ARIC Manuscript Proposal #2656

PC Reviewed: 10/13/15 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Pharmacogenomics of apparent treatment resistant hypertension

   b. Abbreviated Title (Length 26 characters): Pharmacogenomics of aTRH

2.   Writing Group: Eric A. Whitsel, Christy L. Avery, Til Sturmer, James D. Stewart and attempting to maintain symmetry across contributing cohorts, other members of the CHARGE Pharmacogenomics Working Group

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

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3.   Timeline:
   Statistical analyses: October 2015 – December, 2015
   Manuscript preparation: January, 2016 – March, 2016
   Manuscript revision: April, 2016 – June, 2016
   Manuscript submission: July, 2016

4.   Rationale:

Treatment-resistant hypertension (TRH) is an extreme form of elevated blood pressure characterized by (i) use of three different antihypertensive medication classes and blood pressure above goal or (ii) use of ≥ four medication classes, regardless of blood pressure control.[1] When anti-hypertensives are prescribed at optimal doses, a diuretic is in the treatment regimen, and pseudo-resistant hypertension (characterized by poor blood pressure measurement technique, medication non-adherence, and / or white-coat hypertension) is excluded, misclassification of TRH can be minimized.[1]

The prevalence and incidence of TRH have only recently been reported although overall, population-based studies cannot account for all the factors required to define true TRH.[2-5] Recognizing such limitations, Egan et al. coined the term, *apparent treatment resistant hypertension* (aTRH). Using data from NHANES 2005-2008, they estimated that 11.8% of hypertensive U.S. adults have aTRH;[3] identified risk factors for it (age, obesity, poor kidney function, and African American race); and found that African-Americans were two times more likely to be affected. Other groups have reported similar general population-based prevalence estimates and noted increased risk among African-Americans,[4-5] but until recently, few prospective studies of cardiovascular disease among persons with aTRH and less severe forms of hypertension have been published.[2]

Using Kaiser Permanente data, Daugherty *et al.* reported that cardiovascular disease risk was 50% higher in TRH cases ($P < 0.001$) than in non-resistant hypertensive comparators. The fact that the study was conducted among persons with incident hypertension at baseline who were clinically managed following standarized Kaiser Permanente protocols bolsters support for unique pathophysiologic mechanims in TRH above and beyond accumulated blood pressure burden, i.e. damage due to chronic hypertension.[6]

Although two candidate gene studies have reported that the AGT M235T allele is associated with aTRH,[7-8] no genome-wide association study (GWAS) of aTRH has been published, to our knowledge. Low sample size among individual epidemiological cohorts has likely hampered such efforts. We therefore propose genetic studies to shed light on potential mechanisms of disease underlying aTRH.

Our proposal to do so is part of a larger effort examining pharmacogenetic associations in the CHARGE consortium, formed to facilitate GWAS meta-analyses and replication opportunities among multiple, large, population-based prospective cohort studies.

5.   Main Hypothesis/Study Questions:

Hypothesis A genome-wide analysis of common genetic variants will uncover novel gene variants associated with aTRH.

6. Design and analysis

Design We will take a period prevalence approach to cohort-specific analyses and then meta-analytically combine results across cohorts (see below).

Time Period Visits 2-4, representing the era of increasing diversity and availability of anti-hypertensive classes, which are alphabetically listed here: aldosterone receptor blockers, alpha blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, central acting agents, diuretics, and vasodilators.

Exposures Autosomal, single nucleotide polymorphisms (SNPs) imputed to the 1000G reference panel.

Outcome The aTRH outcome will rely on the following information, where n is the count of visits with available blood pressure and medication data: (i) mean systolic blood pressure across visits (**SBP** = $\sum_{i=1}^{n} SBP_i$ / n for visit i = 1 to n), (ii) mean diastolic blood pressure across visits (**DBP** = $\sum_{i=1}^{n} DBP_i$ / n for visit i = 1 to n), (iii) mean number of anti-hypertensive medication classes used across visits (**Classes** = $\sum_{i=1}^{n} number_i$ / n for visit i = 1 to n), and (iv) proportion of visits at which the participant was treated with a diuretic (**Proportion**). aTRH case status will be defined as follows, allowing participants to contribute data from one to three visits during follow-up:

aTRH = 1 if *any one* of the following conditions hold:
((SBP > 140 or DBP > 90) and (Classes ≥ 3.0 and Classes ≤ 3.99 and Proportion ≥ 0.5)) or
(Classes ≥ 4.0 and Proportion ≥ 0.5)

aTRH = 0 (normotensive control group 1) if *all* of the following conditions hold:
SBP ≤ 140 and
DBP ≤ 90 and
Classes = 0

aTRH = 0 (treatment-responsive control group 2) if *all* of the following conditions hold:
SBP ≤ 140 and
DBP ≤ 90 and
Classes ≥ 1.0 and
Classes ≤ 2.0

Covariates Mean age ($\sum_{i=1}^{n} Age_i$ / n for visit i = 1 to n), sex, center, principal components.

Exclusions The following will identify visits and / or participants for exclusion: (i) unavailable blood pressure data, (ii) unavailable medication data, (iii) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2, (iv) body mass index (BMI) > 40 kg/m^2), or (v) aTRH = 1, but one anti-hypertensive is not a diuretic at ≥ 50% of the visits

Analysis European and African-American race-stratified, logistic regression with model-based standard errors repeated for control group 1 and control group 2, where: $\ln(\frac{Y_i}{1-Y_i}) = \beta_0 + \beta_1 SNP_i + \beta_2 C_i$, and Y_i is the aTRH indicator for the ith participant, β_0 is the intercept, SNP_i is the imputed dosage of the genetic variant, and C_i is the vector of covariates. The primary parameter of interest is β_1, which will be subjected to inverse variance-weighted, fixed-effects meta-analysis among cohorts. A *P* value < 5×10^{-8} will be used to identify 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? ____ 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.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)?
#2461 Pharmacogenonomics of non-response to blood pressure lowering therapies in the
        CHARGE Consortium (Whitsel)
#2438 Drug*Gene GWAS of Blood Pressure Response to Anti-Hypertensives in the CHARGE
        Consortium (Whitsel)
#1870 Antihypertensive drug-gene interactions and cardiovascular events (Avery)
#1513 Genome-wide association study of blood pressure using genotype-by smoking and
        genotype-by-alcohol intake interactions: the ARIC Study (Franceschini)
#1484 A gene-environment interaction approach to genome-wide association analysis of blood
        pressure in the ARIC study: gene-age interactions in European Americans (Shi)
#1412 GWAS for longitudinal blood pressure levels (Ehret)

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)
    ___ 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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

References
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8. Lynch AI, Irvin MR, Davis BR, Ford CE, Eckfeldt JH, Arnett DK. Genetic and adverse health outcome associations with treatment resistant hypertension in GenHAT. *Int J Hypertens.* 2013;2013:578.