ARIC Manuscript Proposal #2675

PC Reviewed: 12/8/15    Status: A    Priority: 2
SC Reviewed: _________    Status: _____    Priority: _____

1.a. Full Title: Meta-analysis of genome-wide association studies of HDL cholesterol response to statins

b. Abbreviated Title (Length 26 characters): HDL-statins GWAS

2. Writing Group: Eric A. Whitsel, Christy L. Avery, Til Stürmer, Eric Boerwinkle, James D. Stewart, and attempting to maintain symmetry across contributing cohorts, other members of the CHARGE Pharmacogenomics Working Group

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. CLA

First author: Christy L. Avery
University of North Carolina at Chapel Hill
Department of Epidemiology
Cardiovascular Disease Program
CVS Center, Suite 301-A
137 East Franklin Street
Chapel Hill, NC 27514
(T) 919-966-4312
(F) 919-966-9800
christy_avery@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).

Eric A. Whitsel
University of North Carolina at Chapel Hill
Departments of Epidemiology and Medicine
Cardiovascular Disease Program
CVS Center, Suite 301-B
137 East Franklin Street
Chapel Hill, NC 27514
(T) 919-966-3168 or 1967
(F) 919-966-9800
eric_whitsel@unc.edu

3. Timeline:
   Statistical analyses: November, 2015
   Manuscript preparation: December, 2015
   Manuscript revision: January, 2016
   Manuscript submission: February, 2016
4. **Rationale:**
The 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, better known as statins, are widely prescribed and effective for the prevention and management of cardiovascular disease (CVD) (1). While the major CVD benefit of statins is due to reduction in plasma low density lipoprotein cholesterol (LDL-C), statins also produce moderate increases in levels of high density lipoprotein cholesterol (HDL-C), ranging from 4 to 10% (2;3). This is of particular interest since HDL-C levels have been shown to be inversely related with CVD risk in the general population and in patients treated with statins (4;5), however evidence for a causal role for low HDL-C is weak (6).

The increase in HDL-C after statin therapy is variable between individuals (2). This might be explained in part by genetic variation. Previous studies that have investigated genotype associations with statin-induced changes in HDL-C (7-9) have focused primarily on genetic variants within the CETP gene that are known to affect plasma HDL-C levels (10) and risk for coronary artery disease (11). To determine whether additional loci may influence HDL-C response to statins, we conducted a large-scale pharmacogenetic meta-analysis of genome-wide association studies (GWAS) using datasets from both randomized controlled trials (RCTs) and cohort studies in the large Genomic Investigation of Statin Therapy (GIST) consortium that previously identified four loci associated with LDL-C response to statins (12).

5. **Main Hypothesis/Study Questions:**
To determine whether genetic loci may influence HDL-C response to statins

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).**

**Summary of analyses:** We define our **response-to-treatment** variable as the difference between natural log transformed on- and off-treatment measures. For discovery analyses, we will request analyses of response-to-treatment, both without and with adjustment for the (natural log transformed) off-treatment measure. We also will request an analysis of the (natural log transformed) off-treatment measure of HDL cholesterol.

**Phenotypes required:** For each participant, at least one off-treatment HDL cholesterol level measurement and at least one on-treatment HDL cholesterol level measurement is required. On-treatment means prescribed any kind of statin, at any dosage, for any indication. As covariates, we will include age, sex, and any other variables needed to control for potential stratification (such as recruitment or study site, ancestry PC or MDS vectors).

**Individual exclusions:** Participants missing phenotype or covariate data, participants without on- and off-treatment HDL measures, and participants of non-European ancestry.

**1.4 Defining the phenotypic response variable:** For each individual, define $B$ as the off-treatment measure of HDL cholesterol level, and define $A$ as the on-treatment measure of HDL cholesterol level. Because $A$ and $B$ will be transformed prior to analysis, you can use
either mmol/L or mg/dL units, as long as you are internally consistent. If multiple off- and on-treatment measures are available, then $B$ and $A$ can be weighted averages. Then, we will natural log transform to obtain $\ln(B)$ and $\ln(A)$, as well as the response-to-treatment variable:

$$\text{DeltaLn} = \ln(A) - \ln(B)$$

where $\ln()$ denotes natural log.

**Genetic model and coded/noncoded alleles:** Assuming an additive genetic model, we will test for association by regressing the response variable onto the total dose of the coded allele (e.g. AA=0, AG=1, GG=2 if G is the coded allele) at each SNP, assuming a normal linear model. Designation of coded and non-coded allele at each SNP can be arbitrary, as long as you specify which you used. For imputed SNPs, perform regression onto expected allele dosage.

**Analyses required, file format and names:** Perform the following three analyses, where DeltaLn, $\ln(A)$ and $\ln(B)$ are defined above, and naming them as follows in results files:

- **HDLC-UNADJ**
  - DeltaLn ~ SNP_dose+age+sex+...
- **HDLC-ADJ**
  - DeltaLn ~ SNP_dose+age+sex+$\ln(B)$+...
- **HDLC-ONTRT**
  - $\ln(A)$ ~ SNP_dose+age+sex+...

where "+..." denotes additional study specific covariates (e.g. ancestry PCs). Genomic control will be applied centrally.

**Genome-wide threshold**

$P<5\times10^{-8}$

7.a. Will the data be used for non-CVD analysis in this manuscript?

   No __X__ Yes _____

b. If Yes, is the author aware that the file ICTDER04 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?    __X__ Yes _____ No

(This file ICTDER04 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 ICTDER04 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)?
MS1536 – Genotype-by-statin interactions and lipids: the CHARGE Drug-Gene GWAS Consortium
MS2426 – Statin drug-gene interactions and MI

Both proposals originated from the CHARGE Pharmacogenomics working group and were led by Drs. Avery and Whitsel. The manuscript described by MS1536 was recently published (PMID: 25350695).

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

11.b. If yes, is the proposal
\_X\_ A. primarily the result of an ancillary study (AS #2009.10)
\_ \_ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.
References