QTL associated with blood pressure, heart rate, and heart weight in CBA/CaJ and BALB/cJ mice

FUMIHIRO SUGIYAMA,1,3 GARY A. CHURCHILL,1 RENHUA LI,1 LAURA J. M. LIBBY,1,2 TONYA CARVER,1 KEN-ICHI YAGAMI,3 SIMON W. M. JOHN,1,2 AND BEVERLY PAIGEN1
1The Jackson Laboratory and the 2Howard Hughes Medical Institute, Bar Harbor, Maine 04609; and 3Laboratory Animal Resource Research Center, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan

Received 7 January 2002; accepted in final form 29 April 2002

Sugiyama, Fumihiro, Gary A. Churchill, Renhua Li, Laura J. M. Libby, Tonya Carver, Ken-Ichi Yagami, Simon W. M. John, and Beverly Paigen. QTL associated with blood pressure, heart rate, and heart weight in CBA/CaJ and BALB/cJ mice. Physiol Genomics 10: 5–12, 2002.—To better understand the genetic basis of essential hypertension, we conducted a quantitative trait locus (QTL) analysis of a population of 207 (BALB/cJ × CBA/CaJ) F2 male mice to identify genomic regions that regulate blood pressure, heart rate, and heart weight. We identified two loci, Bpq6 (blood pressure quantitative locus 6) on chromosome 15 (Chr 15; peak, 16 cm; 95% confidence interval, 0–25 cm) and Bpq7 on Chr 7 (peak, 42 cm; 95% confidence interval, 35–50 cm) that were significantly associated with blood pressure. We also identified two loci, Hrq1 (heart rate quantitative locus 1) and Hrq2, on D2Mit304 (peak, 72 cm; 95% confidence interval 60–80 cm) and D15Mit184 (peak, 25 cm; 95% confidence interval 20–35 cm), respectively, that were significantly associated with heart rate. A significant gene-gene interaction for heart rate was found between Hrq1 and D1Mit10 (peak, 57 cm; 95% confidence interval, 45–75 cm); the latter QTL was named Hrq3. We identified a significant locus for heart weight, Hwq1 (heart weight quantitative locus 1), at D14Mit67 (peak, 38 cm; 95% confidence interval 20–43 cm). Identification of the genes for these QTL should lead to a better understanding of the causes of essential hypertension.

quantitative trait loci; hypertension

HUMAN HYPERTENSION greatly increases the risk of coronary heart disease, congestive heart failure, stroke, and kidney disease. Additionally, it is often associated with and complicated by obesity, dyslipidemia, and non-insulin-dependent diabetes mellitus (1). More than 50 million Americans suffer from hypertension, and 12.7 million of them alleviate its symptoms by taking hypertensive drugs (27). Although human hypertension exists in a monogenic form, most humans suffer from polygenic or essential hypertension. It is difficult to identify the genes that cause essential hypertension in humans, because the genetic backgrounds and environmental influences are almost impossible to control. On the other hand, both genetic background and environment are relatively easy to control in inbred rodent populations. As a result, multiple studies of hypertension in genetic crosses of inbred strains have identified many quantitative trait loci (QTL) associated with blood pressure in the rat (18, 28) and in the mouse (29, 33). In addition, numerous studies of genetically engineered mouse strains with deficiency or overexpression of proteins thought to be involved in blood pressure regulation have provided insight into the genetic basis of hypertension [reviewed in Sugiyama et al. (30)]. These studies have established the laboratory rat and mouse as powerful models for dissecting the genetic basis of essential hypertension.

Several of the rat and mouse hypertension QTL map to regions that contain homologous genes, suggesting that the genes determining hypertension are also homologous. Likewise, several of the limited number of human hypertension QTL also map to regions that contain genes homologous to those in rat and mouse hypertension QTL (28, 30). This concordance of hypertension QTL across species suggests that common allelic variations occur in only a subset of all the proteins that are involved in blood pressure regulation. These may be mutations in genes that code for rate-limiting or regulatory proteins since most proteins are present in excess, as shown by the large number of recessive diseases. The fact that QTL are concordant across species should help to guide the search for the genetic determinants of human hypertension, since many studies, such as narrowing a QTL region or carrying out expression studies, are more easily carried out in a rodent model.

In this study, we further exploited the mouse as a hypertension model. We conducted a QTL analysis of a population of (BALB/cJ × CBA/CaJ) F2 males to identify genomic regions and gene-gene interactions that regulate blood pressure, heart rate, and heart weight. We identified several significant QTL: two associated with blood pressure, three significantly associated with heart rate, and one associated with heart weight.

Article published online before print. See web site for date of publication (http://physiolgenomics.physiology.org).
Address for reprint requests and other correspondence: B. Paigen, The Jackson Laboratory, 600 Main St., Bar Harbor, ME 04609 (E-mail: bjp@jax.org)
METHODS

Mice. We obtained BALB/cJ (BALB) and CBA/CaJ (CBA) mice from the Jackson Laboratory (Bar Harbor, ME) and produced reciprocal F1 populations (BALB × CBA; CBA × BALB) and 207 (BALB × CBA) F2 males. We housed them in a room with a 14-h light/10-h dark cycle and gave them unrestricted access to acidified water and food (NIH31 6% fat open formula; Purina Mills, Richmond, IN). The cages were covered with a polyester filter and contained pine shavings bedding. The Institutional Animal Care and Use Committee at the Jackson Laboratory approved all animal protocols.

Phenotyping. To measure blood pressure and heart rate, we used a blood pressure analysis system (model BP-2000; Visitech Systems, Apex, NC). The machine accommodated four mice and consisted of a warming plate, which kept the mice at 38°C, and four restraining units (dark metal tunnels open at one end). Computer-automated tail cuffs placed on the tails of each mouse rapidly inflated and deflated, and blood pressure was detected by a photoresistor cell below each tail and recorded by a computer (14). The machine also recorded the heart rate of each mouse.

We reduced the variation in blood pressure by acclimating mice to the room for at least 2 wk, measuring their blood pressures when they were 8 wk (±1 wk) old, and taking all measurements in the morning (9–12 AM). Additionally, we trained the mice to the machine and all the associated measurement procedures for 5 days, designated as days 1–5, without recording blood pressures, then measured blood pressures on days 8–12, each day taking 20 measurements for a total of 100 measurements per mouse (expressed in mmHg as means ± SE). One of us (F. Sugiyama) carried out all blood pressure measurements. Mice were killed, and body and heart weights were determined. The numbers of mice are listed in Tables 1–3 and Figs. 1–5.

To ensure the quality of our data, we eliminated blood pressure readings that were less than 60 mmHg, because these low readings resulted from failure of the machine to detect the pulse of a mouse that was moving. If we were unable to successfully obtain at least eight pressure readings on a given day, then we did not use that day’s data, since failure to obtain readings resulted from mice that were moving and probably were stressed. We used data from mice only if we were able to obtain at least 3 days of data. These criteria eliminated 12 of the 207 (6%) mice, providing a total of 195 mice for analysis. We eliminated blood pressure readings for a given mouse if these were more than 2 standard deviations from the mean for that mouse on that day. We used the same criteria for heart rate; if we were unable to obtain blood pressure, then we were unable to obtain heart rate.

Genotyping. We extracted DNA from the tail of each mouse (31) and genotyped it with 91 simple sequence length polymorphic (SSLP) markers spaced at ~15-cM intervals throughout the mouse genome; 11 additional SSLP markers were added in specific locations after we detected QTL (Fig. 1). We reported map positions in centimorgans using the 2001 Mouse Genome Informatics database (http://www.informatics.jax.org).

Because most genetic information for a quantitative trait is at the extreme ends of its distribution in a population, we selected for genotyping the mice in the upper and lower 20% of each phenotypic trait. Because we measured so many traits, selecting the upper and lower 20% for each phenotypic trait. Because we measured so many traits, selecting the upper and lower 20% for each trait
Table 1. Systolic blood pressures, heart weights, and heart rates of CBA and BALB inbred mouse strains, and of F1 and F2 progeny

<table>
<thead>
<tr>
<th>Strains</th>
<th>Blood Pressure, mmHg</th>
<th>Heart Rate, beats/min</th>
<th>Heart Weight, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BALB</td>
<td>104 ± 2 (12)</td>
<td>484 ± 9 (12)</td>
<td>120 ± 2 (12)</td>
</tr>
<tr>
<td>CBA</td>
<td>96 ± 3 (11)</td>
<td>620 ± 75 (11)</td>
<td>108 ± 23 (12)</td>
</tr>
<tr>
<td>(BALB × CBA)F1</td>
<td>106 ± 1* (11)</td>
<td>587 ± 105 (11)</td>
<td>138 ± 23 (12)</td>
</tr>
<tr>
<td>(CBA × BALB)F1</td>
<td>110 ± 1* (5)</td>
<td>605 ± 16 (5)</td>
<td>155 ± 32 (8)</td>
</tr>
<tr>
<td>F2</td>
<td>105 ± 1* (195)</td>
<td>610 ± 43 (195)</td>
<td>132 ± 43 (207)</td>
</tr>
</tbody>
</table>

Values are means ± SE; n is parentheses. *Significant difference (P = 0.0001) between CBA and other groups. †Significant difference (P < 0.0001) between CBA and other groups. ‡Significant difference (P < 0.0001) between BALB and other groups.

resulted in 162 of the 195 (83%) F2 males being genotyped; all genotyped animals were used for the genome scan.

We purchased primers from Research Genetics (MapPairs, Huntsville, AL). The Allele Typing Service of the Jackson Laboratory genotyped the samples using fluorescent primers and the ABI model 3700 capillary electrophoresis apparatus. We reviewed the genotypes for the presence of double recombinants over short genetic distances, and questionable typings or missing data were repeated in our laboratory using standard procedures (17). The average spacing between markers was 15 cM. Four regions on chromosome (Chr) 10, 12, 13, and X had greater than 30 cM between markers. Since we found no polymorphic markers in these four regions (data not shown), we think these regions may be identical by descent because these two strains do share a common origin. Chromosome lengths were appropriate, and all markers fit a Hardy-Weinberg distribution.

Statistical analyses. To compare blood pressures between parental and F1 mice, we used Student’s t-test. To detect QTL significantly associated with blood pressure, heart rate, or heart weight, we analyzed genome-wide scans in three steps (29). In the first step, we identified main QTL associated with each phenotype by computing a logarithm of the odds ratio (LOD) score at 2-cM steps over the entire genome and compared these to significance thresholds computed by permutation analysis (4). Confidence intervals were computed by the method of Sen and Churchill (24) by finding the region under the posterior density curve (10-LOD) that contains 95% of the total area. In the second step, we identified pairs of loci significantly associated with a phenotype by performing a simultaneous search for pairs analysis (24). Genome-wide scans were implemented in MATLAB software (Mathworks, Natick, MA; source codes available at http://www.jax.org/research/churchill). In the third step, we integrated all the main and interacting QTL-phenotype associations detected in the first two steps into a multiple regression (using SYS/STAT Software, version 8; SAS Institute, Cary, NC). F-statistics based on adjusted (type III) sums of squares were used to determine the contribution of a QTL in combination with all other QTL. These statistical methods have been described previously (24).

To assess the evidence for multiple linked QTL on the same chromosome, we calculated LOD scores for one, two, and three QTL models on each chromosome that showed a significant main effect. The difference in LOD score between the single and multiple QTL models was used to compute a likelihood ratio test (and thus a P value) for the evidence in favor of multiple linked QTL. These test statistics have nonstandard distributions (23), so we conducted simulations to estimate significance thresholds and P values. For the comparison of 2-QTL vs. 1-QTL models, the 95% significance threshold is 3.4 for additive QTL and 3.9 if we allow for interaction between the two QTL. The estimates are based on 1,000 simulated intercrosses with 200 mice and a single QTL with an effect size of 0.5 standard deviations. LOD scores for 3-QTL vs. 2-QTL models in this study were clearly nonsignificant, and no simulations were carried out.

RESULTS

Blood pressure, heart rate, and heart weight in parental strains, F1 and F2 progeny. The blood pressures of BALB mice were significantly higher than were

<table>
<thead>
<tr>
<th>Strains</th>
<th>Blood Pressure, mmHg</th>
<th>Heart Rate, beats/min</th>
<th>Heart Weight, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBA</td>
<td>104 ± 2 (12)</td>
<td>484 ± 9 (12)</td>
<td>120 ± 2 (12)</td>
</tr>
<tr>
<td>BALB</td>
<td>96 ± 3 (11)</td>
<td>620 ± 75 (11)</td>
<td>108 ± 23 (12)</td>
</tr>
<tr>
<td>(BALB × CBA)F1</td>
<td>106 ± 1* (11)</td>
<td>587 ± 105 (11)</td>
<td>138 ± 23 (12)</td>
</tr>
<tr>
<td>(CBA × BALB)F1</td>
<td>110 ± 1* (5)</td>
<td>605 ± 16 (5)</td>
<td>155 ± 32 (8)</td>
</tr>
<tr>
<td>F2</td>
<td>105 ± 1* (195)</td>
<td>610 ± 43 (195)</td>
<td>132 ± 43 (207)</td>
</tr>
</tbody>
</table>

Values are means ± SE; n is parentheses. *Significant difference (P = 0.0001) between CBA and other groups. †Significant difference (P < 0.0001) between CBA and other groups. ‡Significant difference (P < 0.0001) between BALB and other groups.

"Fig. 2. Distribution of blood pressure (A), heart rate (B), and heart weight (C) in the F2 male progeny. Blood pressure and heart rate are based on 100 measurements/mouse. Heart weight and body weight were obtained at the end of the experiment."
those of CBA mice (104 ± 2 vs. 96 ± 1 mmHg, means ± SE; P = 0.0001, Table 1). This is not a large interstrain difference, but the wide distribution of blood pressures in the F2 population suggested that genes were segregating and that QTL analysis would be successful. Blood pressure was similar in the reciprocal F1 progeny ruling out maternal inheritance or imprinting. The genes underlying the lower blood pressure of CBA mice were apparently recessive because blood pressures of F1 and F2 progeny were more BALB-like than CBA-like.

The heart rates of BALB mice were significantly slower than those of CBA mice (484 ± 9 vs. 620 ± 7 beats/min, P < 0.0001, Table 1); those of the F1 progeny were similar to each other and intermediate to the heart rates of the parental strains with a tendency to be more like CBA (Table 1). The hearts of BALB mice weighed significantly more than did those of CBA mice (120 ± 2 vs. 108 ± 2 mg, P < 0.0001, Table 1). The genes underlying the relatively slower heart rates and larger heart weights of BALB mice were probably recessive, because these phenotypes in F1 and F2 progeny were more CBA-like than BALB-like (Table 1). The mean blood pressures, heart rates, and heart weights of the F2 progeny were distributed normally around the mean (Fig. 2).

Identification of QTL for blood pressure. The genome-wide scan indicated significant QTL for blood pressure on Chrs 7 and 15 (Fig. 3A). The Chr 15 QTL, already named Bpq6 (for “blood pressure QTL 6”) was previously found in two QTL crosses between strains A/J and C57BL/6J and between strains BPH and BPL (these latter strains are “blood pressure high” and “blood pressure low” strains developed by Schlager [22]). However, in this cross the Chr 15 QTL is broad as shown by the interval map together with the 95%
confidence interval (Fig. 4A). Confidence intervals were computed by the method of Sen and Churchill (24) by finding the region under the posterior density curve (10 \( \hat{LOD} \)) that contains 95% of the total area. Equivalent results are obtained by the method of dropping down 1.5 units from the peak of the LOD curve.

We calculated the LOD scores for the 1-QTL, 2-QTL, and 3-QTL models for Chr 15 without interaction effects. The difference in LOD scores for 2-QTL vs. 1-QTL models is 1.9 (\( P < 0.51 \)) and is not statistically significant. We note, however, that this does not rule out the possibility of a second QTL on chromosome 15 (see DISCUSSION). The difference between the 2-QTL and the 3-QTL model is a LOD score of 0.5, which is not significant.

The Chr 7 QTL was also found previously in the A/J × C57BL/6 cross as an interaction (24); it is now named Bpq7. The allele effects of Bpq6 and Bpq7 are shown in Fig. 5, A and B. The Bpq6 allele for high blood pressure came from strain CBA, and the Bpq7 allele for high blood pressure came from strain BALB.

The scan for interacting QTL did not reveal any for blood pressure in this cross. The multiple linear regression (Table 2) shows that the Chr 7 and 15 QTL accounted for 22.5% of the variance. Table 3 lists the chromosomal location, LOD scores, allele giving the highest value, and peak markers for each blood pressure QTL and for the heart rate and heart weight QTL discussed below.

**Identification of QTL for heart rate and heart weight.**

The genome-wide scan revealed significant QTL for heart rate on Chrs 2 and 15 (Fig. 3B). The interval maps for these QTL and the 95% confidence intervals are shown in Fig. 4, C and D. The allele effects of the Chr 2 QTL, named Hrq1 (for “heart rate QTL”), and the Chr 15 QTL, named Hrq2, are shown in Fig. 5, C and D. In both cases strain CBA contributed the allele for high heart rate; the CBA allele is additive for Hrq1 but dominant for Hrq2. This is consistent with the heart rates in F1 progeny (Table 1), which show that heart rate is between the two parents but tends to be more like CBA. Hrq2 on Chr 15 appears to be different than Bpq6 on Chr 15; their 95% confidence intervals overlap only slightly (0–25 cM for Bpq6; 20–35 cM for Hrq2).

The Chr 2 QTL is broad with a distinct cusp (Fig. 4C). We calculated the LOD scores for the single QTL model for Chr 2 and Chr 15 QTL in Table 2.
DISCUSSION

Several studies have recently conducted QTL analyses of progeny from crosses between inbred mouse strains that differed in blood pressure and have identified genomic regions associated with polygenic hypertension. Wright et al. (33) conducted QTL analyses of strains inbred for blood pressure differences (BPH for high blood pressure and BPL for low blood pressure). Analysis of the (BPH/2 × BPL/1)F2 progeny and the progeny of two crosses of (BPL/1 × Mus spretus) identified 10 QTL associated with systolic blood pressure, and one associated with ventricular mass. We (29) conducted a QTL analysis of (C57BL/6J × A/J)F1 × C57BL/6J progeny and found six QTL associated with salt-sensitive hypertension. Three of the QTL we identified for salt-induced hypertension appeared to be the same as those identified by Wright and colleagues (Ref. 33): Bpq1 (25–60 cM on Chr 1), Bpq5 (66–80 cM on Chr 6), and Bpq6 (0–30 cM on Chr 15).

In our current study, we conducted a QTL analysis of (CBA × BALB) F2 progeny. Ordinarily, the blood pressure difference of 8 mmHg between the two parental strains with standard deviations in the range of 5 would not be sufficient to justify a QTL analysis, since this represents a strain difference of less than 2 standard deviation units. However, we planned this cross for other purposes, and the wide distribution of blood pressure among F2 progeny encouraged us to search for QTL for this trait. We identified two QTL associated with blood pressure, Bpq6 and Bpq7. The fact that BALB and CBA each contributed one allele for high blood pressure may explain the small interstrain blood pressure difference between the two parents compared with the difference in the F2 population. We identified the effect of Bpq6 on blood pressure in a previous study (29) as an interacting QTL; Bpq6 had an effect on blood pressure through its interaction with Hrq1 pressure. We have assumed that Bpq6 found in this cross and the previous studies identify the same gene, although further data may reveal that these are distinct genes. Bpq7 was also found in our previous cross as an interacting QTL between A/J and C57BL/6, although we did not report it in our original paper (29). It was found and reported later as our methods for finding interacting QTL improved (24). We also identified three QTL significantly associated with heart rate; Hrq1, Hrq2, and Hrq3 and one associated with heart weight, Hwq1.

Two of the QTL (Bpq6 and Hrq1) reported in this study appear to consist of multiple loci. We feel that it is important to report indications that a QTL region may harbor multiple loci, because it is our experience and the two QTL model for Chr 2; the difference between the 1-QTL LOD and the 2-QTL LOD with interaction is 3.15 (P = 0.19). Although the test failed to achieve the standard 0.05 level of significance, we interpret this as suggestive evidence for multiple QTL. The maximal peak for a single QTL on Chr 2 occurs at 72 cM and we name this QTL Hrq1. If a second locus exists, it would localize somewhere in the region 40–80 cM, so it is tightly linked. The two loci appear to interact epistatically, but with tight linkage not all genotype combinations occur in the cross, and it is difficult to characterize the interaction.

The search for gene-gene interaction showed a significant interaction between D1Mit10 (57 cM) and D2Mit304 for heart rate. We named this interacting QTL on Chr 1 Hrq3. The magnitude of the interaction between Hrq3 and Hrq1 (Fig. 5F) shows that heart rate for mice with a D1Mit10 CBA allele in either a homozygous or heterozygous state are very affected by the D2Mit304 allele at Hrq3. The magnitude of the interaction of the BALB allele at D1Mit10, the Hrq3 locus has no effect. The multiple regression analysis for heart rate (Table 2) shows that these three QTL account for 32.2% of the variance in heart rate.

The genome scan for heart weight was carried out on the log of heart weight and also on the log of heart weight adjusted with body weight as a covariate. The two genome scans gave equivalent results; the scan for log heart weight is shown (Fig. 3C). One significant QTL was found at D14Mit67 with the peak at CM 38 and the 95% confidence interval at 20–43 cM (Fig. 4E); we name this QTL Hwq1 for “heart weight QTL 1.” Two additional QTL that reach suggestive significance were also found, both on Chr 12. These were not named because they are only suggestive, but both were included in the multiple regression analysis since we used a high threshold for suggestive. The allele effects of Hwq1 are shown in Fig. 5E, and the regression analysis is shown in Table 2. The significant locus on Chr 14, and the two suggestive loci on Chr 12 account for 13.1% of the variance.

Table 3. Chromosomal location, peak marker, confidence interval, and LOD score for blood pressure, heart rate, and heart weight QTL

<table>
<thead>
<tr>
<th>Trait</th>
<th>Name</th>
<th>Chr</th>
<th>Peak, cM</th>
<th>95% CI, cM</th>
<th>High Allele</th>
<th>Peak Marker</th>
<th>LOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Bpq7</td>
<td>7</td>
<td>42</td>
<td>35–50</td>
<td>BALB</td>
<td>D7Mit31</td>
<td>6.1</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Bpq6</td>
<td>15</td>
<td>16</td>
<td>0–25</td>
<td>CBA</td>
<td>D15Mit175</td>
<td>4.9</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Hrq1</td>
<td>2</td>
<td>72</td>
<td>60–80</td>
<td>CBA</td>
<td>D2Mit304</td>
<td>4.0</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Hrq2</td>
<td>15</td>
<td>26</td>
<td>20–35</td>
<td>CBA</td>
<td>D15Mit184</td>
<td>3.1</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Hrq3</td>
<td>1</td>
<td>60</td>
<td>45–75</td>
<td>CBA</td>
<td>D1Mit10</td>
<td>0.2*</td>
</tr>
<tr>
<td>Heart weight</td>
<td>Hwq1</td>
<td>14</td>
<td>38</td>
<td>20–43</td>
<td>CBA</td>
<td>D14Mit67</td>
<td>2.9</td>
</tr>
</tbody>
</table>

LOD, logarithm of the odds ratio score; QTL, quantitative trait locus; Chr, chromosome; CI, confidence interval. *Hrq3 has no significant effect by itself but the interaction between Hrq1 and Hrq3 is significant. The confidence intervals for Bpq6 and Hrq1 are not reliable, since both of these are on chromosomes with complex loci.
that upon further dissection (e.g., by analysis of congenics) such QTL may break apart into multiple independent effects. The lack of strong statistical support for multiple QTL is likely to be a consequence of low power to detect linked QTL. Although we can provide some indication of the complexity of these QTL using statistical indices, it is difficult to precisely localize multiple effects in an intercross population of this size.

Bpq6, Bpq7, Hrq1, and Hrq3 each harbor promising candidate genes. We previously reported that Bpq6 contains two candidate genes; prostaglandin receptor gene Ptgerep2 and Npr3 (natriuretic peptide receptor 3; cM 6.7). However, further mapping studies showed that Ptgerep2 was really on Chr 14 and the prostaglandin receptor on Chr 15 was a different member of the same gene family, Ptgerep4 (prostaglandin E receptor EP4 subtype; cM 6.4). Like the Ptgerep2, Ptgerep4 codes for a G protein-coupled receptor, and a number of studies support its role in blood pressure regulation (1–3, 7, 20). The most promising candidate genes for Bpq7 are Adm (adrenomedullin; cM 50.5), which encodes a potent vasodilator peptide that exerts major effects on cardiovascular function (21); Pth (parathyroid hormone; cM 52.5), Calc (calcitonin, α-calcitonin gene-related peptide; cM 54), which shares some structural homology with Adm and is a potent vasodilator (2, 20), and Senn1b and Ig (sodium channel, non-voltage-gated 1β and 1γ; cM 56). Mice that lacks calcitonin develop hypertension (8). Senn1b and Senn1g, the sodium channel, non-voltage-gated 1β or 1γ, participate in the control of sodium flux in the kidney; mutations in these proteins have been associated with Liddle syndrome, a rare form of monogenic human hypertension (9, 26). Some interesting candidate genes for heart rate are located on Chr 1 and 2. Acetylcholine is known to affect heart rate (3), and two classes of cholinergic receptors are known; the muscarinic receptors, of which five are known, and the nicotinic receptors, which exists as a pentamer composed of four different subunits. The muscarinic receptors are G-coupled proteins and are known to affect heart rate; the nicotinic receptor is a ligand-gated ion channel that affects sodium and potassium flux and may affect heart rate (3, 10, 11, 25, 32). Chrna1 (cholinergic receptor, nicotinic, polypeptide-α) is located on Chr 2 at cM 43, and two other subunits of this receptor are located on Chr 1 at cM 52.3 (Chrnd, Chrng; cholinergic receptor, nicotinic, polypeptide δ and γ). These subunits and one other form a pentamer that is the receptor. Two of the muscarinic receptors are also located on Chr 2 in the Hrq1 region, Chrm4 and Chrm5 (cholinergic receptor, muscarinic, 4 and 5; cM 49 and 58).

Evidence for the concordance of QTL across species is increasing. Previously, several studies demonstrated that a QTL in one experimental animal model can predict the location of a QTL in a homologous region in another species, especially humans (13, 28, 29). A recent review provides evidence for additional QTL that are concordant in mice, rats, and humans (12). Our current study offers more evidence for this type of concordance: both murine hypertension QTL we identified were concordant with blood pressure QTL in humans. Bpq6 is homologous to human 5p12–14 and 8q22–24; a human hypertension QTL has been found in both of these regions region (7, 19). Bpq7 is homologous to three human chromosomal regions: cM 35–44 is homologous to human 15q23–26; cM 44–54 are homologous to human 11p12–13 and 11q13–21; and cM 55–56 are homologous to human 16p12–13. A human hypertension QTL has been found for 15q25.1–26.1 (16, 34), and a rare form of monogenic human hypertension, Liddle syndrome, maps to 16p12–13 (9, 26). The rat homology to Bpq6 is not known except for a 2-cM region homologous to rat 2; this small region of rat Chr 2 is part of a hypertension QTL (32). Homology to rat Chr 7 begins at the distal edge of Bpq6 at cM 25; this region of rat Chr 7 does contain a hypertension QTL (5, 6), but the most likely candidate gene Cyp11b1 (7) maps to mouse cM 44, which is clearly out of the Bpq6 region. Since the Chr 15 QTL appears to be complex, there may be a second QTL on Chr 15 which is homologous to rat 7, but it is not the region we define as Bpq6. Bpq7 is homologous to rat Chr 1, which does contain a QTL for hypertension (32). A QTL for heart rate has been found in rats (15); its location on rat Chr 3 has a peak homologous to mouse Chr 2, cM 35. This is not the location of Hrq1, which is at cM 72, but we note that the Chr 2 locus appears to be complex and may have a second peak about cM 40; this second peak is homologous with the rat QTL.

These results establish the laboratory mouse as an excellent model for essential hypertension. Further work in additional inbred mouse strains will more clearly characterize quantitative blood pressure and other cardiovascular traits and enable us to elucidate the genes that regulate these traits in humans.

We thank Olga Savinova, Harry Whitmore, and Janice Martin for excellent technical assistance and Ray Lambert for technical writing skills.

This work was supported by grants from the National Heart, Lung, and Blood Institute’s Program for Genomic Applications (HL-66611) and the SCOR program (HL-55001), by the American Heart Association Grant 50564N (G. A. Churchill and R. Li), by the American Health Assistance Foundation G1999023, and by the Japanese Ministry of Education, Science, Sport, Culture, and Technology (F Sugiyama). S. W. M. John is an assistant investigator of the Howard Hughes Medical Institute.

REFERENCES


17. Rapp JP. Genetic analysis of inherited hypertension in the rat. *Physiol Genomics* • VOL 10 • www.physiolgenomics.org