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:
There is now at least three decades of epidemiologic and clinical observational data, in addition to clinical trial data, addressing the question as to whether lowering blood pressure, or using individual anti-hypertensive medications, can reduce the risk of cognitive impairment and dementia. However, neither source of evidence has provided consistent and convincing results favoring lower blood pressure levels, or any one type of anti-hypertensive drug [McGuiness et al., 2009; Duron and Hanon, 2009], although there is evidence [Iadecola et. al., 2016] of direct and indirect mechanisms through which hypertension-related vascular damage could promote neuronal death. Given the evidence of heritability of both AD and blood pressure levels, possibly specific BP regulatory pathways or tissue damage can be identified by big data analytical approaches to genomic and other downstream omics data.

Specific to this NIAGADS request:
Study design
NIAGADS datasets will be used to investigate the relationship between susceptibility for high blood pressure (BP) as measured in a genetic risk score (GRS), and the risk for dementia and separately for MCI, controlling for basic demographic data (age, sex, race, study cohort). We will specifically investigate the interaction between the GRS and age to determine whether high blood pressure susceptibility contributes differently to the risk for dementia/MCI in young old (<70 yrs), old (70-85 yrs) and oldest (>85 yrs) cases. This information will contribute to our understanding of whether, as people age, the contributions of genetic susceptibility for a risk factor, changes dementia risk.

Analysis
The GRS will be based on a list of blood pressure SNP (single nucleotide polymorphisms) drawn from the latest genome-wide discovery and replication analysis of BP traits (systolic - SBP, diastolic – DBP and pulse pressure -PP). The analysis included the UK Biobank (UKB), and the International Consortium of Blood Pressure-Genome Wide (ICBP) Association Studies for discovery, and replication based on previous reports and on data from the Million Veterans Program and the Estonian Biobank. The novel loci were identified using a combination of a one and two-stage study design to test common and low-frequency with minor allele frequency (MAF) $\geq$ 1%. Based on these analyses 1010 SNPs were reported including novel, reported but not replicated, reported and replicated and proxy SNPs for diastolic, systolic and pulse pressure.

GRS scores will be harmonized across cohorts to account for imputation quality, missing SNPs, minor allele frequency (MAF) threshold of 1%, and strand. Only pairwise-independent, linkage disequilibrium–filtered (r^2<0.1) variants will be used for the GRS. A weighted risk score will be calculated for each person using weights of the association of the SNP to blood pressure, which are derived from the published studies. For SNPs that have been replicated we will use the weights (β-coefficients) reported in the latest publication. For novel replicated SNPs, weights will be derived from the publication

reporting the finding. Three blood pressure phenotype genetic risk scores will be calculated: Diastolic BP, Systolic BP and Pulse pressure.

Logistic regression models will be used to estimate the association of case status (AD/MCI) to the GRS, separately for each BP trait, and adjusting for age, sex, race in each cohort separately. Study cohort results will be pooled for an overall meta-analysis for a main effect of BP-GRS, and for an interaction between GRS and age group. We will test for heterogeneity to assess the comparability of the estimates across study cohorts.

References

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Non-Technical Summary for Application for Genomic Data from NIAGADS

High blood pressure possibly plays a role in progression to AD, but studies are mixed: some showing a positive, others a null, and yet others a negative association. We are interested in whether the genetic susceptibility for high blood pressure differs between AD cases and controls, and Mild Cognitive Impairment cases (a prodromal AD stage) and controls. Because the NIAGADS repository includes well characterized AD cases diagnosed according standardized guidelines, it is an ideal resource for an investigation into the hypothesized contribution of genetic susceptibility to high blood pressure to the development of AD.