ARIC Manuscript Proposal # 1509

PC Reviewed: 5/12/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: ICBP GWAS for BP (SBP and DBP) at first visit

b. Abbreviated Title (Length 26 characters): BP_firstVisit GWAS (ICBP)

2. Writing Group: FEHGAS working group

ARIC writing group members: Georg Ehret, Eric Boerwinkle, Josef Coresh, Dan Arking, Aravinda Chakravarti. Other authors from additional ICBP cohorts. The plan is to maintain symmetry across cohorts.

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

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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: autumn 2009

4. Rationale: Persistent elevated blood pressure (BP), diagnosed as hypertension (HTN), is quantitatively the major cardiovascular risk factor with a population prevalence of ~30%. Pathogenic pathways that lead to HTN remain poorly understood. A distinct fraction of the hypertension risk is genetic and this opens the possibility for genetic investigations to contribute to a better understanding of this trait and possible identification of new molecular targets for drug therapy.

ARIC has recently published a first genome-wide association study (GWAS) on SBP and DBP within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. The corresponding manuscript proposal was named “CHARGE GWAS for BP (SBP and DBP) at first visit”. The total sample size of this consortium including AGES, CHS, FHS, and ERGO is ~25,000.

Several genome-wide significant variants in hypertension genes were identified and replicated in a similar study by a consortium of mainly European cohorts (named “global BP GEN” (GBPGEN)). The total sample size of GBPGEN is similar to CHARGE.

We now propose to draft a manuscript using the data for SBP and DBP combining CHARGE and GBPGEN in a single meta-analysis. The new consortium is termed “International Collaboration for Blood Pressure GWAS” (ICBP-GWAS) and the total sample size of the combined cohorts is ~80,000.

This proposal only covers the data from a meta-analysis of GWAS findings related to a cross-sectional BP assessment (n=8,047 in ARIC). We analyze SBP and DBP at the first ARIC visit (sbpa21 and sbpa22), including a 15/10mmHg treatment correction algorithm.

5. Main Hypothesis/Study Questions:
Additional gene variants can be identified that associate with SBP and DBP at the first ARIC visit increasing the sample size from ~25,000 to ~80,000.

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: Fixed effects meta-analysis of GWAS studies

Participating groups:
Framingham Study
Rotterdam Study (ERGO and ERGO PLUS)
CHS
AGES
17 cohorts from the GBPGEN consortium

Phenotypes: SBP and DBP at first visit

a) Model: Linear regression for cross-sectional analysis
The main analysis will include only self-reported whites (no self-reported African Americans included)

Genetic model: additive.

b) Transform: no transform, no scaling.

c) Covariates: age, age^2, sex, bmi, study-center

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

e) Control for multiple comparisons: Bonferroni adjustment

f) Imputation
Imputation to Hapmap 2.5 M using MACHv1.0.16.

g) Meta-analysis:

Meta-analysis based on 2.5 M observed and imputed SNPs

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
Yes (based on list circulated in July 2008)

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/

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.