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A Meta-Analysis of Hippocampal Transcriptional Profiling Studies in a Selectively-Bred Rat Model Converges with Genetic Sequencing to Implicate Specific Candidate Genes and Pathways in the Liability for Internalizing and Externalizing Psychiatric Disorders

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For over 16 years, we have selectively-bred rats to show either high or low levels of exploratory activity within a novel, anxiety-inducing environment. These “bred High Responder” (bHR) and “bred Low Responder” (bLR) rats serve as a model for temperamental extremes, exhibiting large differences in many internalizing and externalizing behaviors relevant to mood and substance abuse disorders. The current study elucidated persistent differences in gene expression related to bHR/bLR phenotype across development (P7, P14, P21) and adulthood in the hippocampus, a region critical for emotional regulation. We meta-analyzed eight transcriptional profiling datasets (microarray, RNA-Seq) spanning 43 generations of selective breeding (*n*=2-6 rats per group per dataset; total *n*: adult: *n*=46, P7: *n*=22, P14: *n*=49, P21: *n*=21). By cross-referencing these results with exome sequencing performed on our colony, we pinpointed genes that are strongly implicated in bHR/bLR behavioral phenotype, including two associated with metabolism and mood: Thyrotropin releasing hormone receptor (Trhr) and Uncoupling protein 2 (Ucp2). Our results also highlighted bHR/bLR functional differences in the hippocampus, including a network essential for neurodevelopmental programming, proliferation, and differentiation, with hub genes Bone morphogenetic protein 4 (Bmp4) and Marker of proliferation ki-67 (Mki67). Finally, we observed differential expression (DE) related to microglial activation, which is important for synaptic pruning during development and adulthood, including two genes within implicated chromosomal regions: Complement C1q A chain (C1qa) and Milk fat globule-EGF factor 8 (Mfge8). These functional pathways have the capability to direct bHR/bLR rats along different developmental trajectories and promote a widely-different reactivity to the environment.