1.a. Full Title: Association of the HOXA locus with clinical and structural cardiovascular outcomes

b. Abbreviated Title (Length 26 characters): HOXA and cardiovascular disease

2. Writing Group:
ARIC co-authors: Sara Seidelmann, Nora Franceschini, Eric Boerwinkle, Aravinda Chakravarti, Amil Shah, Brian Claggett, Scott Solomon, [others welcome]

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

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4. Rationale:

We recently identified significant associations for genetic variants at the EVX1/HOXA locus with SBP, DBP and HTN in a genome wide association study (GWAS) of individuals of African ancestry\(^1\). These associations also replicated in individuals of
European ancestry. Little is known about the mechanisms relating genes at this locus and hypertension. However, a patient with a 5.6 Mb deletion of 7p15 including HOXA cluster presented with congenital heart defects, suggesting a role of the genes in heart development. We propose to study the association of two independent variants identified in our GWAS with cardiac structural and functional measures in white and black ARIC participants, in addition to testing their association with clinical outcomes.

5. **Main Hypothesis/Study Questions**: Variants in the EVX1/HOXA locus associate with functional and structural heart measures from echocardiogram and cardiovascular disease events.

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).**

**Exposures:**
Common variants in and around the EVX1/HOXA locus (n=13,087 on Affymetrix 6.0 array) will be analyzed.

**Outcomes:**
**Clinical events**--The outcomes analyzed will be cardiovascular events and death since the first visit. New stroke (fatal or non-fatal) or incident CHD (fatal or non-fatal MI or CHD death) since the first visit to the fifth visits (2011-2013) among subjects who were free of these outcomes at the beginning of visit one. HF, including both systolic heart failure and heart failure with preserved ejection fraction will also be evaluated. HF treatment prior to event (ACEi, ARB, beta blocker, MRA, digoxin, statins, diuretics) will be evaluated.

**Blood Pressure** - systolic and diastolic blood pressure measured at visits 1-5 and hypertension status will be evaluated.

**Echocardiographic measures**--Left ventricular dimensions and volume, systolic function, LV diastolic measures, LA dimensions, tissue Doppler and speckle tracking based strain (longitudinal, circumferential and radial), RV dimension, volumes, and function.

**Covariates:**
Age, gender, race. ARIC center, cardiovascular risk factors (diabetes mellitus, dyslipidemia, smoking status)

**Analysis plan:**
Visit 1 will serve as the baseline for these analyses. Data will be reported as percent frequencies and compared by chi-squared or Fischer exact tests. Mean and standard deviation will be used to display continuous normally distributed data; non-normally
distributed data will be displayed as median and 25th-75th percentile. Incident HF, CHD, stroke and death will be presented as events per 1000 person-years at risk. Analysis of genetic variants with cardiovascular events and death will be performed using Cox proportional hazards models. The association of EVX1/HOXA variants with HTN will be analyzed using logistic regression models. Univariate and multivariable models will be created to identify both unadjusted and adjusted risk of the outcomes. Interactions for age, sex, and race on the EVX1/HOXA variants and cardiovascular outcomes will be assessed. Stratified analysis by age, sex and/or race strata will be performed if a significant interaction is apparent. The association between EVX1/HOXA variants and echocardiography measures will be analyzed with multivariable linear regression controlling for potential confounders such as age, sex, race, BMI, ARIC center, and diabetes mellitus.

Limitations
There are likely many genetic modifiers affecting cardiac structure and cardiovascular risk susceptibility; our proposal analyzes specific candidate genes only.

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 ICTDER 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 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 MS 1868: Discovery and fine-mapping of loci in African American and Hispanics. (Franceschini)
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? ____ Yes    __x__ No

11.b. If yes, is the proposal
___  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)* __________ __________

*ancillary studies are listed by number at [http://www.cscc.unc.edu/aric/forms/](http://www.cscc.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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.

References