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Triangulating Genotyping, RNAseq, and Spatial Transcriptomics in a Rat Model of Temperament and Addiction

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Selectively-bred High Responder (bHR) and Low Responder (bLR) rats represent temperament extremes that model the externalizing and internalizing behavior accompanying many psychiatric disorders. We have been investigating the genetic basis of temperament via a multi-pronged genetic, epigenetic, and transcriptomic approach. Bulk RNA-Seq in the hippocampus and nucleus accumbens has revealed robust bHR/bLR differential gene expression, with spatial transcriptomics (i.e., Visium-FF) providing increased anatomical specificity. A F0-F1-F2 cross has shown that key bHR/bLR behaviors are heritable and differential gene expression predicts expression patterns associated with F2 behavior. This differential expression is also successfully predicted based on F0 genotype using cis-expression quantitative trait loci (cis-eQTLs) identified in the F2s. Colocalization of these cis-eQTLs with behavioral Quantitative Trait Loci (via summary data-based mendelian randomization) pinpointed 16 differentially expressed genes that are strong candidates for mediating the influence of genetic variation on behavioral temperament. Many of these candidate genes are consistent with the bHR/bLR differentially enriched pathways highlighting bioenergetic regulation of oxidative stress, microglial activation, and growth-related processes. We are triangulating these findings with our newly acquired PacBio HiFi long-read sequencing data, including methylation calling, and chromatin accessibility data (via ATAC-Seq). Extending our basal genetic and transcriptomic characterization of bHR/bLR brains to those following cocaine self-administration is underway. The richness of this multi-pronged approach will enhance our understanding of genetic contributions shaping behavioral temperament that modulate vulnerability to psychiatric disorders.