Genome Scan for Blood Pressure Loci in Mice

Fred A. Wright, Daniel T. O’Connor, Elizabeth Roberts, Greg Kutey, Charles C. Berry, Lisa U. Yoneda, David Timberlake, Gunther Schlager

Abstract—Hypertension is a complex trait of unknown cause in humans. Mice of the inbred strain BPH/2 serve as a rodent model of human hypertension and display elevated blood pressure compared with the hypotensive strain BPL/1. An F2 intercross of BPH/2 and BPL/1 and 2 backcrosses of BPL/1 with Mus spretus were used to perform interval linkage mapping for systolic blood pressure in a genome scan. Significant linkage was observed in the F2s on chromosome 10 (logarithm of the odds score [LOD]=4.9) and on chromosome 13 in the Mus spretus backcross (LOD=3.3), with additional suggestive LODs on chromosomes 2, 6, 8, and 18. In addition, several suggestive linkages were observed for phenotypes associated with human hypertension. Our study is the first reported genome-wide linkage scan for blood pressure genes in the mouse. (Hypertension. 1999;34:625-630.)

Key Words: linkage ■ hypertension, genetic ■ mice ■ genes

Hypertension in humans is a prevalent and major predisposing factor to a host of illnesses, including cardiovascular disease, renal impairment, and stroke. Although dietary and lifestyle factors have been associated with hypertension, heredity also plays a strong role, and essential hypertension appears to be a complex polygenic trait. Several candidate genes have been investigated in humans, and blood pressure linkages have been observed in isolated hereditary syndromes. However, with heritability estimates in the range of 25% to 50%, a substantial portion of the genetic variation in blood pressure remains unexplained.

Rodent models provide another approach, in which genetic synteny or homology may be used to elucidate genetic mechanisms in human hypertension. Crosses of the spontaneously hypertensive rat (SHR) with normotensive strains and recombinant inbred analyses have provided evidence for blood pressure involvement of several chromosomal regions. Congenic strains have recently provided more definitive evidence in several chromosomal regions by introducing segments from hypertensive rat strains into a normotensive background. Unfortunately, positional cloning strategies in animal models of human hypertension have thus far yielded definitive characterization of few if any loci.

In contrast, few linkage analyses have been reported for blood pressure in the mouse, perhaps because of its small size and the difficulty in assessing the phenotype. However, when properly performed, noninvasive tail-cuff systolic blood pressure measurements are closely correlated with intra-arterial measurements. The genetic analysis of newly identified candidate genes in the mouse may provide independent and corroborative evidence of the genetic components of rodent hypertension. Mice of the inbred hypertensive strain BPH/2 and hypotensive strain BPL/1 have been described, with comparison of blood pressures and related phenotypes. These strains were developed by 2-way selection (high blood pressure versus low blood pressure) from an initial cross of 8 inbred strains, and inbreeding of the unselected control population resulted in an additional, normotensive strain BPN/3. By use of these strains and a standard biometric method for estimating the minimum number of involved quantitative trait loci (QTLs), 3 to 5 major genes were estimated to contribute to the 55 mm Hg strain difference in blood pressure, with heritability of 30% to 60%. Interestingly, the BPH/2 strain also exhibits elevated pulse rate, left ventricular mass, and hematocrit (percent) compared with BPL/1. Phenotypes that have also been associated with human hypertension and its cardiovascular sequelae.

A previous report examined cosegregation of blood pressure with 2 candidate genes on chromosomes 8 and 12 in the BPH/2×BPH/1 intercross. Although the BPH/2 and BPL/1 strains are well described, their genetic similarity and the possibility of random common gene fixation may limit the number of blood pressure genes that vary across the strains. Inbred Mus spretus have relatively high blood pressure, and interspecific crosses of this species with BPL/1 may elucidate additional genes that contribute to variation in blood pressure.
We undertook a genome-wide QTL linkage scan for systolic blood pressure in intraspecific F2 crosses of 247 BPH/2×BPL/1 mice, 92 interspecific backcross (BC) mice designated BCBL (M spretus×BPL/1)×BPL/1, and 84 interspecific backcross mice designated BCMS (M spretus×BPL/1)×M spretus. Blood pressure was determined from tail-cuff measurements, with multiple observations averaged for each mouse. A microsatellite map was used to cover the genome with 91 markers in the F2s and 95 markers in the backcrosses, at an average spacing of ∼16 cM. Additional phenotypes associated with mouse and human hypertension were also examined for linkage as available.

**Methods**

**Intercrosses**

The BPH/2 and BPL/1 strains have been described; they were produced from 23 generations of 2-way blood pressure selection followed by >20 generations of brother-sister inbreeding. The 2 inbred strains were mated reciprocally to produce an F1 generation. From the 2 matings using BPH/2 females, 5 brother-sister matings produced 68 F2s. From the 3 matings using BPL/1 females, 7 brother-sister matings produced 98 F2s. Of these 166 mice, 149 produced DNA of sufficient quality for genotyping (77 males, 72 females). These mice are designated “set A.” In addition, 98 F2 mice with extreme blood pressures were selected for genotyping from previous sets of 221 F2s as a means of improving power to detect linkage. Of these mice, 49 were selected from the lowest quartile of blood pressure (26 males, 23 females) and 49 from the highest quartile (23 males, 26 females). These mice are designated “set B.” Thus, the total number of genotyped F2 mice was 149+98=247. In addition, the phenotypes of the remaining 123 nonextreme mice from the set of 221 F2s were used to provide valid likelihood estimates as described below.

**Blood Pressure Measurement**

Systolic blood pressures of the mice in set A were measured during the summer of 1994 beginning when the mice reached 100 days old. These determinations were tail-cuff measurements (8-mm ID, 15 mm long) taken on unanesthetized restrained mice with the Narco-Biosystems Physiograph. Five determinations were made on each of 3 days at approximately weekly intervals and then measured once or twice again when the mice were 7 to 8 months old. The blood pressures of the mice in set B were determined in fall and winter of 1992/1993 when the mice were 100 days old, at weekly intervals for a total of 15 measurements. All the mice were anesthetized and killed at 150 days old by cervical dislocation. The heart was removed and cleaned and the left ventricle separated and weighed on a Mettler balance.

**DNA Preparation and Genotyping**

A simple 3-step DNA extraction was performed from mouse tail tissue by use of a Qiagen kit and column (protease K step, RNAse A step, and QIAamp spin column; Qiagen Inc). By this procedure, we routinely obtained 160 μg of DNA/tail in 400 μL of Tris-EDTA buffer. Samples were sent to the J.L. Weber laboratory for genotyping.

Markers were scored by at least 2 independent reviewers. In addition, genotypes were reexamined in regions of significant linkage. Markers were spaced as evenly as possible and extended to within 15 cM of both chromosome ends for all but the X chromosome. The mean±SD for marker interval widths was 16.1±7.1 cM for the F2 intercrosses and 16.2±5.1 cM for the backcrosses. Additional intervals were made to close the gaps ≥50 cM apart in 3 such chromosomal regions for the F2s and 1 region for the interspecific backcrosses remained uninformative at all microsatellites examined.

**Linkage and Statistical Analyses**

Linkage analysis was performed for each of the 3 crosses with the Mapmaker/QTL program 1.1 (Whitehead Institute) on a UNIX workstation. The precise phenotype for each cross was chosen before analysis. Statistical power calculations for a genome-wide scan were performed by use of both simulation and analytic approximations, which were in close agreement. The F2 intercross data were shown to have ≥80% power to detect QTLs contributing 10% of the variation in blood pressure, whereas the backcrosses BCBL and BCMS had power of 73% and 70%, respectively, to detect loci contributing 20% of the phenotype variation. The crosses were expected to provide little power to detect epistatic interactions among the loci. Mapmaker/QTL allows the inclusion of covariates in the linkage analysis, and sex was introduced as an additive effect to reduce error variation. The covariate also appears in the denominator of the likelihood ratio and thus does not inflate the type I error. Statistical power for the F2s was enhanced by genotyping of the 98 phenotypically extreme (for blood pressure) mice of set B, with the phenotypes of the remaining 123 nongenotyped mice also entered to provide valid likelihood estimates and combined with the mice of set A. Pulse rate was analyzed for the F2s in the same manner. The mice in the remaining crosses were not chosen on the
basis of extreme phenotype, and all available individuals were used in the analysis.

Linkage analyses used Haldane’s map function and marker map locations reported by Research Genetics, which agrees well with other published maps. Additional marker ordering and mapping was performed on the data by use of Mapmaker/EXE. Maps of mammalian homology reported by the Jackson Laboratory (http://www.informatics.jax.org) were used to compare syntenic regions. Linkage results are reported according to published conservative standards for the maximum LOD in a dense genome scan. LODs of 4.3 and 3.3 are considered significant at the 0.05 level for F2 and backcross populations, respectively. Thresholds of 2.8 and 2.3 are considered “suggestive,” in that they are expected to occur approximately once in a full genome scan. To facilitate communication, all regions with LODs >2.0 are reported here.

### Additional Statistical Analyses

Additional statistical analyses were performed with the S-Plus 3.4 statistics package (MathSoft, Inc). A χ² contingency table test of Mendelian ratios revealed a statistically significant imbalance in parental strain origin of allele marker D13 Mit78 in the F2 cross, in a region not showing evidence of blood pressure linkage. Linkage results were also confirmed by interval mapping regression and permutation-based tests of linkage significance. ANOVA tests of 2-way genetic interactions of all pairs of markers were also performed, with permutation tests used to construct a genome-wide P value.

### Results

#### Blood Pressure

Systolic blood pressure measurements in the F2 intercrosses and BCBPL mice were performed with tail cuffs on conscious, restrained mice; the BCMS mice were measured while regaining consciousness from metofane anesthesia. The measurement procedures varied (see Methods) according to the restraint and anesthetic procedures necessary for each cross. The systolic blood pressures in males were as follows (mm Hg, mean ± SD): 111.7 ± 11.4 in the F2 intercross, 95.2 ± 12.5 in the BCBPL backcross, and 94.0 ± 34.5 in the

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### Table 1: Regions With LODs > 2.0 for Blood Pressure and Related Phenotypes

<table>
<thead>
<tr>
<th>Cross</th>
<th>Chromosome</th>
<th>Marker</th>
<th>LOD</th>
<th>Phenotypic Effect of BPL/1 Alleles</th>
<th>Variance Explained, %</th>
<th>Genetic Model*</th>
<th>Human Homologous Region</th>
<th>Rat Homologous Region</th>
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<tbody>
<tr>
<td><strong>Systolic blood pressure</strong>†</td>
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<td>F2 (n = 247)</td>
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<td>D1Mit303</td>
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<td>Increase</td>
<td>4.2</td>
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<td>9</td>
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<tr>
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<td>D8Mit64/205</td>
<td>3.2‡</td>
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<td>7.7</td>
<td>Recessive</td>
<td>8q, 4q</td>
<td>16q</td>
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<td>BPH/2 × BPL/1</td>
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<td>D10Mit123/117</td>
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<td>Additive</td>
<td>6q, 10q, 22q, 21q, 19p</td>
<td>1, 20, 7</td>
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<td>D12Mit156</td>
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<td>Recessive</td>
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<td>6q2</td>
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<td></td>
<td>4.2</td>
<td>Additive</td>
<td>21q</td>
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<td>D2Mit92/274</td>
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<td>Decrease</td>
<td>18.8</td>
<td>Dominant</td>
<td>2q, 11</td>
<td>3</td>
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<td>BCBPL</td>
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<td>D6Mit15</td>
<td>2.5‡</td>
<td>Decrease</td>
<td>11.9</td>
<td>Dominant</td>
<td>12p</td>
<td>4</td>
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<tr>
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<td>D13Mit198</td>
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<td>15.2</td>
<td>Recessive</td>
<td>1q, 6p, 7p</td>
<td>17</td>
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<tr>
<td>BCMS (n = 84)</td>
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<td>D2Mit149/92</td>
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<td>26.6</td>
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<td>10p, 9q, 2q</td>
<td>17, 3</td>
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<td>14.6</td>
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<td>18q, 5q</td>
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<td><strong>Pulse rate</strong></td>
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<tr>
<td>BPH/2 × BPL/1</td>
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<td>D3Mit60/22</td>
<td>4.2‡</td>
<td>Decrease</td>
<td>11.6</td>
<td>Additive</td>
<td>8p, 3q, 4q</td>
<td>2</td>
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<td>7.8</td>
<td>Dominant</td>
<td>5, 15q</td>
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<td>BPH/2 × BPL/1</td>
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<td>D14Mit20/19</td>
<td>3.5‡</td>
<td>Decrease</td>
<td>7.9</td>
<td>Recessive</td>
<td>14q</td>
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<td>Backcrosses</td>
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<td>BCBMS (n = 84)</td>
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<td>D9Mit85/52</td>
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<td>24.8</td>
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<td>8</td>
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<td>Dominant</td>
<td>18q</td>
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<td>DXMit35</td>
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<td><strong>Left ventricular mass</strong> (percent of total body mass)</td>
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<td>BPH/2 × BPL/1</td>
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<td>D15Mit17/18</td>
<td>2.5</td>
<td>Decrease</td>
<td>24.0</td>
<td>Dominant</td>
<td>8q</td>
<td>7</td>
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<td><strong>Hematocrit</strong></td>
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<td>F2 (n = 71, males only)</td>
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<tr>
<td>BPH/2 × BPL/1</td>
<td></td>
<td>D4Mit255/12</td>
<td>3.2‡</td>
<td>Decrease</td>
<td>23.2</td>
<td>Additive</td>
<td>1p</td>
<td>5</td>
</tr>
</tbody>
</table>

*Genetic model of highest likelihood among 1-df models. Backcross designs cannot distinguish between additive and dominant models.
†Measurement of phenotype described in Methods.
‡Suggestive linkage in a genome scan according to the standards proposed by Lander and Kruglyak.
§Significant linkage in a genome scan.
Blood pressures in females were 110.5 ± 6 in the F2 intercross, 91.9 ± 9.3 in the BCBPL backcross, and 100.1 ± 37.9 in the BCMS backcross. The larger variances in the BCMS cross may reflect the influence of the anesthetic.

Interval mapping was performed with Mapmaker/QTL 40 for each of the 3 crosses and revealed 10 regions with LOD scores ≥ 2.0 (Table 1). Two regions provided significant linkage evidence according to conservative standards: the interval D10 Mit123–D10 Mit117 (LOD = 4.9) in the F2 intercross and D13 Mit198 (LOD = 3.3) in the BCBPL backcross. Additional suggestive loci were identified on chromosomes 2, 6, 8, and 18, including a region, D2 Mit192/274, that approached significant linkage in the BCBPL backcross with LOD = 3.2. A moderate amount of phenotype variation (10% to 25%) may be attributed to these loci individually, and the summed contribution of the suggestive or significant loci (between 30% and 50% in each cross) is consistent with previous heritability estimates. The Figure plots the LOD scores for blood pressure on the 4 chromosomes that achieved suggestive or significant linkage.

BCMS backcross. Blood pressures in females were 110.5 ± 13.8 in the F2 intercross, 91.9 ± 9.3 in the BCBPL backcross, and 100.1 ± 37.9 in the BCMS backcross. The larger variances in the BCMS cross may reflect the influence of the anesthetic.

Interval mapping was performed with Mapmaker/QTL 40 for each of the 3 crosses and revealed 10 regions with LOD scores ≥ 2.0 (Table 1). Two regions provided significant linkage evidence according to conservative standards: the interval D10 Mit123–D10 Mit117 (LOD = 4.9) in the F2 intercross and D13 Mit198 (LOD = 3.3) in the BCBPL backcross. Additional suggestive loci were identified on chromosomes 2, 6, 8, and 18, including a region, D2 Mit192/274, that approached significant linkage in the BCBPL backcross with LOD = 3.2. A moderate amount of phenotype variation (10% to 25%) may be attributed to these loci individually, and the summed contribution of the suggestive or significant loci (between 30% and 50% in each cross) is consistent with previous heritability estimates. The Figure plots the LOD scores for blood pressure on the 4 chromosomes that achieved suggestive or significant linkage.

BPL/1 alleles are present in all the crosses, and QTL alleles from this strain would be expected to reduce blood pressure relative to any other parent strain. Although this is true for most of the regions identified, the BPL/1 allele near D13 Mit198 appears to increase blood pressure relative to M. spreitus. A similar phenomenon has been reported in the rat, 47 in which alleles at some loci from the SHR strain appeared to decrease blood pressure. There was no evidence of chromosome 13 involvement in the BCMS cross, suggesting that the BPL/1 allele may be dominant or due to differing genetic background between the strains (ie, other interacting loci).

The LOD score analysis for the significant loci was supported by additional statistical procedures. 45,46 However, the LOD score of 4.9 was achieved only in a relatively large interval between markers (although an LOD = 3.0 was observed at flanking marker D10 Mit123). Interestingly, the locus on chromosome 10 does not show evidence in either of the interspecific backcrosses, suggesting that M. spreitus may not have an allele conferring high blood pressure in this region.

**Multiple Gene Models**

Additive models 38 with multiple genes were explored with Mapmaker/QTL, but no new loci were identified beyond those listed in Table 1. Using ANOVA with interaction terms, 48 we examined all pairs of markers for evidence of epistatic effects on blood pressure. None of these interaction effects were statistically significant when permutation testing was used to apply a multiple-comparison adjustment.

**Comparison of Blood Pressures Across Strains**

Measurements performed under inhaled metofane anesthetic provide a uniform condition under which blood pressures can be compared across strains and crosses. All of the BCMS mice in this report were measured under metofane anesthetic (see Methods). A few mice from the other strains were chosen to be measured under metofane anesthetic (in addition to their unaesthetized measurements) and are presented for comparison in Table 2. This table exhibits the anticipated differences across strains, with the exception of the BCMS cross. The average blood pressure for BCMS females was greater than that of both of the parent strains (not significant). Metofane phenotypes for F1 females were unavailable.

**Additional Phenotypes**

In addition to blood pressure, the phenotypes pulse rate, relative left ventricular mass (left ventricular mass/body mass), and hematocrit (percent) were examined. Pulse rate was measured concurrently with blood pressure. Left ventric-
ular mass was measured in \( \approx 50\% \) of the F2 mice (\( n = 126 \)) when they were killed at 180 to 250 days old, and hematocrit (percent) was measured only in males of this group (\( n = 71 \)). The procedures for obtaining these phenotypes are discussed in greater detail elsewhere.\(^{30}\) The linkage results are given in Table 1. None of the regions showed significant linkage, although a LOD of 4.2 for pulse rate was highly suggestive for a locus in the interval D3 Mit60/22 among the F2s.

**Discussion**

Hypertension is a complex trait\(^{49}\) with multiple genetic and environmental determinants.\(^{50}\) We demonstrated that several regions of the mouse genome show significant or suggestive cosegregation with systolic blood pressure, and these apparent loci vary across the 3 experimental crosses examined (Table 1). A LOD score of 4.9 was observed on chromosome 10 in an F2 intercross and a LOD of 3.3 on chromosome 13 in an interspecific N2 backcross, surpassing rigorous standards\(^{44}\) for establishing linkage. The comparatively large interval between the markers flanking the area of peak LOD score=4.9 (Table 1; Figure) on chromosome 10 in the F2 cross has thus far resisted attempts to identify further microsatellite polymorphisms distinguishing the parental strains (BPL/1 and BPH/2) in this region; nonetheless, the presence of a LOD \( >3.0 \) at flanking marker D10 Mit123 supports linkage in the region.

Other suggestive\(^{44}\) blood pressure linkages were found on chromosomes 2, 6, 8, and 18. Interestingly, only chromosome 2 shows evidence of involvement in multiple crosses (Table 1 and Figure), and 1-LOD-unit support intervals in the 2 backcrosses exhibit some overlap. The overall results are consistent with the complex, polygenic nature of blood pressure.\(^{51}\)

Loci encoding components of the renin-angiotensin system are leading candidate genes for hypertension, and affected sib-pair methods have found evidence for linkage of the angiotensinogen (\( AGT \)) locus to human hypertension.\(^{52}\) Some alleles at the angiotensin II receptor type I locus (\( AGTR1 \)) are associated with human hypertension,\(^{53}\) and alleles at the angiotensin-converting enzyme (\( ACE \)) locus are associated with adverse myocardial events in hypertension.\(^{54}\)

In the spontaneously hypertensive rat, linkage established the role of a major locus (\( BPH1 \)) near \( ACE \) on rat chromosome 10;\(^{55,56}\) the mouse homologue is probably on chromosome 11. In the mouse, renin-angiotensin components include \( Agt \) at 68 cM (angiotensinogen, renin substrate) on mouse chromosome 8, \( Ren \) (renin) on mouse chromosome 1 at 70 cM, angiotensin-converting enzyme mouse homologue \( Ace \) not assigned but probably on chromosome 11 by synteny, and \( Agtr2 \) (angiotensin II receptor type II) on the mouse X chromosome. None of these regions displayed significant linkage to blood pressure in our data. In the mouse genome, there are 2 angiotensin II receptor type I loci\(^{57}\): \( Agtr1a \), at 16 cM on mouse chromosome 13, and \( Agtr1b \), at 2 cM on mouse chromosome 3. Mouse chromosome 13 showed significant linkage to blood pressure in the BCBL (backcross to BPL/1; Table 1 and Figure), with the support interval containing \( Agtr1a \).

These syntenic comparisons do not provide support for mouse homologues to the candidate regions in humans and rat models. However, to aid future comparisons, we list in Table 1 the presumed homologous regions in the human and rat genomes to the mouse loci identified in this study. The resolution of syntenic maps varies according to region, and in many cases, the mouse blood pressure locus is not well localized, so the syntenic region may include multiple chromosomal regions in the comparison organism.

In conclusion, this study is the first reported genome-wide linkage scan for blood pressure genes in the mouse. Linked regions of mouse-human chromosomal synteny may suggest novel loci that influence blood pressure in humans. As the genetic maps of mammals improve, investigators can increasingly take a positional candidate approach, testing logical candidate genes in linked regions.

**Acknowledgments**

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**References**


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