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Shared Sources of Genetic Variation Underlying the Transmissible Liability Index for Substance Use Disorders and Subsequent Cannabis Use

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Abstract:

We employed the Transmissible Liability Index (TLI), a latent construct indicated by a breadth of childhood/adolescent characteristics, to understand its utility as an indicator of genetic mechanisms related to cannabis use (CU). Data (N=4726 unrelated European Ancestry) were from the National Longitudinal Study of Adolescent to Adult Health. TLI was based on behaviors assessed during early adolescence (e.g., mood and socialization, property damage, and stealing). Factor analysis was used to construct and validate TLI. GCTA-GREML was used to: (1) characterize the SNP-heritability (h^2_{SNP}) across several CU phenotypes, and (2) examine the phenotypic and genetic covariance between TLI and CU. Analyses employed 6,671,511 autosomal SNPs (MAF>1%) and controlled for linkage disequilibrium (LD), sex, age, and stratification/sampling weights. Logistic regression analyses indicated a 75% increase in odds of ever using cannabis per standard deviation increase in TLI. Lifetime CU (use 5+ times; $h^2_{\text{SNP-LDMS}}=0.24$ [SE=0.10]), and TLI ($h^2_{\text{SNP-LDMS}}=0.20$ [SE=0.11]) were heritable when stratified across LD quartiles and MAF bins. Cannabis use (>5 times) was genetically correlated with TLI score, $r_G = 0.73$ [SE = 0.39, $p = 0.048$]. Overall, our results indicated consistent support for the heritability of lifetime CU, with the majority of genetic variance attributable to SNPs with low MAF. Moreover, TLI is heritable and genetically correlated with CU. While these results are promising, the narrow operationalization of the TLI potentially limits the generalizability of this work to prior literature. Future research should continue to examine the genetic architecture of composite traits like TLI.