ARIC Manuscript Proposal #2068

PC Reviewed: 2/12/13 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Exome chip and exome sequencing analyses for BP phenotypes

b. Abbreviated Title (Length 26 characters): Exome chip / squencing BP

2. Writing Group:
ARIC writing group members: Aravinda Chakravarti (convener)
(alphabetical) Eric Boerwinkle, Georg Ehret, Myriam Fornage, Santhi Ganesh, C. Charles Gu, Sharon Kardia, Alanna Morrison, KD Nguyen, DC Rao, Elias Salfati, Xiaofeng Zhu.

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

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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: end of 2013

4. Rationale: Persistently elevated blood pressure (BP), diagnosed as hypertension (HTN), is a major cardiovascular risk factor with a population prevalence of ~30%. A large proportion of individuals with HTN (~97%) have high BP without identifiable cause, termed “essential hypertension”. Because of its frequency we will refer to essential HTN simply as HTN in the following. Pathogenic pathways that lead to HTN remain poorly understood. A distinct fraction of hypertension risk can be attributed to genetic factors and this opens the possibility for genetic investigation to contribute to a better understanding of BP regulation and possible identification of new molecular targets for drug therapy. Since 2009, there has been substantial progress in the identification of genetic variants associated with high BP and HTN, notably driven by multiple contributions of this study group. In total ~43 variants associated with BP have been

identified so far. But a large proportion of the variability of BP and HTN remains unexplained, similar to other phenotypes, and we therefore propose additional experiments that aim at uncovering additional genetic contribution.

The analytical plan outlined here proposes experiments that will follow the scheme of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) analyses: The analyses will be conducted in ARIC first and then, if appropriate, meta-analyzed with results from additional studies from CHARGE, studies beyond CHARGE (CHARGE+), and the International Consortium on Blood Pressure GWAS (ICBP).

Using the datasets from the Illumina Exome chip and datasets from exome sequencing on ARIC blacks and whites, we propose 3 types of experiments:

1) Single marker association analyses
Single markers of a suitable frequency (>~1%, depending on the total sample size) will be analyzed for their association with the phenotype in regression models / logistic models. The phenotypes and covariates are described below.

2) Gene-wide analyses (burden and non-burden tests)
Where single marker cannot be analyzed because of their low frequency, one method currently used has become the analysis of multiple rare markers at the same time. We will use SKAT and T1 tests in their conventional form as well as after weighting for evolutionary conservation. For SKAT both common and rare variants will be combined in the meta stage. Alternatively, we will use meta-SKAT for pooling results from separate analyses of rare variants within defined gene regions for optimal power. Additional methods are under development and will also be applied.

Meta-analysis and/or replication
Meta-analysis will be conducted by inverse variance weighting across the participating studies for single-variants. Meta-analysis of burden tests will also be conducted using methodologies developed or applied by the CHARGE Analysis committee.

Data distribution
In order to permit the different participating centers to contribute optimally to the overall project with their individual interests and specificities, we request that the primary data be distributed by the ARIC DCC or the genotyping laboratory to the following sites: Johns Hopkins, Washington University in St Louis, University of Michigan, and Case-Western Reserve University. Data distribution agreements are not yet in place at all of these sites, but will be in place before work on this manuscript proposal will begin.

5. Main Hypothesis/Study Questions
Genotype data from the exome chip and from exome sequencing can be used to identify additional blood pressure loci that were not discovered using the current datasets with frequent variants.

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: A two stage design followed by meta-analysis/replication analysis is chosen.

Phenotypes: SBP, DBP, MAP, PP levels or HTN status at the first visit.

Model: linear regression (cont. phenotypes), logistic regression (HTN), SKAT, T1, others

Populations: The analyses will include African American and white participants of ARIC.

Genetic model: additive (additional models might be explored)

Transformation: no transform, no scaling.

Covariates: age, age^2, sex, BMI, study-center, principal components if suitable; the phenotypes will be adjusted for the presence of anti-hypertensive treatment (adding 15mmHg to SBP and 10mmHg to DBP in the presence of ≥1 anti-hypertensive therapy).

Exclusions: outliers of the SBP/DBP distribution (>/< +/- 4SD)

Control for multiple comparisons: Bonferroni adjustment

Meta-analysis: Meta-analysis based on the result of each gene of each cohort.

7.a. Will the data be used for non-CVD analysis in this manuscript?
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?
NA
(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?
Yes

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"?
Yes

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?
Yes

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

We are in continuous discussion with ARIC investigators in the BP genetics field are not aware of any overlap with existing projects.

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?
Yes

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

_x__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.03

*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.