

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:

Novel treatments for Alzheimer's Disease (AD) are urgently needed. Observational data indicate that hypertension and hypercholesterolemia are associated with increased risk of both AD and cognitive status (CS) in non-demented persons. However, it is not clear whether these relationships are causative or associative. Because hypertension and hypercholesterolemia can be treated effectively, confirmation of causal links between them and AD/CS would provide an appealing therapeutic opportunity. Population genetics offers powerful tools for causal inference. Inherited genetic variation provides numerous "experiments of nature" that connect specific mutations – and underlying genes and cellular pathways – to human disease. Because mutations are randomly distributed during meiosis, mutation-disease associations are immune to confounding by postnatal exposures. In this setting, mutations strongly associated with an exposure of interest constitute ideal instrumental variables to evaluate the causal effect of that exposure on an outcome of interest. This is an appealing strategy for hypertension/hypercholesterolemia (exposures of interest) and AD/CS (outcomes of interest) because genetic variation explains a substantial proportion of the variance of these two vascular risk factors. We will combine novel methods in statistical genetics and well-established instrumental variable techniques to test the overarching hypothesis that genetically-determined hypertension and hypercholesterolemia influence risk of both late-onset AD and CS in non-demented persons. Our proposal leverages our team's expertise and successful track record of impactful contributions in the fields of Aging; the robust research infrastructure available through Yale's OAIC; and access, through the NIA Genetics of Alzheimer's Disease Data Storage Site and UK Biobank, to clinical and genomic data from 550,990 persons to pursue the following aims: determine whether genetically-determined hypertension and hypercholesterolemia are associated, individually or jointly, with increased risk of late-onset AD; and determine whether genetically-determined hypertension and hypercholesterolemia are associated with CS in community-dwelling individuals not yet diagnosed with dementia. This administrative supplement to Yale's OAIC will deploy an innovative strategy for causal inference based on genetic information to clarify whether observed associations between hypertension/hypercholesterolemia and AD/CS reflect true causal relationships.

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.

Novel treatments for Alzheimer's Disease are urgently needed. Observational data indicate that hypertension and hypercholesterolemia are associated with increased risk of both late-onset Alzheimer's Disease and cognitive decline in non-demented persons; however, it is not clear whether these relationships are causative or associative. We will combine novel methods in statistical genetics and well-established instrumental variable techniques to test the overarching hypothesis that genetically-determined hypertension and hypercholesterolemia influence risk of both late-onset Alzheimer's Disease and cognitive decline in nondemented persons.