CHRD 2024: Abstract Submission Form

Presenter Name
Alana Slike

Presenter Status
PhD Student

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Studying the human relevance and druggability of genetic modifiers in Rett syndrome

Background
Genetic modifiers are non-primary disease-causing genes that alter disease severity and may act as therapeutic targets. Rett syndrome (RTT) is a rare neurodevelopmental disorder caused by mutations in the X-linked MECP2 gene and exhibits inter-individual severity in clinical presentation. A large RTT modifier screen in Mecp2/Y mice recently assessed phenotype improvement following mutagenesis and identified 31 RTT modifiers. We aimed to examine each candidate modifier for human gene-trait associations and drug tractability to help inform future therapeutic assessments.

Objective
We aimed to examine the human gene-trait associations and drug tractability of each of these genes to help inform future therapeutic assessments.

Methods
Modifiers were assessed using GeneWalk to determine the important functions of a specific biological context via machine learning. Human phenotypes were analyzed using v6 of the Open Targets Genetics (OTG) database. Genetic constraint was examined via gnomAD observed/expected scores and gene variance intolerance ranks to inform tractability. The temporal gene expression patterns of the modifiers were also evaluated in BrainSpan. Finally, druggability was assessed using genomic characteristics associated with clinical trial success.

Results
The biological processes attributed to RTT modifiers involve regulation of transcription and double-strand break repair. OTG fine-mapped signals were detected for 16 genes, representing 215 human-trait associations. Traits associated with cognition and neurological function were found. CD22, FAN1 and APOA5 were the least genetically constrained modifiers. FAN1, RAD50, BIRC6 and DENND4A showed temporal expression profiles similar to MECP2. CD22 and HCN2 were the top theoretically druggable genes.

Conclusion
These analyses have revealed novel human-relevant biology underlying RTT modifiers and will help prioritize functional genomics work to confirm modifier effect in human stem cell models.

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No

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