

**ARIC Manuscript Proposal #1794**

**PC Reviewed:** 5/10/11  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:**

Interaction between HMGCR and LIPC affects High-Density Lipoprotein Cholesterol in both European Americans and African Americans

**b. Abbreviated Title (Length 26 characters):**

Interaction affecting HDL-C

**2. Writing Group:**

Writing group members:

Li Ma, Alon Keinan, Eric Boerwinkle, Charles Sing, Ariel Brautbar, Andrew Clark

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

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**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).

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### **3. Timeline:**

Data are collected and the analysis plan has been tested.  
Manuscript will be ready for submission by **06/2011**.

Initial target journal: Nature Genetics

### **4. Rationale:**

Plasma lipoprotein levels are associated with risk of CHD: LDL-C is positively associated and HDL-C is inversely associated. The independent relationship with triglycerides is less clear. Previous analyses within ARIC and elsewhere have identified genes (or gene regions) associated with LDL-C, HDL-C and triglycerides. However, the combined additive effect of these loci accounts for less than 5% of the heritability of the traits. This experience is shared with other CHD risk factors and CHD itself. Using plasma cholesterol levels in ARIC as a model system, we will test whether gene-gene interaction account for some of the “missing heritability” underlying cardiovascular disease risk.

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

Can we identify significant and well-replicated gene-gene interactions affecting lipid traits in ARIC.

### **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 manuscript uses ARIC Affymetrix 6.0 data to test for gene-gene interactions affecting four lipid traits (total cholesterol, low-density lipoprotein cholesterol, triglyceride, and high-density lipoprotein cholesterol). ARIC European American samples are used for discovery and, ARIC African American samples as one of the replication data sets. To increase power to detect gene-gene interactions affecting these phenotypes, we considered the interaction for pairs of SNPs according to the following criteria: (i) both have been previously associated with the level of any of the four lipids; (ii) are found in interacting genes according to a curated human protein-protein interaction network; and (iii) are involved in the pathway of metabolism of lipids and lipoproteins.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**     Yes  
 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.csc.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 with GxG

**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.csc.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.**

Agree.