ARIC Manuscript Proposal #2662

PC Reviewed: 11/10/15 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Exome analysis of phenotypes influencing body fat

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Writing group members: Kristin Young, Kari North, Ruth Loos, Claudia Schurmann, other investigators welcome

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

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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).

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3. Timeline: 1 year
Study-level statistical analyses: November 2015
Interpretation and meta-analyses Fall 2015

Manuscript preparation Summer 2016

Manuscript submission Fall 2016

4. Rationale:

Over the past years, several large-scale GWAS meta-analyses have been performed to discover common variants associated with anthropometric and obesity-related traits to understand the biology that underlies obesity. In this context, also leptin and adiponectin, two hormones (adipokines) secreted by adipose tissue and that respond in a reciprocal manner to changes in fat mass and insulin resistance, respectively, have been studied thoroughly [PMID 20011104; 22479202; 24105470]. Leptin acts as a chronic signal to 'inform' the brain about the stored body fat and as such it is involved in the regulation of long-term energy homeostasis. Adiponectin is involved in regulating glucose levels as well as fatty acid breakdown and is inversely correlated with insulin resistance. Higher levels of leptin and lower levels of adiponectin correlate with increased body fat and insulin resistance, respectively. In contrast to common genetic variations, the contribution of low-frequency and rare (coding) variants has not been assessed. Also identifying the causal gene/variant of GWAS loci has been challenging and it has been suggested that low-frequency and rare variants might help in pinpointing out the causal gene/variant. Therefore, we aim to test the hypothesis that rare coding variation contributes to inter-individual variability in obesity and obesity-related traits, adiponectin and leptin levels in particular, using the novel genotyping array known as the "ExomeChip".

5. Main Hypothesis/Study Questions:
Aim: We hypothesize that by combining summary statistics of a large number of ExomeChip studies we will identify low-frequency and rare variants associated with leptin and adiponectin level. We furthermore speculate that these markers will provide new insights in the biological pathway that underlies inter-individual variation in these hormones and in the risk of obesity and type 2 diabetes.

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).

Study design: Cross-sectional analysis using data taken from **visit 1** in the ARIC population-based cohort, and previously used in a case-cohort study design of novel diabetes risk factors.

Inclusion:
- Adults ≥ 18 years of age
- European ancestry

Exclusion:
- Individuals < 18 years of age
- Pregnant women
- Participants not of European ancestry
- Missing exome data
- Missing outcome (leptin, adiponectin) data
- Missing covariate (BMI) data

Outcome: Circulating leptin levels (ng/ml), plasma adiponectin levels (μg/ml), circulating leptin levels adjusted for BMI, plasma adiponectin levels adjusted for BMI.

Leptin and adiponectin outcomes will be natural log transformed, and then regressed on the following covariates to create residuals (Models 1-4). These residuals will then be inverse normally transformed. Regression analyses and inverse normal transformation will be done in men and women separately and then combined.

Hormone data:
- Circulating leptin levels (ng/ml), natural log transformed
- Plasma adiponectin levels (μg/ml), natural log transformed

Genotype data:
- Illumina ExomeChip QCed using the GIANT ExomeChip Project protocol (CHARGE protocol).

Summary data analysis:
Linear regression models performed in Stata will be used in this study to test the following models:

Model 1:
ln (**LEPTIN**) ~ age + PCs + center → residuals → inverse normal transformation
Model 2:
ln (**LEPTIN**) ~ age + PCs + **BMI** + center → residuals → inverse normal transformation
Model 3:

ln (**ADIPONECTIN**) ~ age + PCs + center → residuals → inverse normal transformation
Model 4:
ln (**ADIPONECTIN**) ~ age + PCs + **BMI** + center → residuals → inverse normal transformation

These inverse normally transformed residuals will then be analysed for association with ExomeChip variants using RVTests software, to generate summary level statistics for future meta-analysis with other cohorts.

Limitations/challenges:

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 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 ICTDER 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

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? ____ 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/

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.