ARIC Manuscript Proposal # 1634

1.a. Full Title: Associations of subclinical atherosclerosis genetic variants with carotid plaque morphology

b. Abbreviated Title (Length 26 characters): Gene variants and carotid plaque morphology

2. Writing Group: Nora Franceschini, Kari E North, Gerardo Heiss, Anna M Kucharska-Newton, Vijay Nambi, Eric Boerwinkle, Lynne Wagenknecht and Kelly A Volcik

Suggested co-author: Richey Sharrett.

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

First author: Nora Franceschini, MD, MPH

Department of Epidemiology
University of North Carolina Chapel Hill
137 E. Franklin St., Suite 306 CB #8050
Chapel Hill, NC 27514
(919) 966-1305 (Voice)
(919) 966-9800 (Fax)
noraf@unc.edu

Corresponding/senior author (must be an ARIC investigator for the proposal but can be different in the published paper; correspondence will be sent to both the first author & the corresponding author):

Gerardo Heiss, MD PhD
Address: 137 E. Franklin St., Suite 306 CB #8050 Chapel Hill, NC 27514
E-mail: gerardo_heiss@unc.edu

3. Timeline: 1-2 years
4. **Rationale**: Ongoing genomewide association (GWA) studies have identified several loci influencing subclinical carotid artery intima media thickness and presence of plaques in Caucasians through the CHARGE Consortium and in African Americans in CARe. We propose to study the association of validated SNPs identified in subclinical carotid artery disease GWAS in Caucasians and African Americans with carotid artery plaques morphology in data from the ARIC Carotid MRI Study. We are particularly interested in the following features: presence of lipid core, maximum lipid core area and total lipid core volume, and mean fibrous cap thickness.

Several of the authors in this proposal are investigators in the subclinical atherosclerosis working groups in CHARGE and CARe. The study will be performed using ARIC data and we will pursue collaborations with MESA for carotid artery morphology (n~400) and with the Framingham Heart Study for abdominal aorta abnormalities. The authorship list will be updated to reflect these collaborations.

5. **Main Hypothesis/Study Questions**:

**Study Questions/Hypotheses**

1. Are SNPs recently identified in subclinical carotid artery wall thickness and presence of plaque GWAS associated with carotid artery wall and plaque characteristics in ARIC white and black participants of the ARIC Carotid MRI study? Are these genetic variants associated with wall thickness, presence of a lipid core, maximum lipid core area, total lipid core volume, and mean fibrous cap thickness?

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)**.

We will use data from the ARIC Carotid MRI study of white and African American individuals with available genotyped data for the target SNPs.
**Study design:** cross-sectional, race-stratified analyses of the association of SNPs with carotid artery wall and plaque characteristics (i.e., presence of a lipid core, maximum lipid core area and total lipid core volume, and fibrous cap thickness. The carotid artery MRI study used a stratified sampling design.

**Exposure:** Validated SNPs from GWAS of subclinical atherosclerosis in Caucasians and African Americans. SNP list is not finalized since studies are now performing replication of findings.

**Outcomes:** carotid artery wall and plaque characteristics (i.e., presence of a lipid core, maximum lipid core area and total lipid core volume, and mean fibrous cap thickness).

**Genotyping:** Affymetrix 6.0 genotyped SNPs or IBC-Chip SNPs.

**Statistical analyses:** All SNPs will be tested for significant deviation from Hardy-Weinberg equilibrium (HWE) in race-stratified samples, using an alpha=0.001 and the Exact test (Wigginton, Cutler et al. 2005). Quantitative trait distributions will be inspected for normal distribution. We will fit linear regression models in race-stratified samples (SAS 9.1) using additive models or general genetic models (2-degree of freedom test, df), adjusting for covariates as described below. All analyses will be adjusted for the effects of age, sex, and their interactions and study center, within each race-stratified population sample. We will implement models adjusting for hypertension, type 2 diabetes, body mass index and smoking exposure, baseline LDL and HDL levels in a secondary analyses, if appropriate. We will use logistic and linear regression methods to test for the association of SNPs and the qualitative and quantitative measures of carotid artery morphology, respectively. All analyses will incorporate the appropriate weights to
account for the stratified probability sampling utilized by the ARIC Carotid MRI study.

We will correct for multiple testing using Bonferoni methods.

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

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)?
ARIC manuscript proposal #1405, Subclinical Measures GWA Collaboration: Carotid 
Intima-Media Thickness , North, Heiss et al.

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

11.b. If yes, is the proposal 
A. primarily the result of an ancillary study (list number)
  X  B. primarily based on ARIC data with ancillary data playing a minor 
role (usually control variables; list number(s)*  __2004.11-CARMRI ________ 
________________________)

*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.