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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.