Cross-Ancestral Genome-wide analysis of Broad Addiction Vulnerability Leads to Additional Insight Over European GWAS Alone

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Background. Comorbidity across substance use disorders (SUDs) is partially due to genetic factors. We recently demonstrated that in individuals of European ancestry a common addiction risk factor underlies covariance in 4 SUDs. Here, we present cross-ancestry findings for common loci for alcohol use disorder, opioid use disorder, tobacco dependence, and cannabis use disorder.

Rationale/Significance. Pleiotropic loci underlying comorbidity of SUDs in populations of non-European descent have not been evaluated.

Study Design and Methods. We conducted a multivariate genome-wide association study via subset search and random effects meta-analysis, and combined information across problematic alcohol use, problematic tobacco use, and cannabis and opioid use disorders in a sample of 1,025,550 individuals of European (EUR) and 92,630 individuals of African (AFR) descent.

Results. Several loci related to addiction that have previously only been seen in EUR were also found in the cross-ethnicity analysis, including at PDE4B, SEM6D, and CADM2. However, there were different patterns of pleiotropy between the two samples; for example, PDE4B influenced alcohol and cannabis use disorder in both, but additionally influenced smoking in EUR. The most strongly associated gene in EUR, DRD2, did not show cross-ancestry effects. Instead, the most associated cross-ancestry variant was positionally mapped to FUT1, and has not been previously observed in European sample genome-wide association studies. These analyses demonstrate the importance of including samples of differing ancestries when searching for causal genes, pleiotropy in behavioral traits, and polysubstance use disorder manifestations.