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Genetic Loci Associated with Cocaine Use Identified using Novel Approach to Detect Epistasis

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Heritability estimates for cocaine use disorder (CUD) suggest that 50% of risk for this disease is genetic, yet no genetic variants have been robustly associated with CUD. Deaths by overdose surpassed 100,000 in 2021 with a third due to psychostimulants. Genetic variants that underlie CUD would be informative for diagnostics and treatments. The inability to explain trait heritability has been attributed to small sample sizes, models that are unable to incorporate small effect sizes of common variants, and the exclusion of large effects such as copy number variants that are difficult to identify. Epistasis is also a likely source of heritability, but is difficult to measure genome-wide. Here we focused on the role of epistasis in CUD by using the custom correlation coefficient in the program BlocBuster to build allele-networks from eQTL SNPs. A test for association of these regulatory eQTL haplotype networks with use of cocaine in a cohort of 9,737 individuals with opioid use disorder identified four statistically significant allele haplotypes distributed amongst three ancestries. For one of the significant alleles, analysis of raw intensity values from the genotyping array indicates that the haplotype associated with cocaine use tags copy number increases at the *CYP2D6* locus in those of European ancestry. Paradoxically, further analyses that leveraged recently released long-read human genomes suggests a model in which non-functional copies of *CYP2D6* alter the dopaminergic, glutaminergic, and kynurenine pathways in the brains of individuals that use cocaine, contributing to addiction.