CHRD 2022: Abstract & Poster Submission Form

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Presenter Status

○ Undergraduate Students

◉ Masters Student

○ PhD Student

○ Post-Doctoral Fellows

○ Residents

○ Non-Trainee

Research Category

◉ Basic Science

○ Clinical

○ Community Health / Policy

Role in the project

☐ Design

☑ 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. Previous studies have implicated genetic modifiers in neurological disease and shown their potential 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 genetic modifiers.

Objective

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

Methods

Human phenotypes were assessed using v6 of the Open Targets Genetics database. This resource aggregates results from unbiased genome-wide association studies (GWAS) and performs machine-learning-based fine-mapping of significant association signals using the Locus2Gene model. GWAS information for each gene is extracted and the results were filtered for signals which were most likely attributable to these genes. To further examine tractability, genetic constraint was examined via gnomAD observed/expected scores and gene variance intolerance ranks. The set of modifiers was 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

Of the genes analyzed, 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 RTT modifiers. FAN1, RAD50, BIRC6 and DENND4A showed a similar temporal expression profile to that of MECP2. The top biological processes attributed to RTT modifiers involved regulation of transcription and double-strand break repair.

Conclusion

These analyses have therefore revealed novel human-relevant biology underlying RTT modifiers. We have used this information to prioritize functional genomics work to confirm the modifier effect in human stem cells.

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Authors

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