ARIC Manuscript Proposal # 1412

PC Reviewed: 08/12/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: GWAS for longitudinal blood pressure levels
b. Abbreviated Title (Length 26 characters): BP_longitudinal GWAS

2. Writing Group: ARIC-LONGITUDINAL BP working group (FEHGAS study)
ARIC writing group members: Georg Ehret, Eric Boerwinkle, Alanna Morrison, Anna Kottgen, Josef Coresh, Sharon Kardia, C. Charles Gu, David Couper, Aravinda Chakravarti. Other authors from additional American or European cohorts. The plan is to maintain symmetry across cohorts.

Also invited to join the author group: Santhi Ganesh, Yan Sun, Dan Arking, Richard Olshen, DC Rao

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 2008

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. Until now only one very large genome-wide association study (GWAS) on hypertension has been published (WTCCC trial) and although some suggestive variants were identified, none proved to be genome-wide significant. Past data suggests that longitudinal BP levels have higher heritability. In addition to our work on the ARIC first visit BP (separate proposal), we set out here to

study genetic association with several longitudinal measures of SBP and DBP in ARIC in a GWAS study.

The results of this investigation will be combined with appropriate US and/or European cohorts for replication. We are in active collaboration with CLUE, CHARGE (ARIC, CHS, Rotterdam, Framingham, and selected other cohorts) and with the European BRIGHT study to perform a meta-analysis of GWAS findings related to a longitudinal BP assessment. The analysis is focusing on a) SBP, b) DBP, and 3) HTN at multiple visits.

5. Main Hypothesis/Study Questions:
Gene variants can be identified that are associated longitudinal BP traits.

6. Design and analysis
Design: meta-analysis of GWAS studies with comparable longitudinal data.

Possible participating groups:
CHARGE (AGES, Framingham Study, Rotterdam Study, CHS)
BRIGHT study
CLUE study – provides data in CLUE I at 1973 and CLUE II at 1989 on a subset (n~1,700 at each date) of ARIC participants. This extends the blood pressures in middle age to younger ages where the role of genes compared to environment may be larger.

The focus will be on pooling results from cohorts with comparable longitudinal data.

Phenotypes: SBP, DBP, and HTN status across the four ARIC visits. Additional data from CLUE I and II will be included after initial exploration to check if the incremental data is likely to increase power.

1.
Model: Linear regression for blood pressure at each visit and mean blood pressure (or residuals) across visits. Longitudinal analysis using GEE examination and other methods for a mean effect across multiple visits allowing for correlation within individuals is likely to be the primary analysis. Associations (z-score and p-values) across visits will be compared and exploratory and confirmatory methods for making comparisons and increasing power will be explored.
ARIC cohort: All ARIC white participants with extension to data in African-Americans for comparison if this increases the scientific impact of this research and does not overlap other existing papers. Use of GWAS data in African-Americans will follow CARE procedures. Specifically, loci discovered in whites will also be examined in blacks, but loci discovered in blacks that do not replicate among whites will be the focus of other papers. We are also aware that the CARE GWAS paper might include blood pressure as a continuous trait.
Genetic model: additive.

2. Transformation: no transformation, no scaling; for BP phenotypes transformation as suitable

3. Covariates: age, age^2, sex, bmi, study-center as suitable
Blood pressure medication use is a critical covariate for which there is no perfect adjustment. We will compare analyses which include individuals using BP-lowering

medications (adding an estimated effect of the medication) and analyses which exclude these individuals.

4. Exclusions: outliers of the SBP/DBP distribution (>SD from the mean), extreme BMI (>40 or <19kg/m2), severe renal disease (based on creatinin cutoff); the impact of excluding heart failure patients will be investigated

5. Control for multiple comparisons: Bonferroni adjustment

6. Imputation
Imputation to Hapmap 2.5 M using MACHv1.0.16 and genotyped SNPs only

7. Meta-analysis:
Meta-analysis based on 2.5 M observed and imputed SNPs and genotyped SNPs only

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

_x__ A. primarily the result of an ancillary study (2006.03, 2007.02)

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.