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From Genetic Risk to Brain Mechanisms: Multi-Omics and Imaging Insights into Cannabis Use and Addiction

Background and Significance:

Cannabis addiction represents a growing public health burden worldwide. Large-scale genome-wide association studies (GWAS) have identified critical genetic risk factors associated with cannabis use and cannabis use disorder, however, the neurobiological and molecular mechanisms linking genetic liability to brain structure, function, and psychiatric comorbidity remain less understood.

Hypothesis and Methods:

We conducted GWAS on lifetime and frequency regular cannabis use in the UK Biobank (UKB; N=486,195) and are extending analyses to the All of Us (AoU) cohort to enhance ancestral diversity and generalizability. We performed comprehensive post-GWAS analyses, including transcriptome-wide association study (TWAS), bidirectional Mendelian Randomization and co-localization analysis using multi-omics Quantitative Trait Locus (QTL), and imaging genetics-based mediation analysis. We hypothesized that genetic liability to cannabis use influences gene expression, epigenetic regulation, and brain structural and functional phenotypes, while pre-existing molecular and neurobiological factors may also causally predispose individuals to cannabis dependence.

Results and Discussion:

In UKB, we replicated genome-wide significant loci mapping to CADM2 gene associated with frequency of cannabis use. Genetic correlation analyses revealed moderate shared heritability between cannabis use frequency and schizophrenia, anxiety and post-traumatic stress disorder ($r \sim 0.2-0.3$). TWAS and pathway enrichment analysis implicated CADM2 and related neural signaling pathways. Ongoing validation in AoU across multiple ancestries, together with multi-omics colocalization and neuroimaging mediation analyses, will help delineate molecular-to-brain mechanisms underlying cannabis addiction risk and advance cross-ancestry genetic insights into cannabis addiction.

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