD severity in AI, MA, and EA respectively. Ten pleiotropic loci were shared between the cohorts although the exact variants from each cohort differed. While majority of the pleiotropic genes were distinct in each cohort, they converged on numerous enriched biological pathways including Wnt/beta-catenin signaling, lipoprotein assembly, response to UV radiation, and the complement system. The enriched gene ontology terms were predominately related to synaptic functions and neurodevelopment. The pleiotropic genes were the most significantly differentially expressed in frontal cortex and coronary artery, up-regulated in adipose tissue, and down-regulated in testis, prostate, and ovary. They were significantly up-regulated in most brain tissues but were down-regulated in the cerebellum and hypothalamus. Our study is the first to attempt a large-scale pleiotropy detection scan for CUD severity. Our findings suggest that the different population cohorts may have distinct genetic factors for CUD, however they share pleiotropic genes from underlying pathways related to Alzheimer's disease, neuroplasticity, immune response, and reproductive endocrine systems.