1.a. Full Title: Candidate gene associations, epistatic interactions, and pleiotropy in MRI-defined structural brain injury: The Atherosclerosis Risk In Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): ARIC MRI GWAS

2. Writing Group:
   Writing group members: Myriam Fornage, Tom Mosley, Eric Boerwinkle, (Additional ARIC authors to be added)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MF_ [please confirm with your initials electronically or in writing]

First author: Myriam Fornage, PhD
Address: University of Texas Houston Institute of Molecular Medicine
        1825 Pressler Street
        Houston, TX 77030

        Phone: 713-500-2463     Fax: 713-500-2447
        E-mail: Myriam.Fornage@uth.tmc.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
    Name: Thomas H. Mosley, PhD
    Address: 2500 North State Street
             University of Mississippi Medical Center

    Phone: 601-984-2763     Fax: 601-815-3422
    E-mail: tmosley@medicine.umsmed.edu

3. Timeline: Analyses completed; First draft to be circulated July/Aug. 2008

4. Rationale:
Stroke and dementia are major causes of mortality and morbidity in the US. The burden of injury to the aging brain, however, is far greater than that of these clinically-recognized neurological conditions, and the deleterious effects of brain vascular disease begin well before clinical symptoms become apparent. Brain imaging techniques, such as magnetic resonance imaging (MRI), have contributed important insights about the prevalence of covert brain abnormalities in the population, the risk factors contributing to their occurrence and progression, and their health implications. Covert brain infarcts, white matter hyperintensities (WMH), and cerebral atrophy detectable by MRI are common in asymptomatic populations beginning in middle age. They share several risk factors, including age, hypertension, and a history of cardiovascular disease. Although the majority of these MRI findings do not produce clinical symptoms, there is growing evidence that they cannot be considered benign accompaniments of aging. Indeed, they have been associated with an increased risk for cognitive deficits, motor function impairment, and future stroke, and are commonly considered part of the spectrum of vascular-related brain injury. The pathophysiology of these MRI measures of structural brain injury is poorly understood. Nonetheless, there is evidence that they may share common pathogenetic mechanisms related to disease of the small vessels of the brain. Measures of MRI-defined structural brain injury, including WMH and cerebral atrophy, have been reported to be under strong genetic influence, with similarly high heritability estimates. To date, very little is known about the specific genes underlying the pathophysiology of these conditions or whether some of the predisposing genes are shared among them. Given the role of cardiovascular risk factors in predicting susceptibility to these conditions, we conducted an association study of 282 polymorphisms in genes related to cardiovascular disease with MRI measures of structural brain injury, including covert brain infarcts, WMH, and sulcal and ventricular size, two markers of cerebral atrophy, in 1,920 African-American and white participants of the Atherosclerosis Risk in Communities (ARIC) study.

5. Main Hypothesis/Study Questions:

Hypothesis 1. Common SNPs in CVD-related genes are associated with MRI-defined prevalent brain infarcts, variation in white matter grade, and sulcal and ventricular grade in African-Americans and Whites.

Hypothesis 2. Pairwise interactions among common SNPs from CVD-related genes are associated with MRI-defined prevalent brain infarcts, variation in white matter grade, and sulcal and ventricular grade in African-Americans and Whites.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Outcome variables: MRI prevalent brain infarcts (BI); Log-transformed white matter grade; Log-transformed ventricular grade; Log-transformed sulcal grade at V3; individuals with prevalent stroke and TIA will be excluded.

Covariates: Age, sex, hypertension status, and field center

Analytical method: Within race categories, linear (quantitative variables) or logistic (presence/absence) regression models adjusting for age, sex, center, and hypertension
status will be used to evaluate the association between SNPs and MRI variables. For each SNP, statistical significance will be assessed based on the point-wise and family-wise (corrected for multiple tests) empirical p-values derived by permutation. A point-wise P-value of 0.005 will be considered significant. With this P-value threshold, the expected number of false positive tests will be less than 1 for each of the traits examined. Moreover, consistency of association across multiple traits or among racial groups will also be considered in evaluating significance of association.

To determine whether interactions among SNPs may influence variation in MRI measures of structural brain injury, we will test pairwise interactions among all possible pairs of SNPs that have a point-wise empirical p-value < 0.20 in the respective single-SNP association analyses. A p-value of 5x10^{-4} will be considered significant, corresponding approximately to an expected false positive rate of 1.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ___X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  ____ Yes  ___X__ No

(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  ____X___ Yes  ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____X___ Yes  ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  ____X___ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.csec.unc.edu/ARIC/search.php

   ____X___ Yes  ____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)? Other GWAS proposals not on the same phenotype
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  _X_ Yes    ____ No

11.b. If yes, is the proposal
   _X_ A. primarily the result of an ancillary study (list number*)
   Brain MRI Study 1991.01
   ___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________  __________)

*ancillary studies are listed by number at [http://www.cscc.unc.edu/aric/forms/](http://www.cscc.unc.edu/aric/forms/)

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

7. Starr JM, Leaper SA, Murray AD, Lemmon HA, Staff RT, Deary IJ, Whalley LJ. Brain white matter lesions detected by magnetic resonance imaging are associated with balance and gait speed. *J Neurol Neurosurg Psychiatry*. 2003;74:94-98