Genetic Influences on the Increase in Blood Pressure with Age in Normotensive Subjects in Barbados

Miguel T. Robinson, PhD; Nathan Fischel-Ghodsian, MD; Henry S. Fraser, MBBS, PhD; George D. Nicholson, MD; Carlene M. Grim, RN, MSN, SpDN; Dorothea M. Wilson, MA; Thomas W. Wilson, PhD, MPH, DrPH; Clarence E. Grim, MS, MD

The authors tested the single and combined effects of nuclear and mitochondrial DNA genotypes on the phenotypes of systolic blood pressure (SBP) and weight, and their changes over 5 years in normotensive subjects living in Barbados. The nuclear genotypes were gender (Y chromosome), haptoglobin (HP), and group specific component (Gc). A mitochondrial genotype was chosen as a marker for maternal lineage. Baseline clinic SBP and weight ($N=78$), 24-hour SBP ($N=28$) were measured. Five years later, clinic SBP and weight were measured again in 28 participants. Male participants generally had higher pressures than female participants. The HP genotype was associated with 5 of the 8 SBP phenotypes.

The haptoglobin-1(HP1) allele was associated with higher clinic ($P=.024$) and evening SBP at baseline ($P=.020$). The effect of HP1 appears to be dominant. Haptoglobin-2 (HP2) was associated with the increase in weight over 5 years ($P=.002$). Group specific component (Gc) genotype was associated with 6 of the 8 SBP phenotypes. The Gc polymorphism 2 was associated with higher 24-hour SBP, sleep SBP (midnight–6 AM), afternoon SBP (noon–6 PM) and evening SBP (6 PM to midnight). Furthermore, we found a significant association between the haptoglobin/mt-DNA and Gc/mt-DNA polymorphisms with SBP between 6 PM and midnight ($P=.009$ and $P=.011$, respectively). The 5-year changes in SBP were significantly associated with the haptoglobin/mt-DNA and Gc/mt-DNA polymorphisms ($P=.005$ and $P=.011$, respectively). Multivariate analysis for genetic effects on change in weight and change in BP suggested the rise in BP, but was not suggestive of change in weight. Furthermore, multivariate analysis was associated with Gc, but not Haptoglobin genotype. In normotensive subjects of African descent living in Barbados, the increase in blood pressure with age is significantly influenced by both nuclear and mitochondrial genotypes that are more common in African derived populations. (*Ethn Dis*. 2004;14:57–63)

Key Words: Haptoglobin, Gc, Blood Pressure, mt-DNA

From the Department of Psychiatry, UC San Diego, La Jolla (MTR), Pediatrics, Cedars-Sinai Medical Center, Los Angeles (NFG), California; University of the West Indies, Barbados (HSF); University of the West Indies, EC (GDN); Shared Care Research, Milwaukee, WI (CMG); Wilson Research, LLC, Loveland, Ohio (DMW, TWW); Internal Medicine Medical College of Wisconsin, Milwaukee, Wisconsin (CEG).

Address correspondence and reprint requests to Clarence E. Grim, MD; Professor of Medicine; Medical College of Wisconsin; 9200 W Wisconsin; Milwaukee, WI 53226; 414-750-5614; 414-374-9927 (fax); lowerbp2@aol.com

Introduction

The tendency for blood pressure (BP) to rise with age aggregates in families and twin and adoption studies suggest a major influence of genetic factors on BP variation.[1] One of the hopes of genetic researchers is that we will be able to find markers that predict who will experience a rise in blood pressure with age. Once such a marker is discovered, researchers can begin to test intervention strategies in a much smaller sample. However, efforts to link specific genetic markers with cross-sectional BP variation have not met with great success; the exception to this has been when another phenotypic marker, such as low potassium, as well as BP, could be measured in families.[2] To date, no studies have tested genetic factors analyzing their influence on the increase in BP with age. Studies attempting to link genetic factors to BP variation among the African Diaspora have also met with mixed results. The distinguishing feature of the syndrome called essential hypertension is the tendency for BP to rise with age. To learn more about this phenomenon, we conducted a study of genetic links to the changes in BP over 5 years in a sample of normotensive subjects of African descent living in Barbados. Heritability computations estimated that approximately 50% of BP variability in this population is related to heritable factors[3] and differed by mitochondrial genotype.[4,5] By design, we initially incorporated a set of standard genetically determined protein markers in our candidate genetic screening pool and then added mitochondrial genetic markers when they became available.[6–8] Many have reported an association between the Haptoglobin 1 allele and increased BP.[9–11] Group specific component (Gc) proteins, which differ widely around the world, are now known to be the human-plasma-protein, vitamin-D-binding, alpha globulin.[12] Mourant et al[13] concluded that the high frequency of the Gc (20 alleles) and their geographic variation were related to levels of sunlight. Because of the likelihood that the genotype leading to the greater rise in BP with age in AAs is from Africa,[14,15] we became interested in mitochondrial DNA (mt-DNA), which has a unique pattern of inheritance. Since mt-DNA is only transmitted through the egg, it is clearly a marker of biological maternal lineage of an individual.[16] Preliminary results suggested that Blacks in Barbados with African maternal lineage have higher BP than those with a non-African maternal lineage.[4]

The purpose of this study was to evaluate the single and combined effects of the haptoglobin (HP), Gc, and mitochondrial DNA polymorphisms on baseline and longitudinal changes in BP and body weight in an African-derived population in the Western Hemisphere.

Because of the likelihood that the genotype leading to the greater rise in BP with age in AAs is from Africa,[14,15] we became interested in mitochondrial DNA (mt-DNA), which has a unique pattern of inheritance.

MATERIALS AND METHODS

The total study population at baseline consisted of 78 normotensive Black Barbadians, 50 of whom had one or more genetic markers determined.[3] Of these 50 participants, 32 were male subjects and 18 were female subjects with a mean age of 30.7 ± 10.7 years. Five years after baseline, data was available on 40 subjects; 28 of these 40 individuals had genetic markers determined at baseline. Weights, heights, and manual BPs were determined by methods previously described.[3] Participants' BPs were taken in the supine position to minimize effects due to cuff-position and height. Clinical BPs were taken with an appropriate size cuff on the right arm after the subjects had been lying down for at least 5 minutes. The BP was taken by 2 separate observers (one male and one female), who were blinded to each other's readings. The observers had been re-certified within 2 weeks of the study using the Shared Care videotape method[17] to assure that their ability to hear Korotkoff sounds to within ± 2 mm Hg was intact. Because diastolic blood pressure (DBP) was frequently heard to zero, we did not analyze the diastolic pressures. Six BP readings were, taken during each visit; the average of these 6 readings was used as the clinic supine BP for that visit. The ambulatory 24-hour BP was obtained in 24 participants using the Delmar Avionics PllI device with techniques previously described.[18] This 24-hour BP was completed at baseline only.

Methodologies for nuclear and genotypic determinations of human subjects have been previously reported.[19,20]

The observations taken in 1989 are labeled as the baseline readings, while those taken in 1994 are called the follow-up or 5 year values.

Statistical analysis of these data was performed using the software program SPSS for Windows version 5.0. Standard analysis of variance (ANOVA) statistical procedures were used to determine if there were significant differences in group means for BPs across the various genotypes. The independent variables were: gender and Gc; HP; and mitochondrial DNA genotypes. The dependent variables were: clinical BP; weight and systolic/diastolic BP at the various time intervals in the 24-hour cycle; BP in 1994; and the change in BP and body weight at follow-up. The difference between the observed number of individuals and the expected number of individuals of each Gc, and HP genotype was examined by chi-square analysis (Hardy-Weinberg equilibrium). All variables were normally distributed. The statistical corrections and standard Bonferroni corrections for multiple comparisons were as follows: the level of significance for clinic BPs was 0.025; the level of significance for 24-hr BPs was 0.0125; the level of significance for weight was 0.025; and the level of significance for the change in weight and BP was 0.05 in each genetic polymorphism model.

For identification, the model that contains mt-DNA and HP will be referred to as the Hapto model; and the one that contains mt-DNA and Gc will be known as the Gc model.

RESULTS

The detailed results are seen in Tables 1–4. The statistical results are summarized in Table 3 for the HP model and Table 4 for the Gc model. Readers may obtain the complete reference tables listing the results of the ANOVA from the authors. When gender differences were noted, male participants always had a higher pressure; thus, the Y chromosome appears to result in higher BP and a greater increase in BP with age. However, in this sample, the Y chromosome did not appear to affect cross-sectional weight.

The average age was 30 in the baseline group and 33 in those followed for 5 years. Although, more male than female participants were seen at both times, the numbers of male participants remained similar at baseline and 5 years thereafter. Body weight was not significantly different at baseline or at follow-up. Weight gain over the years was significant and similar in both men and women.

Clinic Blood Pressure (BP) and Changes Over 5 Years

Systolic blood pressure (SBP) was higher in men at base line and at the 5-year follow-up. While BP increased significantly in men, women in this sample did not show an increase in BP. Systolic BP at baseline and at 5 years was not correlated with weight, but was affected by gender and genotype as described below.

Ambulatory Blood Pressure (BP)

Ambulatory blood pressure was obtained in only 4 women; yet their BP was lower than men in this measure. The 24-hour average BP reading obtained in these 4 women was correlated with the clinic BPs (P=.05). Systolic blood pressure (SBP) was lower during sleep in these subjects, but did not differ from the 24-hour average BP during the rest of the day.

Genetic Effects on Blood Pressure (BP) and Change in BP

The study population was not found to be in Hardy-Weinberg equilibrium

Table 1. Demographics and blood pressures at baseline and at follow-up

Variable	Baseline	Follow-up	P
Number (males + females)	(32 + 18)	(18 + 13)	
Age (range)	29.9 ± 9.6 (17–44)	32 ± 7 (22–49)	
Clinic BP supine			
Men	123 ± 10 (103–166)	127 ± 11 (109–155)	*P*<.0007
Women	107 ± 10 (94–133)	109 ± 12 (99–152)	*P*=.554
24 hr systolic blood pressure (X ± SD) (range)			
Men (*N*=21)	122 ± 10 (91–131)		
Women (*N*=4)	112 ± 9 (90–125)		
Sleep systolic blood pressure	109 ± 9.8 (88–127)		
Morning systolic blood pressure	124 ± 11.4 (103–149)		
Afternoon systolic blood pressure	120 ± 10.4 (108–148)		
Evening systolic blood pressure	120 ± 10.4 (95–139)		
Change in clinic systolic blood pressure (5-year baseline)			
All		4.8	.007
Men (*N*=18)		8.6 mm Hg	.007
Women (*N*=13)		0.5 mm Hg	NS
Weight (kg)			
All	70 (*N*=50)	74 (*N*=28)	NS both times
All men	71	72	NS both times
All women	67	72	NS both times
Change in weight (5-year baseline)			
All		6.5	.041
Men		5.2	.05
Women		7.9	.05

for the 2 diploid polymorphisms associated with BP. The significance statistics of the chi-square analysis of the HP, and Gc polymorphisms were all <0.001.

Haptoglobin (HP) and Blood Pressure (BP) Phenotypes

As Table 2 illustrates, the HP genotype showed a significant or near significant effect in 5 of the 8 systolic BP phenotypes; and the HP1 allele was associated with the higher BP in 6 of the 8 phenotypes. Both homozygous genotypes were associated with an increase in BP with age. Haptoglobin (HP) had an effect on the clinic BP measured at baseline, but not at follow-up. For the clinical SBPs, the effect was clearly due to a higher pressure in those with the 1 allele. Unquestionably, for the baseline (1989) SBP, where most subjects had both BP and genotyping (*N*=50), the fact that 1-1 and 1-2 genotypes have a higher BP than the 2-2 suggests a dominant effect for HP. The rise in BP was also affected by HP genotype; but the effect of the homozygous genotypes had the greater BP increase with age. While there was no effect on cross-sectional weight, the increase in weight was influenced by HP genotype; and it was the HP2 allele that had a dominant effect.

Table 3 lists the influences of the Gc genotype on the same phenotypes as Table 2. Systolic blood pressure (SBP) was influenced by the Gc2 allele in 6 of the 8 BP phenotypes. The clinic BPs did not show a clear significant effect of Gc, nor did the change in BP with age. For the 24-hr SBP, there appears to be a

Table 2. The effect of Haptoglobin genotype on systolic blood pressure (SBP) and weight phenotypes over 5 years of follow-up

	HP Genotype			
Phenotype	1–1	1–2	2–3	*P*
24 hr SBP	124	123	116	NS
6 AM–12 noon (morning)	127	125	127	NS
Noon–6 PM (afternoon)	127	129	119	.044
6 PM–midnight (evening)	124	124	110	.020
Midnight–6 AM (sleep)	115	109	103	.076
Systolic 1989 clinic	118	118	111	.024
Systolic 1994 clinic	124	119	113	NS
Change in SBP	7.3	−0.4	7.8	.039
Weight 1989	66	73	70	NS
Weight 1994	66	84	74	NS
Change in weight	3.2	10.8	9.6	.002

Table 3. The effect of Gc Genotype on systolic blood pressure (SBP) and weight phenotypes over 5 years of follow-up

	Gc Genotype			
Phenotype	**1–1**	**1–2**	**2–2**	***P***
24 hr SBP	116	122	127	.013
6 PM–12 noon	119	121	135	.095
Noon–6 PM	118	126	135	.017
6 PM–midnight	114	125	121	.017
Midnight–6 AM	103	110	115	.04
Systolic 1989 Clinic	113	117	115	.073
Systolic 1994 Clinic	126	119	114	NS
Change in SBP	13	1.5	−0.28	NS
Weight 1989	61	71	74	NS
Weight 1990	67	75	73	NS
Change in weight	7.7	6.8	3.8	NS

dominant effect for the 2 allele. No effect of Gc on the weight phenotypes was evident.

Weight and Changes in Weight Influenced by mt-DNA and Gender

As seen in Table 1, the baseline weight was 70 kg increasing to 74 kg 5 years later (P=.05). As seen in Tables 2 and 3, no detectable effects of any of the genetic markers on cross-sectional weights were observed in 1989 or 1994. The weight at either time did not differ between men and women in this data set. The change in weight was the factor that appeared to be most notably under HP influence. When the mt-DNA effects were tested (no table), the change in weight averaged 6.7 kg; and this varied by gender (male subjects 5.2, female subjects 8.4; P=.041). In mt-DNA Type 3, weight increased by 8.2 while Type 2 increased only by 5 kg (P=.021). In men with Type 3, the gain was 3.5 kg. In Type 2, it was 6.5 kg; and in women with type 3, it was 11.2. However, in type 2 it was only 6.4 kg (P=.05). Haptoglobin genotype had a significant effect on weight gain (Table 2) (1-1=3.2 kg, 1-2=10.8 kg, 2-2=9.6 kg; P=.002). The similar gain by those with type 2 suggests a dominance effect of the system on weight gain. This phenomenon was true in men and women (data not shown). With the Gc model, there were no effects on the baseline, 5-year weights on increases in weight. In this sample, the results suggest that change in weight is the factor most influenced by the genetic influences of mt-DNA and HP.

Haptoglobin Model

Hapto Model (Table 4): Male participants had higher SBP than female participants in both their clinic readings and in SBP increases with age. Male subjects also had higher 24-hour and evening SBP than female subjects. Mt-DNA did not affect the 24-hr BP. Haptoglobin (HP) affected the baseline SBP and the change in SBP.

Table 3 lists the influences of the Gc genotype on the same phenotypes as Table 2. Systolic blood pressure (SBP) was influenced by the Gc2 allele in 6 of the 8 BP phenotypes. The clinic BPs did not show a clear significant effect of Gc, nor did the change in BP with age. For the 24-hr systolic BP, there appears to be a dominant effect for the 2 allele. No effect of Gc on the weight phenotypes was noted.

Five year change in SBP: gender and HP contributed to the main effects. Taking a look at this 5-year change in BP, the Hapto 1-2 had the lowest BP rise. Although the numbers were small (and not significant), the male partici-

Table 4. Haptoglobin Model: *P* values from analysis of variance; effects of gender, mt-DNA, and haptoglobin on systolic blood pressure and weight measurement at baseline in 1989 and at 5 years of follow-up in 1994

Effects	**89 Clinic Ave Sys mm Hg**	**Ave 24 hr Sys mm Hg**	**Sleep Sys 12–6 AM mm Hg**	**Morning Sys 6–12 AM mm Hg**	**Afternoon 12–18 PM mm Hg**	**Evening 18–24 PM mm Hg**	**94 Clinic Ave Sys**	**5 yr Sys Change mm Hg**	**Wt 89 kg**	**Wt 94 kg**	**5 yr Wt Change kg**
N	**50**	24	24	24	24	**24**	**28**	**28**	50	28	**28**
Mean value	**117**	122	111	124	127	**122**	**121**	**4.9**	69.9	73.6	**6.6**
Main effects	**<.001***	.101	.067	.511	.051	**.007***	**<.001***	**.007***	.289	.305	**.001***
Gender	**<.001***	**.035**	.076	.114	.072	**.017***	**<.001***	**.012***	.244	.301	**.041***
Mt-DNA	.453	.959	.321	.456	.511	.087	.052	.083	.957	.903	**.021***
Higher allele											**3**
Hapto	**.024***	.172	.076	.960	.044	**.020***	.303	**.034***	.165	.138	**.002***
Higher allele	**1**					**1**		**1–1, 2–2**			**2**
Explained (*P*)	**<.001***	.101	.067	.511	.051	**.007***	**<.001***	**.007***	.155	.305	**.001***
% Explained	**60%**	NS	NS	NS	38%	**51%**	**60%**	**44%**	NS	NS	**54%**

Bold type and * indicates P=.05.
Main=main effects, gender, mt-DNA genotype (2 or 3), haptoglobin genotype (1–1, 1–2, or 2-2).

Table 5. Gc Model: *P* values from analysis of variance; effects of gender, mt-DNA, and Gc on systolic blood pressure measurement at baseline in 1989 and at 5 years of follow-up in 1994

Effects	89 Clinic Ave Sys	Ave 24 hr Sys	Sleep Sys 12–6 AM	Morning Sys 6–12 AM	Afternoon 12–18 PM	Evening 18–24 PM	94 Clinic Ave Sys	89–94 Sys Change	Wt 89 kg	89–94 Wt Change	Wt 94 kg
Number	49	24	24	24	24	24	28	28	49	28	28
Mean value	116	121	108	122	125	121	120	**4.9**	69	6.4	72.3
Main	**<.001***	**.004***	**.027***	.054	**.013***	**.001***	**<.001***	**.001***	.127	151	.821
Gender	**<.001***	**.004***	**.024***	.087	**.037***	**.001***	**<.001***	**.004***	.254	.167	.451
Mt-DNA	.414	.606	.651	.117	.197	.091	**.046***	**.041***	.974	.047	.908
Higher allele							**3**	**3**			
Gc	.073	**.013***	**.040***	.085	**.017***	**.017***	.681	**.007***	.053	.618	.639
Higher allele		**2**	**2**		**2**	**2**		**1**			
Explained (*P*)	**<.001***	**.004***	**.027***	.054	**.013***	**.001***	**<.001***	**.001***	.365	.151	.821
% Explained	**58%**	**58%**	**42%**	NS	**47%**	**59%**	**60%**	**54%**	NS	NS	NS

Bold type and * indicates *P*=.05.

Main=main effects, gender male, female, mt-DNA genotype (2 or 3). Gc genotype 1 or 2. Explained contains the *P* for the % of variance explained by the variables and % explained is the % explained by the variables.

pants in this category were homozygous for HP1, had the "African" mt genotype 3, and manifested an increase in SBP of 18.4 mm Hg among male subjects in this model.

Five year change in weight: the average increase in weight was 6.6 kg. These changes in weight were affected by gender (women gained more), mt-DNA (type 3 gained more), and by HP genotype (Hapto-2 was associated with a greater weight gain).

Gc Model

Table 5: gender influenced all but one of the BP phenotypes. Male subjects always had the higher BPs, and the greatest increase in BP. Group specific component (Gc) did not influence the clinic BPs. A significant effect was observed on the 24-hr systolic and for all BPs, except the morning SBP. For the cross-sectional BPs, the type 2 allele was associated with higher BP. However, the increase in systolic pressure over 5 years was greater in those with the Type 1 allele. Within the Gc model, there were no gender or genetic influences on body weight fluctuations.

Our results now add 3 genetic influences: (mt-DNA, HP, and Gc) to those genetic factors associated with increase in hypertension with age, at least in those individuals of African descent.

Multivariate Analysis

A model with HP and mt-DNA reflecting simultaneous changes in SBP and weight (wt) was analyzed separately by gender. In male subjects, the change in BP was significantly affected by mt-DNA ($P<.0001$) and haptoglobin ($P=.006$) genotype, but the change in weight was not affected by mt-DNA. In females, increases in weight and BP were not influenced by mt-DNA genotype; however, haptoglobin genotype influenced both (wt $P=.018$, BP $P=.048$).

DISCUSSION

Essential hypertension is defined as the increase in BP with age. Increasing blood pressure (BP) with age is a pervasive phenomenon seen in all societies in the world except those that consume a low-sodium diet. A long-term goal of genetic researchers is to identify who will develop this condition; this crucial information will aid researchers as they test intervention strategies for prevention. The rise in BP with age in adult populations is a function of dietary salt intake as shown by the INTERSALT; those with the highest sodium intake had the greatest rise in BP with age. The rise in BP with age and/or migration has also been shown to be familial.[22] Our results now add 3 genetic influences: (mt-DNA, HP, and Gc) to those genetic factors associated with increase in hypertension with age, at least in those individuals of African descent. The increase in body weight is another important risk factor associated with the increase in BP with age; and this risk factor shows wide population variation. On average, our subjects gained weight, but this did not predict the rise in pressure. In addition, joint genetic influences on body weight and the increase in BP with age were identified.

Most studies looking at the effects of genetic factors on BP in Blacks and Whites have been cross-sectional; thus, the phenotype has generally been based on a few BP measurements on only one or a few days. These measurements are subject to many sources of environmen-

tal effects. On the other hand, the tracking of BP over time may be a more stable estimate of the phenotype of BP that leads eventually to a level that is called hypertension. Ambulatory BP may be a better phenotype, as many more BP readings are available. Therefore, our study showed significant genetic effects on the ambulatory measurements and the change in BP with age. The failure to find effects on variations in BP during certain times of the day may be the result of our small sample size; or it may mean that diverse genetic mechanisms influence BP at different times of the day. A more likely explanation may be that genetic factors exert influences on the rhythms of the 24 hour BP.[23] Due to our small sample size, we did not analyze the effects on 24-hour rhythm patterns.

Hypertension and Haptoglobin

The authors have shown a clear effect of HP on BP and the increase in SBP over a 5-year period. An association of a protein in human plasma associated with human hypertension was first reported in 1981[23] and with HP in Australian Whites in the same year.[24] The protein was identified as the same protein as HP[25] by German investigators in 1985. Delanghe et al[26] showed that hypertensives with the 2-2 phenotype required more complex drug combinations to gain BP control. In 1987, Weinberger et al[9] reported an effect of the HP1 allele on BP in White adults and their children. In subjects tested for salt sensitivity (SS) using the Grim-Weinberger protocol, those with the HP1 allele had greater changes in BP when going from a high-sodium to a low-sodium state and were thus more SS. On the other hand, Weder et al[10] did not find an effect of HP on BP variation in a large population based sample of Whites in Michigan. Kojima et al[27] tested SS using a dietary protocol in Japanese hypertensives and found more SS subjects in those with the FP-1 allele.

If the heterozygote is indistinguishable from one of the homozygotes, then one of the alleles is referred to as dominant to the other. In our study, it appears as though the HP1 allele is dominant to the HP2 allele in BP regulation. No significant difference in average BPs between the Hp 1-1 homozygote and Hp 2-1 heterozygote were observed; however, there is a significant difference in BP between the Hp 1-1 and HP-21 genotypes and the HP 2-2 genotypes. The evidence for dominance was first pointed out to us by our reviewers for this journal. The authors have reviewed the literature for evidence of dominance. Several large studies reported an effect of HP1, but did not mention the dominance effect. Thus, Weinberger et al[9] studies also clearly show a dominance effect of HP1 in adults and this same effect in White children. The change in BP with acute sodium balance changes also shows dominance. Furthermore, Kojima[27] tested SS utilizing a 14-day protocol and also found a greater number of SS subjects in those with HP1. The data from this study suggests a dominant allele. Kojima et al also found that the SS subjects had lower renin and aldosterone levels on the low-sodium intake protocol.

Additionally, our study reports a dominance effect of HP2 on the increase in weight over 5 years. Our observations reflect that increases in BP with age were neither correlated with weight gain, nor with the differing effects of the HP genotype on the weight gain. These findings suggest that both gain in weight and increase in SBP over time are likely under the control of different genetic mechanisms.

Individuals of African descent in the Western Hemisphere have higher rates of obesity than those living in West Africa today. Although differences are almost certainly related to environmental effects, such as increased calories and less exercise, our studies suggest that 2 genotypes that are more common in Africa (mt-DNA Type 3 and HP1) also have an effect on the weight gain over 5 years. This gain in weight was not correlated with an increase in BP.

Vitamin D Alpha-binding Globulin (Gc) and Blood Pressure (BP) Variation

Although we report an association of the Gc polymorphism with 24-hour BP, this finding did not apply to the increase in BP over a 5-year period in Afro-Caribbeans. Other reports that have tested the effect of Gc on BP have not been located. As Gc also plays a key role in Vitamin D metabolism, it should likewise be investigated for a possible role in the effect of sunlight exposure on BP variation. Both Rostand[28] and Callivari-Sforza have suggested that the world-wide genotype variation appears to be related to level of UV light exposure.

Mt-DNA and Blood Pressure (BP) Variation

Two patterns are detected with the Hpa I enzyme: Denaro Morph 3, which is found only in those of African descent (85.7%) and within African populations (Bushman, 92.7%; Pygmy, 95.5%; Bantu, 70.8%); and Morph 2 which is found much less commonly in Africans (1.5%), but is found in 98.1% of Caucasians and 81.3% of Asians. Our first report of an effect of mt-DNA genotype suggested that the Type 3 genotype was associated with a higher BP.[4] This finding is strengthened by our observation that this same genotype is associated with a greater increase in BP with age. The authors are not aware of other published reports of the effect of mitochondrial genotype on BP in other populations.

Limitations of the Study

Although our sample size was, in some respects, relatively small, this limitation was likely overcome by our careful measurement of BP, our 24-hour BP data, and by the longitudinal data included in the study.

SUMMARY

The authors have found individual and epistatic effects of 2 nuclear and one mitochondrial genotype on the phenotypes of supine and ambulatory BP and weight, as well as on the rise in supine SBP and weight over a 5-year period in an Afro-Caribbean population.

These findings suggest that the high prevalence of hypertension in African derived populations in the new world may be related to a higher frequency of these polymorphisms in African in contrast to European populations.

ACKNOWLEDGMENTS

This research was supported in part by the following grants: NIH RCMI G12RR-03026, 7K, 4HL-01885, T32M-HL07655, RR 03026, and the American Heart Association, Minority Scientist Development Award (Dr. Robinson).

REFERENCES

1. Grim CE, Robinson M. Blood pressure variation. In: Goldbourt U, De Faire U, Berg K, eds. *Genetic Factors in Coronary Heart Disease.* Netherlands: Kluwer Academic Publishers; 1994:153–177.
2. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell.* 2001;104(4):545–556.
3. Grim CE, Wilson TW, Nicholson GD, et al. Blood pressure in Blacks: twin studies in Barbados. *Hypertension.* 1990;15:803–809.
4. Grim CE, Miller RW, Fischel-Ghodsian N, et al. Mitochondrial genotype is related to cardiovascular risk factors in Blacks. *Hypertension.* 1991;18:377–378.
5. Arevalo R, Saldana G, Visnawanathan A, et al. Mitochondrial genotype is related to mean systolic blood pressure in Blacks. *Am J Kidney Dis.* 1993;21(suppl 1):75.
6. Knuiman MW, Divitini ML, Welborn TA, Bartholomew HC. Familial correlations, cohabitation effects, and heritability for cardiovascular risk factors. *Ann Epidemiol.* 1966;6: 188–194.
7. Fuentes RM, Notkola IL, Shemeikka S, Tuomilehto J, Nissinen A. Familial aggression of blood pressure: a population-based family study in eastern Finland. *J Hum Hypertens.* 2000;14:441–445.
8. Wang X, Wang B, Chen C, et al. Familial aggregation of blood pressure in a rural Chinese community. *Am J Epidemiol.* 1999;149: 412–420.
9. Weinberger MH, Miller JZ, Finebert NS, Luft FC, Grim CE, Christian JC. Association of haptoglobin with sodium sensitivity and resistance of blood pressure. *Hypertension.* 1987;10:443–446.
10. Weder AB, Schork NJ, Julius S. Linkage of MN locus and erythrocyte lithium-sodium counter transport in Tecumseh, Michigan. *Hypertension.* 1991;17:977–981.
11. Luft FC, Miller JZ, Grim CE, et al. Salt sensitivity and resistance of blood pressure. Age and race as factors in physiological responses. *Hypertension.* 1991;17(suppl):1102–1108.
12. Daiger SP, Cavalli-Sforza LL. Detection of genetic variation with radioactive ligands. II. Genetic variants of vitamin D-labeled group-specific component (Gc) proteins. *Am J Hum Genet.* 1977;29:593–604.
13. Mourant AE, Tills D, Domaniewska-Sobczak K. Sunshine and the geographical distribution of the alleles of the Gc system of plasma proteins. *Hum Genet.* 1976;33:307–314.
14. Grim CE. On slavery, salt, and the greater prevalence of hypertension in Black Americans. *Clin Res.* 1988;36:430.
15. Grim CE, Wilson TW. Salt, slavery, and survival: physiological principles underlying the evolutionary hypothesis of salt sensitive hypertension in western hemisphere Blacks. In: Fray JCS, Douglas JG, eds. *The Pathophysiology of Hypertension in Blacks.* New York, NY: Oxford University Press; 1993:22–48.
16. Cann RL, Stoneking M, Wilson AC. Mitochondrial DNA and human evolution. *Nature.* 1987;325:31–35.
17. Grim CE, Grim CM. A curriculum for training and certification of blood pressure measurement for healthcare providers. *Can J Cardiol.* 1995;11(suppl H):38H–42H.
18. Harshfield GA, Hwang C, Grim CE. Circadian variation of blood pressure in Blacks: influence of age, gender, and activity. *J Hum Hypertens.* 1990;4:43–47.
19. Field LL, Heckenlivity JR, Sparkes RS, et al. Linkage analysis of 5 pedigrees affected with typical autosomal dominant retinitis pigmentosa. *J Med Genet.* 1982;19:266–270.
20. Anderson S, Bankier AT, Barrell BG, et al. Sequence and organization of the mitochondrial genome. *Nature.* 1981;290:457–465.
21. Ward RH, Chin PG, Prior IA. Tokelau Island Migrant Study. Effect of migration on the familial aggregation of blood pressure. *Hypertension.* 1980;4:43–54
22. Moore JH. *Genetic Analysis of Dynamics of Quantitative Traits* [PhD thesis]. Ann Arbor, Mich: University of Michigan; 1999.
23. Nardi R, Sawa H, Caretta R, Bianchi M, Fernandes M. Characteristic variation in electrophoretic pattern of plasma proteins in essential hypertension. *Lancet.* 1980;182–183.
24. Buckton K, Lai LYC, Gibson JB. A search for association between gene markers and serum cholesterol, triglyceride, urate, and blood pressure. *Ann Hum Biol.* 1981;8:39–48.
25. Henke JA, Morich FJ. Identification of a so far not characterized human serum protein associated with essential hypertension. *Electrophoresis.* 1985;6:292–295.
26. Delanghe JR, Duprez DA, De Buyzere MI, et al. Haptoglobin polymorphism and complications in established essential arterial hypertension. *J Hypertens.* 1993;11:861–867.
27. Kojima S, Inenaga T, Matsuoka H, et al. The association of blood pressure with some polymorphic factors. *J Hypertens.* 1994;12:797–801.
28. Rostand SG, Drueke TB, Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int.* 1999;56: 383–392.

AUTHOR CONTRIBUTIONS

Design and concept of study: Robinson, Fischel-Ghodsian, Fraser, Nicholson, CM Grim, DM Wilson, TW Wilson, CE Grim

Acquisition of data: Fischel-Ghodsian, Fraser, Nicholson, CM Grim, DM Wilson, TW Wilson, CE Grim

Data analysis and interpretation: Robinson, TW Wilson, CE Grim

Manuscript draft: Robinson, CE Grim

Statistical expertise: Robinson, TW Wilson, CE Grim

Acquisition of funding: CE Grim

Administrative, technical, or material assistance: Robinson, Fischel-Ghodsian, CM Grim, DM Wilson, CE Grim

Supervision: Fraser, Nicholson, CM Grim, TW Wilson, CE Grim