manitoba neuroscience network

Functionalization of Neuro-developmental Disorder Variants Using Drosophila

NEUROSCIENCE GRAND ROUNDS

DATE

Friday, April 11th, 2025

9:00 AM - 10:00 AM

LOCATION

Psychiatry Bldg. 2nd Floor Rm PX236/238

SPEAKER

Paul Marcogliese, PhD

Assistant Professor, Biochemistry & Medical Genetics, Rady College of Medicine Rady Faculty of Health Sciences, University of Manitoba Investigator - Children's Hospital Research Institute of Manitoba (CHRIM)Co-lead – Multi-OMICS pipeline for Mainstreaming Genomics in Manitoba (MGM).

BIO

Dr. Marcogliese conducted his doctoral studies at the University of Ottawa with Dr. David Park. There, he co-developed a new mouse model of Parkinson's disease (PD) that recapitulates aspects of the human disease. Moreover, he studied the mechanism of action of the PD gene LRRK2 in Drosophila, mice, and cell culture. These studies identified the molecular pathways mediating neurodegeneration implicating LRRK2 in glia as well as a neuro-immune axis in PD. Findings from his doctoral studies resulted in the publication of nine articles including first authorships in Human Molecular Genetics and PNAS. During his postdoc (2016-2022), Dr. Marcogliese was a CIHR (Canadian Institutes of Health Research)-funded postdoctoral fellow in the lab of HHMI Investigator, Dr. Hugo J. Bellen at the Baylor College of Medicine (BCM), Neurological Research Institute. There, he expanded his background in flies including learning sophisticated genetic techniques such as humanization strategies to assess variant function in vivo as well as emerging gene-editing techniques like CRISPR/Cas9. His approach using flies to functionally discern the role of variants of uncertain significance has helped in the discovery of ten novel human neurological disease genes including first authorships published in AJHG, Nature Communications, Cell Reports, and Science Advances. He started his lab in the Department of Biochemistry & Medical Genetics at the University of Manitoba in Winnipeg, Canada in 2022. There he continues to use fruit flies and mice to study variant impact, understand molecular mechanism of disease, and test therapeutics.

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ABSTRACT

In the past decade, next-generation sequencing technology has allowed for a rapid increase in the identification of new human disease genes. This has mostly been in the rare disease space where collectively rare disorders affect 3 million Canadians. It is thought that over 80% of these conditions are genetic in origin and an estimated minimum of 6000 genes remain to be associated with human disease. In both rare neurodevelopmental disorders as well as common disorders of neurodevelopment like autism spectrum disorder (ASD), there is an increased burden of de novo coding variants in affected individuals. Yet large-scale sequencing studies have generally failed to ascribe pathogenic meaning to these variants. Similarly, cohort studies of patients with similar phenotypes and variants in the helped identify causative genes in disease. Again, in many of these reports, functional studies are lacking. Model organisms, and particularly the fruit fly (Drosophila melanogaster) have been critical in providing in vivo evidence for the functional impact of putative disease variants. We have used flies to assess variants implicated in ASD as well as assessed variants in rare neurodevelopmental disorders (EMC1, GLRA2, IRF2BPL, ACOX1, CDK19, TIAM1). Functional studies can shed light on the biological role of the protein product as well as the nature of the variants (loss or gain of function, dominant negative status). This is important as many neurodevelopmental disorders show a range of symptom severity and challenges remain when interpreting variants, particularly missense changes. This talk will present our recent work on variant testing in IRF2BPL, CSNK2A1, CSNK2B, KAT6A, and KAT6B related disorders. We can study the conserved biological mechanisms in these flies and have platformed them for drug testing. Together with clinical collaborators, strategies in flies can be readily employed to assign functional consequences to variants, uncover biology, and advance therapeutic leads in the clinic.

OBJECTIVES

1. Understand how Drosophila can be used to assess variant impact.

2. Gain an appreciation for functional studies in rare neurological disease

3. Understand how flies can be used as a drug screening tool in rare disease

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