1.a. Full Title: GWAS of ST segment and T wave amplitude: the CHARGE consortium

b. Abbreviated Title (Length 26 characters): ST-T wave amplitudes GWAS

2. Writing Group:
   Writing group members: Dan Arking, Alvaro Alonso, Elsayed Soliman, others
   welcome

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]

First author: Alvaro Alonso
Address: Division of Epidemiology and Community Health
         University of Minnesota
         1300 S 2nd St, Suite 300, Minneapolis, MN 55454
         Phone: 6126268597
         E-mail: alonso@umn.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: Dan Arking
Address: Johns Hopkins University School of Medicine
         733 N. Broadway
         Miller Research Building, Room 447
         Baltimore, MD 21205
         Phone: (410) 502-4867
         E-mail: arking@jhmi.edu

3. Timeline:
   Analysis to be completed as soon as proposal is approved.

4. Rationale:
   The ST segment and adjacent T wave amplitudes of the electrocardiogram are quantitative characteristics of cardiac repolarization. Repolarization abnormalities have been linked to ventricular arrhythmias and sudden cardiac death. Duration of cardiac repolarization has been previously studied by genome wide association studies and led to the discovery of 14 associated loci. However, abnormalities of repolarization are not
limited to changes in duration but concern changes in amplitudes as well. Deviations of ST-T wave amplitudes can be indicative of a variety of cardiac pathologies, including myocardial ischemia, ventricular hypertrophy, early repolarization (ER), and Brugada syndrome. Despite the prognostic importance of these conditions, no earlier attempts have been undertaken to identify common genetic variants that are associated with ST-T wave amplitudes. Recently, a consortium of European cohorts identified 17 genome wide significant loci (P<6.26E-9, based on 8 independent phenotypes) and 15 suggestive loci (P<6.25E-7) associated with ST-T wave amplitudes. We propose to (1) replicate in ARIC whites the loci recently identified and (2) to execute a larger-scale follow-up discovery meta-analysis of ARIC with other CHARGE cohorts.

5. Main Hypothesis/Study Questions:
We hypothesize that loci associated with ST-T wave amplitudes in European cohorts will be also associated with similar traits in ARIC whites, and that inclusion of the ARIC cohort in a GWAS of these phenotypes will contribute to identify additional loci.

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 population
We will include eligible ARIC participants from visit 1. All phenotype information will correspond to visit 1.

Phenotype definition
For this analysis, amplitudes at T wave and ST segment amplitudes at 60ms after J-point are requested on every lead from the 12-lead ECG. There are 10 traits of interest; each will be used in the regression analysis. To calculate the Traits, the amplitudes in each lead will be summed according to the 5 clinical leads (Table 1). For example, the lateral ST-segment trait will be calculated as the total amplitude add the ST amplitudes (at 60ms after J) of I + aVL + V₅ + V₆

<table>
<thead>
<tr>
<th>Trait</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST segment Lateral</td>
<td>I + aVL + V₅ + V₆</td>
</tr>
<tr>
<td>ST segment Inferior</td>
<td>II + III + aVF</td>
</tr>
<tr>
<td>ST segment Septal</td>
<td>V₁ + V₂</td>
</tr>
<tr>
<td>ST segment Anterior</td>
<td>V₃ + V₄</td>
</tr>
<tr>
<td>ST segment aVR</td>
<td>aVR</td>
</tr>
<tr>
<td>T wave Lateral</td>
<td>I + aVL + V₅ + V₆</td>
</tr>
<tr>
<td>T wave Inferior</td>
<td>II + III + aVF</td>
</tr>
<tr>
<td>T wave Septal</td>
<td>V₁ + V₂</td>
</tr>
<tr>
<td>T wave Anterior</td>
<td>V₃ + V₄</td>
</tr>
<tr>
<td>T wave aVR</td>
<td>aVR</td>
</tr>
</tbody>
</table>

Phenotype modelling:
- Exclusions (when available):
- Non-Whites
- Phenotype not available
- QRS>120 and/or bundle branch block
- Atrial fibrillation, flutter
- Electronic pacemaker rhythm
- WPW (if available)
- History of Myocardial Infarction
- Also participants with extreme measurements, more than ±4SD from mean on a per phenotype basis.

- Transformation:
  - Standardize the traits to a mean of zero and a standard deviation of one (also referred to as Z-score).

- Covariates for linear regression:
  - Linear adjustment for age, sex and BMI
  - Study site specific
  - PCA if applicable

**Analysis**
Additive genetic models of autosomal SNPs adjusted for covariates / residuals using linear regression (see above).
Do not adjust test statistics by applying genomic control or other method.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ 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 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?  ____ 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.cscn.unc.edu/ARIC/search.php](http://www.cscn.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)?

No related 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/](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.

REFERENCES