Published in final edited form as:
Biol Res Nurs. 2010 October ; 12(2): 149–155. doi:10.1177/1099800410371225.

Gene–Environment Interaction for Hypertension Among African American Women Across Generations

Jacquelyn Y. Taylor, PhD, PNP-BC, RN[1], **Yan V. Sun, PhD**[2], **Steven C. Hunt, PhD**[3], and **Sharon L.R. Kardia, PhD**[2]

[1]School of Nursing, Yale University, New Haven, CT, USA

[2]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA

[3]School of Medicine, University of Utah, Salt Lake City, UT, USA

Abstract

African American women have the highest prevalence of hypertension and obesity of any group in the United States. African American girls have the highest incidence of obesity of any groups of children in the nation, and diagnoses of hypertension have been rising among this group. Because both genetic heredity and body mass index (BMI) are important risk factors for hypertension, this study examined the gene-BMI interaction for hypertension across the lifespan in two generations of African American women. Participants comprised of 868 African American women in the parent cohort and 322 in the offspring cohort from the Hypertension Genetic Epidemiology Network (HyperGEN) study, part of the Family Blood Pressure Program (FBPP). A total of 115 single-nucleotide polymorphisms (SNPs) were evaluated among the parent cohort and 491 among the offspring cohort for tests of SNP-BMI interaction using methods of false discovery rate (FDR; <.20) and examination of minor allele frequency (MAF; >.05) and Hardy-Weinberg equilibrium (>.10). One SNP (located in the *CAPN 13* gene, rs1879282) passed adjustments for the multiple testing mentioned above and had a significant ($p < .01$) gene-BMI interaction on both systolic blood pressure (SBP) and diastolic blood pressure (DBP) among African American female offspring. The rs1879282 SNP is located on chromosome 2 on the calpain (CAPN) 13 gene, which is part of a family of cytosolic calcium-activated proteases involved in apoptosis, cell division, modulation of integrin–cytoskeletal interactions, and synaptic plasticity. This SNP was not available for testing in the African American parent cohort.

Keywords

blood pressure; body mass index; genetic; women; African American

It is estimated that more than 970 million people have been diagnosed with hypertension worldwide (Kearney et al., 2005). According to the American Heart Association (AHA, 2006), approximately 74 million American adults have high blood pressure (BP). African American women have a greater prevalence of both hypertension and obesity than any other group. The AHA reported the prevalence of hypertension among this group at 44% and the

Corresponding Author: Jacquelyn Taylor, 100 Church Street South, Room 295, New Haven, CT 06536, USA jacquelyn.taylor@yale.edu.

Declaration of Conflicting Interests The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

2001–2002 National Health and Nutrition Examination Survey (NHANES) reported that 41.5% of African American women were considered obese, compared to 19.3% of Caucasian women (Rosamond et al., 2008). Diagnoses of hypertension and obesity among children, particularly African American girls, have also been on the rise. In the period between 2003 and 2004, 22.8% of African American girls aged 6–11 years and 23.6% of those aged 12–19 years were considered obese (Taylor, Maddox, & Wu, 2009). In both instances, obesity rates among African American girls were higher than those of Caucasian boys and girls and African American boys. Because the development of hypertension has been closely related to overweight and obesity, it is important to examine both among African American women and girls to reduce the disparity in the prevalence of hypertension.

Lack of exercise and improper diet have been identified as modifiable risk factors for hypertension (Forman, Stampfer, & Curhan, 2009; Taylor, Washington, Artinian, Lichtenberg, 2008). Yet it has also been well established that genetic heredity plays an important role in the development of hypertension. An examination of plausible genetic and environmental interactions for hypertension risk is, therefore, warranted. Researchers have identified genetic factors that influence inter-individual variation in BMI, but there is also a large environmental component to weight that contributes to high BP remaining to be explored. In either case, BMI represents a partial internal metabolic and physiological environment that plays a key role in the development of hypertension for many Americans. In the study described here, we examined BMI as a partial internal environment in the gene–environment interaction for hypertension in African American women across two generations. Early detection of genetic and environmental influences on the development of hypertension development may help reduce the disparity between African American women and other groups in prevalence of hypertension and obesity.

BMI and Hypertension

The correlations among obesity, complex disease, and mortality rate have been well documented (AHA, 2006; Rosamond et al., 2008). For adults, the term *overweight* is defined as a BMI of 25.0 to 30.0 kg/m^2 and *obesity* as a BMI ≥ 30.0 kg/m^2 (Lewis et al., 2009). NHANES data (Ogden et al., 2006) indicate that two third of adults were overweight or obese in 2003–2004. Mean BMI as well as population BMI distributions shifted upward from 1999 to 2004, suggesting that overweight people are becoming obese and normal weight individuals are moving toward the overweight category. Although some researchers insist that advocating for weight loss in the overweight population is unwarranted because most health complications are associated with obese patients (Jackson, Doescher, Saver, & Hart, 2005), overweight and obesity have both been linked to systemic hypertension (Lewis et al., 2009).

Like inactivity and improper diet, obesity has long been associated with hypertension and cardiovascular disease (CVD). CVD related to obesity has been attributed to borderline or elevated risk factor levels among Caucasian Americans. In African Americans, however, it appears that it is a greater prevalence of risk factors that explains the higher CVD rates (Hozawa, Folsom, Sharrett, & Chambless, 2007). Hozawa et al. (2007) found that the percentage of African American men and women with hypertension was higher than that of Caucasian men and women (31.6% vs. 28.2%) and that approximately 80% of African American men and 79% of African American women in the study had elevated risk factors for CVD, compared to 60.5% and 62.9% of Caucasian men and women. Overall, African American women had the highest percentage of risk factors associated with hypertension, obesity, and CVD.

Hypertension-related complications lead to more deaths in women than all other preventable chronic diseases (Lowe, Greenland, Ruth, Dyer, & Stamler, 1998). Although hypertension can be fatal, precautions to delay and perhaps prevent its onset are readily available. Forman et al. (2009) examined low-risk lifestyle factors and the risk of developing hypertension to determine the efficiency of preventative measures over a 14-year period, identifying six low-risk factors: a BMI of less than 25 kg/m^2, 30 min of vigorous exercise daily, a high score on the Dietary Approaches To Stop Hypertension (DASH) diet, modest (10 g/day) alcohol intake, use of non-narcotic analgesics less than once per week, and intake of 400 pg/day of supplemental folic acid. At baseline, the mean age was 36 and the mean BMI was 23.7 kg/m^2. Of the 83,882 women surveyed, 12,319 developed hypertension during the 14-year follow-up, and high BMI was the strongest risk factor. Researchers reported that 50% of those new hypertension cases could be attributed to a BMI of 23 kg/m^{2}or greater. Adherence to a low-risk lifestyle was significantly associated with lower incidence of self-reported hypertension. Considering the disproportionately high incidence of obesity and hypertension among African American women, our examination of BMI, hypertension, and genetic determinants among two generations of African American women is an important step toward understanding the genetic and environmental influences on hypertension.

Method

Study Sample

The Family Blood Pressure Program (FBPP), established by the National Heart Lung and Blood Institute in 1996, consists of four research networks that investigate hypertension and CVD (FBPP Investigators, 2002). One of the four networks in FBPP is the HyperGEN study, which recruited hypertensive, non-Hispanic African American and Caucasian sibships for linkage and family-based association studies to investigate genetic contributions to hypertension and hypertension-related target organ damage. African American participants in HyperGEN were recruited from Forsyth County, North Carolina, and Birmingham, Alabama. All available, affected siblings were recruited from each eligible sibship, with a minimum number of two hypertensive sibs required for each sibship. Exclusion criteria for HyperGEN included age of hypertension onset of >60 years, evidence of secondary hypertension (e.g., hypertension secondary to primary kidney disease), hypertension during pregnancy only, or type 1 diabetes mellitus (insulin therapy prior to age 21 years). Untreated offspring of the hypertensive sibs were also recruited if they were 18 years of age or older. Written informed consent was obtained from each participant and approval was granted by participating institutional review boards. Subjects for this particular HyperGEN substudy were 868 female African American participants in the parent cohort and 322 female African American participants in the offspring cohort. The current study will only examine African American women, and not men, because African American women have the highest prevalence of hypertension and obesity of all groups.

Phenotype Measurement

During the clinical visit, trained staff interviewed each participant for demographic information, medical history, clinical characteristics, and lifestyle factors and collected a blood sample for genotyping and biomarker assays. BP was measured with automated Dinamap BP recorders and cuffs appropriate for arm size (Williams et al., 2000). Three readings were taken for each arm after the participant rested in the sitting position for at least 5 min; the last two readings for each arm were averaged, and the maximum of these was used for the analysis. For participants who were taking antihypertensive medication, we corrected the observed systolic blood pressure (SBP) and diastolic blood pressure (DBP) values by adding the mean effect of each antihypertensive medication category (Wu et al., 2005). Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or drug

treatment for hypertension at time of assessment (Chobanian et al., 2003). Height was measured by stadiometer, weight by electronic balance; body mass index (BMI) was obtained by the standard calculation of dividing each weight (kg) by the corresponding height (m^2; Williams et al., 2000).

Genotyping

Single-nucleotide polymorphism (SNP) genotyping for subjects from the HyperGEN study was conducted at University of Texas-Houston, Johns Hopkins University, Medical College of Wisconsin, and the University of Utah. SNPs were selected in positional candidate genes using the public NCBI database (http://www.ncbi.nlm.nih.gov) and the private Celera database (http://www.celera.com). SNP genotyping on a total of 115 loci in the parent cohort and 491 loci in the offspring cohort was obtained using a combination of two genotyping platforms: mass spectrometer-based detection system implemented on a Sequenom MassARRAY system and the fluorogenic TaqMan assay implemented on an ABI Prism 7900 Sequence Detection System. SNPs were excluded if they had a call rate less than 90% or a minor allele frequency (MAF) less than 5%. Genes were selected to represent biological pathways or positional candidate genes from systems known to be associated with hypertension and previously linked to hypertension (Arnett et al., 2009). These quality control filters resulted in 436 SNPs available for analysis in the parent cohort and 95 loci in the offspring cohort.

Statistical Analysis

In each cohort, the residuals for medication-adjusted BP measurements were obtained using multivariable linear regression models. For SBP and DBP, the adjustment variables were age, age^2, and BMI. We then used linear mixed models (Raudenbush & Bryk, 2002) to test for association between each SNP and the multivariable-adjusted, residual phenotypes to account for the family structure within HyperGEN (siblings) and retain a valid type I error rate (Cupples et al., 2007). Each SNP was tested for additive effects in association with the outcome of interest in a test with one degree of freedom. We also tested the SNP × BMI interaction effects of medication-adjusted SBP and DBP using multivariable linear mixed models with age, age^2, BMI, and SNP allele dosage (i.e., additive effect) as covariates. For participants who were taking antihypertensive medication, we corrected the observed SBP and DBP values by adding the mean effect of each of the six major antihypertensive medication categories, including angiotensin-converting enzyme (ACE) inhibitors, α1-blockers, cardioselective β-blockers (β1-blockers), calcium channel blockers, thiazide and thiazide-like diuretics, and loop diuretics. The genetic additive effects model was used in this study. The additive genetic model of two alleles, A and B, shows a trend of an increased number of coded alleles. Assuming B is the coded risk allele, among the three genotypes, AA (0 risk allele), AB (1 risk allele), and BB (2 risk alleles), the risk for AB genotypes (r) is half that for BB genotypes (2r). Data management, descriptive statistics for the covariates and outcome variables, and the regression analyses were conducted using the statistics software package R in version 2.9.0 (http://www.r-project.org/).

Results

The descriptive statistics for the full sample of African American female parents and offspring are presented in Table 1. The mean BMI for African American mothers (34 ± 8 kg/m^2) was similar to that of the African American female offspring (32 ± 9 kg/m^2), with both groups in the overweight category. All of the parents and none of the offspring had been diagnosed with hypertension.

Tables 2A and 2B present a summary of results among parents and offspring testing for SNP main effects with SBP and DBP. Among the parents, 95 SNPs were tested, with 5 SNPs significantly associated with SBP and 3 SNPs significantly associated with DBP. Among the offspring, 436 SNPs were evaluated, and the same 6 SNPs were significantly associated with both SBP and DBP. Table 3 presents a summary of SNP-BMI interactions and the number of associations that remained significant after adjustment for multiple testing (FDR < 0.2). Among the parents, four SNPs (rs4035540, rs10499859, rs3771452, and rs12508955) remained significantly associated with DBP after adjustment for multiple testing and met all three of the following criteria: FDR < 0.2, MAF > .10, and Hardy-Weinberg equilibrium (HWE) >.05. Among the offspring, four SNPs remained significantly associated with SBP and six SNPs with DBP after adjustment for multiple testing, FDR < 0.2, and HWE >.05. However, of those SNPs, only two (rs17005371 and rs1879282) for SBP and four for DBP (rs1879282, rs4952281, rs523349, and rs13408063) had MAF >.10. Additionally, two SNPs among the offspring did overlap for significant findings for SNP-BMI interaction on both SBP and DBP (rs1406229 and rs1879282), but only one (rs1879282) of the two SNPs passed all three multiple tests of FDR < 0.2, MAF > .10, and HWE > .05 for both SBP and DBP. A Supplemental Table has been provided for SNP (online only) annotations for the candidate genes analyzed in this study.

The results among African American mothers' SNPs (rs4035540, rs10499859, rs3771452, and rs12508955) and BMI interaction effects suggest that differences in DBP levels depend on both an African American woman's genotype and BMI. The consistent results among African American female offsprings' SNP rs1879282 and BMI interaction effects suggest that differences in both SBP and DBP, respectively, depend on genetic underpinnings and BMI that is identifiable early in life, prior to diagnosis of hypertension.

Discussion

The current study found only one SNP that met all three test criteria and overlapped for SNP-BMI interaction on SBP and DBP among offspring—rs1879282. The rs1879282 SNP is located on chromosome 2 on the calpain (CAPN) 13 gene, which is part of a family of cytosolic calcium-activated proteases involved in apoptosis, cell division, modulation of integrin–cytoskeletal interactions, and synaptic plasticity (Dear & Boehm, 2001). In essential hypertension, typical increases in calcium in tissues act to promote calpain inhibition and have been observed in hypertensive rats (Averna et al., 2001). According to Dear and Boehm (2001), CAPN 13 is found in human testis and lung tissue. Because all of the participants in the current study are women, we assume that the CAPN 13 gene is restricted to lung. A study of pulmonary hypertension found that calpain inhibition prevents pulmonary resistance by limiting nitric oxide synthase (NOS) activity and can improve organ recovery in ischemic heart disease (Duffy et al., 2005). Therefore, calpastastin deficiency has been implicated as one of the factors linked to organ damage in essential hypertension (Averna et al., 2001).

Findings of the current study suggest associations between genetic polymorphisms and the internal environment of BMI on DBP in African American mothers and on SBP and DBP in African American female offspring. Although the SNP and BMI interactions for BP in the current study differ from what has been reported in the literature previously, the notion that an association exists between genetic polymorphisms and BMI for hypertension among African American women is consistent. Taylor, Sun, Chu, Mosley, and Kardia (2008) found a significant protective effect with the gene–environment interaction of MMP3_rs679620 and BMI on DBP among African American women in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. Taylor et al. (2009) found significant deleterious effects of rs1017783 and rs6731545 (located on *SLC4A5*, sodium bicarbonate transporter gene) with

low physical activity on both SBP and DBP. However, SNP rs8179526 and the internal environment of sodium intake were found to have a protective effect on SBP among African American women.

In their study of gene–environment interaction, Grove et al. (2007) measured the GNB3 825C > T genotype in 14,716 African American and Caucasian participants from the Atherosclerosis Risk Communities Study. African American participants were significantly younger and had higher BMIs and weights than Caucasian participants. Allele frequencies were significantly different between the two groups: the 825T allele was more common among African American participants and the C825 allele was more common among Caucasian participants. However, genotype frequencies were similar among obese and non-obese as well as hypertensive and nonhypertensive individuals, regardless of race. Most pertinent to the current study, each 825T allele was associated with a 20% lower prevalence of obesity among African American participants as a whole, whereas each 825T allele was linked to a 23% higher obesity prevalence among inactive African American participants.

In addition to linkage studies, genome-wide association studies (GWAS) have provided insight into the area of genetics, hypertension, and obesity. The meta-analysis by Lindgren et al. (2009) of 16 GWAS and large-scale replication studies was designed to examine anthropometric measures of fat distribution and central obesity. Scans of 118,691 individuals identified two loci (*TFAP2B* and *MSRA*) related to waist circumference, as well as a locus, circa LYPLA1, associated with waist-to-hip ratio. Isolating *LYPLA1m*, the female-only signal remained highly significant, providing evidence of effect-size heterogenic effects between genders. However, the study was limited to individuals of European descent. Given the noted relationship between obesity risk factors and findings by Lindgren et al., furthering gene–environment studies pertaining to obesity and African American women is imperative.

Wang et al. (2009) conducted a GWAS using data from the Amish Family Diabetes Study to identify genes associated with essential hypertension. SBP and DBP were measured in 542 men and women. Initially, the scan revealed that rs4977950 was significant at the genome-wide level. The authors assert, “Variants in *STK39* may influence BP by increasing STK39 expression and consequently altering renal sodium, thus unifying rare and common BP-regulating alleles in the same physiological pathway.” However, after the Bonferroni correction was applied, the SNP was not significant at the genome-wide level.

The GWAS by Newton-Cheh et al. (2009) studied 34,433 participants of European descent for the purpose of identifying genetic variants influencing BP. The authors identified the following genes as being significantly associated with BP: CYP17A1, CYP1A2, FGF5, SH2B3, MTHFR, c10orf107, ZNF652, and *PLCD3*. However, researchers determined that each association explained but a fraction of the total SBP or DBP variation. However, these loci do have a meaningful effect on BP, acting throughout the range of values. A CHARGE (Cohorts for Heart and Aging Research in Genetic Epidemiology) consortium study conducted by Levy et al. (2009) examined genetic variation associated with complex traits. With 29,136 participants of European descent, researchers used standardized measurements to observe SBP, DBP, and hypertension to assess their relationship to genetics. The authors identified genome-wide significance for four loci with SBP, six loci with DBP, and one with hypertension. Among the genome-wide significant loci identified in both Levy et al. and Newton-Cheh et al., only two overlapped (*CYP17A1* and *SH2B3*) between the studies.

Adeyemo et al. (2009) published the first study that involved a GWAS among African American subjects, which examined the associations among genetic variants, hypertension, and obesity. Hypertensive participants were older (54 vs. 41 years) and heavier (BMI 31.7

vs. 29.3 kg/m^2) than normotensive subjects. Results pertaining to hypertension were less than desirable. The SNP with the lowest *p* value (5.10×10^{-7}) was rs9791170 located on chromosome 5, but this SNP did not have genome-wide significance nor did the other SNPs. No one locus for gene-environment interaction for BMI and BP using GWAS has been identified as of yet.

Some limitations of the current study need to be considered. The BMI interactions under examination in this study used a small set of biological or positional candidate genes and not GWAS SNPs. Because most of these genes were not found to be associated with BP, they are less likely to show interaction with BMI. The approach was based on the premise that susceptibility alleles for common diseases were not under strong negative selection, and common variants contributed to common disease traits (i.e., the "common disease-common variant" hypothesis; Reich & Lander, 2001). However, the allelic spectrum for genes associated with complex quantitative traits, such as BP, was not fully delineated. It was possible that multiple rare polymorphisms in the biological and positional candidate genes that were studied could influence BP. Due to a lack of statistical power, identifying associations with BP using such alleles would not be possible using approaches employed in this study. The inferences may not be generalizable to individuals who are younger than 18 years of age, of other ethnic groups, or men. Despite some limitations, the approach used in the current study illustrates the use of SNPs in candidate genes to construct a more complete picture of the genetic architecture of complex traits, such as BP.

Identification of the CAPN13_rs1879282 SNP as a risk factor for increases in SBP and DBP in normotensive African American female offspring is clinically important when considering early interventions and appropriate treatment plans. Genetic screening and identification prior to expression of the hypertension phenotype early in life are imperative to delaying development of hypertension in this at-risk population. This early identification could lead to noninvasive lifestyle interventions that could prevent hypertension and promote well-being across the lifespan. Clinicians need to be knowledgeable about the gene–environment effects of rs1879282 among normotensive patients when assessing and treating African American women and girls with a family history of high BP and high BMI. Nurses need to take into account both the genetic and environmental underpinnings of hypertension risk that may exist in some populations, even when the phenotype has not yet been expressed. Risk reduction and health promotion are the keys to reducing hypertension and obesity disparities. These findings add to the body of evidence suggesting a role for rs1879282 in high BP among African American women across the lifespan.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article: Funding for this research was provided in part by the Robert Wood Johnson Foundation–Nurse Faculty Scholars Grant 64193 and National Institutes of Health cooperative agreements (U10) with NHLBI: HL54471, HL54472, HL54473, HL54495, HL54496, HL54497, HL54509, HL54515, and two R01 HL55673-12.

References

Adeyemo A, Gerry N, Chen G, Herbert A, Doumatey A, Huang H, Rotimi C. A genome-wide association study of hypertension and blood pressure in African Americans. PLoS Genetics 2009;5:1–11.

American Heart Association. High blood pressure statistics. 2006. Retrieved August 5, 2009, from http://www.americanheart.org/presenter.jhtml?identifier=4621

Arnett DK, Devereux RB, Rao DC, Li N, Tang W, Kraemer R, Broeckel U. Novel genetic variants contributing to left ventricular hypertrophy: The HyperGEN study. Journal of Hypertension 2009;27:1585–1593. [PubMed: 19593212]

Averna M, De Tullio R, Salamino F, Minafra R, Pontremoli S, Melloni E. Age-dependent degradation of calpastatin in kidney of hypertensive rats. Journal of Biological Chemistry 2001;276:38426–38432. [PubMed: 11485997]

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Roccella EJ. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC-7 report. Journal of the American Medical Association 2003;289:2560–2572. [PubMed: 12748199]

Cupples LA, Arruda HT, Benjamin EJ, D'Augustino RB, Demissie S, DeStefano AL, Atwood LD. The Framingham Heart Study 100K SNP genome wide association study resource: Overview of 17 phenotype working group reports. BMC Medical Genetics 2007;8(Suppl 1):1–19. [PubMed: 17227582]

Dear TN, Boehm T. Identification and characterization of two novel calpain large subunit genes. Gene 2001;274:245–252. [PubMed: 11675017]

Duffy JY, Schwartz SM, Lyons JM, Bell JH, Wagner CJ, Zingarelli B, Pearl JM. Calpain inhibition decreases endothelin-1 and pulmonary hypertension after cardiopulmonary bypass with deep hypothermic circulatory arrest. Critical Care Medicine 2005;33:623–628. [PubMed: 15753756]

FBPP Investigators. Multi-center genetic study of hypertension: The Family Blood Pressure Program (FBPP). Hypertension 2002;39:3–9. [PubMed: 11799070]

Forman JP, Stampfer MJ, Curhan GG. Diet and lifestyle risk factors associated with incident hypertension in women. Journal of the American Medical Association 2009;302:401–411. [PubMed: 19622819]

Grove M, Morrison A, Folsom A, Boerwinkle E, Hoelscher D, Bray M. Gene environment interaction and the GNB3 gene in the Atherosclerosis Risk in Communities Study. International Journal of Obesity 2007;6:919–926. [PubMed: 17299380]

Hozawa A, Folsom R, Sharrett R, Chambless E. Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors: Comparison of African American with white subjects—Atherosclerosis risk in communities study. Archives of Internal Medicine 2007;167:573–579. [PubMed: 17389288]

Jackson JE, Doescher MP, Saver BG, Hart LG. Trends in professional advice to lose weight among obese adults, 1994 to 2000. Journal of Internal Medicine 2005;20:814–818.

Kearney P, Whelton M, Reynolds K, Muntner P, Whelton PK, He D. Global burden of hypertension: Analysis of worldwide data. Lancet 2005;365:217–223. [PubMed: 15652604]

Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, van Duijn CM. Genome-wide association study of blood pressure and hypertension. Nature Genetics 2009;41:677–686. [PubMed: 19430479]

Lewis CE, McTigue KM, Burke LE, Poirier P, Eckel RH, Howard BV, Pi-Sunyer FX. Mortality, health outcomes and body mass index in the overweight range: A science advisory from the American Heart Association. Circulation 2009;119:3263–3271. [PubMed: 19506107]

Lindgren C, Heid I, Randal J, Lamina C, Steinthorsdottir V, Qi L, McCarthy MI. Genome-wide association scan meta-analysis identifies three loci influencing adiposity and fat distribution. PLoS Genetics 2009;5:e1000508. doi:10.1371/ journal.pgen.1000508. [PubMed: 19557161]

Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. Archives of Internal Medicine 1998;158:2007–2014. [PubMed: 9778200]

Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochurd M, Coin L, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. Nature Genetics 2009;41:666–676. [PubMed: 19430483]

Ogden C, Carroll M, Curtin L, McDowell M, Tabak C, Flegal K. Prevalence of overweight and obesity in the United States, 1999–2004. Journal of the American Medical Association 2006;295:1549–1555. [PubMed: 16595758]

Raudenbush, SW.; Bryk, AS. Hierarchial linear models: Applications and data analysis methods. 2nd ed. SAGE; Thousand Oaks, CA: 2002.

Reich DE, Lander ES. On the allelic spectrum of human disease. Trends in Genetics 2001;17:502–510. [PubMed: 11525833]

Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hong Y. Heart disease and stroke statistics—2008 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:e25–146. [PubMed: 18086926]

Taylor JY, Maddox R, Wu CY. Genetic and environmental risks for high blood pressure among African American mothers and daughters. Biological Research for Nursing 2009;11:53–65. [PubMed: 19487301]

Taylor JY, Sun Y, Chu J, Mosley T, Kardia S. Interactions between metallopeptidase 3 polymorphisms rs679620 and BMI in predicting blood pressure in African American women with hypertension. Journal of Hypertension 2008;26:2312–2318. [PubMed: 19008710]

Taylor JY, Washington OGM, Artinian NT, Lichtenberg P. Relationship between depression and specific health indicators among hypertensive African American parents and grandparents. Progress in Cardiovascular Nursing 2008;23(2):68–78. [PubMed: 18843828]

Wang Y, O'Connell JR, McArdle PF, Wade JB, Dorff SE, Shah SJ, Chang YP. Whole-genome association study identifies STK39 as a hypertension susceptibility gene. Proceedings of the National Academy of Sciences of the United States 2009;106:226–231.

Williams RR, Rao DC, Ellison RC, Arnett DK, Heiss G, Oberman A, Hunt SC. NHLBI family blood pressure program: Methodology and recruitment in the HyperGEN network. Annals of Epidemiology 2000;10:389–400. [PubMed: 10964005]

Wu J, Kraja AT, Oberman A, Lewis CE, Ellison RC, Arnett DK, Rao DC. A summary of the effects of antihypertensive medications on measured blood pressure. American Journal of Hypertension 2005;18:935–942. [PubMed: 16053990]

Table 1

Descriptive Statistics (Mean [*SD*]) for Participating African American Mothers and Daughters

Characteristic	Parent (*N* = 855)	Offspring (*N* = 322)
Age (years)	51 (11)	32 (9)
BMI (kg/m^{2}0)	34 (8)	32 (9)
SBP (mmHg)	134 (23)	116 (17)
DBP (mmHg)	74 (11)	69 (11)

Note. BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 2

Top Associated Single Nucleotide Polymorphisms (SNPs) for Systolic and Diastolic Blood Pressure (SBP and DBP) Among Mothers and Female Offspring (Main Effects)

SNP	β	SE	p	FDR	Chr.	Position	Gene
Among mothers							
SBP							
rs5051	11.69	4.51	.01	0.69	1	227156607	*AGT*
rs7597971	−3.40	1.45	.02	0.69	2	167113679	*SCN7A*
rs10499859	3.31	1.46	.03	0.69	7	79903461	*CD36*
rs2493132	−7.12	3.42	.04	0.87	1	227150292	*AGT*
rs2493134	−8.47	4.28	.05	0.87	1	227156094	*AGT*
DBP							
rs12339491	−1.72	0.78	.03	0.91	9	134523175	*RXRA*
rs3775597	2.49	1.15	.03	0.91	4	143007260	*IL15*
rs2820037	1.27	0.63	.04	0.91	1	235625583	-
Among female offspring							
SBP							
rs6706122	5.54	1.60	<.01	0.30	2	33300596	*LTBP1*
rs17012778	−5.30	1.60	<.01	0.30	2	33375138	*LTBP1*
rs11685486	−5.03	1.59	<.01	0.30	2	29504534	*ALK*
rs12468769	3.60	1.31	.01	0.65	2	33319987	*LTBP1*
rs2288697	−12.00	5.34	.03	0.66	2	23771820	*FLJ14126*
rs6707371	3.38	1.57	.03	0.66	2	29928908	*ALK*
DBP							
rs6706122	1.01	2.65	.01	0.72	2	33300596	*LTBP1*
rs17012778	1.02	−3.64	<.01	0.23	2	33375138	*LTBP1*
rs11685486	1.00	−2.4	.02	0.72	2	29504534	*ALK*
rs12468769	0.82	1.78	.03	0.72	2	33319987	*LTBP1*
rs2288697	3.46	−8.52	.01	0.72	2	23771820	*FLJ14126*
rs6707371	0.98	2.07	.04	0.72	2	29928908	*ALK*

Note. SBP and DBP adjusted for antihypertensive medication in parents only. Chr. = chromosome; FDR = false discovery rate.

Table 3

Single Nucleotide Polymorphism (SNP) × Body Mass Index (BMI) Interaction With FDR < 0.2

SNP	β	SE	p	FDR	Chr.	Position	Gene	MAF	HWE
Parent									
SBP (none)									
DBP									
rs4035540	−0.31	0.10	<.01	0.10	22	27411595	*CHEK2*	0.22	0.64
rs10499859	−0.29	0.10	<.01	0.10	7	79903461	*CD36*	0.29	0.31
rs3771452	0.28	0.09	<.01	0.10	2	70848516	*ADD2*	0.25	0.13
rs12508955	−0.33	0.12	.01	0.14	4	143007856	*IL15*	0.19	0.06
Offspring									
SBP									
rs1406229	0.77	8.38	<.01	0.10	2	29435266	*ALK*	0.06	0.52
rs1879282	−0.60	6.45	<.01	0.14	2	30941486	*CAPN13*	0.15	0.30
rs17005371	−0.51	4.72	<.01	0.10	2	26599412	*OTOF*	0.49	0.19
rs1406233	0.97	9.92	<.01	0.10	2	29368013	*ALK*	0.07	0.89
DBP									
rs1406229	0.57	0.14	<.01	0.06	2	29435266	*ALK*	0.06	0.52
rs1879282	−0.40	0.12	<.01	0.14	2	30941486	*CAPN13*	0.15	0.30
rs13000043	0.55	0.14	<.01	0.06	2	29423066	*ALK*	0.06	0.48
rs4952281	0.37	0.11	<.01	0.14	2	33091027	*LTBP1*	0.22	0.37
rs523349	−0.32	0.10	<.01	0.16	2	31717357	*SRD5A2*	0.26	0.08
rs13408063	0.30	0.09	<.01	0.16	2	33629906	*RASGRP3*	0.38	0.20

Note. SBP and DBP adjusted for antihypertensive medication in parents only. DBP = diastolic blood pressure; FDR = false discovery rate; HWE = Hardy-Weinberg equilibrium; MAF = minor allele frequency; SBP = systolic blood pressure.