ARIC Manuscript Proposal #1957

PC Reviewed: 7/10/12  Status: A  Priority: 2
SC Reviewed: _________  Status: ______  Priority: ______

1.a. Full Title: Adiponectin allele score and risk of type 2 diabetes

b. Abbreviated Title (Length 26 characters): Adiponectin allele score and T2D

2. Writing Group:
   Writing group members: Jim Pankow, Na Zhu

This is a consortium analysis involving selected studies, including ARIC, participating in the DIAGRAM (Diabetes Genetics Replication And Meta-analysis Consortium). Jim Pankow is responsible for overseeing analysis in ARIC and will handle communications with the ARIC Publications and Steering Committees. The final composition of ARIC authors is still under negotiation, and the final list of all participating studies is not yet available.

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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3. **Timeline:**  
   Analysis to begin June 2012  
   Draft paper August 2012

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).

Adiponectin may serve as a biomarker of adiposity and other diabetes risk factors, or may contribute directly to risk through glucose regulation and metabolic processes. Associations between adiponectin gene (ADIPOQ) SNPs known to affect adiponectin level and diabetes may provide better evidence of a causal role for adiponectin in the etiology of the disease.

5. **Main Hypothesis/Study Questions:**

A genetic risk score for adiponectin is associated with risk of 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).**

Analysis will follow a standard plan developed for the project; summary estimates will be submitted for meta-analysis at the University of Exeter. Results from ARIC will be based on a cross-sectional analysis of prevalent diabetes cases and non-cases identified at the baseline exam, and restricted to Caucasians.

**Exclusion criteria:**
• In CASES exclude:
  - Individuals aged at diagnosis before 35
  - If age at diagnosis was not known, those aged <45 years at the time of study

• In CONTROLS exclude:
  - HbA1c > 6.4% and/or fasting glucose > 7mmol/l

We will create a weighted allele score using real or imputed (dosage) genotypes for each individual:

\[ s_j = \sum_{i=1}^{4} w_i g_{ij} \]

where \( s_j \) is the score for individual \( j \), \( g_{ij} \) is the number of risk alleles (0, 1, 2 or dosage of the risk allele) for SNP \( i \) carried by individuals \( j \) and \( w_i \) is the effect size for SNP \( i \) (See Table below for values of \( w_i \); i.e. \( w_i = -0.527 \) for SNP rs17366653).

<table>
<thead>
<tr>
<th>SNP</th>
<th>Effect Allele</th>
<th>Weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs17366653</td>
<td>C</td>
<td>-0.527</td>
</tr>
<tr>
<td>rs17300539</td>
<td>G</td>
<td>-0.330</td>
</tr>
<tr>
<td>rs3774261</td>
<td>G</td>
<td>-0.354</td>
</tr>
<tr>
<td>rs3821799</td>
<td>T</td>
<td>-0.352</td>
</tr>
</tbody>
</table>

* Weights have been calculated from meta-analysis of adiponectin-4SNPs association in a multi-variable regression model.

We will create allele score in 3 models using different SNPs (different models because rs17300539 and rs17366653 are often poorly imputed in many standard GWAS datasets):

allele_score_1: use rs17366653, rs17300539, rs3774261, rs3821799
allele_score_2: use rs17300539, rs3774261, rs3821799
allele_score_3: use rs3774261, rs3821799

Only SNPs with imputation quality > = 0.3 (imputed to hapmap) will be included in the analysis.

Logistic regression will be used to relate diabetes to allele score. Covariates will include age, sex, and center.

Analyses will include sex-combined and sex-specific models:

1- diabetes_status ~ allele_score_x * age, sex (in men and women combined)
2- diabetes_status ~ allele_score_x * age (in women only)
3- diabetes_status ~ allele_score_x * age (in men only)

7.a. Will the data be used for non-CVD analysis in this manuscript? ______ Yes ______ 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
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.cscu.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)?

1470 (Li): Genome-wide association study of prevalent type 2 diabetes in the Atherosclerosis Risk in Communities Study

Primary results from the GWAS of type 2 diabetes in ARIC are included in a DIAGRAM consortium paper recently accepted by Nature Genetics (Morris et al.). Although the outcome (prevalent type 2 diabetes at visit 1) is the same, this analysis will be distinct from the GWAS because of its focus on a small number of SNPs summarized in an allele score.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

_x__ Yes  ____ No

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 (Stampeded and Geneva genotype funding in Caucasians)

*ancillary studies are listed by number at http://www.cscu.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.