Supervisor & Project Information Form

Please complete and return via email ONLY to gdip.hres@utoronto.ca by ***Monday September 30, 2019***

Supervisor Information

MUST have unrestricted SGS appointment (appointment to supervise graduate students)

Name: Ryan Yuen	**Email: ryan.yuen@sickkids.ca**
SGS Department: Molecular Genetics	**Field of Research: Genetics**
Research Institution affiliation (if applicable): The Hospital for Sick Children	**Location of Work: Peter Gilgan Centre for Research and Learning**
Student contact time (number of hours per week YOU are available to the student for any concerns or to review progress:	**2 hours**

Project Information (will be posted on GDipHR website for student access)

TITLE: Genomic analysis of individuals with epilepsy

DESCRIPTION (MAX 500 WORDS):

There is a well-known connection between epilepsy and autism spectrum disorder (ASD). The prevalence of developing epilepsy for ASD individuals range from 3 to 40%, while the prevalence of ASD in epilepsy was estimated to be ~6%. Both ASD and epilepsy have substantial genetic susceptibility, and the use of next generation sequencing has allowed the identification of many susceptible genes or loci in both disorders. ASD-risk genes and epilepsy-risk genes shared common biological pathways, such as synaptic functions and transcriptional regulation. While there are susceptible genes in common between the two disorders, most of the genetic variants involved display highly variable penetrance and in many cases it is still unclear if the mutation identified alone can fully explain the associated phenotype.

One of the recently identified genes that links between ASD and epilepsy is SCN2A. Intriguingly, mutations identified in early infantile epilepsies are mostly gain-of-function, but mutations found in late-onset epilepsy and ASD (epilepsy-ASD) are predominantly loss-of-function. A retrospective review of treatment regimen in these patients revealed that sodium channel blockers are effective treatments only for patients with early infantile epilepsies, but not for those with late-onset epilepsies. Therefore, understanding of the presentation and better characterization of the underlying genetic variants in epilepsy-ASD can potentially facilitate the development of personalized treatments for epilepsy. It may also provide clues for developing more effective drug treatments.

This project aims to investigate the genetic/genomic profiles in individuals that present with epilepsy-ASD and establish a correlation between genomic abnormality, ASD and epilepsy phenotypes. It will be the first to comprehensively look at the genomic profiles of individuals with epilepsy-ASD, which provide valuable insight into our understanding of the genetic and molecular mechanisms that lead to the epilepsies in this population. This in turn may allow for identification of disease-modifying factors, provide earlier diagnosis of epilepsy and result in personalized intervention and improved outcomes.

If human subjects are involved, have the appropriate Research Ethics Board approvals been obtained?

☒Yes ☐No ☐Application Submitted (Date: _____)

Do you expect this work will be published within the 20 months?

☒Yes ☐No ☐Uncertain / Other

Student Roles & Responsibilities (*please be as specific as possible****)***

Please indicate who will serve as the student's direct report for daily oversight (PI, PhD student, technician, etc…)

The student will report directly to the PI with the following activities:

Activity 1: Investigating mutation characteristics of subjects with and without epilepsy. The student will perform burden analysis on the rare predicted damaging variants (single nucleotide and copy number variants) in coding and non-coding regions. The effects of the variants will be evaluated using our latest WGS data annotation pipeline.

Activity 2: Comparing the detection rate of clinically relevant variants in known neurodevelopmental genes. The student will use our developed comprehensive medical annotation strategy to identify the mutations that are most likely to be relevant to epilepsy and ASD in the subjects. The burden of rare variants in known neurodevelopmental disorder-related genes, and the molecular diagnostic yield between individuals with and without epilepsy will be investigated.

Activity 3: Elucidating the functional characteristics of different rare variants identified in subjects with and without epilepsy. The student will compare function and pathway enrichment on gene-sets with rare variants between individuals with and without epilepsy. Genotype-phenotype correlation will be performed based on the relevant variants identified in the participants.