ARIC Manuscript Proposal # 1281

PC Reviewed: _8_/21_/07 **Status:** __A__ **Priority:** _2__
SC Reviewed: _____ **Status:** _____ **Priority:** ___

1.a. Full Title: ANGPTL4 variants and CVD events

  b. Abbreviated Title (Length 26 characters): ANGPTL4 and CVD events

2. Writing Group:
  Writing group members: Aaron Folsom, Jim Peacock, Ellen Demerath, Eric Boerwinkle

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

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3. Timeline: paper by fall 07

  4. Rationale:
Over the years there has been controversy about whether an elevated plasma triglyceride level is an independent cardiovascular risk factor. Triglycerides are part of the "metabolic syndrome" and are inversely correlated with HDL-C levels, but they have substantial within person variability. A recent meta-analysis, which

involved 10,158 incident coronary heart disease cases from 29 studies and corrected for within person measurement error, reported triglycerides carry a moderate independent association with CHD (1). For the top versus the bottom third of usual log-triglyceride values, the adjusted odds ratio of CHD was 1.72, 95% CI, 1.56 to 1.90. Yet, genetic forms of hypertriglyceridemias do not uniformly increase CHD or total CVD risk. and clinical trial do not convincingly show that lowering triglycerides, in isolation, prevents CVD incidence or recurrence.

A recent paper involving ARIC, the Dallas Heart Study, and the Copenhagen Study showed that the E40K variant in ANGPTL4, a gene involved in partitioning of fatty acids between sites of storage and sites of oxidation, is associated with substantially reduced plasma levels of triglyceride and increased HDL cholesterol in whites (2). In ARIC, E40K was also associated with modestly decreased LDL-cholesterol and insulin levels. The minor allele frequency was 4% in whites but very rare in blacks. Whether ANGPTL4 variants are associated with CVD events was not explored and therefore unknown. Via the theory of "mendelian randomization," if the triglyceride lowering E40K variant were associated with reduced risk of CVD, this would provide further support for the etiologic importance of plasma triglycerides in CVD.

ARIC can address this question. With 343 heterozygous and 7 homozygous whites with E40K and 8376 non-carriers, we expect to have adequate power to examine moderate associations with carotid IMT and incident CHD. We will also explore associations with prevalent PAD and incident ischemic stroke, for which there will be lower power.

5.   Main Hypothesis/Study Questions:
The ANGPTL4 E40K variant is associated with reduced CVD occurrence 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).

Exclusions: No permission for DNA use. Missing independent and dependent variable data. Prevalent CVD will be excluded for incident CVD analyses.

Dependent variables: Visit 1 IMT, incident CHD and stroke, prevalent PAD (ABI <0.9 or Rose claudication).

Independent variable: E40K variant

Covariates: should be little confounding by other factors, but will consider main risk factors: age, sex, smoking, BMI, hypertension, drinking status, diabetes, etc. Lipids are intervening variables, not confounders.

Analysis: We will re-verify associations between risk factors and the E40K variant. We will use linear regression for analysis of IMT, logistic regression for analysis of prevalent PAD, and proportional hazards for incident CHD and ischemic stroke. If any association is observed, we will add lipids to the model to see if they may contribute to the association as intervening variables. For the most part, covariates will be modeled as baseline variables.

Refs
1. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007 Jan 30;115(4):450-8.

2. Romeo S, Pennacchio LA, Fu Y, Boerwinkle E, Tybjaerg-Hansen A, Hobbs HH, Cohen JC. Population-based resequencing of ANGPTL4 uncovers variations that reduce triglycerides and increase HDL. Nat Genet. 2007 Apr;39(4):513-6.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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

   ____xx__ 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)?

Romeo S, Pennacchio LA, Fu Y, Boerwinkle E, Tybjaerg-Hansen A, Hobbs HH, Cohen JC. Population-based resequencing of ANGPTL4 uncovers variations that reduce triglycerides and increase HDL. Nat Genet. 2007 Apr;39(4):513-6

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.