Genome-wide association study of cocaine use in Heterogeneous Stock rats

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Cocaine use disorder (CUD) is a complex condition with varying clinical presentations that can range in severity. Human genetic studies have established that vulnerability to CUD is a highly heritable trait, but the identification of specific genes mediating that risk remains limited. Furthermore, the absence of FDA-approved medications to treat CUD underscores the urgent need to better understand the underlying genetic etiology. In order to identify genetic loci associated with CUD-like traits, we conducted a genome-wide association study (GWAS) using outbred N/NIH Heterogeneous Stock (HS) rats. HS rats represent an ideal model system for GWAS because they have high genetic diversity, and they exhibit a range of addiction-like behaviors. To date, this large collaborative project has resulted in comprehensive phenotyping of approximately 900 HS rats for CUD-like behaviors. Using an extended-access model of cocaine self-administration, rats were exposed to cocaine in two-hour sessions over 10 days, then six-hour sessions over 14 days. Rats were evaluated for CUD-like traits, including escalation of intake of cocaine over time, and varying time between self-administered cocaine infusions. Importantly, GWAS for these traits resulted in multiple significant loci associated with CUD-like behaviors. One locus on chromosome 19 contains several genes of interest, including the protein coding genes for carboxylesterase 1, which are orthologous to the human *CES1* gene. Carboxylesterase 1 functions as a drug-metabolizing enzyme that acts on a wide range of drugs, including cocaine; and variations in this gene could influence individual differences in cocaine metabolism. This GWAS is the largest genetic study of cocaine use in rats to date, and identification of the *Ces1* locus represents a novel finding with functional implications that could be leveraged in the development of pharmacological strategies and targeted interventions to prevent and treat CUD.