ARIC Manuscript Proposal # 1591

PC Reviewed: 1/12/10  Status: A  Priority: 2
SC Reviewed: _________  Status: ______  Priority: ______

1a. Full Title: Beta blocker Drug-Gene Interactions and Heart Rate: the CHARGE Drug-Gene GWAS Consortium

b. Abbreviated Title: CHARGE Drug-Gene GWAS of RR

2. Writing Group: Christy L. Avery, Eric A. Whitsel, Til Stürmer, Eric Boerwinkle, (and attempting to maintain symmetry across contributing cohorts), other members of the CHARGE Drug-Gene GWAS Consortium, as well as other interested members of the ARIC ECG Phenotype Working Group.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

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3. Timeline:
   Statistical analyses: January 2010 – February, 2010
   Manuscript preparation: March, 2010 – April, 2010
   Manuscript revision: May, 2010 – July, 2010
   Manuscript submission: August, 2010

4. Rationale:

   Electrocardiographic (ECG) measures such as resting heart rate (HR, or equivalently, the RR interval) reflect autonomic control of sinuatrial pacemaker activity, as well as the rate of atrioventricular conduction and repolarization. Elevated HR has been consistently associated with cardiovascular disease morbidity and mortality in patients with pre-existing disease, the latter presumably reflecting increased sympathetic activity. Likewise, interventions for lowering HR have been shown to increase survival, including exercise and beta-blocker use.
Several lines of evidence suggest a genetic component for HR. Family studies have suggested that HR is heritable\textsuperscript{14-16} and population-based candidate gene studies have identified a handful of genetic variants in a few candidate genes influencing phenotypic variation.\textsuperscript{17,18} Findings from meta-analyses of SNP-RR genome-wide association studies across consortia of predominantly Caucasian study populations are also forthcoming or have been published recently.\textsuperscript{19}

Although genetic and environmental foundations for HR have been established, few investigators have examined whether common genetic variants modify the association between beta-blocker use and HR. A large number of genetic polymorphisms have appeared in genes that code for what are now commonly called drug receptors, drug metabolizing enzymes, drug transporters, and drug effector pathways. This is especially relevant given that over the last 50 years, exposure to therapeutic drugs has reached epidemic proportions. Between 1980 and 2005, prescription drug expenditures in the US increased from $12 to $200 billion. This massive population exposure to prescription drugs has provided the opportunity for common drug-gene interactions that may be responsible for some of the 2.2 million adverse drug reactions (ADR) and 106,000 ADR-related deaths that occur each year in the US.\textsuperscript{20} Identifying potential drug-gene interactions is the first step in a translational research effort to use genomics to improve public health. Several applications are emerging in the treatment of breast, colorectal, and lung cancer\textsuperscript{21-25} as well as perhaps hepatitis C.\textsuperscript{26}

The goal of the proposed analysis is to systematically examine within a common working group resting, standard twelve-lead ECG measures of heart rate as they relate to interactions between beta-blocker use and common genetic variants in the CHARGE consortium. The consortium was formed to facilitate GWAS meta-analyses and replication opportunities among multiple large population-based prospective cohort studies, including the Age, Gene/Environment Susceptibility (AGES) -- Reykjavik Study, the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), Rotterdam Study (RS), and HealthABC (HABC). With genome-wide data on more than 40,000 participants (>5000 of them African Americans), this collaboration represents a unique resource for evaluating drug-gene interactions and heart rate in the “real world” of community-based studies.

5. Main Hypotheses/Study Questions:
To examine gene-drug interactions as they relate to ECG measures of heart rate.

6. Design and Analysis:
The approach is first to conduct within-study analyses of the association between phenotype and genotype for each of the 2.5 imputed autosomal CEPH HapMap SNPs and then to combine the findings from the within-study analyses by the method of meta-analysis. Imputation for the African-American populations requires data becoming available through the extended HapMap project. Analyses will be conducted separately for the major ethnic groups (European and African-Americans). At least initially, use of GWAS data in African-Americans will follow CARE procedures.

Outcome. The proposed work focuses on HR (or equivalently, the RR interval) and will be examined in participants without conditions that affect availability or accuracy of HRV measures:
poor ECG quality grades; < 5 or 50% normal-to-normal RR intervals; atrioventricular conduction defects; electronic pacemakers; ventricular ectopy; arrhythmias; or use of digoxin, non-dihydropyridine calcium channel blockers, or sotalol. Participants with prescriptions for ophthalmic β-blocker preparations will be considered non-users.

**Exposures.** SNPs will be evaluated using an additive model of inheritance. β-blocker use will be considered as a binary indicator, excluding sotalol. The approximate prevalence of β-blocker use among CHARGE studies is presented in the table. As shown in the table, we expect to have good power to detect β-blocker-gene interactions across CHARGE studies.

<table>
<thead>
<tr>
<th>Table. Prevalence of β-blocker use among CHARGE studies (%)</th>
<th>AGES</th>
<th>ARIC</th>
<th>CHS</th>
<th>FHS</th>
<th>RS</th>
<th>HABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>02-06</td>
<td>96-99</td>
<td>99-00</td>
<td>98-02</td>
<td>2000</td>
<td>2000</td>
</tr>
<tr>
<td>β-blocker</td>
<td>35</td>
<td>17</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>16</td>
</tr>
</tbody>
</table>

*FHS data from the Offspring cohort, n=3536.

**Model**
We propose using an ordinary least squares (OLS) approach that examines visit 1 cross-sectional RR measures. The OLS model is given by
\[ Y_i = \beta_0 + \beta_1 SNP + \beta_2 Drug + \beta_3 SNP* Drug + \beta_4 C, \]
where \( Y_i \) is RR measured at visit 1, SNP is the genetic variant of interest, Drug is a binary indicator of β-blocker use and C is a vector of covariables that includes age, sex, BMI, prevalent CHD, systolic blood pressure, study site, and principal components for ancestry. The parameter of interest for the fixed effects meta-analysis is \( \beta_3 \).

**Genome-Wide Significance Level.** \( 1 \div \text{number of tests} \)

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 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?

___ 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”?

___ 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)? Manuscript proposal #1483 (Morrison, “Genome-wide association analysis of heart rate identifies novel genetic variants: findings from the RRGEN Consortium”). This manuscript does not focus on drug-gene interactions as they relate to the RR. Although this proposal is distinct from #1483, we invited investigators named in this manuscript proposal to collaborate.

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; #2007.02; #2006.03)
___ 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/

The following acknowledgment will appear in the published manuscript

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12. 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.
REFERENCES


