Genomewide Linkage Scan of Resting Blood Pressure
HERITAGE Family Study


Abstract—The purpose of this study was to search for genomic regions influencing resting systolic (SBP) and diastolic (DBP) blood pressure (BP) in sedentary families (baseline), and for resting BP responses (changes) resulting from a 20-week exercise training intervention (post-training–baseline) in the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study. A genomewide scan was conducted on 317 black individuals from 114 families and 519 white individuals from 99 families using a multipoint variance-components linkage model and a panel of 509 markers. Promising results were primarily, but not exclusively, found in the black families. Linkage evidence ($P<0.0023$) with baseline BP replicated other studies within a 1-logarithm of odds (LOD) interval on 2p14, 3p26.3, and 12q21.33, and provided new evidence on 3q28, 11q21, and 19p12. Results for several known hypertension genes were less compelling. For response BP, results were not very strong, although markers on 13q11 were mildly suggestive ($P<0.01$). In conclusion, these HERITAGE data, in conjunction with results from previous genomewide scans, provide a basis for planning future investigations. The major areas warranting further study involve fine mapping to narrow down 3 regions on 2q, 3p, and 12q that may contain “novel” hypertension genes, additional typing of some biological candidate genes to determine whether they are the sources of these and other signals, multilocus investigations to understand how and to what extent some of these candidates may interact, and multivariate studies to characterize any pleiotropy. (Hypertension. 2002;39:1037-1043.)

Key Words: exercise • race • genes • growth substances • receptors, adrenergic
• renin-angiotensin system • sodium channels

High blood pressure (BP) is a risk factor for coronary heart disease (CHD), with a relatively high prevalence of hypertension in the United States. Estimates vary from as low as 14% in Hispanics, 24% in whites, and 28% in blacks up to 70% among individuals aged 65 years and older. There are multiple forms of essential hypertension, ranging from rare monogenic disorders to multifactorial forms that probably involve multiple susceptibility genes and that constitute the majority of cases. Although some of these genes have been identified (see O’Shaughnessy and Luft for reviews), there remains a great deal of unexplained variability in BP levels. The genomewide linkage scan is one method that may lead to detection of regions harboring novel susceptibility loci that can fill in these gaps. However, the power of this method for detecting true signals is generally low when the effect is modest, as expected for complex traits like BP. Therefore, more liberal criteria for claiming linkage than recommended by Lander and Kruglyak are often adopted but with a greater reliance on replication across studies to confirm true positive signals that warrant more detailed study. Several recent genomewide scans for BP or hypertension have been published. Regions that replicate across these studies provide a fertile ground for further work to identify novel hypertension genes.

One “environmental” factor that is reported to improve BP and reduce the risk for CHD is exercise training. Moreover, recent data from the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study suggests that genetic factors, in part, may underlie the resting BP response to such environmental intervention. Although identification of genes underlying the BP response to exercise has important health implications in the nonpharmacological treatment of hypertension, no other studies investigating linkage hypotheses for the BP responses to exercise training intervention have been reported to date.

The purpose of the current study is 2-fold. First, we report a genomewide scan for resting systolic (SBP) and diastolic...
(DBP) blood pressure, with the goal of identifying genomic regions that replicate across studies, as well as validating the effects of several known genes. Second, we report the first genomewide scan for resting SBP and DBP responses to exercise training.

Methods

Study Design

Black and white participants in the HERITAGE Family Study were measured in a sedentary state and after 20 weeks of endurance exercise training. The criteria for participation are described elsewhere15 (see expanded Methods section in an online data supplement available at http://www.hypertensionaha.org); individuals who were on antihypertensive medications or classified as hypertensive (SBP >159 and/or DBP >99) were excluded from the study design. The Institutional Review Boards of the participating clinical centers previously approved the study protocol and informed consent was obtained from each participant.

Exercise Training

Each participant trained on a cycle ergometer 3 times per week for 20 weeks, as detailed elsewhere15 (see expanded Methods section in an online data supplement available at http://www.hypertensionaha.org). Sessions were supervised on site, and adherence to the protocol was strictly monitored at the participating laboratories.15

Measurements

Multiple BP measurements were made at the baseline visit and after 20 weeks of exercise training as detailed elsewhere16 (see expanded Methods section in an online data supplement available at http://www.hypertensionaha.org). The response was computed as the difference between posttraining values and baseline values.

Data Adjustments

BP measures were adjusted for the effects of covariates using stepwise multiple regression. In summary, a phenotype was regressed on several covariates (separately within age, gender, and racial groups), only significant terms (P<0.05) were retained, and the residual was standardized to zero mean and unit variance. Covariates for baseline measures included the body mass index (BMI) and up to a third degree polynomial in age. The response to exercise (ΔSBP; ΔDBP) was computed as the difference between posttraining and baseline values and was adjusted for a polynomial in age, baseline BP value, and baseline BMI.

Marker Data

PCR conditions, genotyping methods, and checks for Mendelian incompatibilities are outlined elsewhere17 (see expanded Methods section in an online data supplement available at http://www.hypertensionaha.org). Markers were selected from the Location Database (LDB) (http://cedar.genetics.soton.ac.uk), and map locations are expressed in LDB composite units. A total of 509 markers, with an average intermarker spacing of 7 LDB units, was used.

Linkage Analysis

Linkage analysis was performed using a multivariate variance-components model in SEGPATH,18,19 which is more fully described elsewhere9 (see expanded Methods section in an online data supplement available at http://www.hypertensionaha.org). We regard logarithm of the odds (LOD) scores of about 1.75 (P<0.0023) as promising, which represents one false positive per scan for experiments involving approximately 400 markers.6 Linkage analysis was conducted separately in each of the black and white families.

Results

Sample Description

Family structures consisted of parents and offspring. For the baseline visit, there were 317 individuals (114 families) in the black sample (including 136 sibling pairs) and 519 individuals (99 families) in the white sample (including 370 sibling pairs). For the response data, sample sizes were somewhat lower in blacks (249 individuals leading to 91 sibling pairs) and whites (480 individuals yielding 320 sibling pairs). The maximum number of DNA samples was 779 per marker. Means, standard deviations, and sample sizes are given in Table 1. Mean group differences were examined using a standard error comparison. There were ethnic differences for most variables, and generation and gender differences were more prevalent for baseline than response BP measures (see footnotes in Table 1).

Covariate Adjustments

The results for the covariate adjustments are found elsewhere (see expanded Methods section in an online data supplement available at http://www.hypertensionaha.org). For the baseline measures, age and/or BMI account for 4% to 19% of the variance in about half of the groups but is not a significant predictor in the remaining groups. For response BP, the baseline value generally accounts for the most variance (5% to 25%) in most groups.

Linkage

An overview of the linkage results is given in Figures 1 (Baseline) and 2 (Response) in terms of LOD score plots. LOD scores greater than about 1.75 (P<0.0023) are summarized in Table 2. The largest LOD scores for baseline SBP are on 2p14 (D2S441, LOD=1.88), 3p26.3 (D3S2387, LOD=1.84), 3q28 (D3S262, LOD=1.80), 11q21 (D11S2002, LOD=1.98), and 19p12 (D19S215, LOD=2.14). Only one finding at P<0.0023 was noted for DBP, on 12q21.33 (D12S1064, LOD=2.35). Figure 3 graphically depicts each of these 6 regions, with a 1-LOD confidence interval drawn around each peak. We note that there is no replication across HERITAGE black and white samples in any of these regions. A complete set of results, in terms of LOD scores and probability values, is available from the first author (T.R.). A table of results for measured biological candidates (if P<0.05) and for secondary peaks (if P<0.01) is found elsewhere (see expanded Methods section in an online data supplement available at http://www.hypertensionaha.org).

Discussion

The current study yields several promising results (P<0.0023) for baseline BP on chromosomes 2p, 3p, 3q, 11q, 12q, and 19p, with the strongest evidence on 2p, 3p, and 12q involving replication with other studies within a 1-LOD interval. Moreover, there was some confirmation of linkage with markers near plausible biological candidates for hypertension. Results were less compelling for responses to training.

The region on 2p14 (D2S441) replicates at least 3 other studies. Two of them7,9 reported linkage exactly at marker D2S441, and one reported promising results within the 1-LOD interval12 at D2S1394, <5 LDB units downstream. In
addition, preliminary results from a large multicenter study of hypertensive subjects (Rao et al, personal communication, 2002) reported linkage at D2S1356, 10 LDB units upstream. Two plausible candidates in this region include the transforming growth factor (TGFA) and adducin 2 (ADD2) genes. ADD2 was found to be a modulator of a missense mutation in ADD1 (adducin) in Milan hypertensive rats (see, for example, Zagato et al 20), and in humans ADD1 was associated with hypertension (see, for example, Cusi et al 21). TGFA, among other functions, is involved in development of the vascular supply as a regulator of angiogenesis (see, for example, Ferrara22). Because there is now replication across at least 4 studies, further investigation involving fine mapping in 2p14 appears warranted to narrow the region that may contain genes that regulate or affect resting blood pressure.

Promising linkages were also observed on each end of chromosome 3 at 3p26.3 (D3S2387) and 3q28 (D3S1262). The result on 3p was the most extreme marker measured on the p-terminal and, thus, less convincing. However, another study8 also reported linkage less than 1 LDB units from D3S2387 and within the 1-LOD interval, which gives our finding more credibility in terms of replication. The second result on chromosome 3 (D3S1262) does not replicate other studies. However, there is a secondary peak about 100 LDB units upstream (D3S2459, 115 LDB units, LOD=1.22, P=0.0087) that is very close to several other reports. For example, linkage was reported for D3S3045, which is within the 1-LOD interval of D3S2459. Although 2 possible candidates lie between our 2 peaks (dopamine receptor D3 at 3q13.32, 130 LDB, and angiotensin II type 1 receptor at 3q24, 163.3 LDB, involved in hypertension4), only dopamine receptor D3 (DRD3) was within a 1-LOD interval of either peak. Dopamine is a regulator of sodium transport and the D3 receptor inhibits renin release in knockout mice.23 Thus, regions on both 3p and 3q may warrant further investigation involving fine mapping because of the fact that there is now replication across studies.

On 11q21 (D11S2002, 102 LDB units), we found no other reports of linkage within the 1-LOD interval. However, <1 LDB units from D11S2002 is a gene encoding angiotensinase C (PRCP) that is a candidate for essential hypertension and was recently mapped to the 11q21 region.24 Thus, regions on both 3p and 3q may warrant further investigation involving fine mapping because of the fact that there is now replication across studies.

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We also note a secondary peak about 40 units upstream, at D11S4075 (60 LDB units, LOD = 1.38, P = 0.0059), for which there is replication by 2 other studies (within 1 LDB unit) for D11S2019 (59 LDB units) and for D11S2006 (61 LDB units). Together, these results suggest that the 11q region warrants further investigation. More dense typing, including the PRCP locus near our primary signal at D11S2002, is needed to determine whether it or other unidentified loci near our secondary replicated peak are the sources of the linkage.

In absolute values, the strongest findings in the current study were on 12q21.33 (D12S1064, LOD = 2.35) and 19p12 (D19S215, LOD = 2.14). Although no candidates are known on 12q, there was a mildly suggestive replication in an Amish sample within the 1-LOD interval of D12S1064. On 19p, no other genome scans replicated in this region, and the only known candidates were outside of the 1-LOD interval (ICAM1, an intercellular adhesion molecule, and KLK1, a kallikrein protein, both involved in blood flow or coagulation). Because there is now replication for chromosome 12q, this region may also warrant follow-up studies involving additional dense typing to locate the source of the signal. Confirmation of linkage on the 19p region is needed in other studies.

Several other anonymous marker results were noted in the current study; these did not produce convincing LOD scores but nevertheless were mildly suggestive (P < 0.01, see online data supplement at http://www.hypertensionaha.org). At least 2 of these secondary peaks (on 8q and 16q) are close to some known biological candidates and involve linkage with SBP in the black HERITAGE families. For example, the 11β hydroxylase steroid gene (CYP11B2 at 8q24.3, 154 LDB units) is <15 LDB units upstream from D8S1179 (8q24.21, 140 LDB units), which was linked (LOD = 1.61) to baseline SBP in blacks. However, a closer marker to CYP11B2 (D8S373, 154 LDB units) showed no linkage evidence. CYP11B2 is part of the glucocorticoid-remedial aldosteronism disorder.

Two interesting regions were observed on chromosome 16. The 11β2 hydroxysteroid dehydrogenase gene (HSD11B2 at 16q22.1, 73 LDB units) is <10 LDB units upstream from D16S2624 (16q21, 65 LDB units), which was linked (LOD = 1.25) to baseline SBP in blacks. Two HERITAGE markers (D16S2624 and RRAD, which is a renin-angiotensin system [RAS]-related gene associated with diabetes) cover the region of HSD11B2. Although the results for RRAD were nominally suggestive (LOD = 1.04, P = 0.014), those for D16S2624 were not. HSD11B2 is one of several responsible for the apparent mineralocorticoid excess disorder, an inher-
ited form of human hypertension caused by sodium retention. An even closer candidate to D16S3253 (<1 LDB units) is the thiazide-sensitive NaCl cotransporter (SLC12A3, 16q13, 65 LDB units) that relates to the Gitelman and Bartter syndromes.

It is interesting to note that SLC12A3 encodes a molecule that is a target for thiazide diuretics, a common antihypertension drug. There was another region involving 2 markers on 16p near genes involved in Liddle’s syndrome for mutations in the \( SCNN1B \), 16p11.2, 33 LDB units) and \( SCNN1G \), 16p11.2, 32 LDB units) subunits of the epithelial sodium channel. These channel genes were previously associated with hypertension in blacks. In HERITAGE, we now report that D16S261 and D16S753 (16q11.1–q11.2) located about 10 LDB units from \( SCNN1 \), were nominally linked with baseline SBP in blacks (LODs of 1.51 and 1.25, respectively).

The HERITAGE panel of over 500 markers included some candidates for BP (see online data supplement at http://www.hypertensionaha.org) in the renin-angiotensin system relating to vascular or arterial homeostasis (\( AGT \), \( ACE \), \( REN \), \( AGTR1 \)) as

![Figure 2. Multipoint LOD score plots for response SBP and DBP on each of chromosomes 1 through 22. See Figure 1 for further detail.](Image)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Location</th>
<th>LDB Units</th>
<th>Trait</th>
<th>Sample</th>
<th>LOD</th>
<th>( P ) Value</th>
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</thead>
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<td>D2S441</td>
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<td>0.00182</td>
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<td>3q28</td>
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<td>11q21</td>
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<td>White</td>
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<td>19p12</td>
<td>26.051</td>
<td>SBP</td>
<td>Black</td>
<td>2.14</td>
<td>0.00084</td>
</tr>
</tbody>
</table>

Best result for responses on 13q11 with SBP in blacks: D13S175 (16.201 LDB units, LOD = 1.40, \( P<0.00561 \)); D13S250 (17.067 LDB units, LOD = 1.53, \( P<0.00401 \)).

LDB indicates location data base; LOD, logarithm of odds.
well as others previously linked or associated with BP or essential hypertension (eg, \textit{ADRB2}, \textit{GNB3}, \textit{NOS3}, \textit{INSR}) (see O’Shaughnessy\textsuperscript{3} and Luft\textsuperscript{4} for reviews). Other than those already discussed (\textit{UCP2}, \textit{UCP3}, \textit{RRAD}), none evidenced convincing linkage nor replicated across black and white samples, although nominal evidence (\(P=0.01\)) was noted for the \(\beta_2\) adrenergic receptor (\textit{ADRB2}, 5q32) with DBP (\(P=0.0128\)) in blacks, and also for an anonymous marker (\textit{D5S1480}) less than 5 LDB units upstream (LOD=1.41, \(P<0.0055\)). Two SNPs not generally recognized as BP candidates also were nominally linked: insulin-like growth factor binding protein 1 (\textit{IGFBP1}, 7p11.2) with DBP (\(P=0.0084\)) and insulin-like growth factor 1 receptor (\textit{IGF1R}, 15q26.2) with SBP (\(P=0.0081\)) in blacks.

For BP responses to training, no results reached \(P=0.0023\), although 2 markers were nominal. On 13q11, \textit{D13S175} (16.2 LDB units, LOD=1.40, \(P=0.0056\)) and \textit{D13S250} (17.1 LDB units, LOD=1.53, \(P=0.0040\)) were linked with response SBP in blacks. We note that for the resting BP responses, there was no significant change with training in whites and only marginal responses in blacks.\textsuperscript{16} Thus, it is not surprising that no strong linkage signals were detected for the BP responses to training.

In conclusion, multiple regions provided moderate evidence of linkage with resting BP as may be expected for complex traits. However, at least 3 of these regions are highly likely to harbor genes for baseline resting BP by virtue of cross-study replication. In contrast, linkage evidence was not as promising for training responses and may be explained in part by 2 factors. First, the HERITAGE participants were selected to be primarily normotensive and consequently exhibited only small changes in training responses. Second, responses were adjusted for baseline values, so they presumably are specific to how individuals respond to environmental intervention (eg, gene by environment interaction) and independent of the baseline BP levels. These factors constitute a possible explanation for the lack of strong results for responses.

\textbf{Perspectives}

We do not expect striking linkage evidence for complex traits like BP because these traits are likely to be influenced by multiple genes, each having only a modest effect. Thus, there is a greater reliance on replication of moderate results across
studies to guide selection of the most promising regions for further work. In the current study at least 3 regions provide sufficient cross-study replication within a 1-LOD interval: 2p14 (D2S441), 3p26.3 (D3S2387), and 12q21.3 (D12S1064). Further, the known etiologic complexity underlying BP variation suggests that multilocus and multivariate methods are warranted to determine the relationships among contributing genes. That is, consideration of gene-by-environment and gene-by-gene interactions may be necessary to detect linkage signals. For example, hypertension was demonstrated in mice transgenic for both the human angiotensinogen locus (AGT) and human renin (REN) loci, but not in mice transgenic for only one of the human genes.23 The current study suggests several genes to consider by virtue of their nominal levels of linkage (UCP3, RRAD, ADRB2, IGFBP1, and IGFI1R), and others because of their proximity to anonymous markers with suggestive signals (ADD2, TGF A, DRD3, CYP11B2, PRCP, HSD11B2, SLC12A3, and SCNN1B and SCNN1G).

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References

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