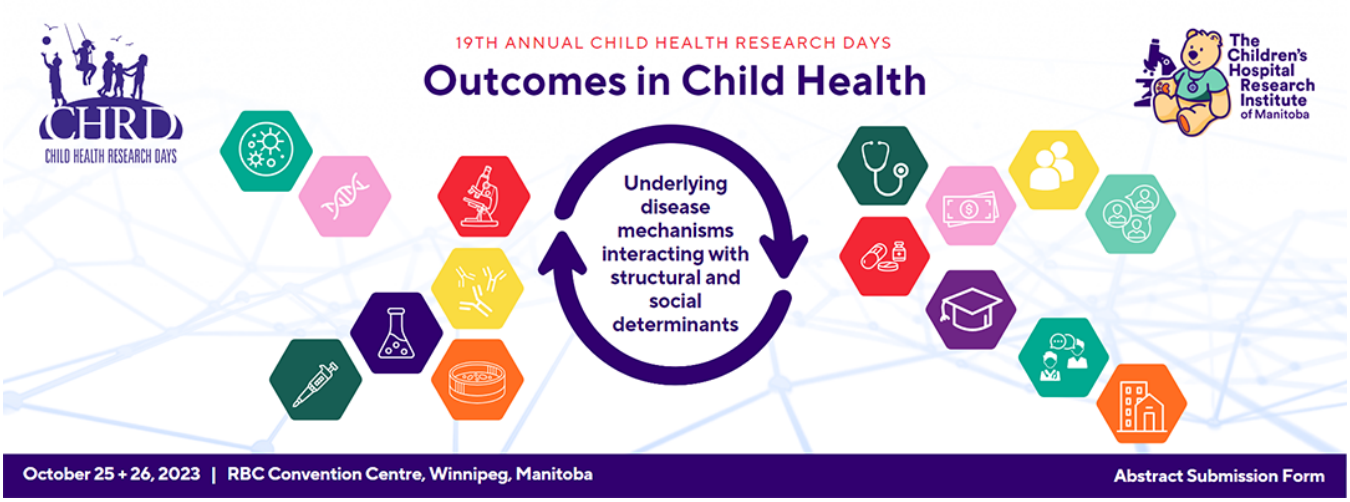

CHRD 2023: Abstract Submission Form

Submitter Name
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Presenter Name
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Presenter Status
PhD Student

Research Category
Basic Science

Role in the project
Perform Experiments
Analyze Data
Write Abstract

Title
Genomic Characteristics of Rett Syndrome Modifier Genes

Background
Genetic modifiers are non-primary disease-causing genes that alter the severity of genetic diseases and therefore may act as therapeutic targets. Rett syndrome (RTT) is a rare neurodevelopmental disorder caused by mutations in the X-linked MECP2 gene. Recently, a large RTT modifier screen in Mecp2/Y mice assessed phenotype improvement following mutagenesis and identified 31 RTT modifiers.

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
Human phenotypes were assessed using v6 of the Open Targets Genetics (OTG) database. To further examine tractability, genetic constraint was examined via gnomAD observed/expected scores and gene variance intolerance ranks. The set of modifiers were also examined by GeneWalk, to determine the important functions of a specific biological context via machine learning. The temporal gene expression patterns of the modifiers were also assessed in BrainSpan.

Results
OTG fine-mapped signals were detected for 16 genes, representing a total of 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 a

similar temporal expression profile to MECP2. The top biological processes attributed to RTT modifiers involve regulation of transcription and double-strand break repair.

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

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