ARIC Manuscript Proposal #2461

PC Reviewed: 11/11/14  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Pharmacogenomics of non-response to blood pressure lowering therapies in the CHARGE Consortium

b. Abbreviated Title (Length 26 characters): GWAS of BP Non-Response in CHARGE

2. Writing Group: Eric A. Whitsel, Christy L. Avery, Til Stürmer, Eric Boerwinkle, James D. Stewart, Chi-Yu (Jack) Yen 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_

First author: Eric A. Whitsel
University of North Carolina at Chapel Hill
Departments of Epidemiology and Medicine
Cardiovascular Disease Program
CVS Center, Suite 301-B
137 East Franklin Street
Chapel Hill, NC 27514
(T) 919-966-3168 or 1967
(F) 919-966-9800
eric_whitsel@unc.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Christy L. Avery
University of North Carolina at Chapel Hill
Department of Epidemiology
Cardiovascular Disease Program
CVS Center, Suite 301-A
137 East Franklin Street
Chapel Hill, NC 27514
(T) 919-966-4312
(F) 919-966-9800
christy_avery@unc.edu

3. Timeline:
   Statistical analyses: November 2014 – February, 2015
   Manuscript preparation: March, 2015 – April, 2015
   Manuscript submission: August, 2015
4. **Rationale:**
Only 30% of patients with hypertension are treated to target,\(^1\)\(^-\)\(^2\) a phenomenon often attributed to e.g. noncompliance, inadequate dosing, drug intolerance, and/or resistance. Such heterogeneity of response to antihypertensive therapy has been noted by investigators for more than half a century,\(^3\)\(^-\)\(^4\) prompting efforts to identify factors underlying it. To date, these efforts have focused on e.g. phenotypic and biochemical factors such as age, race, renin, or insulin sensitivity,\(^5\)\(^-\)\(^7\) but none of them have been extensively employed in the clinical setting. However, pharmacogenomics holds promise for identifying genetic biomarkers of antihypertensive non-response with potential therapeutic implications. We therefore plan to investigate the genetics of non-response to blood pressure-lowering therapies within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, including the Atherosclerosis Risk in Communities study.

5. **Main Hypothesis/Study Questions:**
Among participants treated with a given class of antihypertensive (see below), are genetic variants associated with non-response to treatment?

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).**

**Design**
The general approach is to conduct within-cohort analyses of drug-gene interactions for autosomal single nucleotide polymorphisms (SNPs) imputed to the 1000G reference panel and then meta-analytically combine the findings across cohorts.

**Anti-Hypertensive Classes**
1. Beta Blockers (BB)
2. Calcium Channel Blockers (CCB)
3. Angiotensin-Converting Enzyme Inhibitors (ACE) including receptor antagonists
4. Diuretics (DIU) thiazide diuretics only, not loop diuretics

**The Non-Response Phenotype**
Within each participant subgroup defined by Anti-Hypertensive Classes 1-4 (above), the Non-Response Phenotype (below) will be based on systolic blood pressure (SBP, mm Hg) and dichotomized according to whether a specific treatment target has been reached:
1. Non-response: not treated to target (SBP ≥ 150 mm Hg) = 1
2. Response: treated to target (SBP ≤ 139 mm Hg) = 0
3. Excluded: SBP = 140-149 mm Hg

The simple phenotypic definition and exclusion reflect the imperfect reliability of SBP (intra-class correlation coefficient ≈ 0.75), which usually varies around its true value (±2-5 mm Hg), and therefore allow for greater distinction between non-response and response.

**Inclusions**
1. European or African-American ancestry
2. Available GWAS data passing quality control
3. Treated with one of the listed Anti-Hypertensive Classes (above)
4. Available Non-Response Phenotype (above)
5. Available covariables (below)

**Covariables**
1. Age (visit-specific)
2. Sex
3. Center
4. Principal components for ancestry

**Analyses of Non-Response**
1. To BB
2. To CCB
3. To ACEI
4. To DIU

**Models**
Cross-sectional, logistic regression models of the Non-Response Phenotype at Visit 1, by race.
\[
\log \left( \frac{\hat{p}}{1-\hat{p}} \right) \sim \beta_0 + \beta_1SNP_i + \beta_2C_i, \quad \text{where:}
\]
- \( \hat{p} \) = probability of non-response
- \( \beta_0 \) = intercept
- \( \beta_1 \) = increase in log odds of non-response per unit increase in SNP dosage
- \( SNP_i \) = SNP dosage
- \( \beta_2 \) = increase in log odds of non-response per unit increase in covariate \( i \)
- \( C_i \) = vector of covariates

**Quality Control & Meta-Analysis**
We will follow CHARGE quality control and meta-analysis protocols. Briefly, quality control may include e.g. filtering of variants based on imputation quality or minor allele frequency, applying genomic control, reviewing results of the pairwise comparisons separately using Manhattan and QQ plots, etc. Race-specific, fixed-effects, inverse variance-weighted meta-analysis will be used to combine information across studies.

**Genome-wide threshold**
P<5x10^{-8}

7.a. Will the data be used for non-CVD analysis in this manuscript?
No X Yes ___

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?  
  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 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.cscce.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)?

#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.cscce.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.cscce.unc.edu/aric/index.php, under
Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

**References**