RESEARCH SCHOLAR PROGRAM – 2018

SUPERVISOR & PROJECT INFORMATION FORM

Please complete and return, via email only (crems.programs@utoronto.ca) by ***November 3rd 2017*** *(forms received after this date will not be posted).*

Supervisor Information

Name: Andrew Lim

Email: andrew.lim@utoronto.ca

Degree: MD, MMSc

SGS Appointment (IMS, IHPME, LMP etc..): IMS

Academic Rank: Assistant Professor

Field of Research: Sleep, Circadian Rhythms, Dementia, Genetics, Epigenetics

Research Institution Affiliation (if applicable): Sunnybrook Research Institute

Allocation of student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): I am available in the laboratory at least 30 hours a week. At least 2 hours per week is spent in formal group lab meetings. An addition 2-4 hours a week is available for formal face-to-face instruction of each student.

Project Information

Title: Genetic Determinants of Human Sleep and Circadian Traits

Description (max 500 words):

Sleep and circadian rhythms affect many aspects of human physiology and performance and impact several chronic diseases. Strokes, for instance, show a marked circadian variation in onset risk, with a nearly 7-fold increase in the risk of stroke at peak clock times. However despite substantial progress in understanding the genetic regulation of sleep and circadian rhythms in animal systems, our knowledge of the genetic networks regulating human sleep and circadian rhythms is incomplete. There is considerable inter-individual variability in sleep and circadian phenotypes and twin and family-based studies suggest that some sleep and circadian phenotypes are trait-like and partly heritable. However, genetic association studies using subjective self-report phenotypes have identified relatively few robustly associated gene variants and technical factors have limited the ability to collect quantitative sleep/circadian measures in large cohorts with concomitant genotyping. *The overall goal of this study is to identify genetic variants associated with clinically important sleep and circadian phenotypes, to explore potential mechanisms linking these variants with their associated phenotypes, and to apply these findings to the prediction of sleep and circadian phenomena in community-based and clinical populations*. Objective measures of sleep and circadian behavior in the community setting will be derived from the continuous measurement of individuals' rest-activity patterns for up to 10 days using a wristwatch-like actigraph. We are leveraging available genomic and transcriptomic data from several complementary existing cohorts - the Rush Memory and Aging Project (MAP), the PhenoGenetic Project (PGP), and the Ontario Health Study (OHS). We are using a genome-wide association approach to identify gene variants associated with actigraphic sleep and circadian behavior in the MAP and PGP cohorts with validation in the OHS cohort. We are then test the hypotheses that these associations may be mediated at the molecular level through modulation of gene expression, particularly cis-effects on nearby genes or trans-effects on canonical clock genes. Identifying novel genetic variants associated with sleep/circadian traits and delineating the mechanisms by which they act will deepen our understanding of the generation and regulation of human sleep and circadian rhythms. This in turn has the potential to lead to new mechanistically informed treatments and management strategies for shift-work, jet lag, and sleep disruption that have social and medical consequences for millions of Canadians. Moreover, by facilitating prediction of individual-level sleep and circadian rhythms, this study may facilitate genetic personalization of school, work, travel, medical and other schedules to optimize human performance and clinical outcomes.

This project is funded by CIHR grant MOP 125934 (PI. Lim)

If human subjects are involved, have Ethics been obtained?

☒ YES ☐ NO ☐ Application Submitted ☐ N/A

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

☒ YES ☐ NO ☐ Uncertain

Student's roles and responsibilities (please be specific)

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

The MD student will report directly to the PI. All collection of sleep and circadian rhythm phenotypic data is already complete (n=3000 participants) and genome-wide genotyping is complete on n=1000 participants. The student's primary roles will include participating in developing and overseeing the strategy for genotyping the remaining samples, carrying out analyses relating genotype to phenotype using PLINK and R, and writing up the resulting manuscripts. Anticipated manuscript(s) will describe identification of common gene variants associated with sleep duration, sleep fragmentation, and circadian phase and describing their impact on clinical outcomes. As the work will involve a reasonable degree of programming and data analytics, the ideal student will have programming (especially R and MATLAB, although any language acceptable) and statistics experience, coupled with an undergraduate-level knowledge of mathematics and neurobiology.

Recent manuscript from the laboratory related to this project include:

1. Lim AS, Klein HU, Yu L, Chibnik LB, Ali S, Xu J, Bennett DA, De Jager PL. Diurnal and seasonal molecular rhythms in human neocortex and their relation to Alzheimer's disease. Nat Commun. 2017 Apr 3;8:14931.
2. Lim AS, Srivastava GP, Yu L, Chibnik LB, Xu J, Buchman AS, Schneider JA, Myers AJ, Bennett DA, De Jager PL. 24-Hour Rhythms of DNA Methylation and Their Relation with Rhythms of RNA Expression in the Human Dorsolateral Prefrontal Cortex. PLoS Genetics. 2014 Nov 6;10(11):e1004792.
3. Lim AS, Chang AM, Shulman JM, Raj T, Chibnik LB, Cain SW, Rothamel K, Benoist C, Myers AJ, Czeisler CA, Buchman AS, Bennett DA, Duffy JF, Saper CB, De Jager PL. A common polymorphism near PER1 and the timing of human behavioral rhythms. Annals of Neurology. 2012 Sep 1;72(3):324-34.