

Genome-wide mapping of intermittent-access cocaine self-administration in heterogenous stock rats

Addiction vulnerability is influenced by a combination of genetic and environmental factors. A significant challenge in understanding the genetic predictors of substance use disorders (SUDs) is the complex nature of the human environment. However, genome-wide association studies (GWAS) with animal models offer a solution to identifying genetic associations with SUDs. We performed a GWAS in 989 genetically diverse Heterogeneous Stock (HS) rats for multiple measures of cocaine directed behavior, including key measures for acquisition, cue-seeking, and motivation. Cocaine intake was higher in female rats compared to males. Cocaine motivation was strongly genetically correlated with punished drug intake ($r_g = 0.934$) and cocaine cue seeking ($r_g = 0.899$); punished drug intake was moderately genetically correlated with cocaine cue seeking ($r_g = 0.601$). There was moderate heritability for traits such as acquisition of drug taking ($h^2 = .227$), total lifetime cocaine intake ($h^2 = .256$), and cocaine motivation ($h^2 = .217$), whereas punished drug taking ($h^2 = .174$) and cocaine cue-seeking ($h^2 = .118$) had lower heritability estimates. Three quantitative trait loci (QTL) on chromosomes 1, 5, and 20 were associated with several cocaine directed behaviors, with multiple key traits clustered on chromosome 1. The QTL on chromosome 1 that was associated with both acquisition of drug taking and lifetime cocaine intake contains genes such as *Cpxm2*, *Gpr26* and *Chst15*, which have been previously implicated in smoking initiation, alcohol use (Saunders et al., 2022; Liu et al., 2019) and opioid use (Gaddis et al., 2022) in human GWAS. Phenome wide analyses (PheWAS) linked this SNP which locomotor activity during a social interaction test, as measured in a separate cohort of rats. Separately, an additional QTL on chromosome 1 was linked to cocaine cue-seeking and contains *Dock1*, previously linked to psychiatric conditions including depression, anxiety and schizophrenia (Goes et al., 2015; Tian et al., 2021). The QTL on chromosome 5 was associated with cocaine motivation, contained *Tgfr1* and *Nr4a3* which are both highly expressed in the central nervous system, and linked with depression (Tsai et al., 2018), smoking, and alcohol consumption (Knobloch et al., 2019) respectively in human GWAS. These data shows that GWAS in HS rats are useful in understanding genetic basis of SUDs, as well as highlighting psychiatric conditions associated with SUDs. Additional animals are being tested in an ongoing project to increase power to detect additional loci associated with cocaine directed behaviors. Furthermore, we are applying CRISPR mediated approaches to validate already identified genes and demonstrate their causal links to addiction-related traits.

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