Research Use Statement for Application for Genomic Data from NIAGADS

Please limit to 2,200 characters max. The statement should include the following components:

- Objectives of the proposed research;
- Study design;
- Analysis plan, including the phenotypic characteristics that will be evaluated in association with genetic variants

Research Use Statement:

Objectives of the Proposed Research:
The MAPT locus at 17q21.31 associated with multiple neurodegenerative diseases, including progressive supranuclear palsy (PSP), although the specific causal variants at this locus remain unknown. This region of the genome contains abundant structural variation, including a large genomic inversion as well as multiple copy number variants. We are creating a more detailed map of the structural haplotypes at this locus as well as improved statistical methods for imputing structural variation from genotype data. We propose to combine these two approaches at the 17q21.31 locus to impute a high-resolution map of structural variation into a PSP case/control cohort. We believe this work can help increase our understanding of the role of structural variation at this locus in PSP.

Study Design:
We will build a detailed map of structural variation at the 17q21.31 locus using available whole-genome data sets, including data from the 1000 Genomes Project and other available long-read data. We will build an imputation panel for the structural variation at this locus using this existing data and increase imputation power by incorporating samples from other studies with appropriate consent, such as the Whole Genome Sequencing in Psychiatric Disorders (WGSPD) consortium. We will use this imputation panel to impute structural variation into the PSP case/control cohort we are applying to access.

Analysis Plan:
We will create a map of structural variation and structural haplotypes using existing whole-genome sequencing data sets and publicly available long-read data, utilizing our existing analysis methods (Genome STRiP) and enhancements versions thereof. We will employ new statistical imputation methods we are developing to impute the structural haplotypes at this locus into the PSP case/control cohort and test for association to disease. We will further attempt to fine map any association signals to particular structural features and perform conditional analyses on single-nucleotide variants at the locus to determine the contribution of specific structural features and their relationship to other genetic variation at the locus.

Non-Technical Summary for Application for Genomic Data from NIAGADS

Investigators will provide a non-technical summary of their proposed research. If the project is approved, this statement will be publicly available for lay audiences to read the purpose and objectives of the research. Please limit to 1,100 characters.

The region on chromosome 17 containing the MAPT gene is known to be

associated with multiple neurodegenerative diseases, including progressive supranuclear palsy (PSP). However, the specific genetic variants that influence disease risk and how they might influence disease risk is currently unknown. This region of the human genome is particularly complex: It contains a number of structural changes (copy number changes as well as a large genomic inversion) that vary from person to person. We have developed a new, high-resolution map of structural variation at this locus along with new mathematical techniques to more accurately “project” these maps of structural variation from one group of people to another. This approach has proven effective in other complex regions of the genome in other diseases including schizophrenia, lupus and Sjögren’s syndrome. We will apply these approaches to PSP using previously generated genotype data on PSP patients and controls to attempt to better understand how the genetic variation on chromosome 17 contributes to this disease.