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A Large-Scale Genome-Wide Association Meta-Analysis Study of Cocaine Use Disorder

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Genome-wide association studies (GWAS) of cocaine use disorder (CocUD) have been small by current standards. GWAS discovery for other substance use disorders (SUDs) has been foundational in understanding the genetic and biological components of SUD risk. Although cocaine is one of the most used and addictive illicit drugs in the United States, our biological understanding of CocUD is limited, and not well informed from genetics data. We address this by conducting the largest GWAS of CocUD to date.

This meta-analysis included participants from the Million Veteran Program, Yale-Penn, iPSYCH, and BioVU. The AFR meta-analysis included 117,627 individuals (Ncase=22,163) and the EUR meta-analysis consisted of 441,591 subjects (Ncase=14,909) yielding a total sample of 574,127 subjects (Total Ncase=37,072). Ancestry-specific and cross-ancestry GWAS meta-analyses were performed using an effective sample-size weighted meta-analysis.

The EUR meta-analysis identified a single risk locus at DRD2 on chromosome 11 (lead SNP: rs11214607; p=1.02e-11). The AFR meta-analysis resulted in 3 loci; the top AFR association was with rs10467348 (p=7.58e-09) in HS6ST3 on chromosome 13. The cross-ancestry meta-analysis yielded 11 loci; the top cross-ancestry association was with rs2471851 (p=2.65e-12) in DRD2. Gene-set and tissue expression analyses identified processes involved in neurosynaptic functioning and showed enrichment in brain tissue.

We identified multiple novel findings including DRD2 that has now been identified across multiple SUDs. This effort advances our understanding of the genetic architecture of CocUD and holds promise for understanding better the neurobiology of CocUD and its relationship with other traits.