

## Blood Pressure and Cerebral White Matter Share Common Genetic Factors in Mexican Americans

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**Abstract**—Elevated arterial pulse pressure and blood pressure (BP) can lead to atrophy of cerebral white matter (WM), potentially attributable to shared genetic factors. We calculated the magnitude of shared genetic variance between BP and fractional anisotropy of water diffusion, a sensitive measurement of WM integrity in a well-characterized population of Mexican Americans. The patterns of whole-brain and regional genetic overlap between BP and fractional anisotropy were interpreted in the context the pulse-wave encephalopathy theory. We also tested whether regional pattern in genetic pleiotropy is modulated by the phylogeny of WM development. BP and high-resolution ( $1.7 \times 1.7 \times 3$  mm; 55 directions) diffusion tensor imaging data were analyzed for 332 (202 females; mean age  $47.9 \pm 13.3$  years) members of the San Antonio Family Heart Study. Bivariate genetic correlation analysis was used to calculate the genetic overlap between several BP measurements (pulse pressure, systolic BP, and diastolic BP) and fractional anisotropy (whole-brain and regional values). Intersubject variance in pulse pressure and systolic BP exhibited a significant genetic overlap with variance in whole-brain fractional anisotropy values, sharing 36% and 22% of genetic variance, respectively. Regionally, shared genetic variance was significantly influenced by rates of WM development ( $r = -0.75$ ;  $P = 0.01$ ). The pattern of genetic overlap between BP and WM integrity was generally in agreement with the pulse-wave encephalopathy theory. Our study provides evidence that a set of pleiotropically acting genetic factors jointly influence phenotypic variation in BP and WM integrity. The magnitude of this overlap appears to be influenced by phylogeny of WM development, suggesting a possible role for genotype-by-age interactions. (*Hypertension*. 2011;57:330-335.) • **Online Data Supplement**

**Key Words:** population science ■ genetics ■ blood pressure ■ pulse pressure ■ white matter integrity ■ fractional anisotropy ■ diffusion tensor imaging ■ DTI

Elevated blood pressure (BP) is a well-known risk factor for atrophy of cerebral white matter (WM), and this can lead to cognitive decline and disability in the elderly.<sup>1</sup> BP and the integrity of cerebral WM are under strong genetic control, with up to 80% of individual variance explained by genetic factors.<sup>2–8</sup> We hypothesized that the genetic factors responsible for elevation in BP were also responsible for decline in WM integrity. This hypothesis was tested in a well-characterized population of Mexican Americans randomly selected from large extended families.<sup>9</sup> WM integrity was gauged as fractional anisotropy (FA) using diffusion tensor imaging (DTI), a fully quantitative technique that is capable of ascertaining subtle decline in WM integrity.<sup>10</sup>

First, we investigated whether shared genetic variance between BP and FA measurements was consistent with the pulse-wave encephalopathy (PWE) theory, as suggested previously.<sup>5,6</sup> PWE posits the direct and indirect biological

effects to explain the regional pattern of BP-related decline in the integrity of cerebral WM.<sup>11–13</sup> The direct PWE effect suggests that an increase in arterial pulse pressure (PP) can lead to gliosis of periventricular WM resulting from mechanical damages associated with increased amplitude of cerebrospinal fluid movement.<sup>5</sup> The indirect PWE effect suggests that an increase in systolic BP (SBP) can lead to focal gliosis in subcortical WM because of stenosis and loss of permeability of small cerebral blood vessels.<sup>13,14</sup> Next, we investigated whether shared genetic variance between BP and FA was influenced by a difference in WM development rates.<sup>15</sup> Previous studies suggested a connection between the rates of cerebral development and the genetic contribution to the variance of several brain structures.<sup>16,17</sup> Development of WM tracts associated with higher cognitive function follow a more protracted trajectory, with larger FA increases per year than sensory and motor tracts.<sup>15</sup> We therefore investigated

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whether WM tracts that exhibit high maturation rates would be more susceptible to detrimental effects of elevated BP and would therefore show more genetic overlap with the BP measurements.

## Methods

### Subjects and Measurements

Analyses were performed in 332 (202 females) active participants in the San Antonio Family Heart Study (SAFHS)<sup>9</sup> for whom DTI and BP measurements were available. Participants in the SAFHS study are urban-dwelling Mexican Americans from large extended pedigrees selected randomly from the community. These subjects are characterized by a relatively adverse cardiovascular risk profile, including increased rates of obesity, dyslipidemia, glucose intolerance, and hyperinsulinemia, compared with non-Hispanic whites in San Antonio.<sup>9</sup> Subjects ranged in age from 19 to 79 years (47.9±13.3 years) and were part of 45 families (9.2±8.1 individuals per family; range 2 to 35). Among the 400 subjects recruited for this study, 39 were excluded from MRI for MRI contraindications (n=31), history of neurological illnesses (n=5), or stroke, transient ischemic attack, or other major neurological event (n=3). DTI data were not collected for 29 subjects because a subject was unable to complete the MRI session (n=22), scanner malfunction (n=4), and other reasons (n=3). At the time of collection of BP measurements, 117 subjects (35%; 72 females; average age 54.8±13.0 years) were diagnosed with hypertension, including 44 subjects (31 female; average age 58.7±12.2 years) who were observed to be taking antihypertensive medications (all antihypertension drugs were directly visually verified and recorded). There was no evidence for hypotension in this cohort, with none of the individuals exhibiting BPs with an SBP of <90 mm Hg and/or diastolic BP (DBP) <60 mm Hg. In addition, 133 subjects were obese (body mass index >30), 96 subjects had elevated cholesterol levels (total cholesterol levels >200 mg/dL), 22 subjects had elevated blood lipids (>150 mg/dL), 63 subjects were reported to have type 2 diabetes, and 12 subjects were reported to have coronary heart disorders (supplemental Table I, available online at <http://hyper.ahajournals.org>). Alcohol and depression disorders were not exclusion criteria, with 26 subjects reporting alcohol dependence and 99 subjects reporting a lifetime major depressive episode (supplemental Table I). All subjects provided written informed consent on forms approved by the institutional review board of the University of Texas Health Science Center at San Antonio.

### BP Measurements

Collection of SBP and DBP measurements was detailed in Rutherford et al<sup>2</sup> and proceed the imaging by an average of 3.0±0.8 (maximum 5.3) years. In short, SBP and DBP measurements were performed using a random-zero sphygmomanometer on the left arm. Three measurements were performed with 5-minute intervals, and the average of the last 2 measurements was used as trait value. PP was calculated as the difference between SBP and DBP. The average ±SD SBP, DBP, and PP values were 122.6±16.6, 71.3±10.8, and 51.3±14.2, respectively.<sup>2</sup>

### DTI and Processing

DTI was performed at the Research Imaging Institute, University of Texas Health Science Center at San Antonio, on a Siemens 3T Trio scanner. A single-shot, single refocusing spin-echo, echo-planar imaging sequence was used to acquire diffusion-weighted data, with a spatial resolution of 1.7×1.7×3.0 mm. The sequence parameters were echo time/repetition time=87/8000 ms; field of view=200 mm; 55 isotropically distributed diffusion-weighted directions; 2 diffusion-weighted values; b=0 and 700 s/mm<sup>2</sup> and 3 b=0 (nondiffusion-weighted) images. These parameters were calculated using an optimization technique that maximizes the contrast to noise ratio for FA measurements.<sup>18</sup>

Details for the processing of DTI scans have been discussed previously.<sup>3,19,20</sup> In short, the tract-based spatial statistics software<sup>21</sup>

**Table 1. WM Tracts Used in the Analysis**

Tract	Fiber Type	Connections
Genu of corpus callosum	C	Cerebral hemispheres
Body of corpus callosum	C	Cerebral hemispheres
Splenium of corpus callosum	C	Cerebral hemispheres
Cingulum	A	Cingulate gyrus/hippocampus
Corona radiata	P	Cortical/subcortical
External capsule	A	Frontal/temporal/occipital
Internal capsule (including thalamic radiation)	P	Subcortical/brainstem/cortex
Superior/inferior fronto-occipital fasciculi	A	Frontal/parietal/occipital
Superior longitudinal fasciculus	A	Frontal/temporal/occipital
Sagittal stratum	A/P	Subcortical/temporal/occipital

C indicates commissural; P, projection; A, association.

was used for multisubject analysis of FA images. FA images were created by fitting the diffusion tensor to the raw diffusion data.<sup>22</sup> All FA images were nonlinearly aligned to a group-wise, minimal-deformation target brain.<sup>23</sup> Next, individual FA images were averaged to produce a group-average anisotropy image. This image is used to create a group-wise skeleton of WM tracts that encodes the medial trajectory of the WM fiber tracts. Finally, FA values from each image were projected onto the group-wise skeleton of WM structures. This step accounts for residual misalignment among individual WM tracts. FA values are assigned to each point along a skeleton using the peak value found within a 20-mm distance perpendicular to the skeleton. The FA values vary rapidly perpendicular to the tract direction but very slowly along the tract direction. By assigning the peak value to the skeleton, this procedure effectively maps the center of individual WM tracts on the skeleton.

The whole-brain (WB) average FA value for each subject was calculated as the average FA value for the entire WM skeleton of ≈300×10<sup>3</sup> voxels. Next, the tract-wise average FA measurements were calculated for 10 major WM tracts (Table 1) as described in our previous publications.<sup>3,20</sup> In short, the population-based, 3D, DTI cerebral WM tract atlas developed at Johns Hopkins University and distributed with the FSL package<sup>21</sup> was used to calculate population average diffusion parameter values along the spatial course of the 10 largest (volume ≥5 cm<sup>3</sup>) WM tracts (Table 1). The Johns Hopkins University atlas was nonlinearly aligned to the minimal-deformation target brain, and image-containing labels for individual tracts were transferred to minimal-deformation target space using nearest-neighbor interpolation. Per-tract average values were calculated by averaging the values along the tracts in both hemispheres.

### Genetic Analyses

Two sets of analyses were performed to study the magnitude and regional variations in shared genetic variance between the BP and FA using bivariate genetic correlation analyses methods implemented in the SOLAR software package. First, we analyzed the magnitude of shared genetic effect between BP and WB average FA (WB-FA) values. This was followed by calculation of regional bivariate genetic correlations between BP and tract-wise regional FA values. Beverage genetic analysis calculates the magnitude and significance of genetic correlation coefficient ( $\rho_G$ ), which is the proportion of variability attributable to shared genetic effects. The overall phenotypic correlation ( $\rho_P$ ) between 2 traits A and B (Equation) can be expressed using the correlation attributable to shared additive genetic effects ( $\rho_G$ ) and the residual correlation ( $\rho_E$ ) attributable to shared environmental effects:

$$\rho_P = \sqrt{h_A^2} \sqrt{h_B^2} \times \rho_G + \sqrt{1-h_A^2} \sqrt{1-h_B^2} \times \rho_E,$$

**Table 2. Heritability of WB-FA and BP Indices**

Trait	$h^2$ ( $P$ )	Significant Covariates ( $P$ )	Variance Explained by Covariates
WB-FA	0.52 ( $10^{-6}$ )	Age (1.5E-17), age <sup>2</sup> (0.002)	31%
PP	0.53 ( $10^{-4}$ )	Age (1E-3), age <sup>2</sup> (1E-4)	23%
SBP	0.63 ( $10^{-6}$ )	Age (1E-3)	11%
DBP	0.17 (0.04)	None	0%

where  $h^{2A}$  and  $h^{2B}$  denote the additive genetic heritabilities for each of the traits (ie, the proportion of the total phenotypic variance that is explained by additive genetic factors). If the genetic correlation coefficient ( $\rho_G$ ) is significantly different from zero, then the significant portion of the variance in 2 traits are considered to be influenced by shared genetic factors.<sup>24</sup> All genetic analyses were conducted with age, sex, age $\times$ sex, age<sup>2</sup> age<sup>2</sup> $\times$ sex included as covariates. The health screening data (supplemental Table I) were not used as covariates because of the loss of statistical power to detect genetic effects attributable to their potentially overlapping genetic bases.<sup>24</sup>

### Estimating Confounding Effects of the Antihypertensive Treatment

Genetic analyses can potentially be confounded by the antihypertensive treatment. We estimated the confounding effects of the antihypertensive drugs using 2 approaches, as suggested by Cui et al.<sup>25</sup> First, we used an exclusion approach in which the genetic correlation analyses were performed in a cohort that excluded 44 subjects who were taking antihypertensive medication at the time of BP collection (supplemental Table I). Next, we used a phenotype adjustment approach in which fixed values of 10 and 5 mm Hg were added to the SBP and DBP values, respectively, for the 44 subjects who were taking antihypertensive medication.<sup>25</sup> The estimate of the magnitude of the confounding effect was made based on the significance of the difference in the genetic correlation coefficient among the measurements made in the original versus adjusted cohorts.

### Results

WB-FA values showed a significant negative linear trend with both PP and SBP ( $r^2=0.20$  and  $0.11$ , respectively;  $P<10^{-4}$ ), with no significant relationship observed between WB-FA and SBP (supplemental Figure I). Quantitative genetic analyses estimated that  $>50\%$  of the intersubject variance for the WB-FA, PP, and SBP and  $17\%$  of the variance for the DBP were attributed to additive genetic factors (Table 2). Age and age<sup>2</sup> were significant covariates for PP and WB-FA. Age was a sole significant covariate for SBP. DBP did not have significant covariates. There were no significant ( $P<0.05$ ) age by sex or age<sup>2</sup> by sex interactions detected.

Genetic correlation analyses between BP and the WB-FA values reported that PP and SBP shared  $36\%$  (obtained from

squaring  $\rho_G$ ) and  $22\%$  of genetic variance with the WB-FA values, respectively (Table 3). The negative sign of these correlation coefficients suggested that the same genetic factors associated with higher PP and SBP were linked to progressively lower FA values. Genetic correlation between WB-FA and DBP was not significant (Table 3). The estimates of the confounding effects of the antihypertensive were obtained by excluding 44 subjects who were taking antihypertensive medications and by adding 10 and 5 mm Hg to the SBP and DBP values for the treated subjects. There was no significant difference in either sign or magnitude of genetic correlations (Table 3). Therefore, all further regional analyses were performed in the full pedigree, using the uncorrected BP measurements.

Genetic correlation analyses between BP and the tract-wise FA values (Table 4) indicated that 6 of 10 WM tracts ( genu of corpus callosum, body of corpus callosum, splenium of corpus callosum, fronto-occipital, superior longitudinal fasciculus, and sagittal stratum) showed a statistically significant ( $P\leq 0.05$ ) genetic correlation with PP. Genetic correlation failed to reach statistical significance ( $0.05\leq P\leq 0.10$ ) for 3 more tracts: cingulum, corona radiata, and external capsule (Table 4). Genetic correlation coefficients for FA of 4 tracts ( genu of corpus callosum, body of corpus callosum, fronto-occipital, and sagittal stratum) showed a statistically significant ( $P\leq 0.05$ ) genetic correlation with SBP and approached significance ( $P\leq 0.10$ ) for splenium of corpus callosum (Table 4). There were no significant or suggestive genetic correlation coefficients observed for the genetic correlation coefficients with DBP (Table 4).

The plot of the genetic correlation coefficients ( $\rho_G$ ) for 10 WM tracts versus tract-wise rates of cerebral maturation<sup>20</sup> (Figure) demonstrate that WM bundles with higher rates of maturation shared a progressively higher genetic overlap with both PP and SBP. Linear regression analysis reported that this relationship was statistically significant for both PP and SBP (Pearson  $r^2=0.55$  and  $0.57$ ;  $P\leq 0.01$ , respectively; Figure) but not for DBP (Pearson  $r^2=0.23$ ;  $P=0.16$ ).

### Discussion

This study in a large, well-characterized sample of Mexican American participants in the SAFHS<sup>9</sup> demonstrated that the arterial PP and SBP shared  $36\%$  and  $22\%$  of genetic variance with the WB FA of WM, respectively. In the past, the integrity of cerebral WM was commonly assessed using the T2-hyperintense WM (HWM) lesion imaging techniques.<sup>5-8</sup> HWM lesions are the regions of accumulation of extracellular water attributable to focal degradation of the myelin sheath,<sup>14</sup>

**Table 3. Genetic Correlation Coefficients  $\rho_G$  (95% CI;  $P$ ) Between WB-FA Values and 3 Measurements of Arterial BP: PP, SBP, and DBP**

WB-FA	PP (CI; $P$ )	SBP (CI; $P$ )	DBP (CI; $P$ )
$\rho_G$ ( $P$ )	-0.60 (-0.96, -0.24; $P=10^{-3}$ )	-0.47 (-0.81, -0.13; $P=0.01$ )	0.10 (-0.52, 0.72; $P=0.8$ )
$\rho_G$ ( $P$ )*	-0.62 (-1.0, -0.24; $P=10^{-3}$ )	-0.45 (-0.81, -0.09; $P=0.02$ )	0.12 (-0.05, 0.74; $P=0.7$ )
$\rho_G$ ( $P$ )†	-0.64 (-1.0, -0.22; $P=10^{-3}$ )	-0.43 (-0.79, -0.07; $P=0.03$ )	0.08 (-0.50, 0.64; $P=0.7$ )

\*Calculated after the exclusion of 44 subjects taking antihypertensive medications.

†Calculated after the addition of 10 and 5 mm Hg to the SBP and DBP measurements for subjects taking antihypertensive medications.

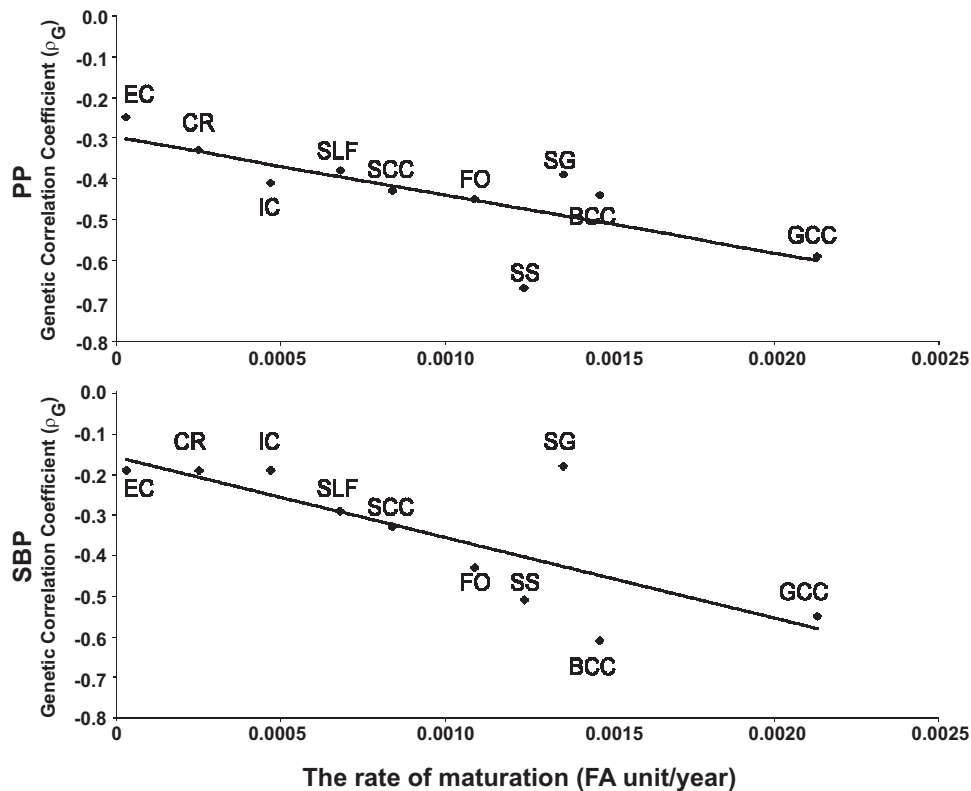
**Table 4. Heritability**

WM Tract	$h^2$ ( $P$ )	Rate of Maturation (FA/Year) <sup>20</sup>	$\rho_G$ (CI; $P$ ) PP	$\rho_G$ (CI; $P$ ) SBP	$\rho_G$ (CI; $P$ ) DBP
Genu of corpus callosum	0.66 ( $10^{-9}$ )	$21.3 \times 10^{-4}$	-0.59 (-0.90, -0.30; $10^{-4}$ )	-0.55 (-0.85, -0.25; $10^{-3}$ )	-0.17 (-1.0, 0.83; 50)
Body of corpus callosum	0.54 ( $10^{-7}$ )	$14.7 \times 10^{-4}$	-0.44 (-0.80, -0.08; 0.01)	-0.61 (-0.97, -0.08; $10^{-4}$ )	-0.32 (-0.92, 0.28; 30)
Splenium of corpus callosum	0.57 ( $10^{-7}$ )	$8.4 \times 10^{-4}$	-0.43 (-0.85, -0.01; 0.04)	-0.33 (-0.71, 0.05; 0.10)	-0.05 (-1.0, 1.0; 0.87)
Cingulum	0.34 ( $10^{-3}$ )	$13.6 \times 10^{-4}$	-0.39 (-0.85, 0.07; 0.10)	-0.18 (-0.64, 0.28; 0.40)	0.37 (-0.23, 0.97; 0.30)
Corona radiata	0.56 ( $10^{-7}$ )	$2.5 \times 10^{-4}$	-0.33 (-0.71, 0.05; 0.08)	-0.19 (-0.55, 0.17; 0.30)	0.23 (-0.70, 1.0; 0.46)
External capsule	0.43 ( $10^{-5}$ )	$0.3 \times 10^{-4}$	-0.25 (-0.65, 0.15; 0.21)	-0.19 (-0.57, 0.19; 0.30)	0.21 (-0.87, 1.0; 0.54)
Internal capsule (including thalamic radiation)	0.43 ( $10^{-6}$ )	$4.7 \times 10^{-4}$	-0.41 (-0.93, 0.11; 0.09)	-0.19 (-0.63, 0.25; 0.40)	0.42 (-0.14, 0.98; 0.28)
Frontal-occipital	0.41 ( $10^{-6}$ )	$10.9 \times 10^{-4}$	-0.45 (-0.85, -0.05; 0.03)	-0.43 (-0.85, -0.01; 0.05)	-0.16 (-1.0, 1.0; 0.65)
Superior longitudinal fasciculus	0.58 ( $10^{-7}$ )	$6.8 \times 10^{-4}$	-0.38 (-0.76, 0.00; 0.04)	-0.29 (-0.67, 0.10; 0.20)	-0.11 (-1.0, 1.0; 0.72)
Sagittal stratum	0.40 ( $10^{-4}$ )	$12.4 \times 10^{-4}$	-0.67 (-1.0, -0.29; $10^{-4}$ )	-0.51 (-0.91, -0.30; 0.01)	0.21 (-0.90, 1.0; 0.54)

The rates of maturation and senescence<sup>20</sup> and the genetic correlation coefficients  $\rho_G$  (95% CI;  $P$ ) were calculated for 10 major WM tracts.

and their volume is an important neuroimaging marker of cerebral integrity.<sup>26</sup> DTI has an advantage over HWM-imaging techniques because it is capable of ascertaining subtle WM damage that precedes formation of HWM lesions.<sup>10</sup> Several recent studies confirmed that DTI is a sensitive neuroimaging marker of WM integrity in hypertensive individuals.<sup>10,27,28</sup> Specifically, FA values were inversely correlated with the arterial PP and SBP in both normotensive and hypertensive individuals.<sup>27</sup>

The PP shared more genetic variance with the WB-FA values than SBP. This is consistent with the PWE theory,<sup>12,13</sup> which suggests that elevation in the arterial pulsativity can lead to cerebral injury even in normotensive individuals.<sup>27</sup> Similar pattern was observed in a previous whole-genome linkage study in this population, in which PP and the volume of HWM lesion shared significant genetic loci, whereas the association between SBP and HWM lesion volume only reached suggestive significance.<sup>5</sup> The regional patterns of



**Figure.** The tract-wise genetic correlation coefficients ( $\rho_G$ ) for PP (top graph) and SBP (bottom graph) are plotted versus tract-wise rates of cerebral maturation (Table 4) in FA units per year taken from.<sup>20</sup> Linear regression analyses (solid lines) indicated that the by-tract variability in the magnitude of genetic overlap was significantly correlated with the by-tract rates of FA increase during maturation for both PP and SBP (Pearson  $r=0.74$  and  $0.76$ ;  $P \leq 0.01$ ).



genetic overlap between BP and FA were in agreement with the direct and indirect mechanisms of BP-related cerebral injury as described by the PWE theory. The direct mechanism is primarily responsible for the gliosis of the periventricular WM.<sup>12,13</sup> This explains the high negative ( $\rho_G = -0.43$  to  $-0.67$ ) genetic correlation between PP and periventricular WM tracts. The highest genetic correlation was observed for the sagittal stratum, which is located in the area that is especially susceptible to the periventricular gliosis.<sup>27</sup> The indirect mechanism of the PWE theory is suggested to be responsible for formation of subcortical WM lesions, most commonly observed in the frontal lobe.<sup>11,27</sup> This may explain high genetic correlations observed between the SBP and the FA of the genu and the body of CC because these tracts contain commissural fibers connecting frontal lobes. The biological pathway of the indirect mechanisms remains unclear. Stenosis of small cerebral vessels, especially in the watershed areas,<sup>29</sup> and high metabolic demands of oligodendrocytes of associative WM contribute to a high vulnerability of the frontal WM to the indirect PWE mechanism.<sup>30</sup> Oligodendrocytes of the associative frontal WM are among the most metabolically active cells in the adult central nervous system and are therefore highly susceptible to damages from hypoxia.<sup>30</sup> In addition, the oligodendrocytes of the associated, frontal WM tracts have reduced rates (per axonal-segment) of myelin production and repair,<sup>31</sup> and this is thought to be responsible for the protracted age-related myelination and sharp age-related decline.<sup>20</sup>

Previous findings suggested that the protracted development and high metabolic demands of associative WM make it more vulnerable to age-related neurodegeneration than sensory and motor WM.<sup>19,27,32</sup> In agreement with these findings, our results showed that WM tracts that continue to myelinate into adulthood, and therefore show higher age-related maturation rates, shared progressively more genetic overlap with PP and SBP. In fact, >50% of regional variability in shared genetic variance was explained by the regional rates of cerebral maturation. We interpret this finding as the evidence for genotype-by-age interaction, with protracted development of associative WM contributing to its higher susceptibility to the neurodegeneration associated with elevated PP and SBP.

Unlike PP and SBP, significant genetic correlations were not observed between DBP and FA. However, given the lower observed heritability of DBP, the current study is relatively underpowered and can therefore fail to identify genetic correlations for this pair of phenotypes. The statistical power of the current study may also have been limited to detect significant genetic correlation for track-wise measurements of FA, in which the magnitude of genetic correlation coefficients for several analyses approached statistical significance. Therefore, the lack of significant genetic correlations cannot be interpreted as evidence against the existence of those pleiotropic relationships. In addition, our study examined Mexican Americans, a population with significant Native American admixture. If relatively rare variants are involved in the determination of quantitative variance, we may expect considerable differences in the degree of shared genetic variance in other populations, such as European Americans.<sup>33</sup>

## Perspective

Our findings in a population characterized by an adverse cardiovascular risk profile demonstrated that genetic factors responsible for elevation in arterial PP and SBP were also responsible for declining integrity of cerebral WM. In agreement with PWE theory, the highest genetic association with WM integrity was observed for PP. Further, our data demonstrated that associative WM tracts that facilitate high-order cognitive functioning showed higher vulnerability to the elevated PP and SBP than motor and sensory WM tracts. The statistical power of this study was not sufficient to localize the individual genes responsible for the pleiotropy between BP and FA, but previous studies in this population provide a likely candidate: *selectin* genes.<sup>2,5,6</sup> The region harboring the constellation of *selectin* genes (*SELP*, *SELL*, and *SELE*) has been identified as a region of significant linkage (LOD=3.82) between PP and HWM volume. In particular, the adhesion molecule *P-selectin*<sup>34</sup> is a marker of potential endothelial dysfunction that has been implicated as a risk factor in essential hypertension<sup>35,36</sup> and stroke.<sup>35,37</sup> Increased blood levels of *P-selectin* have been implicated in formation of atherosclerotic plaque, loss of vascular reactivity, and increase in arterial pulsativity and SBP.<sup>35,37</sup> In addition, platelet-derived gene expression levels of *SELP* were shown to be strongly and positively correlated with arterial BP.<sup>38,39</sup>

## Limitations

Our data indicate that a genotype-by-age interaction is potentially responsible for genetic overlap between BP and FA. Hence, it may be useful to explicitly allow for the potential influences of genotype by age interactions. Although advanced statistical genetic methods for family-based data allow for the formal detection of such interactions within cross-sectional data, longitudinal family studies will have much greater power to localize and ultimately identify the specific genes involved in intersubject differences in the rates of WM atrophy. Therefore, further research is needed to confirm the cross-sectional trends observed here using a longitudinal design.

A potential limitation of this study is that the collection of BP measurements preceded the acquisition of brain images by  $3.0 \pm 0.8$  (maximum 5.3) years. Individual subjects could have experienced a rise in BP during the period between BP and brain assessment, suggesting caution when interpreting these findings.

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## Disclosures

None.

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## Blood Pressure and Cerebral White Matter Share Common Genetic Factors in Mexican-Americans

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Age	N subjects (M/F)	SBP	DBP	PP	N <sub>obese</sub>	N <sub>hyper-cholesterolemia</sub>	N <sub>hyper-lipidemia</sub>	N <sub>heart disorder</sub>	N <sub>diabetes</sub>	N <sub>hypertension</sub>	N <sub>anti-hypertensive meds</sub>	N <sub>AD</sub>	N <sub>MD</sub>
19-29	27 (11/16)	118.7±12.5	68.4±7.7	50.3±10.9	10	3	1	0	1	3	1	3	4
30-39	76 (35/41)	117.9±13.0	72.2±9.2	45.6±9.9	32	8	3	0	3	18	3	8	18
40-49	84 (30/54)	118.9±13.3	72.5±9.7	46.4±9.6	35	20	3	1	13	18	6	6	25
50-59	80 (28/52)	125.4±17.5	72.9±10.5	52.5±13.0	29	27	5	3	15	31	12	4	34
60-69	40 (14/26)	135.0±17.9	73.1±13.5	61.8±16.7	17	24	7	4	18	30	12	4	13
70-79	25 (12/13)	131.1±16.4	71.0±13.3	60.2±16.4	10	14	3	4	13	17	10	1	5

Table S1. Subjects' demographic and health information including systolic (SBP), diastolic (DBP) and pulse pressure (PP), the number of obese subjects (body mass index>30), the number of subjects with hypercholesterolemia (total cholesterol levels > 200 mg/dl) and hyperlipidemia (blood lipids>150 mg/dL), the number of subjects diagnosed with coronary heart disorder, diabetes, hypertension, the number of subjects taking antihypertensive medications, the number of subjects with alcohol dependence (AD) and the number of subject with a lifetime major depression (MD) episode.

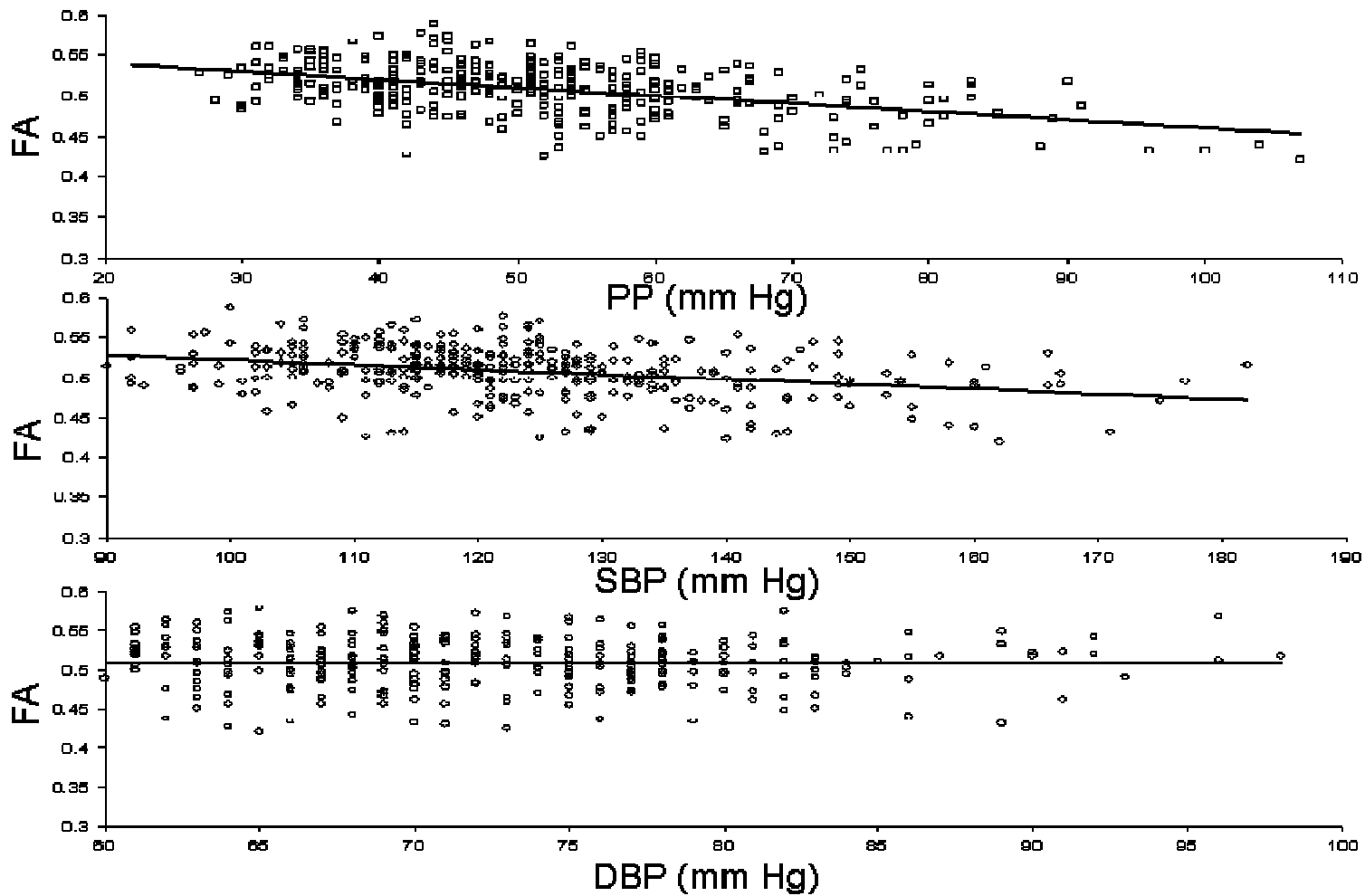


Figure S1. Scatter plots for whole-brain average FA values and results of linear regression, from top to bottom, for pulse pressure (PP) ( $FA = -0.001 * PP + 0.56$ ;  $r^2 = 0.20$ ); systolic blood pressure (SBP) ( $FA = -0.0006 * SBP + 0.58$ ;  $r^2 = 0.11$ ) and diastolic blood pressure (DBP) ( $FA = 1E-6 * SBP + 0.51$ ;  $r^2 = 0.0$ )