Research Use Statement for Application for Genomic Data from NIAGADS
Please limit to 2,200 characters max.

Objectives of the Proposed Research:
We aim to estimate the causal effects of anatomical, cognitive, and physiological factors on the risk of Alzheimer's disease (AD) and AD-related endophenotypes.

Study Design:

Mendelian randomization (MR)

Analysis plan
We aim to examine whether there is an effect of a higher genetic liability for AD on a variety of brain structures in both children and adults. We will use the inverse variance weighted method for MR as well as sensitivity analyses such as MR-Egger, weighted median and mode, and MR Steiger. For adults, we will perform MR, as well as examine AD-related endophenotypes such as genetically predicted age of onset of AD, vascular brain injury, cerebrospinal clusterin, Aβ/ptau levels, neuritic plaques, neurofibrillary tangles. We will also perform bidirectional MR of AD on physiological factors (e.g. proteins) for adults using the same methods and sensitivity analyses. We also intend to investigate whether any of these effects can be observed earlier in the life course (i.e. in childhood). Single nucleotide polymorphisms (SNPs) for these traits will be extracted from the largest genome-wide association studies for the exposures and the outcomes at the time of analysis. For each of the exposure variables, we will include all SNPs at the genome-wide significant level ($p \leq 5x10^{-8}$, $p \leq 5x10^{-2}$ and $p \leq 5x10^{-1}$) and prune the results to remove all SNPs with a pairwise R^2 greater than 0.001.

Explanation of how the proposed research is consistent with the data use limitations for the requested dataset(s):

Use of the data from NIAGADS is limited only by the terms of the data use certification, health/medical/biomedical purposes, does not include the study of population origins or ancestry and is related to AD.

Brief description of any planned collaboration with researchers at other institutions, including the name of the collaborator(s) and their institution(s).
None

List the NIAGADS datasets you are requesting for analysis (ex. NG00017):
NG00052: CLU, A potential endophenotype for AD: Summary Statistics- Deming et al. (2016)

NG00050 - GWAS of CLU, A potential endophenotype for Alzheimer's disease
NG00055: CSF Aβ/ptau Summary Statistics - Deming Y et al. (2017)
NG00058: Summary Statistics of IGAP Age at onset survival GWAS dataset - Huang KL et al. (2017)
NG00075: IGAP Rare variant Summary Statistics by Kunkle et al (2019)

NG00089 - CSF TREM2 Summary Statistics

Non-Technical Summary for Application for Genomic Data from NIAGADS
The aim of the project is to investigate whether and how anatomical, physiological and cognitive factors influence the risk of AD and AD-related endophenotypes and to estimate the magnitude of total effects of these phenotypes on the disease and vice versa. The understanding of the etiology of AD is limited. Studies have previously reported consistent evidence for educational attainment and intelligence on risk of AD. Through disentangling the various mechanisms by which different phenotypes (e.g. brain structures, protein levels) may affect AD, we aim to gain a better grasp of the causal pathway to AD.