ARIC Manuscript Proposal# 1613

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


b. Abbreviated Title: Tri-Tetracyclic-Gene GWAS of QT (CHARGE)

2. Writing Group: Eric A. Whitsel, Christy L. Avery, Til Stürmer (and attempting to maintain symmetry across contributing cohorts), other members of the CHARGE Drug-Gene GWAS Consortium, as well as other interested members of the ARIC ECG Phenotype Working Group.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

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3. Timeline:
Statistical analyses: February 2010 – March, 2010
Manuscript preparation: April, 2010 – May, 2010
Manuscript revision: May, 2010 – Jun, 2010
Manuscript submission: Jun, 2010

4. Rationale:
Repolarization is an active process by which differences in cation concentrations across cell membranes return to their resting levels. The duration of the QT interval (QT) on the resting standard twelve-lead electrocardiogram provides useful information about its temporal dimensions in the ventricular myocardium. This measure has attracted epidemiologic and regulatory scrutiny because abnormalities of the electrophysiological mechanisms underlying its prolongation predispose to a polymorphic form of ventricular tachycardia, torsades de pointes, and sudden cardiac death. Pharmacologic and genetic causes of such abnormalities have been identified. For example, the University of Arizona Center for Education and Research on Therapeutics (UAZ CERT) maintains a publicly accessible, U.S. AHRQ-sponsored list of drugs possessing a definite or possible risk of QT-related torsades, including anti-arrhythmic, anti-psychotic and anti-infective
agents (1). The National Human Genome Research Institute (NHGRI) also catalogues the
discovery of common genetic variants influencing the distribution of QT, including NOS1AP (2-
10). However, few studies have used genome-wide association methods to help identify genetic
variants that may modify the QT-prolonging effects of common treatments, e.g. with tricyclic or
tetracyclic antidepressants (11). Additional research on tri- and tetracyclic anti-depressant-gene
interactions with QT is therefore warranted.

5. Main Hypotheses/Study Questions:
To examine tri-tetracyclic-gene interactions as they relate to time-domain ECG measures of
ventricular repolarization of greatest clinical, pharmaceutical and regulatory interest.

6. Design and Analysis:
Overview
The goal of the proposed analysis is to systematically examine within a common working group
resting, standard twelve-lead ECG measures of ventricular repolarization as they relate to
interactions between tri-tetracyclic anti-depressants and genes in the CHARGE consortium. The
consortium was formed to facilitate GWAS meta-analyses and replication opportunities among
multiple large population-based prospective cohort studies, including the Age, Gene/Environment
Susceptibility (AGES) -- Reykjavik Study, the Atherosclerosis Risk in Communities Study
(ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), and the
Rotterdam Study (RS). HealthABC (HABC), which has had GWAS data since June 2009, recently
joined the effort. With genome-wide data on more than 40,000 participants (>5000 of them
African Americans), this collaboration represents a unique resource for evaluating drug-gene
interactions and ventricular repolarization in the “real world” of community-based studies.

The general approach is first to conduct within-study analyses of the association between
phenotype and genotype for each of the 2.5 imputed autosomal CEPH HapMap SNPs and then to
combine the findings from the within-study analyses by the method of meta-analysis. Imputation
for the African-American populations requires data available through the extended HapMap
project. Analyses will be conducted separately for the major ethnic groups (European and African-
Americans). Use of GWAS data in African-Americans will follow CARE procedures.
To maximize power in the face of infrequent prescription, several initial strategies are proposed.
The first involves working with all tri-tetracyclics at visit 1, tabulated below:

<p>| TRI-TETRACYCLIC ANTI-DEPRESSANT USE @ ARIC V1 BY YEAR, THERAPEUTIC SUBCLASS &amp; MEDICATION |</p>
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</table>
If sample sizes are insufficient to support the cross-sectional analyses described below, triti-tetracyclic-gene interactions will be examined by leveraging e.g. (i) more stringent minor allele frequency (MAF) filters, (ii) the availability of repeated ECG and drug exposure measures over time in longitudinal models, or (iii) a better asymptotic approximator being finalized by our collaborators on the CHARGE Analysis Committee.

**Phenotype**

QT, maximum QT interval duration (ms) across all twelve leads

**Drug exposure definition**

Tri- or tetracyclic anti-depressant use (yes/no)

**Inclusions**

Consenting participants, GWAS data, QT data

**Exclusions**

Poor quality ECG, pacemaker, QRS > 120 ms, atrial fibrillation, 2° or 3° AV block or heart failure

**Exposure**

Additive genetic model of inheritance

**Model**

We propose selecting from two candidate analysis strategies on the basis of available sample size. Adopting longitudinal methods, using repeated measures, and establishing additional collaborations with other studies or consortia that have comparable data may therefore be helpful. The first strategy involves ordinary least squares (OLS) regression of the phenotype. The second involves using generalized estimation equations (GEE) among all participants with genotype data and at least one measurement of the phenotype. The OLS and GEE models are given by

\[ Y_{ij} = \beta_0 + \beta_1 I_{ij} + \beta_2 SNP_i + \beta_3 I_{ij} \times SNP_i + \beta_4 C_{ij}, \]

where \( Y_{ij} \) is the phenotype for the \( i^{th} \) participant at the \( j^{th} \) visit, \( \beta_0 \) is the intercept, \( I_{ij} \) is an indicator of medication use (1,0), \( SNP_i \) is the genetic variant of interest, and \( C_{ij} \) is a vector of covariables. The parameter of interest is \( \beta_3 \), the multiplicative interaction term.

**Adjustments**

Cross-sectional framework: age (yr), gender, where RR = median RR interval duration (s) across all twelve leads (ms), 3-level UAZ-CERT classification of non-tricyclic / non-tetracyclic QT-prolonging medications (as defined in ARIC MS# 1556), and center

Longitudinal framework: + controls for confounding by indication

**Meta-Analysis**

Fixed effects

**Genome-Wide Significance Level**

\[ 1 \div \text{number of tests} \]

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 ICTDER04 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 ICTDER04 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?
8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER04 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.csect.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)?
Manuscript proposals #1434 (Arking, “GWA and candidate gene studies for sudden cardiac death”), #1152 (Post, “Genomic predictors of sudden cardiac death”), and MS# 1556 (Whitsel, “QT-Prolonging Drug-Gene Interactions and Ventricular Repolarization: the CHARGE Drug-Gene GWAS Consortium”) are related to this proposal. However, #1434 and #1152 focus on sudden cardiac death and main effects of selected SNPs. Moreover, neither focuses on drug-gene interactions as they relate to the QT interval or proposes collaboration within the CHARGE consortium. #1556 focuses on UAZ-CERT-classified QT-prolonging medications, which include some, but not all tri-tetracyclic anti-depressants, the exclusive focus of this proposal. Although this proposal is distinct from #1434, #1152 and #1556 for these reasons, we are already collaborating with investigators named in these manuscript proposals.

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

_X_ A. primarily the result of an ancillary study (AS #2009.10; #2007.02; #2006.03)
___ 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/

The following acknowledgment will appear in the published manuscript

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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