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## **Genomic Loci Influencing Addiction-Like Behaviors During Cocaine Self-Administration**

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The complexity of the human environment presents a challenge in studying the genetic underpinnings of drug motivation. Thus, we performed a genome wide association study (GWAS) on intermittent access (IntA) cocaine self-administration in genetically and phenotypically diverse heterogeneous stock (HS) rats of both sexes (n= 688). Measures of drug directed behavior taken included: acquisition of drug taking, cocaine motivation (progressive ratio), cue seeking, punished responding, escalation of drug intake, and cocaine-induced anxiety. We found that rats significantly escalated cocaine intake during self-administration, with females having higher levels of cocaine intake. Genetic analyses revealed that drug-induced anxiety ( $h^2 = .324$ ) and acquisition of drug taking ( $h^2 = .313$ ) had the highest heritability. Other drug-directed traits that showed moderate heritability estimates included total cocaine intake ( $h^2 = .240$ ), punished drug-taking ( $h^2 = .179$ ), and incentive sensitization ( $h^2 = .157$ ). Additional analysis identified nine separate quantitative trait loci (QTL) for several drug-related traits on chromosome 1, 2, 7, 8, 9 and 15. Three traits of interest: cue seeking, responding during punishment, and escalation of cocaine intake were associated with QTL on chromosomes 1, 7 and 9, respectively. The QTL on chromosome 1 that influenced cocaine cue seeking included candidate genes such as *Arntl* (implicated in several psychiatric conditions and alcohol abuse), *Spon1* (associated with heroin dependence), and *Pth* (involved in mitigating anxiety and depression). Also, the QTL on chromosome 7 that influenced punished responding contained candidate genes including *Myh9* and *Cacng2* which have been associated with schizophrenia. Finally, the QTL on chromosome 9 influencing escalation of cocaine intake contained candidate genes *Erb4* (associated with early onset, and recurrence of major depressive disorders, anxiety-like behaviors during nicotine withdrawal, and nicotine sensitivity), and *Xrcc5* (implicated in alcohol dependence in humans and *Drosophila*). These findings demonstrate the importance of GWAS in identifying genetic links associated with cocaine use and addiction-like behaviors. Ongoing work is focused on increasing the power to identify more genomic loci linked to measures of cocaine self-administration, and examining differential gene expression (using RNA sequencing) under intermittent access and long access models of cocaine self-administration. Future research will focus on validating the specific candidate genes associated with cocaine self-administration.