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:

The Tau protein (microtubule associated protein Tau) is the primary component of neurofibrillary tangles (NFTs), long known as a hallmark of Alzheimer's disease. Our research in the transgenic mouse model rTg4510 demonstrated that suppression of Tau led to cognitive improvements despite the accruement of NFTs. Research published by our lab has implicated Caspase 2 (Casp2) cleavage of Tau at aspartate 314 as a key step in the abnormal accumulation of Tau fragments in dendritic spines, leading to synaptic dysfunction. We are currently investigating potential Casp2 inhibitors which may prevent Tau cleavage and thus prevent cognitive impairment. Natural variants in the human Casp2 gene may affect its ability to act on Tau, which could alter susceptibility to the development of AD. To this end, we propose to determine the association, if any, between Casp2 genetic variants and Alzheimer's disease. Our hypothesis is that loss-of-function mutations in Casp2 will decreases the risk of AD. It is known that several caspases are expressed in the brain and that certain caspases have partially redundant functions, thus other caspases may substitute for the loss of Casp2. Therefore, we will include the other caspases primarily expressed in neurons (Casp1/3/6/7/8/9/10) in our analyses.

We will download multiple NIAGADS databases from GWAS studies containing sequence variant information for Casp2 and the other aforementioned caspases. Variant burden associations will be determined for AD cases and controls (Var/CA and Var/CO) and compared to the theoretical variant impact (high, medium, low, etc.) which are given in the datasets. Variants having a significant disease association will be investigated by bioinformatic or structural analysis to determine whether the mutations are likely to impact the Casp2 active site or any aspect of Casp2 docking with Tau, or other loss-of-function mutations such as frame shifts or large deletions of exons or regulatory DNA sequences. Any such positive associations will inform our on-going development of selective Casp2 inhibitor compounds.

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.

We propose to study naturally occurring genetic variations in Caspase 2 (Casp2) and their possible association with Alzheimer Disease (AD) using multiple NIAGADS datasets. We have recently published that the Tau protein is cleaved by Casp2 and the resulting Tau fragment impairs the normal function of neurons, resulting in cognitive impairment. We thus propose to study variants of Casp2 in NIAGADS datasets that may show an increased or decreased association with AD by employing statistical association analyses. Functional predictions based on changes to the DNA and/or amino acid sequence of Casp2 (if any) will be analyzed by *in silico* structural modeling and docking studies.