CHRD 2024: Abstract Submission Form

Presenter Name
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Presenter Status
PhD Student

Role in the project
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Leveraging Large-scale Datasets and Single Cell Omics Data to Develop a Polygenic Score for Cisplatin-induced Ototoxicity

Background
Cisplatin-induced ototoxicity (CIO), characterized by irreversible and progressive bilateral hearing loss, is a prevalent adverse effect of cisplatin chemotherapy. This adverse drug reaction disproportionally affects children, who are at a three-fold higher risk of developing CIO. Genetic variants contribute to CIO and genome-wide association studies (GWAS) have highlighted the polygenicity of this adverse drug reaction.

Objective
To use genomic data to predict CIO.

Methods
We developed a hearing loss polygenic score (PGSHL) using UKBiobank data (n=353,983) and SBayesR. To enhance the relevance of this score to CIO (PGSCIO), we used murine inner ear single nuclei RNA sequencing (snRNA-seq) data and Milo-R to identify cells that exhibited differential abundance post-cisplatin treatment, and selectively included variants mapping to differentially expressed genes. We tested the association between the two PGSs and CIO in two independent CIO cohorts: the PanCareLIFE (PCL) cohort (n=390) and the St. Jude Children's Research Hospital (SJMB) cohort (n=238), using ReACt and logistic regression.

Results
PGSCIO (P=5.54x10-5, R2=0.041) outperformed PGSHL (P=2.93x10-3, R2=0.023) in predicting CIO in the PCL cohort. PGSCIO was also associated with CIO in the SJMB cohort (P=0.043, R2=0.024). The novel scRNAseq data generated through this study has also enhanced our understanding of the cells and biological pathways underlying CIO. Analysis of these data identified cisplatin-induced changes in the proportion of specific cochlear cell types, including specialized auditory cells, supporting cells, immune cells and bone cells.

Conclusion
We developed the first PGS for CIO using a large-scale hearing loss dataset and a biologically-informed filter from inner ear snRNA-seq data. Our approach offers new avenues for developing pharmacogenomic PGSs, and identified cochlear cells that may play critical roles in CIO. This novel genomic prediction model is of particular importance to children, where hearing loss can cause delays in language development, affecting academic and psychosocial outcomes.

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No

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