Name: Nana Amissah
PI Name: Paul Meyer

Email: nanaamis@buffalo.edu
PI Email: pmeyer@buffalo.edu

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

Nana K. Amissah[1], Christopher P. King[1,2], Brady M. Thompson[1], Elizabeth A. Rakowski[1] Luke T. Hannan[1], Apurva S. Chitre[3], Oksana Polesskaya[3], Hao Chen[4], Leah C. Solberg Woods[5], Thiago Sanches[3], Beverl. Peng[3], Abraham A. Palmer[3,6], Paul J. Meyer[1]

[1]Department of Psychology, University at Buffalo, Buffalo, USA.
[2]Clinical and Research Institute on Addictions, Buffalo, USA.
[3]Department of Psychiatry, University of California San Diego, La Jolla, USA.
[4]Department of Pharmacology, Addiction Science and Toxicology, University of Tennessee Health Science Center, Memphis, TN
[5]Department of Internal Medicine, Molecular Medicine, Center on Diabetes, Obesity and Metabolism, Wake Forest School of Medicine, Winston-Salem, USA.
[6]Institute for Genomic Medicine, University of California San Diego, La Jolla, USA.

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 heterogenous 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 (h2 =.324) and acquisition of drug taking (h2 =.313) had the highest heritability. Other drug-directed traits that showed moderate heritability estimates included total cocaine intake (h2 =.240), punished drug-taking (h2 =.179), and incentive sensitization (h2 =.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 Erbb4 (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 of validating the specific candidate genes associated with cocaine self-administration.