Name: Elaine K. Hebda-Bauer, PhD
Email: hebda@med.umich.edu
PI Name: Huda Akil, PhD
PI email: akil@med.umich.edu

Transcriptional Profiling of the Hippocampus in an F2 Cross of a Genetic Rat Model of Internalizing vs. Externalizing Behavior and Addiction Liability

Elaine K. Hebda-Bauer, PhD[1], Megan H. Hagenauer, PhD[1], Peter Blandino, Jr., PhD[1], Fan Meng, PhD[1], Apurva Chitre, MS[2,3], Bilge Ozel, PhD[1], Stanley J. Watson, Jr, MD, PhD[1], Abe Palmer, PhD[2,3], Jun Li, PhD[1], Huda Akil, PhD[1]

[1]University of Michigan Medical School, Ann Arbor; [2]Department of Psychiatry, University of California San Diego; [3]Institute for Genomic Medicine, University of California San Diego

Novelty-seeking and reactivity to psychosocial stress provide two distinct paths to drug seeking, addiction, and relapse. The externalizing versus internalizing behavioral tendencies that promote these paths are highly heritable. To model these heritable tendencies, we have selectively-bred rats for high and low exploration in a novel environment (bred High Responders (bHR) vs. Low Responders (bLR)) for many generations. To identify genes underlying these differences, we created a bHRxbLR F0-F1-F2 cross and then performed behavioral testing, transcriptional profiling (RNASeq), and whole genome sequencing (WGS). For RNASeq, we focused on hippocampus because it mediates stress reactivity, anxiety, and contextual relapse. We found that hippocampal differential expression (DE) associated with increased exploration in F2s was positively correlated with DE associated with the bHR line in both our current F0 RNASeq study and in a meta-analysis of previous bHR/bLR hippocampal RNASeq studies. Amongst bHR/bLR DE genes, there was 3x enrichment for nominally-significant ($p<0.05$) associations between gene expression and exploration in F2s (104 genes) and more than 8x enrichment for stronger associations ($p<0.005$) with exploration (26 genes). Of 104 genes showing DE in association with both F2 exploration and the bLR vs bHR lines, 14 were located within +/-1MB of exploration quantitative trait loci (QTL) identified in our F2s using exon sequencing or WGS. Of these, five had particularly strong relationships ($p<0.005$) with exploration in F2s: ENSRNOG00000052237, Mfge8, Ucp2, Ttc30a1, Fzd6. Next, we will integrate these findings with our WGS data to identify expression QTLs (eQTLs) to pinpoint specific genetic variants driving exploration-related differential expression.