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Basic Science

Abstract Title
Transcriptomic Dysregulation of Synapses in Frontal Cortex Brain Tissues of Human Rett Syndrome Patients

Background
Rett Syndrome (RTT) is a debilitating X-linked neurodevelopmental disorder characterized partially by a loss of purposeful motor control and seizures. Over 90% of cases are caused by mutations in the MECP2 gene, however, the rarity of the disorder means few transcriptomic studies have been performed in human brain tissues. Therefore, the dysfunction of intermediary processes that result in symptoms remain unclear.

Objective
We performed RNA sequencing on frontal cortex samples from five female human RTT patients and age- and sex-matched non-RTT controls to identify processes that are differentially affected by MECP2 mutations.

Methods
Gene Set Enrichment Analysis (GSEA) on the Human Phenotype Ontology (HPO) and Gene Ontology (GO) databases was used to identify sets of genes with known functions (pathways) that are dysregulated in RTT samples. GSEA on the HPO was used to confirm dysregulations of RTT relevant phenotypes, while GO was used to identify novel pathways. Weighted Gene Co-Expression Network Analysis (WGCNA) was then used to extract greater biological signal by identifying modules of highly correlated genes. Pathway analysis of these modules was used to confirm the GSEA results.

Results
HPO results showed dysregulation of several seizure and motor control pathways at adjusted p-value < 0.001. GO results showed numerous robust dysregulations of synapse and synaptic function related pathways at adjusted p-value < 1x10-6. Interrogation of the WGCNA modules confirmed multiple synapse related pathways were dysregulated at adjusted p-value < 0.01.

Conclusion
This study highlights a consistent and robust impairment of synapses in the frontal cortex of human RTT patients. Further, ongoing proteomic and ex vivo work will explain how the dysregulation of synaptic genes presents at the protein level and contributes to overall RTT neurobiology.

We appreciate the donation of the T158M and A201V patient brain tissues and tissues/data for additional RTT and control samples from the NIH NeuroBioBank Program: neurobiobank.nih.gov.

Authors

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