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Possible Locus on Chromosome 18q Influencing Postural Systolic Blood Pressure Changes

James S. Pankow, Kathryn M. Rose, Albert Oberman, Steven C. Hunt, Larry D. Atwood, Luc Djoussé, Michael A. Province, D.C. Rao

Abstract—We conducted a genome-wide scan for quantitative trait loci influencing the systolic blood pressure, diastolic blood pressure, and pulse responses to a postural challenge in 498 white sibling-pairs from the Hypertension Genetic Epidemiology Network, a multicenter study of the genetic susceptibility to hypertension. All participants were hypertensive (systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or on antihypertensive medications) with diagnosis before age 60. Blood pressure and pulse were measured by an oscillometric method after a 5-minute rest in a supine position and again immediately on standing. The genome scan included a total of 387 autosomal short-tandem-repeat polymorphisms typed by the National Heart, Lung, and Blood Institute Mammalian Genotyping Service at Marshfield. We used multipoint variance-components linkage analysis to identify possible quantitative trait loci influencing postural change phenotypes after adjusting for sex, age, and use of antihypertensive medications. There was suggestive evidence for linkage on chromosome 18q for the postural systolic blood pressure response (maximum logarithm of the odds score = 2.6 at 80 centiMorgans). We also observed a maximum logarithm of the odds score of 1.9 for the systolic blood pressure response and 1.7 for the diastolic blood pressure response on chromosome 6p. The marker that demonstrated the strongest evidence for linkage for the systolic blood pressure response (D18S858) lies within 20 centiMorgans of a marker previously linked to rare familial orthostatic hypotensive syndrome. Our findings indicate that there may be 1 or more genes on chromosome 18q that regulate systolic blood pressure during the physiological recovery period after a postural stressor. (Hypertension. 2000;36:471-476.)

Key Words: posture ■ blood pressure ■ heart rate ■ hypertension ■ linkage ■ chromosome mapping

There is some evidence that blood pressure and heart rate responses to psychological and physical stressors are associated with adverse health outcomes. For example, prospective studies have found that a decrease in blood pressure on standing (orthostatic hypotension) is associated with adverse health outcomes. For example, prospective studies have found that a decrease in blood pressure on standing (orthostatic hypotension) is associated with increased coronary heart disease morbidity and mortality and all-cause mortality. Elderly individuals with postural hypotension accompanied by dizziness are also at greater risk of recurrent falls.

Family and twin studies suggest that blood pressure and heart rate responses to laboratory stressors such as a mental arithmetic or cold pressor test are partly under genetic control. By contrast, fewer studies have evaluated familial patterns of blood pressure or heart rate responses to postural stressors. A relatively severe form of orthostatic hypotension with an autosomal dominant mode of transmission has been described in 4 families. Recently, a genome-wide scan in 2 of these families found significant evidence for linkage of this hypertensive trait in a region on chromosome 18q.

Unlike most other laboratory stressors designed to evaluate cardiovascular reactivity, a change in body position from supine to standing is a daily challenge that can lead to either a decrease or an increase in blood pressure. Because the physiological mechanisms leading to an increase in blood pressure on standing probably differ from those leading to a decrease in blood pressure on standing, genetic influences on the blood pressure response to postural stressors may be heterogeneous. In the present study, we report the results of a genome-wide scan in hypertensive sibling-pairs for quantitative trait loci influencing the systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse responses to a change from a supine to a standing position.

Methods

Study Population

Subjects were participants in the Hypertension Genetic Epidemiology Network (HyperGEN) of the National Heart, Lung, and Blood Institute (NHLBI) Family Blood Pressure Program. In HyperGEN, 1142 white subjects from 492 hypertensive sibships (970 sib-pairs)
were recruited in 4 US communities (Framingham, Mass; Forsyth County, North Carolina; the northwest suburbs of Minneapolis, Minn; and Salt Lake City, Utah) by using the database of the NHLBI Family Heart Study. A total of 782 African-American sib-pairs with hypertension were also enrolled in Forsyth County, North Carolina, and Birmingham, Ala.

For the purposes of recruitment into HyperGEN as a member of a hypertensive sibship, eligibility was based on (1) the clinical diagnosis or treatment of hypertension before age 60 (excluding hypertension only during pregnancy), (2) current blood pressure levels \( \geq 140 \) mm Hg systolic or \( 90 \) mm Hg diastolic, (3) current use of recognized antihypertensive medications, or (4) the historical (but not current) treatment for hypertension with prescribed medications for at least 1 year during the past 5 years, all of which occurred before age 60. Individuals with a lifetime history of kidney failure were excluded. To optimize statistical power, all hypertensive full siblings were recruited from each eligible sibship. A random sample of white subjects and their spouses was also recruited from the study communities (n=472).

All participants completed a detailed clinic examination with procedures standardized across centers. Participants were asked to avoid caffeine, eating, and heavy physical activity for 12 hours before the examination. The study was approved by an institutional review committee at each center, and subjects gave informed consent. Procedures followed were in accordance with institutional guidelines.

Blood Pressure and Pulse Measurements
To assess hemodynamic responses to a postural challenge, SBP, DBP, and pulse rate were measured on the dominant arm with a DINAMAP 1846-SX/P oscillometric device. All measurements were directly downloaded to a personal computer. According to arm circumference, measurements were taken with 1 of 5 standardized cuffs: child, small adult, adult, large adult, and thigh. One supine measurement was taken after a 5-minute period of rest. Participants were then instructed to rise as quickly as possible, and standing measurements were taken immediately and again 2 minutes after standing. Between 15 and 35 seconds were required to complete each blood pressure and pulse determination, depending on the heart rate.

Other Measurements
Current use of prescription medications was ascertained, and medication codes were assigned by a computerized protocol administered by trained and certified staff. Codes were collapsed into therapeutic categories (Medispan) by the Data Coordinating Center. The examination also included questionnaires to determine physical activity, history of cigarette smoking, alcohol intake, and reproductive history. Blood samples were collected to determine fasting lipids and lipoproteins and serum chemistries.

Height, weight, and waist girth were measured by a trained and certified technician on shoeless participants wearing scrub suits and nonconstricting underwear, by using a standardized protocol and calibrated instruments. All measurements were recorded to the nearest inch and rounded down, when necessary. Standing height was measured on a fixed stadiometer with the participant’s head in the Frankfort horizontal plane and recorded to the nearest centimeter. Weight was measured on a balance scale and recorded to the nearest point. We used these measures to compute body mass index (BMI, in kg/m\(^2\)). Waist circumference was measured at the umbilicus and recorded to the nearest centimeter at the point of relaxed end-exhalation. Serum insulin was measured by an immunoenzymatic method with the Beckman/Sanofi Access analyzer (Beckman). HDL quantification was performed with the standard cholesterol method after precipitation of non-HDL cholesterol with magnesium/dextran.28

Genotyping
Genotype data on 387 autosomal short-tandem-repeat polymorphisms were provided by the NHLBI Mammalian Genotyping Service at Marshfield. The results presented herein are based on marker data from all participants who have been genotyped to date, representing approximately one half of the white sibships. Because there were fewer African-American sib-pairs enrolled in HyperGEN and statistical power is therefore more limited, genome scan results for these postural blood pressure and pulse phenotypes will not be presented until all African-American participants have been genotyped.

Statistical Analysis
Because maximal hemodynamic responses have been observed within the first minute after a postural stressor,29 our primary analysis focused on the initial response of blood pressure and pulse to a change in posture (ie, a change in blood pressure and pulse measured immediately on rising from a supine to a standing position). We analyzed 3 postural change phenotypes that reflected the difference between standing and supine measures: (1) change in SBP; (2) change in DBP; and (3) change in pulse. We applied a natural-log transformation to normalize the distribution of \( \Delta \text{pulse} \), which was positively skewed. Extreme outliers were deleted (>4 SDs and >1 SD from the nearest point). Sex-specific regression models were developed in participants from the random sample to assess the effects of age (up to cubic terms) and self-reported use of prescription antihypertensive medications in the past 4 weeks. Phenotypes for members of hypertensive sibships were then adjusted by using regression coefficients from these models, and the standardized residuals for each of the phenotypes were used in linkage analysis.

Reported family relationships were compared for consistency with the marker genotype data by using the program ASPEX20 and corrected, as necessary. Any remaining genotype inconsistencies within pedigrees were “zeroed out” (set to missing), marker by marker, by using a fully automated SAS macro that repeatedly called the program MAPMAKER/SIBS.21

We conducted multipoint variance-components linkage analysis by using SEGPATH.22 The expected genetic covariance between relatives was modeled as a function of the identity-by-descent at a given test locus and the kinship coefficient. Heritability (\( h^2 \)) was partitioned into a component attributable to a latent trait locus (\( h_t^2 \)) and residual heritability (\( h_r^2 \)) attributable to other trait genes and/or other sources of familial resemblance. The null hypothesis that there was no effect of the test locus on the trait heritability (\( h_t^2=0 \)) was evaluated by a likelihood-ratio test. MAPMAKER/SIBS21 was used to estimate the allele-sharing proportions among siblings. Population marker allele frequencies were estimated from the random sample. When simulated data from Genetic Analysis Workshop 10 were analyzed under the same set of assumptions,22 SEGPATH and SOLAR23 gave identical results, thus making the variance-components implementations in the 2 programs very comparable.

Results
Including singletons, phenotype and genetic marker data were available for 636 individuals from 285 sibships (498 sibling-pairs). Basic descriptive information is provided in Table 1. The mean age was 60 years, and approximately one half of the participants were women. The vast majority (>90%) of individuals reported use of prescription antihypertensive medications within 4 weeks of the examination. In both men and women, there was an increase in mean DBP and mean pulse but a slight decrease in mean SBP when participants rose from a supine to a standing position.

The distributions of \( \Delta \text{SBP} \), \( \Delta \text{DBP} \), and log \( \Delta \text{pulse} \) were approximately normally distributed after adjusting for sex, age, and antihypertensive medications. In participants from the random sample, \( \Delta \text{SBP} \) and \( \Delta \text{DBP} \) were moderately correlated ([\( r=0.41 \), \( P<0.001 \)]. By contrast, log \( \Delta \text{pulse} \) was only weakly correlated with either \( \Delta \text{SBP} \) ([\( r=-0.07 \), \( P=0.14 \)] or \( \Delta \text{DBP} \) ([\( r=0.13 \), \( P=0.01 \)]. Changes in blood pressure and pulse computed with the first (immediate) standing measure-
oment were moderately correlated with changes computed with the second (2-minute) standing measurement (for ΔSBP, \( r = 0.58, P < 0.001 \); for ΔDBP, \( r = 0.61, P < 0.001 \); and for log Δpulse, \( r = 0.48, P < 0.001 \)).

Generalized heritability estimates (±SE) obtained from SEGPATH were 0.36 (±0.06) for ΔSBP, 0.25 (±0.05) for ΔDBP, and 0.40 (±0.07) for log Δpulse. Map locations and marker names for all locations yielding a maximum log-of-the-odds (LOD) score ≥1.5 are provided in Table 2. Multipoint LOD scores for ΔSBP are plotted by map position in the Figure. The genome-wide scan for ΔSBP indicated suggestive linkage to a broad region on chromosome 18q, with a maximum LOD of 2.6 at marker ATA23G05 (D18S858), \( \approx 80 \) cM from the p terminus. Other regions of potential interest include a LOD of 1.9 for ΔSBP and 1.7 for ΔDBP associated with marker GATA163B10 on chromosome 6p. There were no regions with a LOD ≥1.5 for log Δpulse.

We evaluated other possible predictors of postural blood pressure or pulse responses, including educational attainment, BMI, waist circumference, fasting insulin and glucose, prevalent diabetes, LDL and HDL cholesterol levels, sitting SBP and DBP, and smoking status. However, other than age and use of prescription antihypertensive medications in the past 4 weeks, no other variables were statistically significantly associated \((P<0.05)\) with ΔSBP. Further adjustments for other variables significantly associated with ΔDBP (waist circumference, fasting insulin) and log Δpulse (BMI, HDL cholesterol) had little impact on the maximum LOD scores described above. We also found evidence of heritability \((0.31±0.05)\) for ΔSBP computed with the 2-minute rather than the immediate standing blood pressure measurement but failed to identify a significant peak on chromosome 18q (maximum LOD=0.6).

**Discussion**

Our genome-wide scan in 498 white hypertensive sib-pairs recruited from 4 US communities in the HyperGEN Study, revealed suggestive evidence for linkage of ΔSBP in a broad region on chromosome 18q (maximum LOD=2.6 at 80 cM). By contrast, there was no evidence for linkage of ΔDBP or Δpulse in this chromosomal region. Although the maximum LOD score for ΔSBP on chromosome 18q did not reach the standard for significant linkage as proposed by Lander and Kruglyak, this finding is important because it overlaps with a region on 18q recently linked to familial orthostatic hypotensive syndrome, a related postural blood pressure trait. The marker with the highest LOD score for ΔSBP in our study (D18S858) lies within 20 cM of the marker with the highest LOD score for orthostatic hypotensive syndrome in the earlier study by DeStefano et al (D18S1367, LOD=3.9).

DeStefano et al investigated a small group of extended families whose members suffered from frequent episodes of dizziness, syncope, headaches, and leg edema on rising from a supine position. Orthostatic hypotension was defined as a drop in SBP by >18 mm Hg and a rise in pulse on standing. Because the familial form of this disorder is thought to be rare, the locus on 18q detected by DeStefano et al may be of little or no importance in regulating postural blood pressure for most individuals or families in the population. On the other hand, identifying and characterizing genes involved in rare familial forms of hypertensive or hypotensive disorders may provide insights into the general physiology of blood pressure control. In a population-based study of Mexican-Americans, Atwood et al recently found suggestive linkage (maximum LOD=2.1) of hypertension to marker D18S844, which is within 30 cM of the linkage found in our study and within 10 cM of the linkage reported by DeStefano et al. Our findings and those of Atwood et al suggest that this region of chromosome 18q may contain 1 or more genes with much broader significance for blood pressure regulation. It is also possible that we have localized a gene that primarily influ-

### Table 1: Sex-Specific Means (±SD) or Percentages for Participant Characteristics and Postural Blood Pressure and Pulse Phenotypes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=309)</th>
<th>Women (n=327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.7±9.0</td>
<td>60.8±9.1</td>
</tr>
<tr>
<td>Use of antihypertensive medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past 4 weeks, %</td>
<td>93.9</td>
<td>91.7</td>
</tr>
<tr>
<td>Past 24 hours, %</td>
<td>54.7</td>
<td>54.1</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine SBP</td>
<td>132.0±17.5</td>
<td>129.8±18.5</td>
</tr>
<tr>
<td>Standing SBP</td>
<td>128.8±19.7</td>
<td>127.3±21.4</td>
</tr>
<tr>
<td>ΔSBP</td>
<td>-3.2±14.8</td>
<td>-2.5±15.5</td>
</tr>
<tr>
<td>Supine DBP</td>
<td>75.1±9.2</td>
<td>67.4±9.2</td>
</tr>
<tr>
<td>Standing DBP</td>
<td>75.5±10.1</td>
<td>69.7±11.2</td>
</tr>
<tr>
<td>ΔDBP</td>
<td>+0.4±7.6</td>
<td>+2.3±8.0</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine pulse</td>
<td>63.4±10.9</td>
<td>67.9±7.8</td>
</tr>
<tr>
<td>Standing pulse</td>
<td>75.4±13.4</td>
<td>79.7±13.9</td>
</tr>
<tr>
<td>ΔPulse</td>
<td>+12.0±8.2</td>
<td>+11.8±7.8</td>
</tr>
</tbody>
</table>

### Table 2: List of All Markers With Multipoint LOD Scores of 1.5 or Greater

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Chromosome</th>
<th>Location, cM</th>
<th>Marker</th>
<th>LOD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔSBP</td>
<td>6</td>
<td>42</td>
<td>GATA163B10</td>
<td>1.9</td>
<td>0.0015</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>64</td>
<td>GATA13</td>
<td>1.6</td>
<td>0.0034</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>76</td>
<td>GATA6D09</td>
<td>2.4</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>80</td>
<td>ATA23G05</td>
<td>2.6</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>89</td>
<td>AT7D07</td>
<td>2.0</td>
<td>0.0011</td>
</tr>
<tr>
<td>ΔDBP</td>
<td>6</td>
<td>34</td>
<td>GATA29A01</td>
<td>1.5</td>
<td>0.0038</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>42</td>
<td>GATA163B10</td>
<td>1.7</td>
<td>0.0025</td>
</tr>
</tbody>
</table>
Multipoint linkage results for postural SBP changes, by chromosome (Chr).
ences normal hemodynamic adjustments to the upright posture because the blood pressure responses of the vast majority of participants included in our analysis would not be characterized as “abnormal” by conventional definitions.

Several factors limit the generalizability of our study and suggest that future studies may have some difficulty replicating our findings, unless comparable study designs, protocols, and instruments are used. First, we found suggestive evidence for linkage only when ΔSBP was determined with measurements taken immediately on standing, but not when the blood pressure response was determined with measurements taken 2 minutes after standing. This finding might indicate that genetic factors that operate early in the physiological recovery period after a postural stressor differ from those that influence compensatory changes in blood pressure at later stages of recovery. The relative impact of genetic factors on SBP levels may be greatest immediately after standing, although in our study heritability estimates for ΔSBP were of similar magnitude when computed with either the immediate or the 2-minute standing measurements. Second, although participants in our study were not selected on the basis of orthostatic hypotension status, the pattern of blood pressure and pulse responses to a postural challenge may be atypical, because only hypertensive sibships were selected for our study. For example, the mean (SD) of ΔSBP was −2.8 (15.1) mm Hg in hypertensive sibships compared with +0.4 (11.6) mm Hg in the random sample. In addition, the percentage of participants with a decrease in SBP of at least 20 mm Hg on standing was also higher in hypertensive sibships (11.7%) compared with the random sample (4.5%), possibly because individuals with hypertension and those using antihypertensive medications are more likely to have postural hypotension. We cannot determine from these data whether genetic factors influencing postural blood pressure and heart rate responses are likely to be similar in hypertensives and nonhypertensives.

Measurement error likely reduced statistical power to detect quantitative trait loci for the blood pressure and pulse phenotypes in our study. Blood pressure and pulse exhibit substantial intr individuality, some of which can be attributed to measurement error. Although the DYNAMAP device has been found to have high repeatability, measurement error is compounded when change scores are computed, because each score is based on 2 blood pressure or pulse determinations, each measured with error. For example, a study of patients >60 years old with isolated systolic hypertension found lower reproducibility for orthostatic changes in SBP compared with the reproducibility of either supine or standing SBP measured by conventional sphygmomanometry. In another reproducibility study in elderly patients, intraclass correlation coefficients were somewhat higher for postural SBP changes (0.72) and pulse changes (0.69) compared with DBP changes (0.50).

In addition to possible measurement error introduced by instrumentatation and study protocol, use of prescription antihypertensive medications may have also obscured normal physiological responses to the postural stressor in some individuals. Our ability to adequately account for possible medication effects is limited because >90% of participants in our study were current users of antihypertensive medications. Although participants were fasting at the time of arrival at the clinic, they were offered a snack before the postural blood pressure determinations, which may have triggered postprandial decreases in blood pressure in some individuals. Some of the participants may have also had other common causes of postural hypotension, such as anemia, hypokalemia, or valvular disease.

In conclusion, our genome-wide scan found a possible locus on chromosome 18q influencing the SBP response to a postural challenge in white hypertensive siblings. DeStefano et al. had previously found significant evidence for linkage of a rare familial form of orthostatic hypotension in this same region. Our analysis suggests that there may be 1 or more genes in this region regulating postural SBP responses in hypertensive individuals not selected on the basis of orthostatic hypotension status. Because complex traits such as sitting blood pressure and postural blood pressure change are likely to be influenced by multiple genes with modest (polygenic) effects, it will be difficult for linkage studies such as ours to produce convincing levels of evidence. Therefore, some of the less significant findings reported herein may also be of interest.

Acknowledgments

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