GENOME-WIDE ASSOCIATION STUDY OF AMPHETAMINE RELATED STIMULANT DEPENDENCE

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Background: Lifetime use of stimulants such as amphetamines has been shown to be highly heritable, however few genetic risk factors have been identified for stimulant-related traits.

Methods: We performed a genome wide association study (GWAS) for DSM-IV stimulant dependence in a cohort of families and unrelated individuals of African American (AA) and European American (EA) ancestry (451 cases among 8,121 participants) who were ascertained for genetic studies of cocaine, opioid and alcohol dependence and carefully phenotyped using the Semi-Structured Assessment for Drug Dependence and Alcoholism instrument. Dependence diagnosis was regressed on imputed SNP allele dosage adjusted for sex, age and the first five ancestry principal components in logistic regression models using generalized estimating equations to correct for correlations among related individuals. Association tests were performed separately within each ethnic group and the results were meta-analyzed.

Results: Two regions with genome-wide significant SNPs were identified in AAs, including rs11122436 between *DISC1* and *RP5-865N13.2* (OR = 28.3, P = 3.0×10^{-9}), and rs114496117 (OR=29.3, P= 2.1×10^{-9}) within *TIAM2*. We also detected suggestive associations in EAs with SNPs in the nicotinic receptor gene cluster, *CHRNA3/A5/B4* (OR= 0.6, P=8.5×10^{-7}).

Conclusion: We identified the first genome-wide significant associations for stimulant dependence with SNPs in *DISC1* and *TIAM2*. *DISC1* has a role in neurite/cortical development and has been associated with cocaine and opioid dependence. *TIAM2* modulates the activity of RHO-like protein affecting neuron development. Previously, *CHRNA3/A5/B4* cluster variants were associated with nicotine and cocaine dependence. Our findings need to be replicated in an independent sample and validated experimentally.