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:

PSP is a neurodegenerative parkinsonian disorder pathologically characterized by tau lesions in the brain. Although largely considered a sporadic disorder, a genetic component has been implicated; most notably a PSP GWAS identified three novel risk loci (NIAGADS dataset NG00045) in addition to the established risk haplotype on chromosome 17. Some of these variants are likewise associated with altered brain expression of specific genes (Allen et al, Acta Neuropathologica, 2016; Ferrari R et al Neurobiol Aging 2014; Rademakers R et al Hum Mol Genet 2005). The goal of this proposal is to determine if genes or eQTL nominated by our ongoing transcriptomics studies, harbor PSP risk variants.

Study Design: We will query the results from the PSP GWAS (NIAGADS dataset NG00045) for variants at loci nominated by our ongoing transcriptomics studies, including but not limited to: variants nominated by eQTL studies; variants within and proximal to (+/-1MB) genes nominated by differential expression studies (Eg: PSP vs Control brain expression) and hub genes in co-expression networks established using gene expression measures from PSP brain samples. We postulate that association of disease risk variants at loci implicated by our transcriptomic studies will provide additional important insights into disease mechanisms underlying risk for PSP.

Analysis Plan: The variant summary results from the case-control PSP GWAS (NG00045) will queried based on rs# (for variants nominated by eQTL studies) or chromosome and position (for genes/loci nominated by transcriptomic profiling studies) using sql and Microsoft access.

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.

PSP is a neurodegenerative parkinsonian disorder pathologically characterized by tau lesions in the brain. Although largely considered a sporadic disorder, a genetic component has been implicated; most notably a PSP GWAS identified three novel risk loci (NIAGADS dataset NG00045) in addition to the established risk haplotype on chromosome 17. Some of these variants are likewise associated with altered brain expression of specific genes. While efforts are currently underway to decipher the genetic complexity of the disorder, the discovery of the actual disease gene(s), the functional genetic variants, and mechanism of action requires additional creative study. We will leverage the PSP GWAS results in conjunction with our expression data to determine additional genetic risk sites. Through this study we hope to nominate genomic regions of functional relevance in PSP which can be further investigated in model

systems to identify novel therapeutics for this currently incurable disease.