ARIC Manuscript Proposal #2670

PC Reviewed: 11/10/15  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Genetic Associations with Mitral Annular Calcification (MAC)

b. Abbreviated Title (Length 26 characters): Genetic Associations with MAC

2. Writing Group:
   Writing group members: Alexandra Gonçalves, Sara B. Seidelmann, Calum MacRae, Amil M Shah, Susan Cheng, Eric Boerwinkle, Scott D. Solomon. Others welcome.

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

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3. **Timeline:** Analysis will begin following proposal approval. A manuscript is anticipated to be completed within 6 months of the date. A second manuscript will be pending on updated database outcomes.

4. **Rationale:**

Mitral annular calcification (MAC) is a frequent echocardiographic finding among elderly, and its prevalence is likely to rise with the increasingly aged population. Community based cohort studies have suggested a strong association between MAC and traditional cardiovascular disease (CVD) risk factors\(^1\)\(^-\)\(^2\) and with an increased risk of CVD events and death in the general population.\(^3\) Moreover MAC may represent an important early phenotype for valvular heart disease, preceding the development of valvular dysfunction, and it increases the risk of mitral valvular repair surgery.\(^4\)-\(^6\)

The pathophysiology underlying valvular calcification presents some similarities to atherosclerosis,\(^7\) but it remains incompletely defined and there are no effective medical treatments capable of prevent or slow its progression. It is expected that identification of causal risk factors as well as a better understanding of the pathophysiology may open opportunities for prevention. Moreover, some previously identified genetic factors may influence the development of valvular calcification. Specifically, ApoB (XbaI, rs1042031, and rs6725189), ACE (rs4340), IL10 (rs1800896 and rs1800872), and LPA (rs1045587) gene polymorphisms may be associated with valvular calcific stenosis with a relatively high level of evidence\(^8\) and recently, two SNPs (rs17659543 and rs13415097) near the proinflammatory gene IL1F9, were indentified with genome wide significance for MAC, although not replicated consistently. However, whether these associations differ by cardiovascular risk profile or by ethnicity is unknown. The ARIC cohort presents a unique opportunity for the evaluation of MAC in the elderly population, to understand ethnic differences in MAC prevalence and the association between previous identified genetic variants and MAC in whites and African-Americans.

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

1. To analyze the genetic background of previously identified SNPs of patients displaying echocardiographic MAC and test the specific hypothesis:
   a. Individuals with rs17659543 and rs13415097 IL1F9 SNPs have higher prevalence of MAC compared to individuals without these SNPs.
   b. The IL1F9 SNPs distribution differs between whites and African-Americans.
   c. The effect of IL1F9 SNPs on MAC is independent of age, gender, and CV risk factors.
d. The effect of IL1F9 SNPs on MAC is superior to ApoB (XbaI, rs1042031, and rs6725189), ACE (rs4340), IL10 (rs1800896 and rs1800872), and LPA (rs10455872) gene polymorphisms.

2. To analyse the association between MAC and overall mortality and cardiovascular outcomes (atrial fibrillation, heart failure, stroke, myocardial infarction), independently of IL1F9 SNPs.

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).

This study will analyze ARIC cohort participants presenting to visit 5, who have acceptable echocardiography image quality. Participants will be excluded if they are neither White nor African American, or if prohibited use of DNA.

**Method for mitral annular calcification evaluation**
Using echocardiography, mitral annular calcification is defined as a dense, highly reflective area at the base of the junction of the atrioventricular groove and posterior mitral valve leaflet. The individuals will classified dichotomously (present or absent).

**Variables of interest**

*Genotype data:* IL1F9 SNPs (rs17659543 and rs13415097), ApoB (XbaI, rs1042031, and rs6725189), ACE (rs4340), IL10 (rs1800896 and rs1800872), and LPA (rs10455872) gene polymorphisms.

*Echocardiographic variables* (Visit 5): presence of MAC (dichotomous variable) and variables related to other valvular disease abnormalities and cardiac structure and function

*Clinical and demographic variables* (Visit 5): Demographic characteristics (age, race, sex, body mass index, socioeconomic status), cardiovascular risk factors (diabetes, arterial hypertension, smoking, dislipidemia, use of antihypertensive medications or statins).

*Laboratory values* (visit 5): C Reactive protein, plasma lipid levels (i.e. HDL and LDL cholesterol, apolipoprotein AI and B, triglycerides), serum creatinine, hemoglobin A1C, total, HDL and LDL cholesterol, triglycerides, 25-hydroxyvitamin D serum calcium, phosphorus, albumin, potassium and magnesium.

*Forthcoming outcomes:* mortality, acute myocardial infarction or revascularization procedure, heart failure, stroke or TIA.
Limitations: Echocardiography is the most commonly used imaging technique for the assessment of valvular calcification, but the evaluation from the ultrasonic images is subjective, dependent on the expertise of the examiner and vulnerable to inter- and intra-observer variability. However, echocardiographic evaluation of valvular calcification has been extensively used and it is correlated with prognosis and with non-coronary cardiac calcium, measured by computed tomography.\(^9\)

Analytical approach:

This study will consider a cross sectional analysis at visit 5. Continuous normally distributed data will be displayed as mean and standard deviation and continuous non-normally distributed data will be displayed as median and interquartile range. Categorical data will be shown as a total sample and proportion. Associations between the IL1F9 SNPs and other genetic polymorphisms of interest and MAC, will be evaluated using mendelian randomization analysis and multivariable logistic regression analyses adjusting for the significant covariates (demographic characteristics, cardiovascular risk factors). The effects will be expressed as odds ratio and 95% CI. We will test for interaction by race if there is any evidence for interaction by race results will be presented stratified.

In addition, in the future, this study aims to analyse prospectively the relation between MAC and mortality and cardiovascular outcomes.

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?
      __x__ 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

   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)?

Proposal #2089 Contemporary Burden of Valvular Disease in the Community
Proposal # 845 Mitral Annular Calcification and Its Association with Cardiovascular Events in African Americans

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.cscc.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


