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**Genetic control of the microbiome and bile acids to influence addiction-related behaviors**

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Increasing evidence suggests that the gut microbiome and bile acids (BAs) are important mediators of the gut-brain axis. However, the interactive network among host genetics, the microbiome and BAs in substance use disorder has not been defined. Using diversity outbred mice, we identified a novel locus that determines the abundance of Turicibacter – a microbe that is highly heritable across mice and human. Turicibacter abundance driven by a locus on chromosome 13, was correlated with anxiety and risk-taking behavior. Candidate gene prioritization identified arylsulfatase B (Arsb) as the most likely gene responsible for Turicibacter abundance. Arsb mutant mice have decreased anxiety-like behavior, accompanied by increased Turicibacter abundance, increased levels of the primary BA chenodeoxycholic acid (CDCA) and specific secondary BAs. In vitro culture revealed a bidirectional regulation between Turicibacter and BAs. Turicibacter colonization or CDCA administration in C57BL/6J mice recapitulated behavioral changes observed in Arsb mutant mice. Our data identified a novel pathway connecting host genetics, the gut microbiome and BAs in addiction-related behaviors and provides novel targets to treat substance use disorder and underlying co-morbidities.