ARIC Manuscript Proposal # 1190

PC Reviewed: ___/___/06	**Status: __A__**	**Priority: _2__**
SC Reviewed: _____	**Status: __A__**	**Priority: _2__**

1.a. Full Title: Population-based resequencing of ANGPTL4 reveals variation that reduce triglycerides and increase HDL

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

2. Writing Group:

Writing group members: Stefano Romeo, Len Pennacchio, Yunxin Fu, Eric Boerwinkle, Anne Tybjaerg-Hansen, Helen H. Hobbs, Jonathan C Cohen

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

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3. Timeline: Imminent

4. Rationale:
Adipocytes secrete a variety of proteins that regulate glucose and lipid metabolism. As a first step towards elucidating the role of these adipokines in lipid metabolism in humans, we examined the effects of sequence variation in ANGPTL4, a gene induced in adipose tissue and liver during fasting. Mice with a genetic deletion of ANGPTL4 have lower plasma triglyceride levels (Koster et al (2005) Endocrinology 146: 4943-4950).

5. Main Hypothesis/Study Questions:
Note: This study has a number of population genetics questions/hypotheses that are not outlined here. These population genetic questions are addressed using data not derived from the ARIC study.

Primary null hypothesis: Fasting plasma triglyceride levels are not different among ANGPTL4 E40K genotypes.

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).

To begin with, we sequenced the ANGPTL4 gene in 3,551 participants in the Dallas Heart Study, a level of sequence depth never achieved before. After analyses of the extremes of the triglyceride distribution, we identified a single amino acid substitution (common in whites) having significantly different allele frequencies in those with high and low triglycerides. This substitution has now been typed in ARIC and the Copenhagen City Heart Study.

All analyses will be carried out in a race-specific manner. Goodness of fit to Hardy-Weinberg expectations will be carried out using a chi-square test. For the genotype-phenotype analyses, age, sex and BMI will be included as covariates. Multivariable linear regression will be the primary analysis tool. Exclusion criteria include those with restricted DNA, missing data, and not fasting. Triglcyerides will be log transformed prior to analysis.

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

___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

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. primiarly 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