ARIC Manuscript Proposal # 3125

PC Reviewed: 03/20/2018          Status: _____          Priority: _____
SC Reviewed: __________          Status: _____          Priority: _____

1.a. Full Title: Candidate Gene Study of Thiazide-Gene Interactions on QT interval using ExomeChip data in the CHARGE Drug-Gene GWAS Consortium

b. Abbreviated Title (Length 26 characters): Tz*Gene Interactions & QT

2. Writing Group: Eric A. Whitsel, Christy L. Avery, Til Sturmer, James Stewart, on behalf of Brenton Swenson, Nona Sotoodehnia, the CHARGE Pharmacogenomics Working Group and interested others

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

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4. **Rationale**: Pharmacologically induced prolongation of the QT interval, which can lead to ventricular tachyarrhythmias and sudden death, is a leading cause of withdrawal of medication from the market. Most medications that prolong the QT interval interfere with the IKr potassium channel. The molecular mechanisms are partially known. The most well-described mechanism is blocking of the ion channel cavity of HERG (alpha subunit of IKr channel). Other less common mechanisms include (1) disruption of HERG protein trafficking leading to loss of IKr channels; (2) rescue of SCN5A channel causing increased inward sodium current; and (3) an increase in inward calcium current. Response to a culprit medication is variable and it is unclear why some individuals have marked prolongation of QT interval in response to pharmacologic therapy whereas others do not. Both common and rare variation in cardiac potassium, sodium, and calcium channel genes are associated with QT interval duration. Whether genetic variants in these genes influence a person’s adverse response to pharmacologic therapy is unknown and only recently being explored.

5. **Main Hypothesis/Study Questions**: We hypothesize that both rare (<1% frequency in the population) and common (>1% frequency in the population) exonic and splice genetic variation, found on the Illumina Human Exome chip, account for some of this variability in pharmacologically induced QT prolongation. Specifically, we hypothesize that variation in the genes responsible for the IKr channel, or its sister channel IKs, will interact with QT prolonging medication resulting in more marked prolongation among individuals with certain genotypes. We secondarily will examine variation in any of the sodium and calcium channels responsible for normal action potential formation, and specific cytochrome p450 genes which are involved in the metabolism of QT altering medications. Because these ion channels are comprised of alpha and beta subunits, we will examine the genes that encode these subunits both separately, as well as in a combined gene-group analysis (outlined below).

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)**.

   **Analysis Overview**: Initial analyses will focus on candidate genes and gene combinations. The primary analyses will examine whether exome variation in the IKr and IKs channel genes interacts with medications (detailed below) to influence the QT interval, as most medications that influence QT duration act through the IK channels. The secondary analyses will examine this type of medication-gene interaction in other candidate genes. These candidate genes include other long QT associated genes, medication metabolism genes, and other genes with known involvement in medication-gene interactions. Final (exploratory) analyses will examine interactions exome-wide.

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<thead>
<tr>
<th>Focus of Primary Analysis</th>
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<tbody>
<tr>
<td>KCNH2</td>
<td>SCN5A</td>
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<tr>
<td>KCNE2</td>
<td>CAV3</td>
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<tr>
<td>KCNQ1</td>
<td>ANK2</td>
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<td>SCN4B</td>
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<td>KCNE1</td>
<td>CACNA1C</td>
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<tr>
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Setting / Samples: Studies from the CHARGE consortium with measures of medication use and ECG data from at least one study visit will contribute to these meta-analyses. For studies of related individuals, only one person from each family will be included in the study population.

Phenotype: QT interval duration (ms) on the resting, standard, twelve-lead ECG at Visit 1.

Genotype Data: Data on non-monomorphic exonic variants from the Illumina Human ExomeChip will be used. All results will be coded to the minor allele as determined by CHARGE Joint Calling to ensure consistency across cohorts. The file "recode_all.txt" on the exome chip wiki page will be used to code all variants to the appropriate allele. Analyses will be limited to variants with TRUE for the indicator column “sc_nonsynSplice” in the exome chip SNPinfo file (i.e., variants with “single_func_region” column labeled as “exonic;stopgain”, “exonic;stoploss”, “splicing”, “exonic;splicing; nonsynonymous”, “exonic;splicing;synonymous”, “exonic;splicing”, “exonic; nonsynonymous”, “exonic;splicing;stopgain”, “exonic;splicing;stoploss”).

Medication Data: Thiazide / thiazide-like diuretic use (with or without concomitant use of a potassium-sparing diuretic or potassium supplementation) on the same day as the ECG recording will define participants as thiazide exposed. Exposure to this therapeutic class of medications is common and of interest because it can affect ion channels, potassium levels, and QT interval duration.

Covariates: Age, sex, RR interval duration (ms), center, ancestry principal components, and use of a University of Arizona Center for Education and Research on Therapeutics (UAZ-CERT)-classified definite, probable or conditional QT-prolonging medication

Exclusions: QRS ≥ 120 (or left or right bundle branch block), atrial fibrillation, pacemaker, second or third degree atrioventricular block, heart failure, use of a loop diuretic, and missingness of phenotype, genotype, medication, or covariate data

Analysis: Race-stratified analyses will be performed using the rareGE package available on CRAN using distributed R code that relies on three data matrices: [1] an n x p genotype matrix (Z), [2] an n x 1 phenotype matrix (Y) containing inverse-normal transformed residuals from a model including all covariates except principal components, and [3] an n x q matrix (X) of the thiazide exposure and principal components.

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? ____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.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)?

#1712 (Whitsel, Thiazide Diuretic-Gene Interactions and Ventricular Repolarization: the CHARGE Drug-Gene GWAS Consortium). Published 2017. Note the differentiating focus of the current proposal on exonic variants in candidate genes.

#1556 (Whitsel, QT-Prolonging Drug-Gene Interactions and Ventricular Repolarization: the CHARGE Drug-Gene GWAS Consortium). Note the differentiating focus of #1556 on UAZ-CERT-classified QT-prolonging medications, which include only a single thiazide-like diuretic, the therapeutic class on which the current 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  

___X__  A. primarily the result of an ancillary study (list number* _#2009.10_)  
___  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/

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/  are posted in  http://www.csc.unc.edu/aric/index.php, under Publications, Policies & Forms.  http://publicaccess.nih.gov/submit_process_journals.htm  shows you which journals automatically upload articles to PubMed central.