Ryan Yuen- Scientific Summary

Project Title: Investigating repeat-mediated RNA dysregulation in autism spectrum disorder

Statement of Purpose: This project will elucidate role and mechanisms of genetic repeat expansions in autism, which will increase understanding of the underlying biology of the disorder.

Project Summary:

Autism spectrum disorder (ASD) is clinically and genetically heterogeneous. To date, genetic studies have identified hundreds of genetic risk factors that are comprised of chromosomal abnormalities, copy number variants, and single nucleotide variants. However, these genetic risk factors collectively can only explain the etiology of about 20% of cases, while family studies indicate a much stronger role of heritable factors. This “missing heritability” can be in part attributed to the inaccessibly of repetitive regions of the genome due to the technical hurdle of the short-read nature of the current high-throughput whole genome sequencing technology. One of the most abundant classes of these sequences are tandem repeats.

We have developed a comprehensive repeat expansion calling strategy, allowing an unbiased genome-wide detection and genotyping of tandem repeat expansions from WGS data. We have recently applied such strategy on ~20,000 genomes of families with ASD, and population controls, and identified 57 loci with large repeat expansions in genes related to nervous system development that are potentially involved in ASD. While this previous study shows that repeat expansions play a role in the etiology of ASD, the biological mechanism of their impact is largely unclear. The current study aims to address this and elucidate this gap in knowledge. Since these loci are predominantly found near splice junctions, we hypothesize that the transcribed tandem repeat expansions gain a toxic function that leads to abnormal development and function of the central nervous system.

Our specific aims in this project are to:
Aim 1. Investigate the potential effect of repeat expansion on RNA dysregulation.
Aim 2. Identify and delineate specific mechanisms of repeat-mediated RNA mis-processing.
Aim 3. Model in vivo the consequences of the AG-rich Cacnb1 RNA repeat expansion.

The scientific significance of the proposed work for neurodevelopmental disorders is twofold: First, by identifying ASD-associated repeat expansions that were previously undetectable, findings of this work will likely reduce the “missing heritability” for ASD. In addition, these findings will provide a strong rationale to examine the possible role of repeat expansions in other complex brain-related disorders. Second, this project may delineate the underlying disorder-causing mechanism involved in repeat expansions, which will broaden the scope by which ASD and its related conditions may be treated.

Since the global effects of repeat expansions in ASD have never been explored, it has the potential to fundamentally change our understanding of the brain and nervous system functions involved.