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:
MAPT is associated with neurodegenerative disease, but it is unclear whether there is a single causal variant at the locus with pleiotropic effects or multiple variants on different sub-haplotypes. We plan to use GWAS data from multiple tauopathies, including Alzheimer's and Parkinson's diseases, Progressive Supranuclear Palsy and Corticobasal Degeneration, to identify specific 17q21 sub-haplotypes associated with disease, and determine whether the incidences of these sub-haplotypes correlate with different tauopathies, or whether risk for all tauopathies is associated with one particular haplotype. This work will help to advance our understanding of the genetic basis of the development of multiple and divergent phenotypes associated with tauopathy.

Study Design:
We will assemble GWAS datasets from studies of four different taupothies (IPDGC, the ADGC and PSP datasets we are requesting here, and a CBD dataset we will be requesting in the future once available). We will identify protective and risk sub-haplotypes within the MAPT locus for each dataset individually, then compare this data between tauopathies in order to identify whether the same MAPT haplotypes may confer risk for multiple diseases, or whether different haplotypes are responsible for different Tau-associated phenotypes.

Analysis Plan:
All datasets will be analyzed individually, and the resulting sub-haplotypes and their association with tauopathies will then be pooled. The 17q21 locus from individual datasets will undergo a stringent quality control pipeline phased using ShapeIt2, and imputed using the Michigan HRC server. Haplotype blocks, based on linkage disequilibrium scores and number of SNPs, will be calculated using Golden Helix SVS. The extent of variation present within each block will then be assessed, and the association of specific variants with a disease phenotype will be calculated. The incidences of specific sub-haplotypes associated with different disease phenotypes will then be compared for similarity or shared features.

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 MAPT gene is associated with multiple different neurodegenerative diseases, named 'tauopathies.' While the risk of developing these tauopathies has been associated with a particular version, or 'haplotype' of this gene, labelled 'H1', it is

currently unknown whether there is one sub-haplotype of H1 that increases risk for developing any one of these tauopathies, or whether different sub-haplotypes are responsible for increased risk of different tauopathies. We will be gathering genotype data from different tauopathies, including Alzheimer's disease, Parkinson's disease, Progressive Supranuclear Palsy and Corticobasal Degeneration. Within each dataset, we will indentify the different MAPT sub-haplotypes that are present, and determine the association with either increased risk or increased protection against developing that tauopathy. Once the sub-haplotypes associated with risk and protection for each tauopathy have been identified, we will pool this data to determine whether the sub-haplotypes increasing risk for tauopathy are the same across all diseases, or whether they differ