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A large-scale genome-wide association study meta-analysis of cocaine use disorder

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, PGC-SUD, and additional informative biobanks and cohorts yielding a total sample size of 727,181 subjects (Total Ncase = 51,932). The AFR meta-analysis included 144,885 individuals (Ncase = 27,916), the EUR meta-analysis included 531,999 subjects (Ncase = 21,318), and the AMR meta-analysis included 43,455 individuals (Ncase = 2,698). Ancestry-specific and cross-ancestry GWAS meta-analyses were performed using an effective sample-size weighted meta-analysis. A comprehensive series of in silico analyses were then performed to inform genomic discovery and biological understanding. The EUR meta-analysis identified 7 loci including DRD2 on chromosome 11 (lead SNP: rs11214607; $p = 2.66e-13$). The AFR meta-analysis resulted in 4 loci; the top AFR association was with rs10467348 ($p = 5.09e-09$) in HS6ST3 on chromosome 13. The cross-ancestry meta-analysis yielded 16 loci; the top cross-ancestry association was with rs2471851 in DRD2 ($p = 3.25e-13$). Gene-set and tissue expression analyses identified processes involved in neurosynaptic functioning and showed enrichment in brain tissue. Many additional insights were drawn from the in silico analyses implicating disease relevant etiology. 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.

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