1.a. **Full Title**: Gene-Body Mass Index Interactions Influencing Blood Pressure in Caucasians

b. **Abbreviated Title (Length 26 characters)**: SNP-BMI Interaction in BP

2. **Writing Group**:
   Yan Sun, Gang Shi, DC Rao, Alanna Morrison, Santhi Ganesh, Georg Ehret, Gerardo Heiss, Eric Boerwinkle, Aravinda Chakravarti, Sharon Kardia

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

YS [please confirm with your initials electronically or in writing]

**First author**: Yan V. Sun
Address: University of Michigan
School of Public Health, Department of Epidemiology
109 Observatory #4605
Ann Arbor, MI 48109-2029
Phone: 734-615-6279 Fax: 734-764-1357
E-mail: yansun@umich.edu

**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).

Name: Alanna C. Morrison
Address: University of Texas Health Science Center at Houston School of Public Health
1200 Herman Pressler Dr.
Houston, Texas 77030
United States
Phone: (713) 500-9913
Email: Alanna.C.Morrison@uth.tmc.edu

3. **Timeline**: Summer and Fall of 2009

4. **Rationale**: Although genetic markers have been identified as precursors for high blood pressure (BP), they only explain a small fraction of the genetic variance for BP. We speculate that this is a result of reliance on simple methods of association looking for the main effects of single SNPs. Accommodating gene-environment interactions as part of the association analysis model will make it possible to identify larger numbers of genetic loci which collectively may begin to explain much larger fractions of the underlying genetic variance. Moreover, lifestyle behaviors can be modified, unlike genetic factors, to prevent or enhance effects of genetic predispositions. It is well known that negative lifestyle behaviors, (e.g., consuming foods with high caloric content) can lead to obesity, high blood pressure and cardiovascular problems. Maintaining optimal weight is a health index of diet/physical
activity/lifestyle choices that may impact gene effects on high blood pressure but no one has systematically studied gene-by-BMI interactions in a genome-wide association on blood pressure. BMI is an applicable predictor of adiposity and a BMI at or greater than 25 is considered overweight, and BMI 30 or greater is indicative of obesity. Common complex traits such as blood pressure have long been thought to be caused by a complex interplay between genes and environment. Recent studies have reported the relatively modest effect sizes of over 300 GWAS papers reported over 1,300 SNPs detected for about 180 human traits\textsuperscript{2}. Although the discovery that individual gene effects are small is not surprising, the next step is to better understand how traditional risk factor interact with these genes, such as modeling gene-environment interactions (GEI), to better elucidate the impact of genes on risk of common chronic disease such as hypertension. This makes BMI one of the most attractive variables for a GEI investigation.

5. Main Hypothesis/Study Questions: We hypothesize that the effects of genetic loci influencing blood pressure measurements are modulated by BMI (which includes both environmental and genetic components). Therefore, investigating genome wide gene-BMI interactions will help discover novel blood pressure loci and provide insights into how to modify individual’s genetic risks.

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: European-American in ARIC population at visit 1 with blood pressure measurements.

Exposure: Affymetrix 6.0 SNP data and 2.5 million HapMap genetic variants identified in HapMap project imputed from Affymetrix 6.0 SNP data

Outcome: systolic BP, diastolic BP, pulse pressure, mean arterial pressure and hypertension status.

Primary statistical approach: Additive model with BMI interaction, adjusting for age, age\textsuperscript{2}, sex, field center, BMI, and population substructure.

Secondary statistical approach: If the primary analysis does not yield positive results based on simple methods, alternative genetic coding (eg. Two dummy variable representing the 3 genotypes of a SNP) that allow more specificity of the SNP-BMI interactions will be considered.

Statistical significance: genome-wide significance\textsuperscript{2} (\(p\)-value < 5\(\times\)10\textsuperscript{-7})

Validation and Replication: Our current plans include replication in other CHARGE cohorts

Major Phenotypes to Analyze: v1age01, gender, racegrp, bmi01, sbpa21, sbpa22, hyptmdcode01, centerid, hypert05;

7.a. Will the data be used for non-CVD analysis in this manuscript? \textbf{X} Yes  
7.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? \textbf{X} Yes  

8.a. Will the DNA data be used in this manuscript?  
  \textbf{X} 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”?  

_____ 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


2. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447;661-78