

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:

Over the past decade, GWAS have contributed to our understanding of the genetic basis of complex human diseases. However, the role of the X chromosome in such diseases remains largely unknown because the vast majority of GWAS have omitted it from analysis. Despite the collective evidence pointing to a possible role played by X-linked genes, no consistent GWAS has clearly addressed their contribution to AD or AD-related biomarkers. We aim to perform the first comprehensive X chromosome-wide association study (XWAS) of AD and related biomarkers.

Study Design:

We will assemble for analysis 11 GWAS datasets (ADNI, NIALOAD/NCRAD Family Study, TGen II, and the ones we are requesting with the present application) that include or might include X-chromosome data. An X-chromosome wide association study (XWAS) will be performed in a case-control setting, analyzing independently each dataset and combining the results by meta-analysis. We will also test the association of X-linked variants with CSF markers (beta-amyloid, Total-Tau and P-Tau) in ADNI and NG00035 datasets.

Analysis Plan:

For each dataset, a stringent quality-control (QC) pipeline will be applied to the data before and after the imputation using XWAS (v1.0). Imputation will be performed using IMPUTE2. The association testing will be carried out by logistic regression (or linear regression for the CSF markers), adjusting for Age, APOE4 status and population structure using PLINK. The analysis will be performed both in the whole sample (by coding male genotypes as 0/2) and in males and females separately.

The results will be combined in a meta-analysis using the inverse variance weighted method implemented in METAL and applying genomic control within each individual study.

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.

Alzheimer's Disease (AD) affects women more than men suggesting that there are important sex-based differences in the biological causes of this disease. Understanding sex-specific risk factors and protective factors for AD may help to develop novel interventions for prevention and treatment.

However, the sex-specific genetic architecture of AD is still an under-explored field. We aim to shed light on the genetic underpinnings leading to sex-specific differences in AD by performing the first comprehensive genetic analysis of the X chromosome in AD.