RUTGERS HEALTH
School of Graduate Studies
Health Sciences Campus - Newark

Office of Student Affairs and Admissions
SGS at New Jersey Medical School
Rutgers, The State University of New Jersey
185 South Orange Avenue, MSB C-696
Newark, NJ 07103

http://njms.rutgers.edu/gsbs/
p. 973-972-4511
f. 973-972-7148

YOU ARE INVITED TO ATTEND THE DEFENSE OF THE DOCTORAL DISSERTATION

"Advanced transcriptomics for diagnostic and translational benefit in rare pediatric neuromuscular disease."

By

Sarah Silverstein
M.D./Ph.D. Program
B.S., Biology, 2016, Lander College for Women, New York, NY

Thesis Advisors: Carsten Bönnemann, MD, habil
Neuromuscular and Neurogenetics Disorders of Childhood Section, NINDS, NIH
&
David R Adams, MD, PhD
Office of the Clinical Director, NHGRI, NIH

Tuesday, March 3rd, 2026
1:00 P.M.
NIH Intramural Campus, Bldg 35, Yellow Skybox

Join Microsoft Teams presentation
https://teams.microsoft.com/meet/28648427275166?p=0sdNikJlNBXH6PDTem
Meeting ID: 286 484 272 751 66
Password: vy36Gj6F

ABSTRACT

Pediatric neuromuscular diseases are clinically and genetically heterogeneous, with 30–60% of cases remaining molecularly undiagnosed after exome or genome sequencing. Diagnostic yields are higher for myopathies and muscular dystrophies, whereas neuropathies have lower diagnostic rates despite being associated with a larger number of disease genes. Short-read transcriptome sequencing can increase diagnostic yield in an estimated 2.5–32% of unresolved cases; however, many patients remain undiagnosed. In clinical practice, short-read RNA sequencing is often interpreted manually in the context of pre-identified variants of uncertain significance and compatible phenotypes, highlighting the need for improved diagnostic strategies. This thesis evaluates advanced transcriptomic approaches -- including computational analytics and long-read RNA sequencing -- to improve diagnostic and translational outcomes.

First, a best-practice pipeline of open-source computational tools was developed for clinical RNA-seq analysis. Using a truth set from a previously diagnosed cohort with muscle- or fibroblast-derived short-read RNA sequencing, a selection of RNA analytical tools was evaluated. Ensemble approaches demonstrated greater sensitivity than individual tools; however, of 68 confirmed diagnoses, only 28 (41%) were detected, indicating that these methods accelerate variant prioritization but do not replace variant-directed manual analysis. Application of this pipeline to 74 previously undiagnosed samples identified nine novel candidate splice-altering variants.

Second, long-read RNA sequencing was applied to deep intronic variants of uncertain significance in intron 8 of *IGHMBP2*, a gene in which biallelic variants cause neuronopathy and neuropathy. Long-read sequencing was required to fully resolve aberrant splicing events incompletely characterized by short-read approaches, enabling accurate variant interpretation. These findings informed development of a splice-corrective antisense oligonucleotide strategy, which was tested in patient-derived induced motor neurons. ASO treatment corrected splicing defects in a subset of variants, restoring full-length IGHMBP2 protein. Transcriptomic and proteomic profiling of successfully treated cells demonstrated rescue of known translational defects and identified pathways that may underlie undiagnosed neuropathies.

Collectively, this thesis demonstrates the diagnostic and translational value of advanced transcriptomic approaches and supports incorporation of long-read sequencing for noncoding variant interpretation in clinical practice.