Research Use Statement for Application for Genomic Data from NIAGADS

Research Use Statement:

Identifying the precise causal risk factors of Alzheimer's disease (AD) is important to reduce social and economic burden. Candidate associated factors suggested by traditional epidemiological studies can be biased by reverse causation, confounding factors, and measurement errors. To overcome these problems and identify causal risk factors, the Mendelian randomization (MR) method has been proposed and is currently widely used. MR analysis is less likely to be influenced by social and economic bias because germline mutations are not affected by confounders.

In this study, we will investigate causal inference between associated risk factors and AD, and identify novel genetic variants for AD. First, we will identify associated risk factors for AD from independent healthcare datasets (Elderly cohort in South Korea, UK biobank, and Korean genome and epidemiology study). We will employ the time-varying Cox hazard model with outcome of overall survival free of AD. All candidate associated factors for AD will be tested as independent variables of interest. This step will be performed independently of the NIAGADS data.

Second, we will identify causality of these associated factors for AD using one-sample Mendelian randomization (OSMR). The OSMR estimates a polygenic risk score (PRS) related to the significant associated factors for each sample using the PLINK software. Summary statistics of genetic association studies of associated factors from LD hub (http://ldsc.broadinstitute.org/ldhub/) will be used to estimate the PRS. Next, we will test for the association of the PRS with incident AD using a logistic-regression analysis adjusted for covariates such as age and sex in the NIAGADS data.

Third, we will investigate biological pathways shared by the causally-related phenotypes. The DEPICT tool can be used to prioritize and suggest associated biological pathways by identifying the most likely causal genes of identified loci using various databases.

Our study will provide evidence for the causal risk factors for AD.

Non-Technical Summary for Application for Genomic Data from NIAGADS

Many people are interested in preventing dementia. For example, people are wondering what diseases should be avoided, whether they should exercise, whether they should quit smoking, and whether they should be on a diet. Epidemiological studies on many people have shown that some diseases or lifestyle habits are associated with dementia, but more evidence is needed to know whether there is actually causal relation. In this study, we use epidemiological and genomic data to investigate which risk factors can control Alzheimer dementia.