1.a. Full Title: Genomewide genotype-by-sex interaction of subclinical atherosclerosis phenotypes: the ARIC Study

b. Abbreviated Title (Length 26 characters): Genomewide genotype-by-sex interaction of subclinical atherosclerosis traits

2. Writing Group: Nora Franceschini, Kari E North, Eric Boerwinkle, Miguel Quibrera, Gerardo Heiss

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]

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

4. Rationale:
To conduct a genome-wide genotype-by-sex interaction of subclinical atherosclerosis traits: ankle-brachial index and carotid intima media thickness among ARIC participants with replication in multiple prospective cohort studies of cardiovascular disease within CHARGe and GENEVA. The collaboration is based on:

CHARGe - carotid intimal media thickness (CIMT) and ankle branchial index (ABI).

We have contacted GENEVA investigators to include samples if the phenotype is available.

Initial interaction analysis, with replication of top findings with other subclinical atherosclerotic measures (CIMT, ABI).

Replication in other cohorts with CIMT and ABI measures if available (CHARGe and GENEVA).

5. Main Hypothesis/Study Questions:

Conduct a genome-wide gene-by-sex interaction analysis for subclinical atherosclerosis measures of ABI and CIMT using the set of genotyped and imputed SNPs.

Primary analysis: ABI and CIMT (internal and common carotid)

Secondary analysis: Peripheral arterial disease, define as ABI <0.90.

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 IMT and PAD. Use of GWAS data in African-Americans will follow CARE procedures.

Variables (phenotype): Baseline measurements of the ABI and common and internal CIMT.

Exclusions: ABI > 1.4 for ABI analysis

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 analysis of continuous variables, additive model. Analyses will be conducted either with covariates included in the model. For analysis of dichotomous variables, we will use logistic regression analysis adjusted for covariates in the model. We will test for genotype-by-sex interaction using interaction terms and 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: In secondary analyses, sex-specific analysis (stratified analysis by sex)

Transform: Log transformed ABI and IMT, if nonnormal distribution, to reduce kurtosis.
**Covariates:** Basic model: age and center adjusted, sex as interaction covariate
We will consider multivariable analysis, restricting to "top hits": 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.

**Statistical significance:** Bonferroni correction adjustment (1/ number of tests performed) (~10^-7)

**Validation and Replication:** We will pursue validation/replication of the top hits within the CHARGE subclinical atherosclerosis group.

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 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

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.csecc.unc.edu/ARIC/search.php](http://www.csecc.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)?

ARIC manuscript #1404: GWAS of the Ankle-brachial index, PI: Heiss
ARIC Manuscript #1405: Subclinical Measures GWA Collaboration: Carotid Intima-Media Thickness, PI: North

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
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/](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.