ARIC Manuscript Proposal # 1390

PC Reviewed: 08/12/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome-wide association study of incident stroke in the CHARGE consortium

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

2. Writing Group:

Writing group members: Myriam Fornage, Tom Mosley, Eric Boerwinkle, Aaron Folsom, Wayne Rosamond, Eyal Shahar, Josef Coresh

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: August 2008

4. Rationale:

Stroke is the third leading cause of death in developed countries, after heart disease and cancer, and the leading cause of severe long-term disability.[1] In middle-aged adults, the lifetime risk of stroke is one in five for women and one in six for men.[2] There is strong evidence supporting a significant genetic component underlying susceptibility to stroke. Studies in twins showed significantly greater concordance rates of stroke in monozygotic twins than in dizygotic twins.[3-5] A meta-analysis of ischemic stroke showed that a positive family history is a significant risk factor for ischemic stroke both in case-control (OR=1.8; 95% CI: 1.7-1.9) and in cohort (OR=1.3; 95% CI: 1.2-1.5) studies.[6] To date, few genes influencing stroke susceptibility have been identified. 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 [7, 8] and, more recently, diabetes [9, 10] and obesity [11, 12] 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 incident stroke 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 incident all strokes in individuals from 4 cohorts of the CHARGE consortium, including ARIC, CHS, FHS, and Rotterdam.

Hypothesis 2. Common SNPs are associated with incident ischemic strokes in individuals from 4 cohorts of the CHARGE consortium, including ARIC, CHS, FHS, and Rotterdam.

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: Incident all-strokes and incident ischemic strokes through 2004.

Exclusions: Prevalent strokes and TIA at baseline. For the analysis of all-strokes, individuals with incident SAH will be excluded.

Covariates: Age, sex, and field center

Analytical method: Genetic effects will be estimated using Cox proportional hazards models assuming an additive model. Specifically, within race categories, hazard rate ratios and 95% confidence intervals will be estimated, and contrasted among the genotypic classes for each SNP tested. 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 $5x10^{-8}$ 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
_X__ A. primarily the result of an ancillary study (list number* 2006.03 (Stampede, 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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