1.a. Full Title: Genome-wide analysis of QRS voltage

b. Abbreviated Title (Length 26 characters): QRS voltage GWAS

2. Writing Group: Alvaro Alonso, Dan E. Arking, other ARIC investigators; investigators from other cohorts

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

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3. Timeline:

Analysis will be completed in the next 2 months. Final submission for publication will depend on when other participating cohorts finish their analysis and whether additional experiments/analyses are conducted
4. Rationale:

Left ventricular (LV) mass detected by electrocardiography (ECG) is a common manifestation of preclinical cardiovascular disease that predicts cardiovascular morbidity and mortality.\textsuperscript{1, 2} A variety of ECG criteria have been introduced to detect LV hypertrophy and LV mass since the early years of ECG. Commonly used LV hypertrophy criteria include the Sokolow-Lyon, the Cornell voltage, Cornell voltage product, and the 12-lead sum.\textsuperscript{3-5} Among LIFE study patients, regression of Cornell product and Sokolow-Lyon voltage criteria was associated with a decreased risk of cardiovascular death, myocardial infarction, stroke, and the composite endpoint of these events, independent of treatment modality and blood pressure lowering.\textsuperscript{6}

A substantial proportion of both echocardiographic (~23%) as well as ECG determined LV mass (Sokolow-Lyon ~40%, Cornell product ~30%) can be explained by heredity.\textsuperscript{7-10} Identification of the specific genes that are associated with an individual’s predisposition to LV mass may lead to advances in the prevention of cardiovascular disease morbidity and mortality. A preliminary genome-wide linkage analysis (400 microsatellites) has only provided moderate evidence for linkage. A locus for Sokolow-Lyon voltage was suggested on chromosome 10q23.1 (LOD 2.21), for Cornell voltage product on chromosome 17p13.3 (LOD 2.67), and for ECG LV mass on 12q14.1 (LOD 2.19).\textsuperscript{11} The question remains whether these are true-positives.

Recently, a meta-analysis of GWA studies was not successful in identifying genetic variants associated with the echocardiographic trait of LV mass or wall thickness.\textsuperscript{12} Studying the ECG indices of LV mass is of great interest as the underlying biology of these phenotypes are different (in addition to being more standardized and more commonly available). ECG voltages reflects the functional (electrical active) cardiomyocyte compartment, whereas anatomical measures of LV mass encompasses all (including non-electrically active) cellular and interstitial components. In addition, the potential number of subjects to be studied is likely to be substantially large for an ECG trait compared to an echocardiographic trait. Finally, the observation that both echocardiography and ECG estimated LV mass predict mortality independently of each other further supports the notion that these parameters are not reflections of identical conditions.\textsuperscript{13}

QRS duration is only weakly correlated to voltage duration products (e.g., Cornell-voltage-product with QRS duration ($r^2 \approx 0.10$, unpublished data). Therefore, in addition to the published QRS duration GWAS (MS #1605, Sotoodehnia et al, Nat Genet 2010), we propose to prepare an independent meta-analysis on QRS phenotypes that takes voltage into account.

5. Main Hypothesis/Study Questions:

We will assess the genetic determinants of QRS voltage using a genome-wide association approach.

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**

Cross-sectional analysis of ARIC participants at baseline with ECG and genetic data.

**Inclusion/exclusion criteria**
The initial GWAS will exclude the following individuals:

- Non-whites
- AFib on baseline ECG
- History of myocardial infarction or heart failure
- QRS interval > 120 ms
- Presence of left or right bundle branch block
- QRS axis < -30 or > +90
- Pacemaker
- Wolf-Parkinson-White syndrome
- Use of class I or class III anti-arrhythmic medications

**Main outcome variable**
QRS voltage will be defined using different approaches:

1.) 12-lead sum product (mm · ms)
   a. 12-lead sum of R to S (or Q whatever greater) in mm for all 12 leads together. The 12-lead sum product us the 12 lead sum multiplied by QRS duration (in ms)

2.) Cornell voltage product (mm · ms)
   a. Cornell voltage is the sum in mm of R in lead aVL added to the absolute mm value of the S (or Q whatever greater) in V3. The Cornell voltage product is the Cornell voltage (mm) multiplied by QRS duration (ms).

3.) Sokolow-Lyon product (mm · ms)
   a. Sokolow-Lyon is the sum in mm of the S (or Q whatever greater) in V1 added to the R in V5. The Sokolow-Lyon voltage product is the Sokolow-Lyon voltage (mm) multiplied by QRS duration (ms).

**Analysis**
We will perform linear regression of QRS-voltage phenotypes on genotype dosage (both types and imputed SNPs) adjusting for age, sex, height, and body mass index. Results from ARIC will be meta-analyzed with those from other cohorts using inverse variance weighted meta-analysis.

In additional analyses, we will perform look-ups of genome-wide hits found in whites to the ARIC African-American participants, and will create a gene score derived from the European-ancestry sample.

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 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”?  
   _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)?

   MS #1605 – QRS GWAS. The current proposal explores a related but different phenotype. The ARIC representatives will be the same as in the QRS GWAS.

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/

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.

Reference List


(4) Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. *J Am Coll Cardiol* 1992 November 1;20(5):1180-6.

(5) SOKOLOW M, LYON TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* 1949 February;37(2):161-86.

(6) Okin PM, Devereux RB, Jern S et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004 November 17;292(19):2343-9.


