ARIC Manuscript Proposal # 1201

PC Reviewed: _11/_21_/06	**Status: _D__**	**Priority: ___**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: A genetic risk score predicts incident stroke in the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Genetic risk score and stroke

2. Writing Group: Alanna C. Morrison, Lance A. Bare, May M. Luke, Jim Pankow, Thomas H. Mosley, James J. Devlin and Eric Boerwinkle

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3. Timeline: Analyses will be completed by November 2006. A manuscript will be in preparation by December 2006.

4. Rationale:

Recent studies (ARIC MS# 1095 and 1142) demonstrate the concept of aggregating information from multiple single nucleotide polymorphisms (SNPs) into a risk score and indicate that it can improve the prediction of incident coronary heart disease (CHD) in the ARIC Study. In order to generate a genetic risk score (GRS) for CHD in ARIC, an initial set of 92 putative functional SNPs were genotyped as a part of Ancillary Study 2004.11. Of these 92 SNPs, 51 were associated with CHD ($p<0.10$) in two antecedent association studies (i.e. prior to testing in ARIC) and had the same risk allele in both antecedent studies. Of the 51 SNPs, 49 were selected based on two case-control studies of myocardial infarction (MI). The other two SNPs were associated with risk of CHD in the placebo arms of two prospective, double blind CHD prevention trials (the CARE and

WOSCOPS studies). This study will assess the contribution of the 51 SNPs to incident stroke in the ARIC Study.

Stroke and CHD share have many traditional risk factors such as smoking, diabetes and hypertension. They may also share certain genetic risk factors, such as variants in genes associated with severe stenosis and thrombotic pathways. The contribution of genetic factors to stroke risk will be assessed by the creation of a stroke GRS. The measure of the predictability of a risk score for the population is the area under the ROC curve (AUC). Race-specific AUCs will be calculated and compared for prediction equations containing traditional stroke risk factors as well as for the inclusion of the stroke GRS in the prediction equation.

5. Main Hypothesis/Study Questions:

Main hypothesis: Putative functional SNPs associated with CHD in antecedent studies are associated with incident stroke in the ARIC Study.

Secondary hypothesis: An individual's stroke GRS improves predictive ability of a stroke event beyond traditional risk factors.

Study Questions:

1. Within Whites and Blacks, the significance of a race-specific stroke GRS will be evaluated by a Cox proportional hazards model for ischemic stroke that includes traditional stroke risk factors (i.e. age, gender, diabetes, hypertension and smoking status).
2. A ROC curve and the corresponding AUC will be determined for a risk score prediction equation containing traditional risk factors, within each race. Similarly, a ROC curve and corresponding AUC will be determined for a prediction equation additionally containing the race-specific GRS. The AUCs will be compared to determine whether inclusion of the GRS improves prediction of a stroke event.

6. Data (variables, time window, source, inclusions/exclusions):

Incident ischemic stroke cases up to 2002 (i.e. 14-year follow-up) will be identified from the istrby02 dataset.

Traditional risk factors at baseline include age, gender, diabetes (DIABTS03), hypertension (HYPERT05) and smoking status (CURSMOK01). Genetic variation contributing to the genetic risk score includes 51 SNPs previously genotyped in the entire ARIC cohort as a part of Ancillary Study 2004.11.

Exclusions prior to analysis involve the removal of individuals with existing or missing data for prevalent CHD at baseline, diagnosis or history of stroke at baseline, Blacks not from Jackson, MS, race other than Black or White, and individuals with restricted DNA

use. Additional exclusions will be performed for individuals missing data for any one of the traditional risk factors.

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 ICTDER02 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 ICTDER02 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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__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)?
None.

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* 2004.11)
___ 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.