ARIC Manuscript Proposal # 1483

PC Reviewed: 03/17/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome-wide association analysis of heart rate identifies novel genetic variants: findings from the RRGEN Consortium

b. Abbreviated Title (Length 26 characters): Heart rate GWAS

2. Writing Group:

ARIC writing group members: Alanna Morrison, Alvaro Alonso, Dan Arking, David Couper, Aaron Folsom, Ervin Fox, Ron Prineas, Eric Boerwinkle

Please note that other authors from additional consortium cohorts will be included. The RRGEN Consortium includes 7 cohorts and up to 5 independent replication cohorts are possible. Manuscript authorship will follow the convention of a starred first author (i.e., Alanna Morrison for ARIC) and starred last author (i.e., Eric Boerwinkle for ARIC) from each cohort.

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

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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: Manuscript drafted by the end of March 2009, plan for journal submission by May 2009.

4. Rationale:

The epidemiologic data for the relationship between resting heart rate and cardiovascular outcomes extends over the last 25 years. Resting heart rate has been related to several cardiovascular outcomes[1,2,3] and this association is believed to be independent of other risk factors and clinical parameters.[4,5] Animal model and experimental studies lend evidence for pathophysiological mechanisms linking heart rate and cardiovascular outcomes such as atherosclerosis, arterial stiffness, myocardial infarction, ventricular arrhythmias, left ventricular dysfunction and heart failure.[6] Most consistently, elevated heart rate has been significantly associated with mortality from coronary disease, all-cause mortality and cancer mortality.[2,6] It has been shown that heredity plays a substantial role in the population variation of heart rate.[7,8] Quantitative trait loci have been identified for heart rate in both animal models[9] and humans through linkage studies[10,11] and candidate gene approaches[12], the latter without convincing replication.[13]

The RRGEN Consortium was convened with the goal of utilizing genome-wide association study (GWAS) data to identify genetic variation associated with resting heart rate in the general population. This study is a meta-analysis of seven heart rate GWAS involving 24,712 white individuals of European ancestry. Heart rate is measured as the RR interval duration on the electrocardiogram (ECG). The seven prospective cohort studies comprising the RRGEN Consortium include the Age, Gene, Environment Susceptibility Study (AGES), the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), the Rotterdam Study (RS1) and the Rotterdam Study Extended Cohort (RS2), and the Cooperative Health Research in the Region Augsburg study cohorts F3 (KORA F3) and S4 (KORA S4). Findings will potentially be replicated in five studies: the SardiNIA study, the Study of Health in Pomerania (SHIP) and three population isolate studies (EUROSPAN: Orkney, ERF and MICROS).

5. Main Hypothesis/Study Questions:

Identification of genetic variation associated with resting heart rate among individuals of European ancestry.

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

This manuscript proposal addresses the analysis of ARIC Whites as a part of the RRGEN Consortium. Analysis of ARIC African Americans will be addressed in a separate manuscript proposal as a part of the CARe Consortium.

For this analysis, individuals are excluded if they have prevalent myocardial infarction, heart failure or atrial fibrillation; second or third degree atrial-ventricular block; heart rate below 50 or above 100 beats per minute (RR interval >1200 milliseconds or <600

milliseconds); use of beta-blocking agents, non-dihydropyridine calcium antagonists or digoxin at the moment of phenotype measurement; and presence of a pace-maker if this data was available, or pacemaker activity on the ECG.

In ARIC, RR interval was measured automatically from 12-lead electrocardiograms performed at baseline. Initial ECG processing was done by the Dalhousie ECG program, and processing was later repeated with the 2001 version of the GE Marquette 12-SL program (GE Marquette, Milwaukee, Wisconsin). Utilizing the ECG data from ARIC visit 1 (ECGRAW), RR interval is computed as 60000/ECGRA078. The phenoytpe for the GWAS analysis is the residual resulting from RR interval adjusted for age (V1AGE01), gender and BMI (BMI01).

Analysis

The association between the residuals and ~2.5 million single nucleotide polymorphism (SNP) genotypes will be tested under an additive genetic model using linear regression implemented in the program ProbABEL. Each cohort will individually evaluate their data and the within-study associations will be meta-analyzed across studies. These analyses include only adults of European ancestry. An *a priori* threshold for genome wide significance was set at $\alpha = 5x10^{-8}$.

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
_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)?

None.

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* _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/

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.

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