ARIC Manuscript Proposal # 1403

PC Reviewed: 08/12/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: ***LDL receptor* gene variants and carotid plaque morphology**

b. Abbreviated Title (Length 26 characters): ***LDLR* and carotid plaque morphology**

2. Writing Group: Nora Franceschini
Nobuyo Maeda, Kari E North, Lynne Wagenknecht, Brad Astor, Hind Muallem, Kelly A Volcik, Christie M Ballantyne, L.E. Chambless, Eric Boerwinkle

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

Research Assistant Professor
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

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Gerardo Heiss
Department of Epidemiology, CVD Program
University of North Carolina at Chapel Hill
137 E. Franklin St, Suite 306
Chapel Hill, NC 27514

Phone: (919) 962 3253 Fax: (919) 966 9800
E-mail: gerardo_heiss@unc.edu

3. Timeline: 12 months

4. Rationale:

The contribution of common variants in the LDL receptor (*LDLR)* gene to coronary heart disease (CHD) risk has been recently documented (Kathiresan, Melander et al. 2008; Polisecki, Muallem et al. 2008; Willer, Sanna et al. 2008). Single nucleotide polymorphisms (SNPs), particularly those located in a regulatory region of the gene, may subtly affect the atherosclerotic process and/or progression through changes in the clearance of LDL cholesterol or by other, yet unknown mechanisms.

We previously demonstrated that SNPs in the regulatory region of *LDLR* are associated with incident CHD in ARIC African American individuals (Franceschini et al., submitted, ARIC ms#1065). In particular, CHD events were increased in African Americans with the rs1433099 T allele. Carrying 1 or 2 copies of the *LDLR* rs1433099 T allele was associated with 23% and 47% increased in CHD compared with carrying no copies of the T allele (hazard ratio [HR] 1.23, 95% confidence interval [CI] 0.93, 1.62, and HR 1.47, 95%CI 1.09, 1.98, for 1 and 2 copies of the T allele, respectively).The association was independent of baseline serum lipid measures, raising the question whether the SNP effects are due to arterial wall lipid deposition.

We propose to study the association of *LDLR* SNPs with morphology of carotid artery plaques, 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 cap thickness.

5. Main Hypothesis/Study Questions:

Study Questions/Hypotheses

1. *LDLR* gene variants (rs1433099 and rs2738466) are associated with carotid artery wall and plaque characteristics.

2. *LDLR* gene variants are associated with wall thickness, presence of a lipid core, maximum lipid core area, total lipid core volume, and 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).

The analyses will be conducted on data from the ARIC Carotid MRI study of white and African American individuals with available genotyped data for the *LDLR* polymorphisms.

Study design: cross-sectional, race-stratified analyses of the association of *LDLR* polymorphisms 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.

Exposure: Two SNPs in the regulatory region of *LDLR* (rs1433099 and rs2738466).

Outcomes: 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.

Genotyping: Two SNPs in the 5' region of the 3'UTR regulatory region of *LDLR* [rs1433099 (C/T) and rs2738466 (A/G)] were genotyped using TaqMan assays. The SNPs are separated by 0.1 Kb and are in complete linkage disequilibrium (LD) in HapMap CEU (D'=1.00, confidence bounds 0.67 to 1.00) and YRB samples (D'=1.00, confidence bounds 0.81 to 1.00).

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 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 fit models adjusting for hypertension, type 2 diabetes, body mass index and smoking exposure, baseline LDL and HDL levels. We will use logistic regression methods to test for the association of *LDLR* SNPs and the qualitative measures of carotid artery morphology. All analyses will incorporate the appropriate weights to account for the stratified probability sampling utilized by the ARIC Carotid MRI study.

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 #1065, "LDL Receptor Polymorphisms and the Risk of Coronary Heart Disease: the Atherosclerosis Risk in Communities Study". Franceschini et al., submitted J Lipid Res

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.