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Early Cannabis Use in Adolescents Associates With High-Order Gene by Environment Interactions Identified by Machine Learning

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Youth cannabis use is associated with increased risk for mental illness, cognitive impairment, and poor social relationships; thus, prevention of early initiation is critical. Several risk factors, including genetics, have been implicated in youth cannabis use. However, polygenicity and complex genetic and genetic by environmental (GxE) interactions challenge translation of genetics to clinical application. This study combined logic forest (LF) and penalized logistic regression to identify multi-order (up to 8 variables) GxE most strongly associated with early cannabis use. To identify GxE associated with early cannabis use among 4,301 youth from the Adolescent Brain Cognitive Development (ABCD) Study, we fit an LF model considering 180 single nucleotide polymorphisms (SNPs) within *CHRNA2*, *DRD2*, *CNR1*, and *CNR2* (genes associated with lifetime CUD among adults), tobacco use, and alcohol use. LF identified 1,398 GxE; odds ratios for cannabis use for interactions ranged from 13.2-110. Penalized logistic regression selected 33 of the 1,398 originally identified interactions; all interactions selected included at least 2 SNPs. The interaction with the largest effect size included 6 predictors: tobacco use & rs7766029 & rs806377 & rs2023239 & rs2280376 & rs79145239. Fourteen (0.34%) of 4,137 children who had not used cannabis met the criterion for this interaction compared to 31 (18.9%) of 164 children who had used cannabis [OR = 68.6]. These results indicate that examining genetic risk for youth cannabis initiation requires consideration of multiple SNPs and that GxE methods can identify youth at significantly elevated risk for cannabis initiation and facilitate targeted prevention interventions.