ARIC Manuscript Proposal #2204

PC Reviewed: 8/13/13                      Status: A                      Priority: 2
SC Reviewed: _________                      Status: _____                      Priority: _____

1.a. Full Title: Association of variation in the PRDM16 gene with adipose tissue, skeletal muscle and myocardial phenotypes in CHF

b. Abbreviated Title (Length 26 characters): PRDM16 variation in heart failure

2. Writing Group:
   Writing group members: Scott Solomon, Calum A MacRae, Christina Quarta, Amil Shah, Susan Cheng, Eric Boerwinkle

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

First author: Calum MacRae, MD, PhD
   Address: Brigham and Women’s Hospital
   75 Francis Street
   Boston
   MA 02115

   Phone: 857 307 0301       Fax: 857 307 0300
   E-mail: camacrae@bics.bwh.harvard.edu

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).
   Name: Scott D. Solomon
   Address: Brigham and Women’s Hospital
            Cardiovascular Division
            75 Francis Street
            Boston, MA 02115

   Phone: 857-307-1960       Fax: 857-307-1944
   E-mail: ssolomon@rics.bwh.harvard.edu

3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4. Rationale:
We have recently shown that mutations in PRDM16 cause left ventricular non-compaction and DCM (Arndt et al. AJHG in press) with effects on cardiomyocyte proliferation, metabolism and intercellular coupling. This gene encodes a transcriptional coactivator that reciprocally regulates the differentiation steps between muscle and brown adipose tissue. Notably it actively suppresses white adipose tissue formation. It also controls a transcriptional cascade which acts as a switch for natriuretic peptide signaling through the NP receptors.

We would propose to test for simple association between rare variants in PRDM16 and LVEF, LV dimensions and LV mass as well as heart failure using allele burden tests. We would also like to test for association with circulating natriuretic peptide levels as we would anticipate that these will be perturbed through feedback regulation via the receptors including the clearance receptor. Finally, we would like to enquire if it is possible to access imaging data that would allow us to assess subcutaneous and visceral fat stores as we would anticipate distinctive correlations between different fat stores, cardiac function and PRDM16 genotype.

5. **Main Hypothesis/Study Questions:**
Rare variation in PRDM16 is associated with LV mass, LV dimensions, LV function and incident heart failure.

PRDM16 variation is associated with skeletal muscle mass and the relative volume of specific adipose tissue stores and that these in turn are associated with circulating natriuretic peptide levels in the general population.

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).**

**Study design:** Simple association for binary phenotypes and linear regression for continuous traits. All analyses will be performed under a dominant model.

**Inclusion/exclusion:** All genotyped subjects who have undergone echocardiography will be eligible for inclusion in the analysis.

**Phenotypes:** LV mass, LV dimensions, LV ejection fraction, LV trabeculation indices, incident heart failure, serum natriuretic peptide levels, regional subcutaneous and visceral adipose tissue volumes, skeletal muscle volume/mass estimates.

**Analysis:** Simple association for binary phenotypes and linear regression for continuous traits. All analyses will be performed under a dominant model, but we will also consider a true additive model. Case control association will be performed across variants using Fisher’s exact test with permutation used to derive locus-wide significance thresholds and p values. We will undertake association analyses for quantitative traits using linear regression of the trait residuals on the variant burden. Again, we will empirically estimate significance using permutation.

**Covariates:** Age, sex, BMI, height, diabetes
Burden testing: We will use both the Combined Multivariate and Collapsing (CMC) method and SKAT. In addition, we will empiric assay of the biologic effects of PRDM16 coding alleles on transcriptional function to stratify variants for these analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript?  __X__ 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?  __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”?  ____ 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)?

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/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

References: