ARIC Manuscript Proposal # 1394

PC Reviewed: 07/30/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome-wide association study of MRI-defined covert infarcts and white matter lesion in the CHARGE consortium

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]**

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3. Timeline: Cohort-specific analyses completed by mid-September. Meta-analyses begin mid-September.

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.[1] 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 and white matter hyperintensities (WMH) 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 [2-5], motor function impairment [6, 7], and future stroke [2, 8, 9], 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.[10-13] 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. Advances in genotyping technologies and SNP discovery have made the pursuit of whole-genome association studies possible and timely. Early successes in identifying genes for age-related macular degeneration [14, 15] and, more recently, diabetes [16, 17] and obesity [18, 19] provide support for this approach to gene discovery in complex disease such as brain vascular disease. We propose to conduct a genome-wide association study (GWAS) of prevalent MRI infarcts and white matter lesion burden in Whites and African-Americans from the ARIC cohort. Meta-analysis of the findings (whites only) will be performed in collaboration with cohorts involved in the CHARGE consortium.

5. Main Hypothesis/Study Questions:

Hypothesis 1. Common SNPs are associated with MRI-defined prevalent brain infarcts in individuals from 6 cohorts of the CHARGE consortium, including ARIC, CHS, FHS, Rotterdam, AGES, and the Austrian Stroke Prevention study.

Hypothesis 2. Common SNPs are associated with MRI-defined variation in white matter grade in individuals from 6 cohorts of the CHARGE consortium, including ARIC, CHS, FHS, Rotterdam, AGES, and the Austrian Stroke Prevention study.

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) and Log-transformed white matter grade at V3; individuals with prevalent stroke and TIA will be excluded.

Covariates: Age, sex, and field center

Analytical method: Within race categories, genetic effects will be estimated using logistic (BI) and linear models (WMH) assuming an additive model. Genotypic classes will be coded as the number of copies of the minor allele of the SNP (additive model). Both observed genotypes and genotypes imputed to the HapMap (Build35) will be modeled. A p-value of $5x10^{-7}$ will be considered statistically significant.
Meta-analyses will be carried out using a 1df fixed effect model (whites only). Each cohort will carry out their own analyses. Only effect size and P-values, not individual data, will be shared across cohorts.

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 ____ 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.cscc.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

___ **A. primarily the result of an ancillary study (list number*** 1991.01, Brain MRI Study; 2006.03, Stampeed, genotyping in Caucasians; 2007.02, CARe, genotyping in African Americans**)**

___ **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/

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.

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