1.a. Full Title: A Gene-Environment Interaction Approach to Genome-Wide Association Analysis of Blood Pressure in the ARIC Study: Gene-Age Interactions in European Americans

b. Abbreviated Title (Length 26 characters): GWAS of BP with SNP-Age Interaction

2. Writing Group:
   Gang Shi, Yan Sun, Sharon Kardia, Alanna Morrison, Santhi Ganesh, Gerardo Heiss, (any other ARIC/FEHGA authors), C. Charles Gu, Eric Boerwinkle, Aravinda Chakravarti, DC Rao

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

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3. Timeline: All genotyping is complete. Data are being processed. Analysis to begin immediately.

4. Rationale: Common complex traits such as blood pressure (BP) have long been thought to be caused by a complex interplay between genes and environment. Recent studies have underscored the relatively modest effect sizes of the ~200 genetic variants detected for nearly 40 common disease traits. Although the discovery that individual gene effects are small is not surprising, it makes it necessary to use more powerful methods for this purpose, such as modeling gene-environment interactions (GEI). Of particular relevance is the observation that some genetic effects seem to be modulated by other covariates, especially age, BMI, and possibly gender. Genetic analysis incorporating gene-age interactions can increase the statistical power substantially for detecting genetic effects even with relatively small effect sizes. Lasky-Su et al. have demonstrated that incorporation of gene-age interaction not only enhances gene discovery, it also renders many non-replications into valid replications. This makes age one of the most attractive variables for a GEI investigation.

5. Main Hypothesis/Study Questions: We hypothesize that the effects of many BP genetic loci are modulated by age. Therefore, incorporation of gene-age interaction will help discover novel blood pressure loci.
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).

**General Analysis Approach:**

**Subjects:** ARIC Whites at visit 1, after excluding outliers for blood pressure. This manuscript proposal addresses the analysis of ARIC Whites as part of FEHGAS. FEHGAS (Familial Essential Hypertension Genetic Association Study) is a collaborative effort between the NHLBI Family Blood Pressure Program (FBPP) and ARIC that was established such that top hits from ARIC GWAS for blood pressure and hypertension could be investigated for replication in FBPP. Analysis of ARIC African Americans will be addressed in a separate manuscript proposal as a part of the CARe Consortium.

**Exposure:** 2.5 million HapMap genetic variants identified in CEPH trios

Outcome: systolic, diastolic, and mean arterial blood pressures.

**Primary statistical approach:** Additive model (2 df test) with age interaction, adjusting for sex, age, bmi, and center.

**Secondary statistical approach:** If the primary analysis does not yield positive results based on simple methods, non-linear gene-age interactions will be considered. Although these analyses entail more df, they have the potential to boost statistical power as our experience with linkage analysis has shown2.

**Statistical significance:** Bonferroni correction (1/ number of tests performed) (~5x10^-8)

**Validation and Replication:** Our current plans include replication in CHARGE

Major Phenotypes to Analyze: v1age01, gender, racegrp, bmi01, sbpa21, sbpa22, hyptmdcode01, centerid;

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

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

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. ____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)?

There are no related manuscript proposals in ARIC since this proposal deals with the application of a new GEI approach to analysis of the GWA genotype data.
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)* __________ __________ __________)

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.

References

