1.a. Full Title: Rare variants of CHARGE GWAS for BP (SBP and DBP) at first visit

b. Abbreviated Title (Length 26 characters): RareVariantFirstVisit GWAS

2. Writing Group: CHARGE-BP working group
   ARIC writing group members: Tao Feng, Yali Li, Zhu X, Georg Ehret, Eric Boerwinkle, Alanna Morrison, Anna Kottgen, Sharon Kardia, Santhi Ganesh, C. Charles Gu, Yan Sun, DC Rao, Aravinda Chakravarti. Other authors from additional CHARGE cohorts. The plan is to maintain symmetry across cohorts.

Also invited to join the author group: Richard Olshen, Neil Risch

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

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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: summer 2010

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. Three large genome-wide association study (GWAS) on hypertension have been published. Although several common genetic variants were identified, the total variation expressed by the variants is limited. It has been debated that multiple rare variants may also contribute complex traits such as hypertension. Here we hypothesize that gene-based haplotypes may capture a portion of variation due to rare variants. We set out to study the association of haplotypes in genes with the first visit BP (systolic BP and diastolic BP, average of the measurements available after discarding the first (sbpa21 and sbpa22)) in ARIC in a GWAS study. We first map a SNP to a particular gene if the SNP is within or less than 500Kb from a gene. We will infer haplotype phases for the SNPs in each gene using the software BEAGLE with the use of the reference haplotypes from HapMap CEU data. The association test between haplotypes and BP/HT will be conducted using the two-stage method: 1) classification of rare risk haplotypes; 2: association test. We will apply p-value of $2.0 \times 10^{-6}$ in order to declare the genome wide significance. However, different significance level will be applied for the genes identified in literatures to be associated with Hypertension and BP.

CHARGE (ARIC, CHS, Rotterdam, Framingham, and selected other cohorts) perform a replication analysis of GWAS findings related to a cross-sectional BP assessment (n=8,047 in ARIC). The analysis is focusing on a) SBP, b) DBP at the first ARIC visit. We will use ARIC Phase I and II data.

5. Main Hypothesis/Study Questions:

A set of haplotypes in a gene can be identified that associate with SBP and DBP at the first ARIC visit. The association may be due to multiple rare 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: two stage design followed by replication analysis. Stage 1: classifying rare risk haplotypes. Stage 2: association test

Participating groups:
Framingham Study
Rotterdam Study
CHS
AGES

Phenotypes: SBP and DBP at first visit

1. Model: ANOVA and haplotype analysis

Main analysis will include only self-reported whites (no self-reported African Americans included)

Genetic model: dominate.
2. Transform: no transform, no scaling.

3. Covariates: age, age\(^2\), sex, bmi, study-center

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

5. Control for multiple comparisons: Bonferroni adjustment

6. Imputation
   No.

7. 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
   Yes (based on list circulated in July 2009)

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.cscce.unc.edu/aric/forms/](http://www.cscce.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.