CHRD 2024: Abstract Submission Form

Presenter Name
Paris Musaphir

Presenter Status
Masters Student

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Investigation of DNA double-strand break repair pathway choice in Rett syndrome

Background
Rett syndrome (RTT) is an X-linked dominant neurodevelopmental disorder caused by mutations in the MECP2 gene. The largest genetic modifier screen conducted in Mecp2-null mice identified genes that were enriched in the repair of double-stranded breaks (DSBs).

Objective
To determine the role of DSB pathway choice as a genetic modifier in RTT.

Methods
Three experimental models are being used: (i) the analysis of a key DSB pathway choice gene (RBBP8) in RTT stem cells (ii) a high throughput DNA repair screen in a neuroblastoma cell line and (iii) use of a bioinformatic approach to identify and prioritize genes implicated in RTT to inform future therapeutic studies. RBBP8 will be knocked out in an iPSC MECP2 null isogenic pair. Following, these cells will be differentiated into NPCs and cortical-like forebrain neurons. In aim (ii), siRNA targeting RBBP8 will be performed in SH-SY5Y human neuroblastoma cells that have undergone CRISPR-Cas9 knockout of MECP2. A high throughput screen of DNA repair genes will be performed to assess the activity of DSB pathway choice.

Results
Edited iPSCs and SH-SY5Y cells are being expanded. Next steps include differentiation to NPCs and siRNA experiments, respectively.

Conclusion
Using approaches that focus on identifying DNA repair-related RTT genetic modifiers and how the RBBP8 genetic modifier affects DNA repair pathway choice, may provide new therapeutic insights for RTT as limited options exist.

Do you have a table/figure to upload?
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