Submitter Name: Jason Bubier Submitter Email:Jason.bubier@jax.org

Host genetics, microbiome composition and addiction/addiction-related behavior in mice.

Jason A. Bubier[1], Dong-Binh Tran[2], Asaf Peer[2], Hoan Nguyen[2], Robyn Ball[1], Vivek Philip[1], Hao He[2], Jane Adams[3], Belinda Cornes[2], George Weinstock,[2] Elissa J. Chesler,[1] Yanjiao Zhou[4]

[1]The Jackson Laboratory 600 Main St. Bar Harbor ME 04609
[2]The Jackson Laboratory for Genomic Medicine, 10 Discovery Dr. Farmington CT 06032
[3]Northeastern University Boston MA 02115
[4]UConn Health, 263 Farmington Ave. Farmington CT 06030

Cocaine use disorder (CUD) is a chronic disease characterized by compulsive drug seeking and use, leading to substantial adverse outcomes. CUD is highly heritable (>70%), and many genes have been associated with addiction; however, these only account for a small proportion of the observed variation, suggesting a role for many other biological and environmental factors. As there are still no viable therapeutics for CUD, there is a pressing need to gain *new* mechanistic insights to identify *new* therapeutic avenues. The gut microbiome and its metabolites have emerged as important players in neuropsychiatric disorders via the gut-brain axis. However, their role in addiction and their relationship with host genetics and underlying molecular processes are largely unexplored. We hypothesize that host genetics influences behavior by altering the composition of the gut microbiome. We leveraged data from the P50 Center for Systems Neurogenetics of Addiction, including extensive phenotyping data and fecal samples, to identify novel associations. We identified microbial abundance QTLs at each level of microbial classification (e.g., family, genus) from the gut microbiome. We determined that microbial genes involved in glutamate metabolism were associated with the propensity for mice to self-administer cocaine. We established that gut metabolites are an important functional output of the microbiome and serve as critical mediators of the gut-brain axis in cocaine response. Using multiple statistical approaches, we have identified numerous microbe and behavior associations. Together, these results support the role of host genetics in controlling the microbial abundance and microbial community composition associated with behavior. U01DA043809-JAB/YZ; P50DA039841-EJC