ARIC Manuscript Proposal # 1455

PC Reviewed: 12/9/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genomewide association of serum albumin and globulins: the ARIC Study

b. Abbreviated Title (Length 26 characters): Genomewide of serum albumin and globulins

2. Writing Group: Nora Franceschini, Laura Loehr, John Eckfeldt, Aaron Folsom, Eric Boerwinkle, Miguel Quibrera, Kari E North

Others welcome

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

First author: **Nora Franceschini, MD, MPH**
Address: Department of Epidemiology
University of North Carolina Chapel Hill
Bank Of America Center
137 E. Franklin St., Suite 306
CB #8050
Chapel Hill, NC 27514
Phone: 919-966-1305 Fax: 919-966-9800
E-mail: noraf@unc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Address: Kari E North, PhD
University of North Carolina
School of Public Health- Department of Epidemiology
Bank of America Center, 137 E. Franklin Street, Suite 306, Chapel Hill, NC 27514
Fax: (919) 966-9800
E-mail: kari_north@unc.edu

3. Timeline: Analyses will begin when all genotyping and QC is completed.

4. Rationale:

To conduct a genome-wide association of serum albumin and globulins traits among ARIC participants with replication in multiple prospective cohort studies of cardiovascular disease within CHARGe.

We will perform genomewide association analysis in ARIC with replication of top findings in other samples within CHARGe. If no genomewide significant findings are identified in the ARIC analysis, we will consider a meta-analysis within CHARGe and GENEVA.

CHARGE participants with available measures:
Framingham - investigators: Caroline Fox
CHS - investigators: Nancy Jenny and Peter Durda
other studies to be invited.

5. Main Hypothesis/Study Questions:
Conduct a genomewide association analysis for serum albumin and globulins using the set of genotyped and imputed SNPs.
Primary analysis: visit 1 serum albumin and globulins (total proteins minus albumin)
Secondary analysis:
Genotype-by-diabetes and genotype-by-smoking interactions. Interaction analysis will be performed when all ARIC individuals have been genotyped and will NOT be restricted to SNPs with significant main effects.

We plan to expand our analyses to African Americans as the genotyping data is available. Use of GWAS data in African-Americans will follow CARe procedures.

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).
Subjects: Individuals of European ancestry and African descent with available measures of serum albumin and total protein. Use of GWAS data in African-Americans will follow CARe procedures.
Variables (phenotype): visit 1 measurements of the serum albumin and total protein.
Exclusions: We will consider excluding individuals with malnutrition (based on BMI) and those with history of cancer (other than skin). The criteria for exclusions will be discussed within CHARGe Working Group.
Exposure: 2.5 million HapMap genetic variants identified in CEPH trios for whites and 1.0 million genetic variants in African American. We will not pursue imputation in African descent samples at this point but would consider it if adequate accuracy of imputation using HapMap YRB samples is demonstrated.
Model: Linear regression for analyses of continuous variables, using a genetic additive model. Analyses will be conducted either with and without covariates included in the model. We will test for genotype-by-diabetes and genotype-by-diabetes interaction using interaction terms and the likelihood ratio test.

We will perform analysis using all available SNPs that pass QC, without pre-screening of SNPs based on significant main effect association.
Subgroups: stratified analysis by diabetes and smoking as described above.
Transform: Serum albumin and globulins have normal distribution and will not be transformed for analysis.
Covariates: Basic model: age, sex and center adjusted. We will consider multivariable analysis using the following covariates: age, sex, cigarette smoking (current, former, never), BMI, dichotomous hypertension (defined by SBP, DBP and treatment status), total cholesterol, HDL cholesterol, lipid lowering therapy, DM, triglycerides, and markers of inflammation available at visit 1 (WBC, fibrinogen, others). We will also look for effect modification by smoking (which is associated with inflammation) and diabetes (associated with low albumin levels).
Statistical significance: Bonferroni correction adjustment (1/ number of tests performed) ($\sim 10^{-7}$)
Validation and Replication: We will pursue validation/replication of the top hits within the CHARGe group.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

none

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* 2006.03 (Stampede and Geneva genotype funding in Caucasians) and 2007.02 (CARe, genotyping in African Americans).

___ 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/

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.