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Closing the loop on *Turicibacter*

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Substance use disorder (SUD) is heritable, and many genes are associated with addiction. These account for a small proportion of variation, suggesting the involvement of other biological and environmental factors. The gut microbiome affects behavioral responses to cocaine, with abundance and variety of microbial metabolites altering behavior. Host genetics can influence behavior by altering composition of the gut microbiome. We hypothesize this contributes to SUD. Leveraging P50 funded Center for Systems Neurogenetics of Addiction, we used fecal samples and phenotype data from Diversity Outbred mice to test our hypothesis. We identified microbial abundance QTLs in fecal boli and the cecal contents, making them accessible through an online QTL viewer. We utilized CC mice and mutant alleles to test haplotype and gene effects of loci on microbial abundance. Using multiple statistical approaches, we identified microbe and behavior associations.

Turicibacter sanguinis expresses a neurotransmitter symporter homologous to mammalian 5-HT transporter and signals bi-directionally with the host serotonergic system to promote its survival. Abundance of *Turicibacter* correlated with % time mice spend in the light in a DO mouse population. QTL mapping identified a suggestive maQTL on chromosome 13. The QTL haplotype confidence interval from the highest LOD scoring SNP model had one protein-coding gene candidate, *Arsb*. Using CC mice and *Arsb* ENU mutant, 16S sequencing on feces and cecum showed mice carrying the WSB QTL driving allele had highest prevalence of *Turicibacter* in feces and a genotype effect on *Turicibacter* abundance between different *Arsb* mice (+/-,+/+,-/-). U01DA043809 to GMW/JAB and P50DA039841to EJC