ARIC Manuscript Proposal # 1265r

PC Reviewed: __8/21_/07	**Status: _A___**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Common Allele on Chromosome 9p21 and Risk of Heart Failure, Stroke, and Atherosclerosis in The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Allele on 9p21 & HF, stroke

2. Writing Group:
Writing group members: Kazumasa Yamagishi, Aaron R. Folsom, Wayne D. Rosamond, Eric Boerwinkle, Jonathan C. Cohen and others

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

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3. Timeline: 4 months
Approval of proposal
Literature review - 2 weeks
Outline paper - 1 week
Data analysis - 3 weeks
Manuscript writing - 4 weeks

Review and edit - 8 weeks

4. Rationale:

Recently, two reports (1-2) independently identified a relatively strong association of myocardial infarction and coronary calcium with a common allele represented by rs2383206, or rs10757274 or other nearby SNPs near the *CDKN2A/B* gene on chromosome 9p21. The mechanisms are largely unknown. These SNPs are near a SNP (rs10811661) associated with diabetes in 3 reports (3-5). We hypothesize these SNPs are also associated with heart failure, stroke and other atherosclerotic diseases, but to date, no prospective study has tested this hypothesis.

The rs2383206 and rs10757274 polymorphisms have been already typed for the entire ARIC cohort. We propose to examine the association between these and incident heart failure, stroke and its subtypes, and prevalence of carotid atherosclerosis and PAD in the ARIC cohort sample.

Reference

(1) McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. *Science 2007* (in press)
(2) Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardioal infarction. *Science 2007* (in press)
(3) Saxena R, Voight BF, Lyssenko V, et al. Genome-wide association analysis identifies loci for type2 diabetes and triglyceride levels. *Science 2007* (in press)
(4) Scott LJ, Mohlke KL, Bonnycastle LL, et al. A genome-wide association study of type2 diabetes in Finns detects multiple susceptibility variants. *Science 2007* (in press)
(5) Zeggini E, Weedon MN, Lindgren CM, et al. Replication of genome-wide association signals in U.K. samples reveals risk loci for type2 diabetes. *Science 2007* (in press)

5. Main Hypothesis/Study Questions:

rs2383206 and rs10757274 are associated with the risk of heart failure and stroke, especially ischemic stroke, but not hemorrhagic stroke. They are also associated with prevalent carotid atherosclerosis and PAD at baseline.

Although this seems like many outcomes for one paper, the coauthors feel this approach is appropriate for this paper.

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).

Sample: ARIC entire cohort samples

Exclusions:
(for HF) missing gene variables, prevalent HF
(for stroke) missing gene variables, prevalent stroke
(for IMT) missing gene variables and IMT
(for PAD) missing gene variables, and ABI or claudication

Dependent variable: incident HF, stroke and its subtypes, and prevalent carotid atherosclerosis, PAD, and IMT. Values at baseline will be used for IMT.

Independent variable: chromosome 9p21 SNPs (rs2383206 and rs10757274)

Covariates: age, smoking, alcohol intake, BMI, blood pressure, antihypertensive medication use, diabetes, plasma total cholesterol, and other factors.
Prevalent/incident CHD will be additionally included into the model to test potential confounding of the association by CHD. Analyses will also be performed stratifying by presence of prevalent/incident CHD.

Analysis plan: Hardy-Weinberg equilibrium will be tested by chi-square test. Sex-specific hazard ratios and 95% confidence intervals of incident heart failure, stroke and its subtypes across the genotypes will be calculated adjusted for age and other covariates using Cox proportional hazard models. A similar analysis will be done using logistic regression for prevalent carotid atherosclerosis and PAD, and linear regression for IMT as a continuous variable.

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)?

#1223 Large-scale genomic association study identifies region of human chromosome 9 influencing risk of CHD

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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.