ARIC Manuscript Proposal # 1306

PC Reviewed: _11/_13/07 **Status: ___A_** **Priority: __2_**
SC Reviewed: _____ Status: _____ Priority: ____

1.a. Full Title:
Longitudinal association between *ANGPTL4* and TG and interactions with change in body weight in the Atherosclerosis Risk in Communities (ARIC) Study

1.b. Abbreviated Title:
ANGPTL4 and longitudinal changes in TG and body weight

2. Writing Group:
Writing group members: Jennifer A. Nettleton, Kelly Volcik, Eric Boerwinkle, Aaron R. Folsom (others welcome)

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

Corresponding/senior author: Jennifer A. Nettleton
Data analyst: Jennifer A. Nettleton

3. Timeline:
Data preparation and analysis will begin upon approval, and manuscript drafting will commence once suitable analytical models are finalized.
Initial drafts will be circulated among writing group members within 4 months of proposal approval.

4. Background & Rationale:

The adipokine angiopoietin-like 4 (ANGPTL4) is thought to regulate fatty acid transport among tissues by inhibiting lipoprotein lipase, a key enzyme in HDL-C and triglyceride metabolism [1-3]. Consistent with its suspected role, a recent cross-sectional analysis including white participants from the ARIC study showed a strong association between baseline triglyceride levels and the nonsynonymous sequence variant [E40K] in the ANGPTL4 gene [4]. Homozygous (K/K) and heterozygous carriers (E/K) of the mutation had significantly lower TG concentrations compared to their homozyogous wild type counterparts (E/E). The influence of this polymorphism on longitudinal changes in TG has not yet been investigated.

Changes in body weight predict changes in TG [5-8], but it is possible that the influence of body weight change on changes in TG concentration may be dampened in individuals with the *ANGPTL4* [E40K] mutation.

Therefore we plan to 1) characterize the longitudinal change in TG across ARIC exams stratified by *ANGPTL4* [E40K] genotype and 2) examine the potential interaction between longitudinal body weight change and *ANGPTL4* [E40K] genotype with respect to longitudinal TG changes in white men and women in the Atherosclerosis Risk in Communities (ARIC) study.

References

1. Li C. Genetics and regulation of angiopoietin-like proteins 3 and 4. *Curr Opin Lipidol.* Apr 2006;17(2):152-156.
2. Merkel M, Eckel RH, Goldberg IJ. Lipoprotein lipase: genetics, lipid uptake, and regulation. *J Lipid Res.* Dec 2002;43(12):1997-2006.
3. Yoshida K, Shimizugawa T, Ono M, et al. Angiopoietin-like protein 4 is a potent hyperlipidemia-inducing factor in mice and inhibitor of lipoprotein lipase. *J Lipid Res.* Nov 2002;43(11):1770-1772.
4. Romeo S, Pennacchio LA, Fu Y, et al. Population-based resequencing of ANGPTL4 uncovers variations that reduce triglycerides and increase HDL. *Nat Genet.* Apr 2007;39(4):513-516.
5. Lloyd-Jones DM, Liu K, Colangelo LA, et al. Consistently stable or decreased body mass index in young adulthood and longitudinal changes in metabolic syndrome components: the Coronary Artery Risk Development in Young Adults Study. *Circulation.* Feb 27 2007;115(8):1004-1011.
6. Norman JE, Bild D, Lewis CE, et al. The impact of weight change on cardiovascular disease risk factors in young black and white adults: the CARDIA study. *Int J Obes Relat Metab Disord.* Mar 2003;27(3):369-376.
7. Siervogel RM, Wisemandle W, Maynard LM, et al. Lifetime overweight status in relation to serial changes in body composition and risk factors for cardiovascular disease: The Fels Longitudinal Study. *Obes Res.* Sep 2000;8(6):422-430.
8. Truesdale KP, Stevens J, Lewis CE, et al. Changes in risk factors for cardiovascular disease by baseline weight status in young adults who maintain or gain weight over 15 years: the CARDIA study. *Int J Obes (Lond).* Sep 2006;30(9):1397-1407.

5. Hypotheses:

1. *ANGPTL4* [E40K] genotype will be associated with longitudinal changes in TG concentrations: individuals with the wild type E/E genotype will experience a greater increase in TG over time compared with E/K and K/K genotypes.

2. The relation between longitudinal changes in body weight and longitudinal changes in TG will be weaker in individuals with E/K and K/K genotypes compared to those with the E/E genotype.

6. Data:

Participant exclusions:

- Non-fasting
- Non-white race (the *ANGPTL4* [E40K] snp is very rare in blacks)
- Diabetic at baseline (ADA fasting criteria)
- Heavy alcohol consumption
- Missing *ANGPTL4* [E40K] genotype information
- Lipid-lowering medication use

Outcome:

- Longitudinal changes in TG concentrations

Exposures:

- *ANGPTL4* [E40K] genotype (E/K and K/K will be combined due to small number of K/K homozygotes)
- Longitudinal change in body weight

STATISTICAL ANALYSIS:

SAS 9.1 will be used for all analyses.

Due to anticipated skewed distribution of TG concentrations, values will be transformed to the natural log scale for analysis.

A repeated measures ANOVA will be conducted using SAS PROC MIXED which allows for missing and correlated individual data. Longitudinal change in TG concentration will be modeled with a genotype x exam interaction term, i.e., if the relationship between *ANGPTL4* genotype and TG varies by exam (significant genotype*exam term), then genotype will be declared a significant predictor of longitudinal TG change. A genotype-stratified, graphic or tabular display of TG concentrations across study exams will be used for presentation.

A stratified analysis will be conducted to characterize the genotype-specific associations between longitudinal changes in body weight and longitudinal changes in TG, i.e., body weight (~4 observations per subject) x exam

interaction term. We will verify the existence of the main effect of body weight change on TG change in our sample, but we anticipate it to be strong based on previous work in ARIC (*Truesdale, Stevens & Cai AJE, 2007*).

The interaction between *ANGPTL4* genotype and body weight change will be formally tested with a genotype x exam x body weight (~4 observations per subject) interaction term. Because we recognize that it may be difficult to formally detect a statistically significant 3-way interaction, (despite that a true difference in the relation between body weight change and TG change may exist between *ANGPTL4* E/E and E/K + K/K) we may also utilize a model which characterizes body weight change over time as simply the difference between exam 4 body weight and baseline body weight (exam 4 wt – baseline wt).
Thus, the interaction would be tested with a genotype x body weight change 2-way interaction with the difference in TG between exam 4 and baseline (exam 4 TG – baseline TG) serving as the dependent variable of interest.

CONFOUNDERS/MODEL COVARIATES:

LONGITUDINAL TG CHANGE & GENOTYPE
Model 1 unadjusted

Model 2 center, age, gender, physical activity, total energy intake, alcohol intake, smoking, education, BMI

LONGITUDINAL BODY WEIGHT CHANGE X GENOTYPE → LONGITUDINAL TG CHANGE
(use Model 2) center, age, gender, physical activity, total energy intake, alcohol intake, smoking, education

7.a. Will the data be used for non-CVD analysis in this manuscript? No

7.b. NA

8.a. Will the DNA data be used in this manuscript? YES, and genotyping has been completed for the ANGPTL4 snp to be studied in this analysis.

8.b. Is the author aware that either DNA data distributed by the Coordninating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? Yes, the author is aware of this issue.

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.
There is no overlap between this proposal and current proposals/published manuscripts.

10. What are the most related manuscript proposals in ARIC?
Romeo S, Pennacchio LA, Fu Y, et al. Population-based resequencing of ANGPTL4 uncovers variations that reduce triglycerides and increase HDL. *Nat Genet.* Apr 2007;39(4):513-516.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use any ancillary study data? No

11.b. NA

12. 1-3 year completion expectation: Yes, the lead author is aware that manuscript preparation is expected to be completed in 1-3 years, and if this expectation is not met, the manuscript proposal will expire.