ARIC Manuscript Proposal # 1605

PC Reviewed: 2/9/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genomewide analysis of QRS interval: the CHARGE consortium

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

2. Writing Group: Dan E. Arking, Alvaro Alonso, coauthors from other cohorts. Additional ARIC coauthors might be included based on interest and participation.

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

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3. Timeline:
Data analysis in ARIC, result sharing with other CHARGE cohort and meta-analysis will be done before summer 2010.

4. Rationale:
The QRS complex in the ECG records the depolarization of the ventricles through the Purkinje system and ventricular myocardium. Increased QRS duration has been associated with mortality in individuals with heart failure (Wang, 2008), hypertrophic cardiomyopathy (Bongioanni 2007) or in the general population (Desai 2006).

A recently published genome-wide association study in deCODE, which included ~10000 individuals in the discovery sample, has identified several genetic loci associated with QRS duration (*TBX5, SCN10A,* 6p21 and 10q21) (Holm 2010). The CHARGE consortium is an excellent setting to replicate these results and identify new variants given its larger sample size.

5. Main Hypothesis/Study Questions:

Gene variants can be identified that associate with QRS duration.

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).

Design:

- Meta-analysis of GWAS studies

Participating groups:

- AGES, Framingham Study, Rotterdam Study, ARIC, CHS, SHIP, MONICA/KORA, ERF, MICROS, ORCARDES, CROATIA, TwinsUK, BRIGHT, PREVEND. Other cohorts will be contacted for replication.

Phenotype:

- QRS complex duration from ECGs conducted during the ARIC first visit.

    a. Exclusions
        i. Non-Whites
        ii. No ECG with QRS duration
        iii. Atrial fibrillation on baseline ECG
        iv. History of Myocardial Infarction or Heart failure
        v. QRS>120
        vi. WPW
        vii. Pacemaker
        viii. Class I and class III anti-arrhythmic medication

    b. Covariates
        i. Linear adjustment for age.
        ii. Gender
        iii. Study site / cohort as relevant (in ARIC and CHS)
        iv. Height
        v. BMI

Analysis:

- Additive genetic model of autosomal SNPs

- Minor and major alleles consistent across cohorts for each SNP
- Linear regression of QRS-interval on genotype dosage (both typed and imputed SNPs) in study specific analyses.
- Adjustment for the following covariates (see above as well): age, gender, height, BMI, study site/cohort if relevant

Meta analysis

- Inverse variance weighted meta-analysis with genomic control per study
- Absolute threshold of P<5x10E-8 for declaring genome wide significance

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? _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

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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X_ Yes ____ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
X B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.03, 2007.02)

*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.**

REFERENCES

Bogioanni S, et al. Relation of QRS duration to mortality in a community-based cohort with hypertrophic cardiomyopathy. Am J Cardiol 2007;100:503-6.

Desai AD, et al. Prognostic significance of quantitative QRS duration. Am J Med 2006;119:600-6.

Holm H, et al. Several common variants modulate heart rate, PR interval and QRS duration. Nat Genet 2010 (advanced online publication).

Wang NC, et al. Clinical implication of QRS duration in patients hospitalized with worsening heart failure and left ventricular ejection fraction. JAMA 2008;299:2656-66.