ARIC Manuscript Proposal # 1093

PC Reviewed: _08/30/05 **Status: _A___** **Priority: _2__**
SC Reviewed: __08/30/05 **Status: __A__** **Priority: _2__**

1.a. Full Title: Nonsense mutations in PCSK9 confer protection against coronary heart disease

b. Abbreviated Title (Length 26 characters): PCSK9 mutations lower CHD risk

2. Writing Group:

Writing group members: Jonathan Cohen, Eric Boerwinkle, Thomas Mosley and Helen Hobbs

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1 **Timeline**: Data have been collected Manuscript ready by September, 2005

2 **Rationale**:

PCSK9 is a member of the subtilisin/kexin serine protease family that is expressed in the liver, intestine and kidney. PCSK9 is in the secretory pathway of cholesterol. Overexpression of PCSK9 in the livers of mice results in a marked reduction in LDLR protein and hypercholesterolemia. Mice lacking PCSK9 have increased levels of hepatic LDLR protein. Rare mutations in the pathway have been associated with hypercholesterolemia. In African-Americans, more common (but still relatively rare from a population perspective) mutations have been associated with low blood cholesterol. Investigators at University of Texas Southwestern have resequenced PCS9 in a sample of African-Americans. The rare and common variations were provided to the ARIC DNA laboratory for genotyping.

The ARIC study has genotyped both rare (relatively) and common variation in the entire ARIC cohort. At this point, we anticipate multiple ARIC manuscripts.

1 Rare variation – Lead by UT Southwestern investigators, including ARIC DNA lab and

Jackson field center.
2 Common variation – Lead by ARIC DNA laboratory, including UT Southwestern and ARIC lipid laboratory
3 Rare and common variation related to post-prandial lipemia. Lead by ARIC lipid lab, including UT Southwestern and ARIC DNA laboratory.

Note: Other manuscripts (stroke and PAD) are expected, but not yet developed. Note: Because the frequency of PCSK9 sequence variation is different between blacks and whites, all analyses will be done in a race-specific manner.

This is the first in the series of manuscript proposals.

5. Main Hypothesis/Study Questions:

1 What is the frequency of the Y142X and C679X mutations in the ARIC cohort.
2 What is the relationship between rare PCSK9 variation and plasma LDL-cholesterol levels.
3 What is the relationship between rare PCSK9 variation and carotid artery wall thickness.
4 What is the relationship between rare PCSK9 variation and incident CHD.

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

Baseline: Self-reported race, sex, age, total cholesterol, LDL-cholesterol (calculated), HDL-cholesterol, Triglycerides, BMI, cigarette smoking, hypertension status, diabetes status, carotid artery wall thickness. Incident CHD: 2002

Exclusion criterion will depend on the exact question being addressed. In general, the exclusion criterion included individuals taking lipid lowering medications, prevalent CHD in the case of hypotheses related to incident CHD, restricted DNA, key missing data, non-black or non-white, and blacks not from the Jackson or Forsyth field centers.

Routine comparison of risk factor levels between cases and non-cases and between *PCSK9* carriers and non-carriers will be carried out using contingency chi-square tests for discrete variables and t-tests for continuous variables. Cox proportional hazards modeling will be used to test the primary null hypothesis that the incidence rates of CHD were no different between *PCSK9* carriers and non-carriers. Hazard ratios (HR) based on the regression coefficients from the Cox modeling will be reported.

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

1 **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)?**
There are no related ms proposals.
2 **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. 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.