ARIC Manuscript Proposal #2438

PC Reviewed: 9/9/14  Status: A  Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title: Drug*Gene GWAS of Blood Pressure Response to Anti-Hypertensives in the CHARGE Consortium

b. Abbreviated Title (Length 26 characters): Drug*Gene GWAS of BP 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_

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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).

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3. Timeline:
Statistical analyses: November 2014 – February, 2015
Manuscript preparation: March, 2015 – April, 2015
Manuscript submission: August, 2015
4. **Rationale:**
Hypertension is a therapeutically modifiable cardiovascular disease risk factor, but therapeutic response to antihypertensive medications varies within populations. We recently examined pharmacogenomic sources of such variation in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT; [http://www.ascotstudy.org](http://www.ascotstudy.org)), a randomized control trial that included 19,257 patients with hypertension randomized at baseline to a calcium channel blocker (amlodipine 5 mg) or beta blocker (atenolol 50 mg). Having done that, our current aim is to extend that analysis to the larger CHARGE Drug-Gene Consortium of observational cohorts, including the Atherosclerosis Risk in Communities study. The proposed extension involves examining whether genetic variants modify associations between use of antihypertensive monotherapies and their blood pressure-lowering responses.

5. **Main Hypothesis/Study Questions:**
Do genetic variants modify associations between use of antihypertensive monotherapies and their blood pressure-lowering responses?

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 each of the 2.5 million imputed autosomal single nucleotide polymorphisms (SNPs) and then meta-analytically combine the findings across cohorts.

**Blood Pressure Phenotypes**
1. Systolic Blood Pressure (SBP, mmHg)
2. Diastolic Blood Pressure (DBP, mmHg)

**Anti-Hypertensive Monotherapies**
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

**Binary Coding of Monotherapies**
Pairwise comparisons of the above monotherapies will be examined separately using binary coding of drug exposures:
1. BB (=1) vs. CCB (=0)
2. BB (=1) vs. ACE (=0)
3. BB (=1) vs. DIU (=0)
4. CCB (=1) vs. ACE (=0)
5. CCB (=1) vs. DIU (=0)
6. ACE (=1) vs. DIU (=0)

**Inclusions**
1. GWAS data available that passed QC
2. European or African-American ancestry
3. Anti-hypertensive treated only
4. Anti-hypertensive monotherapy at each visit specified by a particular pairwise comparison, noting that follow-up will stop and only those measurements from within a treatment period will be included when treatment is (i) stopped at a subsequent visit, (ii) increased from mono to combination therapy at a subsequent visit, or (iii) switched at a subsequent visit from one to another monotherapy not being examined by a given pairwise comparison. In (iii), subsequent measures will instead contribute to pairwise comparisons of the other monotherapy, such that participants can contribute to analyses representing more than one monotherapy if they transition between monotherapies over time. However, participants switching monotherapy at a subsequent visit within a given pairwise comparison will remain in the analysis, and the coding of their drug exposure will change from 1 to 0, or vice versa, to reflect the transition.
5. BP phenotypes available within periods of monotherapy from visit 1, 2, 3 and / or 4, where the number of measurements may vary by participant.
6. Availability of covariables

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

**Model**
For each blood pressure phenotype, we will perform the aforementioned pairwise comparisons, by race. The initial strategy will be to longitudinally model the average of repeated outcomes and thereby facilitate estimation of effects by increasing power using methods we have identified, tested and applied to large-scale genomic data in the CHARGE PWG over the last several years under ARIC AS#2009.10. The strategy relies on conventional generalized estimation equations (GEE) methods. 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 blood pressures on future medication use. Pan and Wall's small-sample GEE extension of Satterthwaite's method of approximating the degrees of freedom (df) associated with the $t$ reference distribution will be implemented in R using the bossWithdf package.

$$E[Y_{ij}] = \beta_0 + \beta_D I_{ij} + \beta_G SNP_i + \beta_{GD} I_{ij} SNP_i + \beta_C C_{ij},$$

where:
- $Y_{ij}$ is the blood pressure of the $i$th participant at the $j$th visit
- $\beta_0$ is the intercept
- $I_{ij}$ is the binary indicator for the monotherapies being compared
- $SNP_i$ is the dosage of the single nucleotide polymorphism
- $C_{ij}$ is the 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 unless early departure of test statistics from the null distribution occurs; then a t-distribution approach will be used. P-values will be recalculated by applying a t reference distribution to the drug-SNP interaction estimates of β (standard error), and then meta-analyzed using a weighted Z-statistic, with weights based on the SNP imputation quality multiplied by the estimated number of independent observations exposed to the drug.

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.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)?
#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)
A gene-environment interaction approach to genome-wide association analysis of blood pressure in the ARIC study: gene-age interactions in European Americans (Shi)
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.