Multi-cohort analysis identifies robust host genetic effects on the rat gut microbiome

Amelie Baud[1], Felipe Morillo[1], Helene Tonnele[1], Denghui Chen[2], Benjamin B Johnson[2], Oliver Stegle[3], Shelly Flagel[4], Terry E. Robinson[4], Jerry B. Richards[5], Keita Ishiwari[5], Paul J Meyer[6], Hao Chen[7], Leah Solberg Woods[8], Oksana Polesskaya[2], Rob Knight[9], Abraham A Palmer[2]

[1] Systems and synthetic biology, Centre for Genomic Regulation, Barcelona, Spain. [2] Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. [3] Genome Biology Unit, European Molecular Biology Laboratory, Heidelberg, Germany. [4] Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA. [5] Department of Pharmacology and Toxicology, University at Buffalo, Buffalo, NY, USA. [6] Department of Psychology, University at Buffalo, Buffalo, NY, USA. [7] Department of Pharmacology, University of Tennessee Health Science Center, Memphis, TN, USA. [8] School of Medicine, Wake Forest University, Winston-Salem, NC, USA. [9] Center for Microbiome Innovation, University of California San Diego, La Jolla, CA, USA.

Host genetic effects on the gut microbiome are notoriously difficult to detect and rarely replicated across studies. Potential reasons for this lack of replication include different protocols used to profile the microbiome, different genetic and/or environmental characteristics of the cohorts studied, and lack of statistical power.

We took advantage of the efforts of the NIDA P50 Center for GWAS in Outbred rats to profile, using the same protocol, the cecal microbiome of 4,154 Heterogeneous Stock rats from four different cohorts. These cohorts differed in several important ways with regard to the microbiome, including age, vendor providing the chow diet, and microbial environments faced by the rats in the different animal facilities. These differences between cohorts are representative of the variation that more generally exists in microbiome studies. Our primary goals were to evaluate whether host genetic effects are shared across cohorts and to identify robust host genetic effects active across cohorts. To do so, we estimated genetic correlations for the same microbiome phenotype measured in different cohorts and searched for genome-wide significant loci replicated across cohorts.

Genetic correlations were generally high, with an average of 0.5, pointing to limited gene by laboratory environment interactions for microbiome phenotypes, provided the same protocols are used. We identified three highly significant loci for microbiome phenotypes that, remarkably, were replicated across three or four cohorts. The genes implicated at these loci highlighted the importance of mucins, glycosyltransferases and anti-bacterial peptides in host-microbiome interactions. While these mechanisms have long been known to be important for host-microbiome interactions, previous results were almost exclusively based on laboratory experiments involving genetically modified models. In contrast, our results demonstrate that natural genetic variants exist that modulate these mechanisms and shape host-microbiome interactions.