

Name: Elaine K. Hebda-Bauer
PI Name: Huda Akil

Email: hebda@med.umich.edu
PI email: akil@med.umich.edu

Bioenergetic-Related Gene Expression in the Hippocampus Predicts Internalizing vs. Externalizing Behavior in a F₂ Cross of Selectively-Bred Rats

Elaine K. Hebda-Bauer¹, Megan H. Hagenauer¹, Peter Blandino, Jr.¹, Fan Meng¹,
Apurva Chitre², A. Bilge Ozel³, Keiko Arakawa¹, Shelly B. Fligel¹, Stanley J. Watson, Jr.¹,
Abe A. Palmer^{2,4}, Jun Li³, Huda Akil¹

¹ Michigan Neuroscience Institute, University of Michigan, Ann Arbor; MI 48109, USA

²Department of Psychiatry, University of California San Diego; La Jolla, CA 92093, USA

³Department of Human Genetics, University of Michigan, Ann Arbor, MI 48109, USA

⁴Institute for Genomic Medicine, University of California San Diego, La Jolla, CA 92093, USA

Using selective breeding, we have produced a rat model focusing on temperament as an antecedent to drug use. The bred Low Responders (bLR) are extremely inhibited and anxious in a novel environment, whereas bred High Responders (bHR) are exploratory and sensation-seeking. These divergent behavioral traits map onto temperamental extremes predictive of internalizing vs. externalizing psychiatric disorders in humans and model two divergent paths to drug abuse.

To elucidate gene expression underlying these heritable behavioral differences, F37 bHR/bLR rats were bred to produce a F₀-F₁-F₂ cross, followed by behavioral testing and RNA-Sequencing of hippocampal tissue. The F₀s exhibited robust bHR/bLR differential expression, and we confirmed many differentially expressed genes (DEG) identified in a previous bHR/bLR meta-analysis (Birt, Hagenauer et al, 2021). Prioritizing these bHR/bLR DEGs led to the identification of 17 genes with expression predictive of F₂ behavior, seven of which were located within related QTLs previously identified in F₂s (Chitre, Hebda-Bauer et al, 2023). Convergence between our study and others targeting similar behavioral traits revealed an additional 6 genes related to behavioral temperament. Gene set enrichment analysis pointed to growth and proliferation upregulated with bHR-like behavior and mitochondrial functions, oxidative stress, and microglial activation upregulated with bLR-like behavior. Our findings implicate bioenergetic regulation of hippocampal function in shaping temperamental differences, thereby modulating vulnerability to psychiatric and addictive disorders. We are following up on this study by examining gene expression in the Nucleus Accumbens of bHR/bLR rats from a more recent generation and will provide preliminary results from this reward-related area.