ARIC Manuscript Proposal # 1223

PC Reviewed: _2_/_13/06	**Status: _A___**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Large-scale genomic association study identifies region of human chromosome 9 influencing risk of CHD (Note to PC: ARIC is one of several participating studies in ancillary study 2006.03)

b. Abbreviated Title (Length 26 characters): GWA of CHD identifies chr 9

2. Writing Group: Ruth McPherson, Alex Pertsemlidis, Karis Hughes, David Cox, David Hinds, Eric Topol, Anne Tybjaerg-Hansen, Eric Boerwinkle, Jonathan Cohen

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

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3. Timeline: Imminent. Genotyping of the two polymorphisms is complete for the entire ARIC cohort. Draft manuscript should be ready for ARIC review by February 12.

4. Rationale: Genetic factors contribute importantly to the development of coronary atherosclerosis, a major cause of morbidity and mortality in Western countries. The goal of ancillary study 2006.03 is to identify genomic regions associated with coronary heart disease using genome-wide association methods. As an early effort in this area and with the collaborators of ancillary study 2006.03, we have performed a large-scale genomic association study using 75,000 SNPs in over 300 subjects with premature, documented coronary atherosclerosis and in 312 asymptomatic elderly controls, both ascertained from Ottowa, Canada. A total of 2,135 SNPs were associated with atherosclerosis at a nominal significance

threshold of 0.025, which significantly exceeded the number expected under the null hypothesis (n=1,615). To determine which of these 2,135 SNPs were systematically associated with atherosclerosis, a second association study was performed with these SNPs in an independent sample, again from Ottawa, Canada. A total of 50 SNPs met the significance threshold (<0.025) and were in the same direction in both studies. The number of significant SNPs observed (n=50) significantly exceeded the number expected by chance and could not be explained by random fluctuations in allele frequency, systematic errors or population substructure. The two SNPs with the smallest p-values in the two samples were validated by further replications in an independent sample of cases (n=183) and controls (n=556) from the Dallas Heart Study. These two SNPs, which are near one another on human chromosome 9 and have common allele frequencies, identify a novel gene region associated with coronary atherosclerosis.

We propose to extent our findings for these two SNPs in the large prospective ARIC cohort and the Copenhagen City Heart Study. Obviously, this manuscript proposal is for ARIC, and a similar manuscript proposal is under consideration by the Copenhagen City Heart Study. Specifically for this manuscript proposal, we will evaluate whether these SNPs are associated with incident CHD in the ARIC study.

Note to PC: The identity of the two SNPs and a detailed map of the region will be part of the draft manuscript. However, the identies are kept confidential at these early stages.

5. Main Hypothesis/Study Questions:

1. Estimate the frequency distribution of the two SNPs in a population-based sample of whites and African-Americans.
2. In a race-specific manner, utilize Cox regression to evaluate the ability of the two SNPs to independently predict incident CHD. Analyses will be carried out taking into account age, gender, field center, BMI, HDL and total cholesterol, smoking, diabetes and hypertension status.

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).

All antecedent analyses have been completed in case-control studies as presented above. The two SNPs of interest have been typed on the entire ARIC cohort and will be evaluated for associations with incident CHD. Goodness of fit to Hardy-Weinberg expectations will be carried out using a chi-square test.

The usual DNA restriction, ethnic group and missing data exclusion criteria will be used. Exclusions will include the following: 1) positive or unknown history of prevalent CHD or stroke or history of TIA/stroke, 2) prohibited use of DNA, 3) ethnic background other than white or African American, as well as African Americans not from Jackson or Forsyth. Cox proportional hazards regression models will be the primary analysis tool. For incident CHD analyses, we will use the variable IN_03SP. Covariates to be included in the analyses include age, gender, race, field center, HDL and total cholesterol, BMI, smoking, diabetes and hypertension status. All analyses will be carried out in a race-specific manner.

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? **____ Yes __X__ No**

11.b. If yes, is the proposal
__X_ A. primarily the result of an ancillary study (list number* _2006.03_)
___ B. primiarly 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. Agreed