

## ARIC Manuscript Proposal # 1906

PC Reviewed: 2/14/12  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Genome-wide association analysis of fetuin-A levels

**b. Abbreviated Title (Length 26 characters):** GWAS of fetuin-A

**2. Writing Group:**

Writing group members:

This is a consortium analysis involving CHARGE and other cohorts. Jim Pankow is responsible for overseeing analysis in ARIC and will handle communications with the ARIC Publications and Steering Committees. ARIC is tentatively allotted three authors for this manuscript.

ARIC: Jim Pankow, Ron Hoogeveen, Maria Ines Schmidt

CHS: David Siscovick, Bruce Psaty, Richard A. Jensen, Joe Zumada, Jerome I. Rotter, Ida Chen, Mark O. Goodarzi, Alice Arnold (Anne Newman) - and fetuin-A working group (Multi-PI R01 for CHS): Kenneth Mukamal, Luc Djousse, Jorge Kizer, Susan Ziemann, Joe Ix

Nurses' Health Study: Kathryn Rexrode, Eric Rimm, Qi Sun, Majken K. Jensen

FHS: Vasan Ramachandran, 2 others

MESA: Ronit Katz, Xiuqing Guo, (Yongmei Liu, Jim Pankow, Joe Ix, David Siscovick)

Health ABC: Yongmei Liu, Anne Newman, 1 more (Joe Ix)

The EPIC Potsdam Study, the KORA study, and the Heart and Soul Study have also been contacted. These cohorts have fetuin-A levels, but not GWAS data. Each has tentatively agreed to provide SNP look-ups.

NOTE: The co-author list is partial at this time and may not be a complete/final list, especially as additional replication cohorts are added, etc.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. \_\_JP (for ARIC authors)\_\_ [**please confirm with your initials electronically or in writing**]

First author: Majken K. Jensen (Nurses' Health Study)

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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:** Analysis to begin in ARIC to begin as soon as approval is granted  
First draft by June 2012

**4. Rationale:**

Fetuin-A is a protein that is produced almost exclusively by hepatocytes and secreted into the bloodstream.<sup>1,2</sup> Fetuin-A directly binds and inhibits the insulin receptor on adipocytes and skeletal muscle cells. When bound, it decreases the rate of insulin receptor tyrosine kinase activity, and downstream intracellular signaling cascades, resulting in insulin resistance.<sup>7,8</sup> This function is conserved in multiple mammalian models *in vitro*<sup>9-12</sup> and *in vivo*.<sup>7,8,12</sup> The fetuin-A knock-out mouse has improved insulin sensitivity by euglycemic clamp experiments, lower triglyceride and FFA levels, resistance to weight gain, and less adiposity.<sup>13,14</sup> We<sup>15</sup> and others<sup>16,17</sup> have shown that higher fetuin-A is cross-sectionally associated with insulin resistance and longitudinally associated with incident diabetes in older adults.<sup>18,19</sup>

The gene encoding fetuin-A (*AHSG*) is located on Chr 3 (3q27); a locus that has been linked with phenotypes of the metabolic syndrome and T2DM.<sup>20,21</sup> A French group conducted a detailed candidate gene association study of the *AHSG* gene by directly sequencing the gene-encoding exons and the flanking regions. They identified 9 single nucleotide polymorphisms (SNPs) with a minor allele frequency of 5% or more, and showed strong linkage disequilibrium (LD) among the SNPs in the entire region. In a case-control study, they found that one SNP (rs1071592) had a significantly higher prevalence among those with T2DM compared to normoglycemic controls. Two other

SNPs that were in almost complete LD (rs4917 and rs2248690) showed the same tendencies, although associations with these SNPs with T2DM did not reach statistical significance.<sup>22</sup>

In the literature, variation in the *AHSG* gene is associated with fetuin-A levels. Carriers of the major alleles of rs2248690 (A; frequency in Caucasians ~74%), rs4917 (C; ~77%), and rs4918 (T ~66%) have higher levels of circulating fetuin-A, compared to carriers of the variant alleles.<sup>23-25</sup> However, it is not known whether other genetic loci can be identified that play a role in the regulation of fetuin-A concentrations. So far, no genome-wide analyses have been performed to identify genetic determinants of fetuin-A. Hence, the current proposal aims to include ARIC GWAS data in a meta-analysis of cohorts with fetuin-A levels available in the CHARGE consortium (FHS, CHS, ARIC), the Health ABC cohort, and the Nurses' Health Study.

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

To identify the common genetic determinants of fetuin-A levels.

## **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).**

In ARIC, fetuin-A concentrations will be taken from measurements performed on visit 1 plasma samples in the random subcohort selected for the “Inflammatory Precursors of Type 2 Diabetes” ancillary study.

### **SAMPLES**

Men and Women.

### **EXCLUSIONS**

1. Missing genotype data
2. Missing data on fetuin-A concentrations

### **STRATIFICATION OF SAMPLE**

Analysis will be conducted separately for Caucasians and African-Americans.

### **TRAIT OF INTEREST**

Fetuin-A (g/L), untransformed.

### **COVARIATES**

Age, age<sup>2</sup>, sex, field center, and principal components, where appropriate.

## **Brief analysis plan and methods:**

Genetic model: additive model

Fetuin-A (untransformed) = age + age<sup>2</sup> + sex + principal components/field center + SNP

QC methods at cohort levels as previously described at

<http://depts.washington.edu/chargeco/wiki/QCprocedures>

**Meta-analysis:**

Cohort-specific results will be meta-analyzed using MetABEL or Metal software.

- a. Fixed Effects
- b. Significance threshold:  $p < 5 \times 10^{-8}$
- c. Final QC step (e.g. filtering MAF at 1%) at meta-analysis stage

**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

(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?**     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”?**  
 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.csc.unc.edu/ARIC/search.php>**  
 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)?**



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