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### **Host Genotype Affects Microbiome Composition and Behavior**

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The intestinal microbiome significantly influences health and disease. Its composition is partly regulated by host genetics, with the heritability of microbial abundance in mice and humans ranging from 5-45%. We utilized the advanced mouse resources of the Collaborative Cross (CC) and Diversity Outbred (DO) mice as a discovery platform for a systems genetics analysis of addiction related behaviors. Leveraging DO data from the NIDA P50 CSNA, we identified genetic loci (QTL) controlling the relative abundance of microbes at the genera level in cecal feces (36 QTL) and fecal boli (34 mQTL). For two QTL, we prioritized candidate genes and, using knockout mouse resources, verified the involvement of two specific genes in the abundance of two microbes. The microbial abundance in both cecal and fecal microbiomes was associated with addiction-related behaviors. Using various statistical approaches, we analyzed the strongest microbe-behavior correlations, associating single microbes with behaviors and clusters of microbes with each addiction-related behavior. Using striatal and cecal eQTL, we identified networks of genes co-expressed and co-varied with the abundance of microbes, helping us understand the mechanistic relationship within the gut-brain axis. Finally, with the CC, we deeply analyzed two phenotypically divergent strains, CC4 and CC41, identifying microbes associated with strong and weak addiction phenotypes (cocaine locomotor sensitization and IVSA). Our work provides compelling evidence that the microbiome, regulated partly by the host genome, plays a crucial role in regulating behavior.

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Hyperlink to relevant publication: <https://pubmed.ncbi.nlm.nih.gov/37114320/>