1.a. Full Title: Genetic analysis of CD36 and cardiac structure and function

b. Abbreviated Title (Length 26 characters): CD36 and echo

2. Writing Group:
   Writing group members: Sara B. Seidelmann, Niek Verweij, Gulum Kosova, Chris Newton-Cheh for CHARGE QRS Exome working group, Amil Shah, Bing Yu, [OTHERS WELCOME], Eric Boerwinkle, Scott D. Solomon

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

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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 will begin following proposal approval with the aim of completing the analysis and associated manuscript(s) within 1 year of data availability.

4. **Rationale:**

   Elevated left ventricular (LV) mass detected by electrocardiography (ECG) is a common manifestation of preclinical cardiovascular disease that predicts cardiovascular morbidity and mortality. We explored the effect of rare and low-frequency coding variants for the three QRS voltage products Cornell*QRS duration, 12 lead Sum*QRS duration and Sokolow-Lyon*QRS duration as proxies for electrically active myocardial mass in 70k individuals; we recently published a common variant GWAS (van der Harst JACC 2016)[1].

   Our current analysis identified novel genes and variants for QRS voltage traits including rs3211938 in CD36 (fatty acid translocase), a variant specific to individuals of African descent; there are some reports that it may have been under positive selection[2]. Based on our analyses, its potential role in fatty acid metabolism and observed effects of increase myocardial mass in unpublished animal models by collaborators, we hypothesize that this variant may be associated with increased left ventricular mass and function in individuals of African descent.

   This work is unpublished and we would propose inclusion of appropriate co-authors from ARIC in the primary publication with the GWAS results for all variants.

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

   1) We hypothesize that genetic variation in CD36 (rs3211938) is associated with increased left ventricular mass and echocardiographic measures of cardiac structure and function.
   2) We further hypothesize that rs3211938 may be associated with heart failure in the ARIC.

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).**

   **Basic Study Design and study population:**
   All subjects with self-reported race of “African American” in the ARIC that have GWAS data available will be included.

   **Exposures and their measurement:**
   The genetic variant rs3211938 in CD36 will be assessed.

   **Outcomes and their measurement:**
   **Primary phenotype to be analyzed:** LV wall thickness and estimated LV mass (by echocardiography at V3 and V5), and incident heart failure.
**Other Echocardiographic measures**—Left ventricular dimensions and volume, systolic function, LV diastolic measures, LA dimensions and function, tissue Doppler and speckle tracking based strain (longitudinal, circumferential and radial), RV dimension, volumes, and function.

**Plasma measures**—brain natriuretic peptide levels, cholesterol levels (total and high density), triglyceride levels

**Other Cardiac outcomes**—atrial fibrillation, stroke, myocardial infarction and mortality will be assessed if primary analysis is significant

**Confounders and their measurement:**
Age, gender, BMI, height, study recruitment center, first 10 principle components, systolic and diastolic blood pressure, hypertension status (categorical variable defined as antihypertensive medications within the past 2 weeks of examination were self-reported or taken from prescription bottles or BP > 140/90), diabetes mellitus status, estimated Glomerular Filtration Rate.

**Exclusions:** Patients with severe valvular heart disease, inadequate echocardiograms, and non-African ancestry.

**Analysis plan:**
Descriptive statistics of the study sample will be presented by genotype. Categorical data will be reported as frequencies and percentages and compared by chi-squared or Fisher exact tests. Mean and standard deviation will be used to summarize continuous, normally distributed data; non-normally distributed data will be summarized as median and 25th - 75th percentile and compared between groups via Wilcoxon rank sum test or nonparametric trend tests as appropriate. Interactions between age, and/or sex, and the relationship between rs3211938 and echocardiographic outcomes will be assessed. Stratified analysis by age and/or sex strata will be performed if a significant interaction is apparent. The association between rs3211938 and echocardiography measures will be analyzed with multivariable linear regression controlling for potential confounders such as age, sex, and BMI. Sensitivity analysis will be performed with adjustment for SBP or anti-hypertensive therapy use if the variant is associated in the primary analysis. Inverse probability weighting will be used to account for the non-randomness of missing echocardiographic data at Visit 5. Basic, age- and gender-adjusted, as well as covariate adjusted hazard ratios will be used to test the association between rs3211938 and the risk of HF and other CV outcomes using Cox proportional hazard regression.

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,
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.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)?

Past (inactive) proposals:

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/

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.cscce.unc.edu/ari/index.php, under Publications, Policies & Forms. 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
