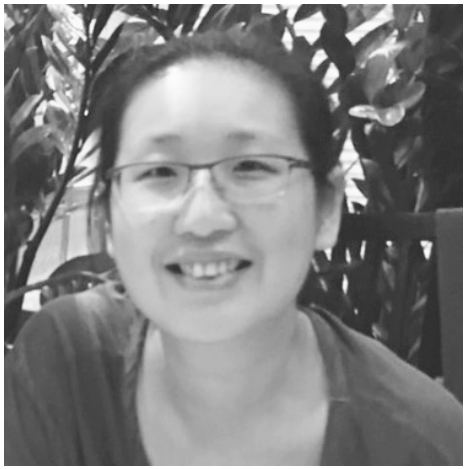
SickKids RESEARCH INSTITUTE

2018
Faculty Candidate Seminar
Rare Disease Genetics and Genomics

Interpreting Sequence Variants in Precision Medicine Era



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2PM
Robert B. Salter Auditorium
Peter Gilgan Centre for Research and Learning
686 Bay St.

Advance in genome sequencing technology has led to an unprecedented speed for variant detection. But progress in functional variant interpretation has been slow and has fallen far behind the demands. While many prediction tools are available to characterize functional variants, none are yet mature. It has been increasingly recognized that variants outside the canonical splice-sites also have the potential to alter splicing and lead to loss-of-function. However, they are severely underreported due to the limitations of the tools to characterize splice variants. We developed Massively Parallel Splicing Assay (MaPSy), a scalable and versatile technology to identify Exonic Splicing Variants (ESV) that can keep pace with variant discovery. We screened ~5,000 exonic variants from Human Gene Mutation Database (HGMD) with MaPSy. Approximately 10% of HGMD coding variants disrupt splicing. Interestingly, ESV often occur in weak exons and share the same mechanism of splicing disruption. ESV and splice-site variants also co-enriched in disease genes, particularly in haploinsufficient genes. MaPSy facilitates the first large-scale genome-wide ESV characterization, which is essential for the maturation of precision medicine.