ARIC Manuscript Proposal # 1741

1.a. Full Title: Genome-wide association study of adiponectin level

b. Abbreviated Title (Length 26 characters): GWAS of adiponectin

2. Writing Group: ADIPOGen Consortium (up to 4 authors per cohort)
   ARIC writing group members: Jim Pankow, David Couper, Christie Ballantyne, Bruce Duncan

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

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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).
   Name:
   Address:

   Phone: Fax:
   E-mail:

3. Timeline: Begin analysis January 2011
   Paper ready for submission April 2011

4. Rationale:

Adiponectin is a protein hormone secreted exclusively by adipocytes that plays a role in inflammation and metabolism. Prospective epidemiologic studies (1), including ARIC
(2, 3), have found inverse, independent associations between circulating adiponectin level and risk of type 2 diabetes. Adiponectin levels are strongly and inversely associated with measures of adiposity. Recent genome-wide association studies have identified variants on chromosomes 3, 5, and 16 that explain some interindividual variability in adiponectin levels (4, 5, 6, 7, 8).

The ADIPOGen Consortium was formed to facilitate gene discovery for adiponectin levels. The participating cohorts plan to perform a genome-wide meta-analysis, in which summary statistics based on a mutually agreed upon analysis plan will be shared across cohorts to allow meta-analysis and identification of variants for replication testing. The consortium is primarily made up of studies from Europe and the US. Member studies from the CARe consortium have recently agreed to join ADIPOGen, which will further extend gene discovery efforts to African American populations. At the moment ARIC will serve as an in silico replication sample for ADIPOGen, although it is possible that future analyses will include ARIC as a discovery cohort.

5. Main Hypothesis/Study Questions:

Gene variants associated with adiponectin in the ADIPOGen consortium will replicate in participants from the ARIC cohort.

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).

The data analysis will be restricted to Caucasian and African American subjects in the “Inflammatory Precursors of Type 2 Diabetes” ancillary study who have total or high-molecular weight adiponectin measures and genome-wide markers available from samples collected at visit 1. The complexity of the case-cohort design will be addressed in the analysis. According to the ADIPOGen analysis plan, adiponectin will be naturally log transformed. Analyses will be race/ethnicity specific and adjusted for age, BMI, and sex, and principal components of ancestry, if appropriate. Sex-specific analyses will also be conducted. Summary results will be deposited in a shared directory on a central server which will be password protected. Meta-analyses will be performed using GWAMA software, calculating fixed and random effects. The fixed effects will be reported as the main results.

In order to further extend gene discovery, results across ethnic groups will be compared using TRANSMAP software. The TRANSMAP software implements Bayesian methodology for the meta-analysis of genetic association studies undertaken in multiple ethnic groups. Traditional fixed-effects meta-analysis assumes allelic effects to be the same in each population. However, we might expect heterogeneity in these effects between different ethnic groups because: (i) causal variants may not be the same; (ii) exposure to interacting environmental risk factors may vary; or (iii) allele frequencies at interacting variants may not be the same. To address this challenge, the TRANSMAP
methodology clusters populations according to their relatedness, thus allowing for the
expected heterogeneity in allelic effects between different ethnic groups. Simulations
suggest that TRANSMAP offers substantial improvements in power and localization
accuracy over fixed-effects meta-analysis, and thus improves the likelihood of identifying
and fine-mapping causal variants within trait loci in trans-ethnic association studies.

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 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?  ____ No
     _x___ Yes

     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.csec.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?  ____ No
     _x___ Yes

11.b. If yes, is the proposal
     _x___ 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)* __________ __________
________)
     2006.03 (Stampede and Geneva genotype funding in Caucasians)
2007.02 (CARe, genotyping in African Americans)
1995.09 (Inflammatory Precursors of Type 2 Diabetes)
*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.

References: