Evidence for a Gene on Chromosome 13 Influencing Postural Systolic Blood Pressure Change and Body Mass Index

Kari E. North, Kathryn M. Rose, Ingrid B. Borecki, Albert Oberman, Steven C. Hunt, Michael B. Miller, John Blangero, Laura Almasy, James S. Pankow

Abstract—Previous analysis in the Hypertension Genetic Epidemiology Network (HyperGEN) of the National Heart Lung and Blood Institute (NHLBI) Family Blood Pressure Program, a multicenter study of genetic and environmental factors related to hypertension, indicated regions of linkage for blood pressure traits together with several coincident regions for phenotypically correlated traits, including systolic blood pressure (SBP) response to a postural challenge and body mass index (BMI). Motivated by these findings and by our desire to better understand the physiology of these traits, we conducted bivariate linkage analysis of postural SBP change and BMI. Sibships in HyperGEN were recruited from 5 field centers in Massachusetts, North Carolina, Minnesota, Utah, and Alabama. All available affected siblings, their parents, and selected nonmedicated offspring were recruited. Among 1636 whites and 1747 blacks, we performed a maximum likelihood bivariate genome scan for quantitative trait loci influencing postural SBP change and BMI, similarly adjusted for race, study center, sex, age, and age-by-sex interactions. Genome scans were performed using SOLAR (version 2.0) and race-specific marker allele frequencies derived from founders. The maximum genome-wide logarithm of odds (LOD) score of 3.2 was detected on chromosome 13 at 24 cM. This marker (D13S493) lies within 20 cM of a marker previously linked to BMI in the Family Heart Study and is substantially higher than the univariate linkage for each trait (LOD scores for BMI and postural SBP change were 2.4 and 0.9, respectively). These findings suggest that a gene(s) on chromosome 13q jointly regulates the SBP response to postural change and BMI. (Hypertension. 2004;43:780-784.)

Key Words: genetics ■ hypotension ■ posture ■ body mass index ■ blood pressure

The response of systolic blood pressure (SBP) to a change in body position has been used in studies as a measure of cardiovascular reactivity. A strong decrease in blood pressure on standing (orthostatic hypotension) is associated with an increased risk of coronary heart disease (CHD),1 stroke,2 incident hypertension,3 and all-cause mortality.4,5 Epidemiological studies assessing the association between the SBP response to postural challenge and BMI have been inconsistent.1,4,6–10 Studies evaluating the association between BMI and orthostatic hypotension, although not consistent, have most often noted lower BMIs among those with a strong SBP decrease in response to a change in posture. The association between BMI and an increase in SBP in response to a change in posture has not been frequently reported. However, in a cohort of middle-aged participants, those with a strong SBP increase in response to a change in posture had higher BMIs.1,10

Studies have identified chromosomal regions harboring quantitative trait loci (QTL) for obesity11 and SBP response to postural challenge,12 with coincident linkage for obesity13 and SBP response to postural challenge at 18q21.12 Moreover, a polymorphism (C825T) in the gene encoding the G protein beta3 subunit (GNB3) has recently been associated with hypertension and obesity in several studies.14–16 Despite the evidence for a possible correlation between these phenotypes, there is still much to be learned about specific loci jointly influencing obesity and SBP response to postural challenge.

Previous analysis in the Hypertension Genetic Epidemiology Network (HyperGEN) of the National Heart Lung and Blood Institute (NHLBI) Family Blood Pressure Program, a multicenter study of genetic and environmental factors related to hypertension, indicated several regions of suggestive linkage for blood pressure traits17 together with several coincident regions for phenotypically correlated traits, including SBP response to postural challenge and BMI.12 However, these previous genome scans were conducted on a subset of the data presented here, considering only affected sibling
pairs. Motivated by these preliminary findings and by our desire to more accurately model the underlying determinants of these traits and make it easier to detect, localize, and identify genes contributing to their variation and co-variation, we conducted bivariate linkage analysis of postural SBP change and BMI.

Methods

Subjects
The Hypertension Genetic Epidemiology Network (HyperGEN) is 1 of 4 networks in the National Heart, Lung, and Blood Institute (NHLBI) Family Blood Pressure Program. HyperGEN study methods have previously been reported. In brief, the original populations were defined and enumerated from the NHLBI Framingham Heart Study, the Minneapolis, Minn and Forsyth County, NC field centers of the Atherosclerosis Risk in Communities (ARIC) Study, the Utah Health Family Tree Study, and from various studies at the Birmingham field center.

The present report includes 1636 white and 1747 black hypertensive siblings and their relatives. Additionally, a random sample of age-matched persons from the same base populations was included to calculate population parameters. The sample of examined individuals included 4453 relative pairs: over 595 parent offspring pairs, 2017 sibling pairs, 850 avuncular pairs (aunt/uncle-niece/nephew), and 192 first-cousin pairs, recruited from the 5 clinical centers.

Phenotypes
Anthropometric measurements were obtained as reported previously. BMI was computed as weight (kg)/height (m)^2. Blood pressure measurements were taken using a DINAMAP model 1846 SX/P automated oscillometric device using a standard protocol. Briefly, after a 5-minute rest period, a supine blood pressure reading was taken using the dominant arm and the participant was asked to stand. On standing, a blood pressure measurement was immediately taken. Two minutes later, a second standing measurement was taken. The SBP response to a postural change was calculated as the first standing measurement minus the supine measurement.

Venipuncture was performed on fasting participants following a previously described standard protocol. Use of antihypertensive medications was determined based on participants' responses to questions about medications regularly used during the 4 weeks preceding the examination. Informed consent was obtained from all participants, and this project was approved by the Institutional Review Boards of all participating institutions.

Genotypes
Genomic DNA was isolated from whole blood using standard procedures. Genotyping was provided by the NHLBI Mammalian Genotyping Service (Marshfield, Wis). Details on gel preparation and polymerase chain reaction conditions are available from the Mammalian Genotyping Service web site (http://marshmed.org/genetics). The CHLC screening set 8 was used, which includes up to 200 microsatellite markers equally spaced (~9-cM distance) throughout the genome. The average marker heterozygosity was 77.7%. Analyses and assignment of the marker alleles were performed using computerized algorithms. Relationship status among the purportedly full sibs was tested using ASPLEX, a likelihood-based method and MERLIN.

Analytical Methods

Variance Components Linkage Analysis
Multipoint linkage analysis as implemented in SOLAR, version 2.0 was performed to detect and localize QTL jointly influencing variation in BMI and postural SBP change. Details of this model have been described previously.

The use of the variance component approach requires an estimate of the identity-by-descent (IBD) matrix. The small size of our families allowed us to compute exact conditional probabilities using the Lander-Green algorithm as implemented in MERLIN. Allele frequencies from founders were calculated separately in black and white groups. The IBD probabilities computed by MERLIN were then combined into a single set of multipoint IBD files in the SOLAR format using the program Mer2sol (http://taxa.epi.umn.edu/mex2sol/) developed by Michael Miller at the University of Minnesota.

Multivariate Linkage Analysis
In the multivariate linkage model, the phenotype covariance is decomposed to include the genetic correlation between traits caused by additive genetic effects and the shared effects of the QTL, such that the covariance among family members for 2 traits is given by:

\[
\Omega = \begin{pmatrix}
\Omega_{11} & \Omega_{12} \\
\Omega_{12} & \Omega_{22}
\end{pmatrix}
\]

\[
\Omega_{ij} = \sum_{k=1}^{n} \sum_{l=1}^{n} \rho_{ij} \sigma_{g_k} \sigma_{g_l} + 2 \rho_{ij} \sigma_{e_k} \sigma_{e_l} + \rho_{ij} \sigma_{g_k} \sigma_{e_l} + \rho_{ij} \sigma_{g_l} \sigma_{e_k}
\]

Where \(a\) and \(b\) can be trait 1 or 2 and \(\rho_{ij}, \sigma_{g}, \sigma_{e}\) are the QTL specific genetic, additive genetic, and individual-specific environmental correlations between the two traits, respectively. \(\sigma_{g}, \sigma_{e}\) are the additive genetic variance due to the major locus, the genetic variance due to residual additive genetic factors, and the variance due to individual-specific environmental effects, respectively. \(H\) is a matrix whose elements \(g_{ij}\) provide the probability that individuals \(i\) and \(j\) are IBD at a quantitative trait locus which is linked to a genetic marker locus. \(P\) is the kinship matrix, and I is an identity matrix. The conversion of a 2-degrees of freedom (df) bivariate logarithm of odds (LOD) score to a 1-degree of freedom effective LOD score is based on the conversion of the \(\chi^2\) with \(\frac{1}{2}\) df, \(\frac{1}{4}\) df, and \(\frac{1}{4}\) point mass at zero. This is then converted to a \(\frac{1}{2}\) df \(\chi^2\) of equivalent probability value, which is divided by 2in10 to get the 1-df effective LOD score (for more details, please see Amos et al).

Results

Application to HyperGEN Data
Only individuals with complete phenotypic data were included in these analyses. We excluded 10 individuals who were part of a monozygotic twin pair and 6 white individuals from Alabama, because the sample size of 6 was too small to consider as a separate race-center grouping. To reduce skewness in the phenotypic data, outliers (any observation more than 4 standard deviations (SD) from the mean and at least 1 SD from the nearest data point) were also excluded. Table 1 presents the baseline characteristics of all study participants. The average age was approximately 58 years in whites and 49 years in blacks (Table 1). Blacks had significantly higher BMIs and were more often female. The mean SBP response

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White</th>
<th>Black</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families (n)</td>
<td>437</td>
<td>686</td>
<td>1124</td>
</tr>
<tr>
<td>Individuals (n)</td>
<td>1636</td>
<td>1747</td>
<td>3383</td>
</tr>
<tr>
<td>% Women</td>
<td>54</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Age ± SD</td>
<td>58.00±13.1</td>
<td>49.0±13.5</td>
<td>53.4±14.0</td>
</tr>
<tr>
<td>Mean BMI ± SD</td>
<td>29.40±5.78</td>
<td>32.05±7.38</td>
<td>30.77±6.78</td>
</tr>
<tr>
<td>Sample size for BMI</td>
<td>1628</td>
<td>1737</td>
<td>3365</td>
</tr>
<tr>
<td>Mean SBP response to postural challenge ± SD (mm Hg)</td>
<td>-0.34±13.5</td>
<td>2.5±13.3</td>
<td>1.2±13.5</td>
</tr>
<tr>
<td>N (%) with hypertension</td>
<td>1190 (76)</td>
<td>1320 (79)</td>
<td>2510 (76)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure.
TABLE 2. Heritability of SBP Response to Postural Challenge and BMI

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Proportion of Variance Caused by Covariates*†</th>
<th>Proportion of Remaining Variance Caused by Genes (h²) ± SD‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.08 ± 0.05‡</td>
<td>0.55 ± 0.04‡</td>
</tr>
<tr>
<td>Black</td>
<td>0.07 ± 0.05†</td>
<td>0.59 ± 0.06‡</td>
</tr>
<tr>
<td>Whites</td>
<td>0.06 ± 0.06</td>
<td>0.53 ± 0.06‡</td>
</tr>
<tr>
<td>SBP response to postural challenge</td>
<td>Combined sample: 0.09 ± 0.05†</td>
<td>0.17 ± 0.05‡</td>
</tr>
<tr>
<td></td>
<td>Black: 0.07 ± 0.05†</td>
<td>0.15 ± 0.07‡</td>
</tr>
<tr>
<td></td>
<td>White: 0.09 ± 0.06†</td>
<td>0.20 ± 0.06‡</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; BMI, body mass index.
*All heritabilities significant at P<0.001.
*Covariates include race (when applicable), study center, sex, age, and age-sex interaction.
†Standard deviation of estimate is not available.
‡All heritabilities significant at P<0.001.

Examination of the phenotypic correlations (Table 3) revealed that SBP response to postural challenge and BMI were similarly adjusted for race, study center, sex, age, and age-by-sex interaction. We evaluated other possible predictors of postural SBP response and BMI, including plasma total cholesterol, educational attainment, smoking status, alcohol consumption, supine blood pressure, serum glucose level, menopausal status, estrogen use, hypertension status, hypertensive medication usage (y/n), use of beta blockers (y/n), use of calcium channel blockers (y/n), and number of antihypertensive medications used. Further adjustments for these variables had little effect on the magnitude of the genetic signal (data not shown); therefore, only the minimally adjusted models were interpreted further. SBP response to postural challenge and BMI exhibited a residual heritability (after accounting for covariate effects) of 17% (h²=0.17 ± 0.05; P<0.01) and 55% (h²=0.55 ± 0.04; P<0.0001), respectively. Heritability did not strongly vary by race (Table 2).

The genetic and environmental correlations between SBP response and BMI in the combined and race-specific samples are given in Table 3. In all 3 analyses, significant genetic correlations were identified.

Table 4 presents the multipoint genome-wide bivariate-adjusted LOD scores (LOD scores converted from a mixed distribution to a 1-degree of freedom distribution) and their location from the variance component analyses for all peaks ≥1.9 (suggestive evidence of linkage). We detected a maximum LOD score of 3.2 at D13S1493 at approximately 24 cM in the combined sample (significant evidence of linkage).

**Discussion**

A QTL jointly influencing the SBP response to a postural challenge and BMI was detected on chromosome 13q (13q11-13q12) (maximum LOD score=3.2 at D13S1493 at approximately 24 cM). This linkage signal is substantially higher than the univariate linkage signal for each trait at this same chromosomal location (LOD scores for BMI and postural SBP change were 0.9 and 2.4, respectively, data not shown).

The mean SBP response to postural challenge was positive (2.5±13.3 mm Hg) in blacks and near zero in whites (−0.34±13.5 mm Hg). In hypertensive participants, the prevalence of severe hypertension was 53% in whites and 59% in blacks.

Postural SBP change and BMI were similarly adjusted for race, study center, sex, age, and age-by-sex interaction. We evaluated other possible predictors of postural SBP response and BMI, including plasma total cholesterol, educational attainment, smoking status, alcohol consumption, supine blood pressure, serum glucose level, menopausal status, estrogen use, hypertension status, hypertensive medication usage (y/n), use of beta blockers (y/n), use of calcium channel blockers (y/n), and number of antihypertensive medications used. Further adjustments for these variables had little effect on the magnitude of the genetic signal (data not shown); therefore, only the minimally adjusted models were interpreted further. SBP response to postural challenge and BMI exhibited a residual heritability (after accounting for covariate effects) of 17% (h²=0.17 ± 0.05; P<0.01) and 55% (h²=0.55 ± 0.04; P<0.0001), respectively. Heritability did not strongly vary by race (Table 2).

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**TABLE 3. Genetic and Environmental Correlations Between SBP Response to Postural Challenge and BMI**

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>ρe</th>
<th>ρr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural SBP change and BMI±SD</td>
<td>0.29±0.11*</td>
<td>0.05±0.05</td>
</tr>
<tr>
<td>Postural SBP change/BMI (blacks only)±SD</td>
<td>0.35±0.15†</td>
<td>0.13±0.09</td>
</tr>
<tr>
<td>Postural SBP change/BMI (whites only)±SD</td>
<td>0.24±0.14‡</td>
<td>0.09±0.07</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; BMI, body mass index.
*P<0.01; †P=0.001; ‡P<0.05.

The mean SBP response to postural challenge was positive (2.5±13.3 mm Hg) in blacks and near zero in whites (−0.34±13.5 mm Hg). In hypertensive participants, the prevalence of severe hypertension was 53% in whites and 59% in blacks.

**TABLE 4. Multipoint Genome-Wide Bivariate Adjusted Multipoint LOD Scores and Approximate Locations of Peaks ≥1.9 From Genome Scan of BMI and SBP Response to Postural Challenge**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Chromosome</th>
<th>cM</th>
<th>Bivariate Adjusted LOD Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>12</td>
<td>149</td>
<td>1.9</td>
</tr>
<tr>
<td>Combined</td>
<td>13</td>
<td>25</td>
<td>3.2</td>
</tr>
<tr>
<td>Combined</td>
<td>18</td>
<td>80</td>
<td>2.6</td>
</tr>
<tr>
<td>Combined</td>
<td>21</td>
<td>9</td>
<td>2.0</td>
</tr>
<tr>
<td>White</td>
<td>13</td>
<td>25</td>
<td>2.7</td>
</tr>
<tr>
<td>White</td>
<td>18</td>
<td>81</td>
<td>2.6</td>
</tr>
</tbody>
</table>

LOD indicates logarithm of odds; BMI, body mass index; SBP, systolic blood pressure.
*Bivariate LOD score converted from a mixed distribution to a 1-degree of freedom distribution.
of 2.7 at 25 cM) participants. Thus, this QTL may be important in both subpopulations.

The marker that demonstrated the strongest evidence for linkage coincides with a signal reported by Rice et al,30 which is a peak linkage signal of 1.5 (P = 0.0040) on 13q11 for blood pressure response to training. Additionally, our signal is within 20 cM of a linkage (at 13q14) to BMI reported by Feitosa et al31 in the Family Heart Study (LOD = 3.2, P = 0.00006) and Knoblauch et al32 in a sample of dizygotic twin pairs (P = 0.0001).

One plausible candidate gene in the 14-cM (1 LOD unit) support interval is Insulin Promoter Factor 1 (IPF1), a key regulator of islet peptide hormone expression that may be involved in several disorders, most notably, diabetes mellitus (13q12.1).33 Altered IPF1 gene expression may contribute to the beta-cell dysfunction that characterizes type 2 diabetes and may also be related to hypertension and obesity, 2 traits often displayed in diabetic subjects, for which common genes have been hypothesized. Indeed, murine models of insulin resistance have shown the importance of impaired insulin action in pancreatic beta cells for normal glucose sensing and the prevention of obesity.34 Moreover, insulin directly affects vascular endothelium or smooth muscle by causing changes in skeletal muscle blood flow.35

Three other bivariate-adjusted LOD scores ≥1.9 (suggestive evidence for linkage) were detected at 12q, 18q, and 21p. The bivariate signal on 18q, although lower than the univariate LOD at the same location (univariate LOD = 3.6, data not shown), overlays an interesting candidate gene for BMI and SBP response to a postural challenge, melanocortin 4 receptor (MC4R). MC4R deficiency is the commonest monogenic form of obesity36 and may play a role in obesity-related hypertension through the action of leptin.37,38 Because the renal sympathetic effects of leptin may depend on the interactions with other neurochemical pathways in the hypothalamus, including MC4R.39,40

Although participants in our study were not selected on the basis of orthostatic hypotension status, the pattern of blood pressure responses to a postural challenge may be atypical, because the study sample is largely hypertensive. Use of some antihypertensive and other medications is often cited as a potential cause of orthostatic hypotension in the clinical literature. However, findings from population studies have been inconsistent.1,7,41 Our ability to assess whether use of prescrip-

tion antihypertensive medications may have obscured normal physiological responses to the postural stressor is limited in our study because 75% of participants in our study were current users of antihypertensive medications. Nonetheless, when correcting for antihypertensive medication use, hypertension status, and class of hypertensive medication, the magnitude of the peaks reported decreased only slightly. For example, LOD scores with and without a correction for antihypertensive medication use, hypertension status, and class of hypertensive medication were reduced by 0.2, 0.1, and 0.5 LOD units, respectively. However, correcting for class of hypertensive medication reduced the sample by >700 participants, therefore substantially reducing the power of the analysis.

In population-based studies, the blood pressure response to a change in posture is reported to be normally distributed and wide, with a mean close to zero and with a substantial portion of individuals having either strong increases or decreases.4,10 Yet very few studies examine this response as a quantitative trait. Indeed, much of the literature to date focuses on the health-related correlates of orthostatic hypotension. Elevated blood pressure has been consistently associated with orthostatic hypotension.4,5,9 Studies have reported a lack of association of BMI with orthostatic hypotension1,7 but predominantly lower BMIs among those with orthostatic hypotension.4–6

In contrast, relatively little is known about health-related correlates of strong postural blood pressure increases. One study of normotensive individuals reported a positive association of BMI with strong postural blood pressure increases.3,10 Similarly, strong increases in blood pressure in response to a change in posture have also been associated with higher BMI.10 We explored the correlation between BMI and SBP response to a change in posture in hypertensive and random participants and found small but significant correlations (r = 0.17, P < 0.0001 and r = 0.15, P < 0.0001, respectively) when adjusted for age sex, age-by-sex interaction, race, center, menopausal, hormone use, alcohol consumption, smoking status, and supine blood pressure. Unfortunately, in examining the 10 families with the highest positive LOD scores, we could not detect a pattern of segregation of low BMI and a strong negative SBP response to a change in posture (data not shown). Clearly, more research is needed to better understand the interrelationship between the full range of BMI and the SBP response to a change in posture. Indeed, the role of genes in the joint regulation of these 2 traits may help us to better understand their interrelationship.

Perspectives

Our findings suggest that one or more genes on chromosome 13q jointly regulates the SBP response to postural change and BMI. Because the HyperGEN study population was not selected based on the SBP response to a change in posture or BMI, this region on 13q may have broader significance for blood pressure regulation and, by virtue of cross-study replication, likely harbors genes jointly influencing BMI and blood pressure regulation. Therefore, future research should type the biological candidate gene identified here, IPF1, to determine whether polymorphisms in this gene are the source of this and other related linkage signals. Identification of the exact functional
mutations may suggest novel mechanisms in the development and regulation of hypertension and body mass.

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References


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