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

UC San Diego PI Steven D. Edland

Objectives of the Proposed Research:

We are requesting GWAS data from NIA-funded Alzheimer's Disease Center subjects who have autopsy data. We are completing a GWAS of an independent dataset, the Honolulu-Asia Aging Study (HAAS) autopsy series. GWAS of the HAAS will establish candidate risk loci for brain autopsy endophenotypes including neuritic plaque, neurofibrillary tangles, and Lewy bodies. We require the ADC GWAS as a validation dataset for our planned study. Loci identified in our HAAS series will be queried in the ADC autopsy series to inform the generalizability and potential relevance of identified loci to the etiology of the pathological processes underlying clinical dementing syndromes.

Study Design:

Study design is standard quantitative trait GWAS. Quantitative autopsy lesion data are typically zero-inflated, so the statistical analysis plan for the HAAS GWAS will accommodate that, either by Poisson modeling or log transformation of count data. ADC phenotypes are ordinal and present different but related challenges. Because distributional assumptions are unlikely to hold regardless of transformations performed, all analyses of HAAS and of ADC data will use permutation test p-values for hypothesis testing. All analyses will be preceded by the usual diagnostics and filtering, include for prohibitively low minor allele frequencies, lack of Hardy-Weinberg equilibrium, and cryptic relatedness.

Analysis Plan:

Quantitative autopsy lesion data are typically zero-inflated lesion count data that may be highly skewed for some outcomes. Primary analysis will be linear models assuming additive genetic effects; analyses will be of log transformed of data to reduce the leverage of extreme values in the outcome measure. Moreover, because least squares model distributional assumptions are unlikely to hold regardless of transformations performed, all analyses of HAAS and of ADC data will use permutation test p-values for hypothesis testing. Analysis will be by plink, with the default adaptive permutation testing option. All analyses will control for age at death and APOE E4 genotype status. Secondary analyses will test for APOE E4 by SNP associations.

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

Proposed analyses are of posted deidentified ADC GWAS and autopsy phenotype data and are consistent with data use limitations of each of the institutions contributing to this series. The purpose of this research falls under allowable uses such as examining: Disease-specific Aging and Dementia, Dementing/Neurodegenerative, and AD and related disorder research, by examining generalizability and possible relevance of brain endophenotypes for better understanding etiology of clinical dementing pathological processes.

NIAGADS

RESEARCH USE STATEMENT AND NON-TECHNICAL SUMMARY

Brief description of any planned collaboration with researchers at other institutions, including the name of the collaborator(s) and their institution(s).

Primary Collaborators are Dr. Tom Montine at Stanford University and Dr. Lon White at the Pacific Health Research and Education Institute. Dr. Montine will assist with interpretation of findings. Dr. White is responsible for the HAAS cohort, including clinical and research criterion brain autopsy phenotyping (n=852). Statistical analyses will be performed at the University of California San Diego Center for Computational Biology and Bioinformatics under the direction of Dr. Kathleen Fisch.

List the NIAGADS datasets you are requesting for analysis (ex. NG00017):

We request access to datasets **ADC1, ADC2, ADC3, ADC4, ADC5, ADC6 and ADC7**

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.

Genome Wide Association Study (GWAS) data from NIA-funded Alzheimer's Disease Center (ADC) subjects who have autopsy data were accessed, for the purpose of validating a new dataset for a planned study. The new, independent study dataset was the Honolulu-Asia Aging Study (HAAS) autopsy series. GWAS of the HAAS is intended to establish candidate genes that may be responsible for brain lesions, including neuritic plaque, neurofibrillary tangles, and Lewy bodies, believed to be responsible for dementia. Loci identified in our HAAS series were queried in the ADC autopsy series to inform the generalizability and potential relevance of identified loci to the etiology of the pathological processes underlying clinical dementing syndromes.