

ARIC Manuscript Proposal #1712

PC Reviewed: 11/9/10

SC Reviewed: _____

Status: A

Status: _____

Priority: 2

Priority: _____

1a. Full Title: Thiazide Diuretic-Gene Interactions and Ventricular Repolarization: the CHARGE Drug-Gene GWAS Consortium

b. Abbreviated Title: Thiazide-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: October, 2010 – December, 2010

Manuscript preparation: January, 2011 – February, 2011

Manuscript revision: March, 2011 – April, 2011

Manuscript submission: April, 2011

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 (1), including the thiazide-like diuretic, indapamide (2). The National Human Genome Research Institute (NHGRI) also catalogues the discovery of common genetic variants influencing the distribution of QT, including *NOS1AP* (2-11). 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 thiazide or thiazide-like diuretics.

Having said that, an unexpected excess of coronary heart disease mortality, primarily sudden death, occurred among special-intervention hypertensive men with electrocardiographic abnormalities who had

received high-dose diuretic therapy in the Multiple Risk Factor Intervention Trial (12), and in a case-control study, the risk of primary cardiac arrest was strongly related to dose of thiazide diuretic (13). Moreover, in a cross-over randomized trial study, hydrochlorothiazide but not amlodipine, bisoprolol or losartan was associated with myocardial repolarization abnormalities (14). In the Cardiovascular Health Study, diuretic use, primarily thiazide diuretics, was a strong predictor of QTc interval even after adjustment for potassium level, female sex and other confounders (15). Additional research on thiazide diuretic-gene interactions with QT is therefore warranted.

Main Hypotheses/Study Questions:

To examine thiazide diuretic-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 thiazide diuretics 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, as have several other cohorts. 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 thiazide diuretics at visit 1, tabulated below:

**THIAZIDE AND THIAZIDE-LIKE DIURETIC USE @ ARIC V1
BY YEAR, THERAPEUTIC SUBCLASS & GENERIC INGREDIENT**

GENERIC / BRAND NAME MEDICATION	YEAR					
	1986	1987	1988	1989	1990	ALL
THIAZIDE & THIAZIDE-LIKE DIURETICS						
> BENDROFLUMETHIAZIDE	0	8	10	3	1	22
> CHLOROTHIAZIDE	0	11	10	8	0	29
> CHLORTHALIDONE	4	109	97	95	5	310
> HYDROCHLOROTHIAZIDE	16	640	781	824	42	2303
> INDAPAMIDE	1	11	15	34	3	64
> METHYLOTHIAZIDE	0	19	21	22	0	62
> METOLAZONE	1	5	5	17	0	28
> QUINETHAZONE	0	0	2	0	0	2
> TRICHLORMETHIAZIDE	0	2	0	2	0	4
> BENZTHIAZIDE	0	1	1	0	0	2
> CYCLOTHIAZIDE	0	1	0	0	0	1
> POLYTHIAZIDE	0	2	1	1	1	5
> HYDROFLUMETHIAZIDE	0	4	1	1	0	6
> ANY	22	809	940	1002	51	2824

If sample sizes are insufficient to support the cross-sectional analyses described below, thiazide diuretic-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

Use of a thiazide or thiazide-like diuretic (yes/no), in a single or combination preparation, with or without potassium-sparing agents, and with or without potassium supplements

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, loop diuretic use

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, β_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 β_3 , the multiplicative interaction term. A robust variance estimator will be used.

Adjustments

Cross-sectional framework: age (yr), gender, median RR interval duration across all twelve leads (ms), 3-level UAZ-CERT classification of non-thiazide / thiazide-like 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?

☒ 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 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.csc.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 #1556 (Whitsel, “QT-Prolonging Drug-Gene Interactions and Ventricular Repolarization: the CHARGE Drug-Gene GWAS Consortium”), MS #1612 (Whitsel, “Sulfonylurea-Gene Interactions and Ventricular Repolarization: the CHARGE Drug-Gene GWAS Consortium”), and MS #1613 (Whitsel, “Tri- and Tetracyclic Anti-depressant-Gene Interactions and Ventricular Repolarization: the CHARGE Drug-Gene GWAS Consortium”) are related to this proposal. MS #1434 and #1152 focus on sudden cardiac death and main effects of selected SNPs. 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 a single thiazide-like diuretic, the therapeutic class on which this proposal is exclusively focused.

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** (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.csc.unc.edu/aric/forms/>

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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.

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