ARIC Manuscript Proposal # 1582

1.a. Full Title: Genetic Variants Altering Individual Plasma Lipid Components and Risk for Myocardial Infarction

b. Abbreviated Title (Length 26 characters): Lipid genetic variants and risk for MI

2. Writing Group for ARIC:
   Writing group members: Maja Barbalic, Ariel Brautbar, Eric Boerwinkle, Christie Ballantyne
   The coauthors from the other cohorts

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

First author: Maja Barbalic
Address: Human Genetics Center
The University of Texas Health Science Center at Houston
School of Public Health
1200 Herman Pressler, E435
Houston, TX 77030

Phone: 713-500-9817       Fax: 713-500-0900
E-mail: maja.barbalic@uth.tmc.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: Eric Boerwinkle
Address: Human Genetics Center
The University of Texas Health Science Center at Houston
School of Public Health
1200 Herman Pressler, Suite RAS-E447
Houston, TX 77030

Phone: 713-500-9816       Fax: 713-500-0900
E-mail: eric.boerwinkle@uth.tmc.edu
3. Timeline:
   Genotyping is complete. Data analysis will begin immediately.

4. Rationale:

Components of the fasting lipid profile (low-density lipoprotein cholesterol – LDL-C, triglycerides – TG and high-density lipoprotein cholesterol – HDL-C) have been associated with risk for myocardial infarction (MI) in multiple epidemiologic studies. By means of Mendelian randomization, it is possible to distinguish if this relationship is causative or a reflection of the underlying pathophysiology. If lipids directly influence MI risk, genetic variation that alters lipids’ levels is expected to change MI risk by a magnitude and direction predicted by the lipid-MI association. In this study, we will use SNPs that have been identified in recent lipids’ GWA studies to determine whether the observed effect of each SNP changes MI risk as would be expected by prediction based on lipids’ association with MI.

Note to Publications Committee: Drs. Boerwinkle and Ballantyne have been discussing a similar manuscript for some time. In the mean time and independently, the MIGen study consortium had executed this analysis and submitted the paper to the NEJM. The editors asked the authors for additional replication and analysis. The senior author Sek Kathiresan contacted us to collaborate on the paper’s resubmission with the inclusion of ARIC data.

5. Main Hypothesis/Study Questions: To investigate the association of 35 SNPs influencing plasma lipid levels with incident myocardial infarction and to assess if the observed effect is well explained by the predicted effect based on the established lipids-MI association

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).

Subjects: ARIC European-Americans
Outcome: Incident myocardial infarction
Primary statistical approach: The association of 35 SNPs with LDL-C, TG and HDL-C will be tested using linear regression. We will use hazard model to examine the association of plasma lipids with the MI event. To follow the existing analysis plan, selected 35 SNPs will be tested for association with MI by logistic regression by defining all incident events as cases and all the others as controls. Because ARIC has true incident MI, we will also investigate the relationship between each SNP and MI using hazard models, and we will compare the results of the hazards model with that obtained via logistic regression. (Note to publication committee: The analysis plan is a compromise between what is best suited for this question in the ARIC study and what has already been done in the existing sample sets contributing to this manuscript.)
Age at baseline, sex and principal components of ancestry will be included in the model. This choice of modeling is driven by the need of combining our results with the large number of case and control studies involved in this study (e.g. FINRISK, WTCCC MI, SHEEP etc.).

Exposure: 35 SNPs involved in lipids’ metabolism

Exclusions: Those without consent for genetic research

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

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  ____ 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)?

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
A. primarily the result of an ancillary study (list number* 2006.03 (Stampede, genotyping in Caucasians))

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. Agreed.