Objectives of the proposed research

We are seeking to further characterize genetic variant associations for Alzheimer's disease and related neurocognitive disease through using GWAS and meta-analysis. We have datasets we are accessing through dbGaP focused on Alzheimer's disease and age-related neurocognitive diseases. Using the datasets requested here and from dbGap we are going to perform meta-analysis after performing GWAS to identify which genetic association signals are truly robust through leveraging the increased power of multiple datasets. We then use colocalization analysis and functional genomics, combining genetic variation with eQTL data, to determine the genetic variants of most phenotypic impact in relevant tissues for Alzheimer's disease and related conditions.

Study Design

We are requesting access to dataset listed in Table 1 so we can perform genetic associations individually within each of these datasets, then we will then combine results through standard meta-analysis approaches that only use summary statistics. We will not be combining individual level data across these datasets and we will not combine individual level data from these datasets with any other datasets, and will not share the individual level data externally.

Table 1 – Datasets for Meta-Analysis

Origin of Dataset	Total Sample Size	Key Phenotypic data
University of Pittsburgh	2440	APOE, Alzheimer's Diagnosis, MMSE, Age at Onset
TGen II Cohort	1599	APOE, BRAAK, Alzheimer's Diagnosis, Age at Onset
Wash U1 GWAS	578	APOE, Alzheimer's Diagnosis, MMSE, Age at Onset
TARCC	625	Longitudinal clinical, neuropsychiatric, AD and MCI
MTC	542	Alzheimer's cases
WHICAP	653	Alzheimer's cases
WashU2	235	Dementia and severity of dementia
ADC7	1462	Alzheimer's case status, Autopsy, APOE, Age last exam, BRAAK, Age at onset
Miami, Vanderbilt, and Medical School of Mount Sinai (UMVUMSSM) GWAS	2462	Alzheimer's diagnosis, APOE, age last exam, diagnosis, age at onset
NIA-LOAD (ADGC subset) GWAS	3843	Age last exam, Alzheimer's diagnosis
NIA-LOAD GWAS	884 (case control), 9396 family dataset	Alzheimers Diagnosis, age at onset, Autopsy
Strem 2	813	Alzheimer's Disease
CSF Tau Levels	1164	Alzheimers Disease, APOE, CSF data

Analysis Plan

We will use the phenotypic outcomes of Alzheimer's case/control status in our main genome wide association study (GWAS) analyses. We will use any available and relevant

covariates for these datasets in the model, such as information regarding age and gender. For datasets with other sub-phenotypes, we will also run comprehensive associations and perform meta-analysis for the subset of datasets that have the same phenotypic measures. We will then colocalization analyses and functional genomics to further refine signals after meta-analysis. We have evaluated the data use requirements of each datasets requested, and will comply with the individual data use requirements of each dataset for this project.

Non-Technical Summary for Application for Genomic Data from NIAGADS

Alzheimer's Disease, dementia, and mild cognitive impairment have a significant impact on the quality of life for individuals, as well as their care givers. Treatments are still few and not very effective. Identifying novel treatments for these conditions is critical to changing patient trajectories and outcomes. Discovery of new drug targets is possible through the identification of genetic targets through genome wide association studies. There is also still more to be discovered of the genetic etiology of these conditions through investigating associations between common genetic variants and outcomes. We are using these NIAGADS datasets to understand the genetic etiology of Alzheimer's, dementia, and mild cognitive impairment, through combining results across multiple datasets. We can then do further analyses to refine results from these meta-analyses to seek new targets for drug development.