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

Objectives of the Proposed Research:

In the U.S. among older adults (aged ≥ 65), ~8% live with dementia.[1] A healthy lifestyle has been shown to offset the genetic risk of dementia among white participants aged ≥ 60 in the large cohort of UK Biobank.[2] Among those in the top quintile of genetic risk, a favorable lifestyle reduced the risk of dementia by 32%.[2] Overall African Americans have 30% higher risk of dementia compared with whites in the U.S.[3] The extent that a healthy lifestyle could offset genetic risk of dementia in African Americans has not been assessed.

Previously our application proposed to use the GWAS summary statistics of Rietz et al.[4] to derive a genetic risk score (GRS) for dementia in the African American cohort of the Atherosclerosis Risk in Communities (ARIC) study. These GRS will be used to evaluate the interplay between genetic risk and lifestyle factors for dementia in African Americans.
Very recently a new GWAS of Alzheimer's disease (AD) among African Americans with larger sample size has been published (Kunkle et al. 2020).[5] Now we would like to revise the application to request the summary statistics from Kunkle et al. 2020 (NG00100).

Although the study of Kunkle et al. is a GWAS of Alzheimer's disease (AD), its summary statistics is acceptable for deriving a GRS for the study of dementia given the lack of large-scale published GWAS of all-cause dementia (one is ongoing in CHARGE) and AD is the most common form of dementia.[6] In addition, patients of AD often present with other dementia pathologies,[7,8] GWAS summary statistics of AD could have captured genetic risk for other forms of dementia.

The ARIC study is a longitudinal cohort study of 15,892 U.S. adults (African Americans n=4,266) aged 45 to 65 at visit 1 (1987-89).[9] Dementia diagnosis for all participants have been carefully assessed by a panel of experts using predefined criteria based on information from cognitive tests, neuropsychological battery, informant interview, and ICD-9 code for dementia at hospital discharge or on death certificate.[10] We will analyze dementia outcome up to September 1, 2013.

Study Design:
Longitudinal cohort study with ARIC visit 1 as baseline

Analysis Plan:

Given the long follow-up time, we will use competing risk survival analysis based on the Fine & Gray method to account for mortality, which can preclude the development of dementia.[11] Significance level will be set at p-value < 0.05.

Given genetic risk for dementia may differ by race, we will conduct competing risk analysis stratified by self-reported race. The methods for meta-analysis to combine the results from the race groups, e.g. fixed or random effects, will depend on the results from the assessment of heterogeneity.[12]

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

The data use limitation of the requested dataset is: Disease-Specific (Alzheimer's Disease and Related Dementias, IRB, NPU) (DS-ADRD-IRB-NPU)

This proposed research is consistent with the data use limitations, which include dementia. In addition, consistent with the limitation of the IRB and NPU codes, our research is not-for-profit and have also obtained IRB approved.

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

The initial analysis will be conducted at UMMC, which is a study site of the ARIC study. Investigators from the other three sites (Forsyth, NC; Mineapolis suburb, MN; and Washington country, MD) will contribute to reviewing and interpretation of the results and do not need direct access to the summary statistics from Kunkle et al. 2020.

In the event that any investigators outside of UMMC need to access the summary statistics from Kunkle et al., we will submit an amendment to this request.

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

ng00039 ADGC African American Summary Statistics- Reitz et al. (2013)

NG00100 - Novel risk loci and pathways associated with Alzheimer disease in African Americans: A GWAS and meta-analysis summary statistics- Kunkle et al. (2020)

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.

Almost 10% of the older adults in the U.S live with dementia. Treatment options are limited and have small benefits. A healthy lifestyle has been shown to offset the genetic risk of dementia among whites in a large study in the UK. Among those in the top 20 percentile of dementia genetic risk, a favorable lifestyle reduced the risk by 32%. Similar studies have not been conducted among African Americans in the US. More research on the interplay between genetic risk and lifestyle improve the use of lifestyle factors for the prevention and treatment of dementia. The proposed research will use the genome-wide summary statistics of Alzheimer's disease to compute a genetic risk score for dementia to study the interplay between lifestyle factors and genetic risk for dementia.

References

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