ARIC Manuscript Proposal #2101

PC Reviewed: 3/12/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Thiazide Diuretic and ACE Inhibitor-Gene Interactions and Serum Potassium Concentration: the CHARGE Drug-Gene GWAS Consortium

b. Abbreviated Title (Length 26 characters): TD & ACEI-Gene GWAS of K+

2. Writing Group:
Writing group members: Whitsel EA, Avery CL, Stürmer T, Boerwinkle E, Del-Aguila JL

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

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3. Timeline:
Anticipated completion is six months once data are available.
4. **Rationale:**

Altered serum potassium (K+) concentrations are well-known adverse effects of thiazide and thiazide-like diuretics (TDs) and occur more frequently among users of these first line antihypertensive agents when compared to other commonly used antihypertensives like beta-blockers (BBs) or calcium-channel blockers (CCBs). Hypokalemic effects of TDs have been implicated in the development and progression of coronary heart disease, diabetes, life-threatening arrhythmia, and sudden death. Though less common, hyperkalemic effects of angiotensin-converting enzyme inhibitors (ACEIs) have also been associated with increased risk of cardiovascular disease mortality among hypertensive patients. For example, a recent report from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial demonstrated that hypokalemia incidence was higher in the chlorthalidone (TD) group versus the amlodipine (CCB) and lisinopril (ACEI) groups: 12.9% vs. 2.1% and 1.0%, respectively. To the contrary, hyperkalemia incidence was higher in the ACEI versus TD and CCB groups: 3.6% vs. 1.2% and 1.9%.

Pharmacogenetic studies of intermediate traits (such as serum K+ concentrations during antihypertensive treatment) may help identify risk loci for hyper and hypokalemia, yet few studies have been performed to date. To help fill this gap, we propose collaboration within a larger effort examining gene-drug interactions in the Cohorts for Heart and Aging Research in Genomic Epidemiology pharmacogenomics working group (CHARGE-PWG). The CHARGE-PWG consists of >70,000 participants predominantly of European American (EA) and African American (AA) descent. CHARGE was formed to facilitate genome-wide association study (GWAS) meta-analyses and replication opportunities among multiple, large, population-based, prospective cohort studies with high quality drug, phenotype, and large scale genomics data. Participating cohorts with available serum K+ data in either EAs or AAs include the Cardiovascular Health Study (CHS), Rotterdam Study (RS), Atherosclerosis Risk in Communities (ARIC) study, Hypertension Genetic Epidemiology Network (HyperGEN), Jackson Heart Study (JHS), and the Genetics of Hypertension Associated Treatment (GenHAT, ancillary to ALLHAT) study. Using these data, we will identify potential pharmacogenetic risk variants in observational, epidemiological cohorts with available measures of serum K+, genome-wide genetic data, and antihypertensive medication data. Results will be replicated in an antihypertensive clinical trial (ALLHAT/GenHAT) with available data on serum K+ measured 1 year after randomization to treatment.

5. **Main Hypothesis/Study Questions:**

**Hypothesis 1.** Common genetic variants modify the association between TD use and serum K+ concentration.

**Hypothesis 2.** Common genetic variants modify the association between ACEI or angiotensin II receptor blocker (ARB) use and serum K+ concentration.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary**
Overview.

Our goal is to use ARIC visit 1 and 2 data to examine interactions between use of TD or ACEI and genes as they relate to serum K+ concentrations. Included participants will have used a TD in a single or combination preparation without concomitant use of an ACEI or ARB as assessed by the medication inventory OR will have used an ACEI or ARB, in a single or combination preparation without concomitant use of a TD. We will use ARIC genotyping data to identify genetic modifiers of the association between TD or ACEI and serum K+ concentration.

Following the CHARGE PWG meta-analysis protocol, we will conduct within-study, race/ethnicity-stratified longitudinal analyses (harnessing repeated drug and K+ measures) and meta-analytically combine them within race-ethnicity across cohorts.

Validity of Pharmacogenomics Research Using Non-Experimental Data

Non-experimental data from ARIC are well-suited for the investigation of pharmacogenomic effects when compared with clinical trials, which can have a run-in phase to exclude participants experiencing early manifestations of drug intolerance prior to randomization. Despite these benefits, we note that the drug-SNP interaction models used to evaluate genetic susceptibility to medications in the context of non-experimental studies may be prone to bias and error, which remain incompletely characterized. In previous simulations, we found that confounding by indication does not appreciably affect cross-sectional, non-experimental pharmacogenomic studies. However, effects on longitudinal models and the influence of measurement error, duration of use, bias, type I error, and statistical power have yet to be quantified. Therefore, we have extended the simulations to accommodate repeated assessments of exposure and outcome. Results from these simulations will inform interpretation of results and selection of the most valid statistical approach.

Study population & Inclusion/Exclusion criteria. The population will include EA and AA men and women with GWAS data, medication data and a serum K+ concentration at visit 1 or 2. Participants will be excluded for the following reasons:
- Non-consent
- Not treated for hypertension
- Missing serum K+
- Treated with any loop diuretic
- Treated with any K+ sparing diuretic
- Treated with ACE or ARB and thiazide in single or combination preparation
- Treated with an aldosterone antagonist
- Presence of renal or heart failure

Drug exposure Definition.

1. **Thiazide**
   a. Thiazide use (yes/no) on the day of serum K+ measurement, i.e. use of a thiazide or thiazide-like diuretic in a single or combination preparation without concomitant use of an ACEI or ARB versus use of another
antihypertensive agent (CCB, alpha-blocker, BB, centrally acting agent, and/or direct vasodilator) as assessed by medication inventory.

2. **ACEI**
   a. ACEI use (yes/no) on the day of serum K+ measurement, i.e. use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, in a single or combination preparation without concomitant use of a thiazide versus use of another antihypertensive agent (CCB, alpha-blocker, BB, central acting agent, and/or direct vasodilator) as assessed by the medication inventory.

**Genetic exposure.** Additive genetic model, ~2.5 million imputed (dosage) SNPs.

**Phenotype:** Serum K+ Concentration.

**Analysis**

1. Cross-sectional (race stratified)

   **Model:** \[ Y_i = \beta_0 + \beta_E I_i + \beta_{G}\text{SNP}_i + \beta_{G:E}\text{SNP}_i + \beta_4 C_i, \]

   where \( Y_i \) is the log-transformed outcome for the \( i^{th} \) participant, \( \beta_0 \) is the intercept, \( I_i \) is an indicator for drug use, \( \text{SNP}_i \) is the (dosage of the) genetic variant, and \( C_i \) is the vector of adjustment variables. The primary parameter of interest is \( \beta_{G:E} \).

   **Covariates:** Age, sex, body mass index, concomitant use of a K+ supplement (yes/no), race-specific principal components and study site.

   **Estimation:** Linear regression with robust standard errors

   The initial strategy is to longitudinally model repeated outcomes and thereby facilitate estimation of interactive drug-SNP effects by increasing power using methods we have identified, tested and applied to large-scale genomic data in the CHARGE PWG over the last two years under ARIC AS#2009.10. The strategy relies on conventional generalized estimation equations (GEE). Although other structures can be accommodated, an independence correlation structure will be used in this context to ensure consistency of the GEE estimates in the presence of time-varying covariates, and protect against potential bias related to the putative effects of past K+ concentrations on future medication use.\(^9,10\) Pan and Wall’s small-sample GEE extension\(^11\) of Satterthwaite’s method of approximating the degrees of freedom (df)\(^12\) associated with the \( t \) reference distribution will be implemented in R using the bossWithdf package.

**Meta-analysis.**

We will follow the meta-analysis protocol proposed by the CHARGE-PWG. Briefly, race-specific, fixed-effects, inverse variance-weighted meta-analysis will be used. Cross-sectional estimates from a minority of cohorts may contribute to meta-analysis. When that is the case and/or Satterthwaite’s df is unavailable, then the df will be estimated as two times the SNP-specific product of the number of independent observations of exposure to the drug, minor allele frequency, imputation quality, and probability of drug exposed.

**Genome-wide Significance Level.** \( 0.05 \div \text{number of tests} \)
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?
      ____ 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.c.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 Thiazide Diuretic-Gene Interactions and Ventricular Repolarization: the
   CHARGE Drug-Gene GWAS Consortium. However, its focus is on QT interval
duration, not serum potassium. Moreover, the authors are members of the same
   CHARGE pharmacogenomics working group.

   #1925 Fasting Glucose, Insulin and Thiazide Diuretic: Gene Interactions. However, its
   focus is on the glucose and insulin phenotype, not serum potassium. Moreover, the
   authors are members of the same CHARGE pharmacogenomics working group.

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.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/ are posted in http://www.cscc.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.

References
7. Psaty BM, O'Donnell CJ, Gudnason V, Lunetta KL, Folsom AR, Rotter JI, Uitterlinden AG, Harris TB, Witteman JC, Boerwinkle E. Cohorts for heart and aging research in genomic epidemiology (charge) consortium: Design of


