Published in final edited form as:
J Cardiovasc Transl Res. 2012 June ; 5(3): 302–308. doi:10.1007/s12265-012-9362-y.

A Review of Genetics, Arterial Stiffness, and Blood Pressure in African Americans

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Abstract

The prevalence of hypertension in African Americans in the United States is amongst the highest in the world and increasing. The identification of genes and pathways regulating blood pressure in African Americans has been challenging. An early predictor of hypertension is arterial stiffness. The prevalence of arterial stiffness is significantly higher in African Americans compared to Caucasians. Approximately 20% of the variance in arterial stiffness is estimated to be heritable. Identifying genes and biological pathways regulating arterial stiffness may provide insight into the genetics underlying the increased risk of hypertension in African Americans. This paper reviews the genetic findings to date in the area of arterial stiffness and blood pressure in African Americans with an emphasis on the current limitations and new efforts to move the field forward.

Keywords

African Americans; arterial stiffness; arterial elasticity; compliance; genetics; DNA; variants; SNP; elastin; collagen; health and medicine

INTRODUCTION

The prevalence of hypertension in African Americans in the United States is amongst the highest in the world and increasing (1). According to the 2005–2006 National Health and Nutrition Examination Survey (NHANES), 27% of African American adults are hypertensive compared to 17% of Caucasians (2). This racial disparity in poorly controlled blood pressure exists after adjusting for demographics, socioeconomic status, clinical characteristics and modifiable health behaviors (2). This difference in hypertension prevalence suggests that other factors, including genetic factors, may play a significant contributing role in blood pressure. Hypertension is the most common risk factor associated with cardiovascular disease and is associated with a three fold increase in age-adjusted death rate (3). Thus, developing effective therapies to decrease hypertension would significantly lower the prevalence of cardiovascular disease. Identifying genes and pathways that predispose African Americans to high blood pressure would represent a major first step in developing new effective therapies to treat hypertension.

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Impaired arterial elasticity is an early predictor of hypertension in asymptomatic individuals (4–9). The prevalence of impaired arterial elasticity (as well as hypertension) is significantly higher in African Americans compared to Caucasians(10–14). Approximately 20% of the variance in arterial elasticity is estimated to be heritable (15,16). Previous studies have identified common variants associated with arterial elasticity across different ethnicities (15–56). Despite these investigations, relatively little of the phenotypic variance in arterial elasticity has been identified through common genetic variants using either candidate gene or genome-wide association scan (GWAS) approaches.

IMPAIRED ARTERIAL ELASTICITY IN AFRICAN AMERICANS

Evidence to date suggests that the prevalence of impaired arterial elasticity and hypertension is significantly higher in African American men compared to Caucasian men (11,12,14,57–60) (Table 1). Duprez and colleagues recently demonstrated that small artery elasticity is an early predictor of hypertension (6). In addition, Duprez showed that small artery elasticity is impaired in African Americans compared to Caucasian- and Asian-American participants in the Multi-Ethnic Study of Atherosclerosis (MESA) (14). The MESA cohort consists of ~ 6800 men and women ages 45–84 years with no clinical evidence of cardiovascular disease. These findings are similar to previously published work in the Bogalusa Heart Study showing decreased pulse wave velocity and decreased small and large artery elasticity in African Americans compared to whites (61). Shah and colleagues showed that arterial stiffness (as measured by pulse wave velocity and Augmentation index) is significantly increased in adolescent African Americans with type 2 diabetes compared to adolescent whites with type 2 diabetes (59). A meta-analysis with five cohorts by Chirinos et al showed that the central augmentation index, defined as a ratio calculated from a blood pressure waveform, is increased in African Americans compared to British whites (57). Heffernan showed that racial differences in low arterial compliance in African Americans compared to whites are unchanged with exercise (58). A lower arterial compliance in African Americans had previously been shown by Zion et al in 2003, Ferreira et al, in 1999 and Din-Dzietham et al in 2004 (60).

Over the last decade, different measurements including augmentation index, pulse wave velocity, pulse pressure and small and large artery elasticity have been utilized by different research groups and separate cohorts to measure arterial stiffness. The overwhelming conclusion is that African Americans exhibit impaired arterial stiffness, starting at a younger age, even after controlling for height, weight, LDL-C, diabetes and blood pressure and other risk factors compared to Caucasians (14,61–63).

GENETICS OF PULSE PRESSURE

To date, there has been little accomplished in defining the role of genetics in arterial stiffness in any ethnic group, but in particular, African Americans. A long-term goal of genetic studies in the area of arterial stiffness is to identify genes and biological pathways that contribute to early hypertension. A genome-wide linkage scan was performed as part of the Family Blood Pressure Program (FBPP) for loci affecting pulse pressure on 10798 participants in 3320 families(64). The Family Blood Pressure Program, FBPP, was established in 1995 to identify the role of DNA variants in hypertension in African-Americans, Hispanic, Asian and non-Hispanic white populations. Four separate networks are combined to form the FBPP: GenNet, Genetic Epidemiology Network of Arteriopathy (GENOA), Hypertension Genetics, Epidemiology Network (HyperGen), and Stanford Asian Pacific Program in Hypertension and Insulin Resistance (SAPPHIRE) (65). All ascertained families in the network include individuals with hypertension or genetic predisposition towards hypertension (64).

Pulse pressure (the difference between systolic and diastolic blood pressure) is not a direct method of measuring aortic stiffness; yet, pulse pressure has been used as a surrogate marker of arterial compliance. The FBPP linkage scan identified a region on chromosome 7 at 75 cM with a LOD = 3.1 in African Americans (LOD > 3 typically suggests a significant region of linkage), a region on chromosome 19 at 0 cM with a LOD = 3.1 in a combined sample of whites and African Americans, and a region on chromosome 18 at 71 cM with LOD = 3.2 in a combined racial sample (whites, African Americans and Hispanics)(64). Simino et al reported more recent results from the FBPP using an overall meta-analysis and four race-specific meta-analyses of genome wide blood pressure linkage scans. These analyses used data from 13,044 participants and identified one locus associated with pulse pressure (Chromosome 6, position 42.27 cM, LOD = 3.23) from the meta-analysis and a second locus (chromosome 1, 212.44 cM, LOD = 3.16) that associated with pulse pressure in one of the FBPP cohorts (HyperGEN) (66). The locus for pulse pressure on chromosome 6p22.3 was later identified as containing the most associated SNP (rs16877320) with systolic blood pressure in a meta-analysis of normotensive African Americans (67).

The HyperGEN (Hypertension Genetic Epidemiology Network) investigators (a component of the FBPP) performed a genome-wide linkage scan on 1251 African Americans (16). This study identified two regions of linkage with pulse pressure on chromosome 1 at 215 cM (LOD = 3.08) and another locus linked to pulse pressure on chromosome 14 at 85 cM with LOD = 2.42 (16). These loci contain many genes, but the ones closest to the linkage peaks were *GPR25* and *SMOC1*. These regions were not sequenced and there has been no follow up studies as of yet to replicate or confirm these findings.

GENETICS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE/ HYPERTENSION

The first GWAS to focus on blood pressure in African Americans was conducted by Adeyemo et al in 2009 in 1017 individuals (509 cases of hypertension and 508 normotensive controls) from the Howard University Family Study (67). No locus met genome wide significance (typically $P < 5\times10^{-8}$) for association with hypertension. Six SNPs met genome-wide significance for association with systolic blood pressure (see Table 1). One of these SNPs (rs3751664) was in a non-synonymous coding region of the gene *CACNA1H* (calcium channel, voltage-dependent, T-type, alpha 1H subunit, that encodes a member of the alpha-1 subunit family in the voltage-dependent calcium channel complex. No SNPs were found to significantly associate with diastolic blood pressure. The SNPs most associated with systolic blood were used for replication in a cohort of non-diabetic West Africans (n=980). Of the six most associated SNPs with systolic blood pressure in the Howard Family study, the non-synonymous coding SNP in the calcium channel protein (rs3751664) was monomorphic in the West African cohort, and the remaining five were not significantly associated with systolic blood pressure (67). Moreover, for the SNPs tested, the direction of the genotypic effect on blood pressure was not always similar in the original and replication study (67). One explanation for the difference in results is admixture between the discovery cohort (African-Americans) and the replication cohort (West Africa), with its effects on LD structure, allelic frequency distributions, and risk factor profiles (68,69). There was no overlap in the genes identified in this study (67) with the loci associated with impaired arterial elasticity or pulse pressure reported earlier (16,64). Associations with pulse pressure were not reported in this study by Adeyemo (67).

An admixture mapping study has implicated two regions, on 6q24 and 21q21, that may contain genes that influence risk of hypertension in African Americans (70). An admixture mapping approach used in the Dallas Heart Study Cohort implicated the gene, vanin 1 (*VNN1*) in the region on 6q24, (rs2272996) as associated with the risk for hypertension in

African Americans (71). The *VNN1* SNP increased risk for hypertension in African Americans yet conferred protection in European Americans (although It did not reach statistical significance in European Americans)(71). Recent transcription profiling work by Blangero and colleagues in lymphocytes suggests that sequence variants in *VNN1* are related to HDL cholesterol concentrations (72).

Fox et al (73) examined both genome-wide and candidate gene associations with systolic and diastolic blood pressure in 8,591 African Americans in the NHLBI Candidate Gene Association Resource (CARe) consortium. None of the SNPs tested using either the Affymetrix 6.0 GWAS panel or the ITMAT-Broad_CARe custom SNP array were replicated in an additional 11,882 African Americans or European Americans (69,899) (73). Previously identified blood pressure SNPs in European Americans were identified in African Americans although with weak significance (*SH2B3, TBX3-5, DBP*) (73). This study highlights many issues currently challenging the field of blood pressure, African-Americans and genetics including the complexity of the phenotype, and the admixture effects in African-Americans. An admixture approach using the CARe consortium in 6,303 African Americans followed by replication in four different African-American populations and one native Nigerian African sample (total n = 11,882) identified a novel SNP, rs7726475, associated with systolic and diastolic blood pressure between genes *SUB1* and *NPR3* (74).

A recent study by the International Consortium for Blood Pressure Genome-Wide Association Studies in multiple ancestries including a cohort of 19,775 African Americans identified multiple novel loci associated with blood pressure (75). These loci were associated with systolic and diastolic blood pressure in 200,000 Europeans, ~19,000 African Americans, ~ 29,000 East Asians, and ~24,000 South Asians. In African Americans, 22 loci were significantly associated with systolic or diastolic blood pressure ($P < 1 \times 10^{-8}$) (75) (see Table 1). Many of these SNPs were also significant in other race/ethnicities. Genes that had been implicated in previous studies but may have not achieved statistical significance were replicated in this study including (but not limited to) *NPR3*, *SLC4A7*, and *SH2B3*. A new gene *SLC39A8*, identified to be associated with both systolic and diastolic blood pressure in African Americans, European Americans and South Asians, is also associated with HDL cholesterol levels (similar to *VNN1*, but not replicated in this analysis). *NPR3* encodes the clearance receptor for natriuretic peptide and mice lacking this receptor have reduced blood pressure (76). *SLC4A7* is expressed in vascular smooth muscle and the nephron and regulates sodium bicarbonate (77). Knockout of this gene induces mild hypertension in mice. *SH2B3* has been implicated in multiple associations with immune and inflammatory diseases as well as hypertension (78,79); however its function remains unknown.

CONCLUSIONS, LIMITATIONS, AND FUTURE DIRECTIONS

In sum, the strength of the genetic studies for associations in systolic and diastolic blood pressure in African Americans is at a very early stage and will continue to improve with increased sample size as well as understanding of the complexities in uniqueness between ancestral genomes. The genetic associations between arterial stiffness in African Americans are also at a very early stage. Utilizing pulse pressure to estimate arterial stiffness may be a weakness of the early studies and the small sample size also represents a major hurdle of the early work done in this field. The potential importance of pairing genetics with phenotypic measurements of arterial stiffness include the identification of new pathways for drug development to prevent or inhibit cardiovascular disease.

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Table 1

Loci and Genes Associated with Pulse Pressure, Systolic and Diastolic Blood Pressure and Hypertension

Study	Race-ethnicity/country	Genotyping Platform	Traits	Discovery
FBPP[1]	AA (n=3962)/Whites (n=3667)/Hispanics (n=1612)/Asian(n=1557) U.S.	Genome-wide linkage	Pulse pressure	chromosome 7 at 75 cM, LOD 3.1 in AA, chromosome 19 at 0 cM LOD 3.1 in combined sample whites and AA, and a region on chromosome 18 at 71 cM LOD score of 3.2 in whites, AA, and Hispanics.
FBPP[2]	AA (n=3962)/Whites (n=3667)/Hispanics (n=1612)/Asian(n=2154): U.S.	Genome-wide linkage, race-specific meta-analyses	Pulse pressure	chromosome 6, 42.27 cM LOD 3.76 Raw PP, LOD 3.23 Medication adjusted PP, (META): chromosome 1 212.44 LOD 2.82 Raw PP, LOD 3.16 Medication adjusted PP, HyperGEN)
HyperGEN[3]	AA(n=1251) U.S.	Genome Scan	Pulse Pressure	Chromosome 1, 215 cM, LOD 3.08, Chromosome 14, 85 cM, LOD 2.42
Howard University Family Study[4]	AA (n=1017) U.S. 2nd cohort of 980 West Africans	GWAS Affymetrix 6.0	Systolic BP	rs5743185, rs16877320, rs11160059, rs17365948, rs12279202, rs3751664
FBPP[5]	AA (n=737) (cases) European Americans (n=573)(controls)	microsatellite markers and a set of informative SNPs: Admixture mapping	hypertension	5 markers on chromosome 6q (near region 6q24); 2 markers on chromosome 21 (near region 21q21) may contain genes influencing risk of hypertension in AA
Dallas Heart Study[6]	AA (n=1743), White (n=1000), Mexican American (n=581)	Admixture mapping 2,270 ancestral informative markers	Hypertension	rs2272996
CARe[7]	AA (n=8591), replication Cohorts: Women's Health Initiative; Maywood, GENOA, Howard University Family Study, native Nigerian African Sample (n=11,882)	GWAS Affymetrix 6.0 50K Cardiovascular gene-centric array	Systolic and diastolic blood pressure	none of the top SNPs replicated
CARe[8]	AA (n=6303), replication Cohorts: Women's Health Initiative, Maywood, GENOA, Howard University Family Study, native Nigerian African Sample (n=11,882)	admixture mapping follow up association	Systolic and Diastolic blood pressure	rs7726475 between genes SUB1 and NPR3
International Consortium for Blood Pressure Association Studies[9]	AA (n=19,775), Europeans (n=200,000), East Asians (n=29,719), South Asians	GWAS Meta-analysis	Systolic and Diastolic blood pressure, Hypertension	rs13082711 (SLC4A7) (SBP/DBP); rs419076 (MECOM), (SBP); rs13107325 (SLC39A8) (SBP/DBP); rs13139571 (GUCY1A3-GUCY1B3) (SBP/DBP); rs1173771 (NPR3-C5orf23) (SBP); rs11953630 (EBF1) (SBP/DBP); rs805303 (BAT2-BAT5) (DBP); rs7129220 (ADM) (SBP/DBP); rs633185 (FLJ32810/TMEM133) (SBP); rs2521501 (FURIN-FES) (SBP/DBP); rs17608766 (GOSR2) (SBP/DBP); rs1327235 (JAG1) (SBP/DBP); rs6015450 (GNAS-EDN3)

Study	Race-ethnicity/country	Genotyping Platform	Traits	Discovery
				(SBP/DBP); rs17367504 (MTHFR-NPPB) (SBP/DBP); rs3774372 (ULK4) (SBP/DBP); rs1458038 (FGF5) (SBP/DBP); rs1813353 (CACNB2(3') (SBP/DBP); rs11191548 (CYP17A1-NT5C2) (SBP/DBP); rs381815 (PLEKHA7) (SBP/DBP); rs3184504 (SH2B3) (SBP/DBP); rs1378942 (CYP1A1-ULK3) (SBP): rs12940887 (ZNF652) (SBP/DBP)

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