Abstract—In a previous study, by using a candidate gene approach, we detected in both Milan hypertensive rats and humans a polymorphism in the α-adducin gene (ADD1) that was associated with blood pressure and renal sodium handling. In the present study, a genomewide search with 264 informative markers was undertaken in 251 (Milan hypertensive strain × Milan normotensive strain) F2 rats to further investigate the contribution of the adducin gene family (Add1, Add2, and Add3) and to identify novel quantitative trait loci (QTLs) that affect blood pressure. The influence of 2 different methods of blood pressure measurement, the intracarotid catheter and the tail-cuff method, was also evaluated. We found evidence that QTLs affected systolic blood pressure (SBP) measured at the carotid (direct SBP) on rat chromosome 1 with a logarithm of the odds (LOD) score peak of 3.3 on D1Rat121 and on rat chromosome 14 on Add1 locus (LOD=3.2). A QTL for SBP measured at the tail (indirect SBP) was found on rat chromosome 10 around D10Rat33 (LOD=5.0). All of these QTLs identified chromosomal regions not detected in other rat studies and harbor genes (Na+/H+ exchanger A3; α-adducin; α1B-adrenergic receptor) that may be involved in blood pressure regulation. Therefore, these findings may be relevant to human hypertension, also in consideration of the biochemical and pathophysiological similarities between MHS and a subgroup of patients of primary hypertension, which led to the identification of α-adducin as a candidate gene in both species. (Hypertension. 2000;36:734-739.)

Key Words: genes ■ rats, inbred strains ■ hypertension, essential

A variety of strategies can be applied to demonstrate the molecular genetic determinants of human essential hypertension. Our approach was to study, in parallel, hypertensive patients and an animal model of genetic hypertension, the Milan hypertensive strain (MHS) rat with its normotensive control (Milan normotensive strain [MNS]). In this way, it may be possible to reduce the enormous complexity that arises from the polygenic nature of hypertension, the environmental and genetic context dependency of each gene effect, and all of the consequences that these 2 confounding characteristics may have at the different levels of biological organization. The main drawbacks of this strategy are that (1) only the genes at work in a particular strain of rats can be detected, and other genes, with their interactions, that may be involved in human hypertension are ignored, and (2) the small degree of polymorphism between 2 strains of rats derived from common ancestors may hamper the detection of a number of polymorphic markers suitable to carry out a total genome search and the congenic strain selection. This last limitation considerably delayed the whole genome screening in the MHS×MNS cross. The continuous improvements and the recent availability of new rat markers allowed us to provide a systematic genome scan for blood pressure (BP) quantitative trait loci (QTLs) in an (MHS×MNS) F2 population.

Biochemical and physiological abnormalities in kidney function and cell membrane ion transport were described in hypertensive rats and humans. The genetic approach allowed us to identify in both rats and humans α-adducin gene (ADD1) functional mutations. A logical sequence of events linked an alteration in the cytoskeletal protein α-adducin with the primary renal alteration responsible for hypertension, that is, increased tubular sodium reabsorption due to hyperactivation of the Na+/K+ pump, which is the driving enzyme responsible for the overall tubular reabsorption. Missense mutations were detected in the rat α and β-adducin genes (Add1 and Add2), and a cause-effect relationship between these mutations and hypertension was supported by genetic studies, gene transfections in tubular cells, and interactions between adducin and the Na+/K+ pump in a cell-free system with the different adducin variants. In addition, in humans, a missense mutation in ADD1 has been associated with hypertension. The increase in BP after saline infusion or its decrease after diuretic treatment is greater in patients with “hypertensive” adducin than in those with “normotensive” adducin.
The aims of the present work were to (1) confirm and define the boundaries of the previously reported BP QTL at Add1 locus and further investigate the contribution of the adducin gene family, (2) map new QTLs by using 2 methods of BP measurement, and (3) evaluate potential interactions among QTLs and analyze the rat–human synteny in the regions associated with BP.

### Methods

#### Animal Procedures and BP Measurement

All MHS (MHS/Gib) and MNS (MNS/Gib) rats were bred in our facilities and maintained under conditions described elsewhere. A large F2 population of 121 males and 130 females was used for BP cosegregation analysis and was described previously. Two different methods of BP determination were used. Indirect systolic BP (indirect SBP) was measured with the tail-cuff method at 12 to 16 weeks of age with a W±W BP recorder (Ugo Basile) with piezoelectric pick-up. Animals were awake and restrained by being lightly wrapped in a small cloth. At least 4 consecutive consistent readings were taken during 4 separate sessions, and the pressures were averaged to give a final BP (indirect SBP). Direct BP measurements were obtained in rats at 16 weeks of age through a cannula inserted into the carotid artery of the rats while under light halothane anesthesia and externalized at the back of the neck through a subcutaneous tunnel. The animals recovered within 3 to 5 minutes. Four hours later, the rats were connected via a catheter to a Gould BS3200 BP recorder under unrestrained conditions. The SBP and diastolic BP (DBP) of each rat were recorded simultaneously for 1 hour, and 1-minute tracings were taken every 3 to 4 minutes. These values were averaged to provide a single systolic or diastolic measurement for each animal (direct SBP or direct DBP).

#### Polymorphic Markers and Genotyping

The majority of polymorphic markers used were SSLPs (single strand length polymorphisms); a few markers were represented by single base-pair differences. SSLPs were selected from Serikawa et al., Steen and Kwitek-Black panels. D14N52 single base-pair differences. SSLPs were selected from Serikawa et al., Bihoreau et al., and Steen and Kwitek-Black panels. D14N52 single base-pair differences. SSLPs were selected from Serikawa et al., Bihoreau et al., and Steen and Kwitek-Black panels. D14N52 single base-pair differences. SSLPs were selected from Serikawa et al., Bihoreau et al., and Steen and Kwitek-Black panels.

TABLE 1. Blood Pressure Values in MNS, MHS, F1, and F2 Cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Direct SBP</th>
<th>Direct DBP</th>
<th>Indirect SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MNS</td>
<td>138.3±2.6 (14)</td>
<td>96.9±2.8 (15)</td>
<td>131.2±1.1 (17)</td>
</tr>
<tr>
<td>MHS</td>
<td>163.7±1.9 (22)</td>
<td>113.4±5.3 (22)</td>
<td>169.4±1.0 (23)</td>
</tr>
<tr>
<td>F1</td>
<td>145.0±2.8 (10)</td>
<td>106.9±3.1 (10)</td>
<td>141.7±1.9 (11)</td>
</tr>
<tr>
<td>F2</td>
<td>147.8±0.7 (251)</td>
<td>107.7±0.7 (251)</td>
<td>151.4±0.7 (251)</td>
</tr>
</tbody>
</table>

Estimated degree of genetic determination* 0.42 0.25 0.45

*The estimated degree of genetic determination is calculated as a ratio of genetic to total variance.

Blood pressure values are expressed in mean±SEM mm Hg (number of animals studied).

For the PCR, primers for typing the polymorphic markers were obtained from Genosys, Research Genetics, and Primm. Genotyping was performed with PCR with a microtiter plate-type apparatus (Techne). The reaction volume was 20 μL with 100 ng genomic DNA, 0.25 to 0.4 μmol/L concentration of each primer, 200 μmol/L dNTPs, NiCl2, or KCl 10× buffer, 1.5 to 3 mmol/L MgCl2, and 1 U Taq polymerase (Bioline). PCR products of SSLP markers were resolved in 4% agarose gel and detected with ethidium bromide staining. Markers that could not be resolved under these conditions were amplified with 32P end-labeled primers and resolved on denaturing polyacrylamide gels.

F316Y polymorphism of Add1, Q529R polymorphism of Add2, Stul polymorphisms at Sa and Na/Kal loci, C573W polymorphism of Scnn1g, and a trinucleotide repeat in Gr exon 2 were typed in previous works. Q572K polymorphism of Add3 and Stul polymorphism at the ATPB2S locus were typed as described previously. A GATA repeat in 3′ noncoding region of Cyp11b1 and a TaqI Agt polymorphism (D. Lodwick and N.J. Samani, personal communication, 1999) were analyzed.

LOD surfaces for direct (solid line) and indirect (dotted line) SBP are reported for chrs 1 (A), 10 (B), 14 (C), and 20 (D). Marker D15Rat45 on chr 1 (indicated by asterisk) has a chromosomal assignment different from that on published maps.
Ppy coding region direct sequencing of MHS and MNS revealed a polymorphic site in A673G (GenBank M27450). Genotypes were determined with allele-specific oligonucleotide hybridization by using 5'-GTATCCTGCTCCTCTGGC-3' and 5'-ATTGTTGGTGCCTCTGCTTCTGGC-3' as PCR primers and 5'-CTCTCTGCCAGTCTGGCT-3' as ASO probes.

Linkage and Statistical Analysis

Genetic markers were mapped with the MAPMAKER/EXP 3.0 computer package with an error detection procedure. 21,22 Genetic distances were calculated with the Kosambi mapping function. QTLs that affected a given phenotype were mapped relative to the genetic map, the markers were on average 9.7 cM apart and at maximum distance of 26 cM (except for chr 15, for which we were limited by availability of informative markers) (Table 2). The overall genome coverage was 85%.

Results

BP Measurements

BP measurements in 251 F2 rats (121 male, 130 female) were obtained both directly via the intracarotid catheter method and indirectly via the tail-cuff method. The degree of genetic determination (ratio of genetic to total variance) in the F2 cohort was estimated as 0.42 for direct SBP, 0.25 for direct DBP, and 0.45 for indirect SBP (Table 1). 24 Direct SBP and DBP were strongly correlated (r=0.93), whereas direct and indirect SBP measurements showed just a weak correlation (r=0.24; P<0.01). We refer to the direct SBP and indirect SBP, whereas data on direct DBP have been omitted because the same pattern as that of direct SBP was followed. Within each cohort, the BP values of males were not significantly different from those of females (data not shown).

Genomewide Scan

DNA samples from MHS and MNS rats were screened for all of the microsatellite markers of the Wellcome Trust Center Oxford and the Whitehead Institute/MIT Center for Genomic Research panels. Of 5317 markers, 1527 were found to be polymorphic between MHS and MNS. These 2 strains of rats were selected from the same colony of outbred animals. For this reason, the low degree of polymorphism (28.7%) may be due to the sharing of many chromosomal regions inherited from common ancestors. In this work, 264 polymorphic markers were mapped on our total F2 progeny, including intragenic polymorphisms for some candidate genes in hypertension: Sa, Scnn1g, Adh1, Add2, Add3, Atplab1, Cyp11b1, Ppy, Atplab2, Gr, and Agt. The vast majority of the markers retained their relative map order as reported, 23, 24 but some differences were found in chromosomal assignment for D15Rat45 and 37.RHAP181FB9.seq (http://www.genome.wi.mit.edu) assigned in our linkage map to chromosomes (hrs) 1 (Figure) and 18 (data not shown), respectively. In our genetic map, the markers were on average 9.7 cM apart and at maximum distance of 26 cM (except for chr 15, for which we were limited by availability of informative markers) (Table 2). The overall genome coverage was 85%.

QTL Detection

In the (MHS×MNS) F2 intercross, we detected suggestive linkage (2.8≤LOD≤4.3) for direct SBP on chrs 1 and 14 and for indirect SBP on chr 20, and we detected significant linkage (LOD≥4.3) for indirect SBP on chr 10 (Figure and Table 3).

We found evidence for a QTL on the short arm of chr 1, affecting direct SBP with an LOD score peak of 3.3 on D1Rat121 marker (Figure, A, and Table 3).

The LOD surface for linkage of indirect SBP on chr 10 was very wide with a major peak on D10Rat33 (LOD score=5.0) and minor peaks: 1 within D10Rat81 and D10Rat116 (LOD score=3.3), 1 within D10Wox12(Abp) and D10Wox13(Syb2) (LOD score=3.3), and 1 within D10Rat59 and D10Wox5 (LOD score=.3.0). Multiple QTL analysis conducted with “simultaneous search” function of MAPMAKER/QTLM software confirmed the presence of a QTL only on D10Rat33 marker (data not shown). No significant association was observed along the chr 10 for direct SBP (Figure,B, and Table 3).

Using the candidate gene approach, we had already identified an F316Y polymorphism in the Add1 gene on chr 14, associated with direct SBP and modulated by a Q529R polymorphism in the Add2 gene. 6 To better localize the position of Add1 gene on the chromosome and to estimate the statistical confidence interval of the QTL, the genetic map of chr 14 was constructed. The LOD surface for linkage to direct SBP showed a blood pressure QTL with a maximum LOD of 4.3 on D14Rat35 marker (data not shown). 7 No significant association was observed along the chr 10 for direct SBP (Figure,B, and Table 3).

![Image](http://hyper.ahajournals.org/)

**TABLE 2. (MHS×MNS) F2 Genomic Coverage**

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>No. of Markers</th>
<th>Maximum Distance Between Adjacent Markers, cM</th>
<th>Maximum Distance to End of Map, cM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>22.5</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>24.6</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>26.5</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>24.3</td>
<td>16</td>
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<td>11</td>
<td>25.7</td>
<td>4</td>
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<td>7</td>
<td>12</td>
<td>25.6</td>
<td>7.8</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>26.1</td>
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<td>9</td>
<td>9</td>
<td>23.6</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>15.2</td>
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<td>17.4</td>
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<td>7</td>
<td>26</td>
<td>7</td>
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<tr>
<td>14</td>
<td>24</td>
<td>14.3</td>
<td>24</td>
</tr>
<tr>
<td>15</td>
<td>8</td>
<td>35.1</td>
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<td>26.8</td>
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<td>6</td>
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<td>18</td>
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<td>19.9</td>
<td>19</td>
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<td>24.8</td>
<td>3.7</td>
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<tr>
<td>20</td>
<td>9</td>
<td>17.9</td>
<td>11.3</td>
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<tr>
<td>X</td>
<td>5</td>
<td>19.9</td>
<td>16.7</td>
</tr>
</tbody>
</table>

*The distances between telomeres and first marker on our genetic map are calculated referring to those reported by the WIBR/MIT CGR panel (final release January 2000).*
3.2 on the Add1 locus (Figure, C, and Table 3). No significant association was observed along the chromosome for indirect SBP.

With multilocus linkage analysis, we also localized Add2 gene on rat chr 4 at 0.2 cM from D4Wox18/Tgfa and 0.5 cM from D4Rat51 (data not shown), but no association with BP was observed along the chromosome.

The cytogenetic localization of Add3 gene on chr 1q55 and the K572Q polymorphism previously reported allowed the linkage analysis of the F2 and the exclusion of an involvement of this polymorphism per se in BP determination.

On chr 20, we found suggestive evidence for QTL with an LOD peak of 3.0 for indirect SBP on D20Rat40 (Figure, D, and Table 3).

Interactions

Two-by-two factorial ANOVA of BP was performed on all F2 rats with the markers at each BP QTL against all other markers representatively spaced (20 to 25 cM) throughout the genome. The results, shown in Table 4, suggest that other than the QTLs identified on chrs 1, 10, 14, and 20, additional loci can be taken into account for BP-regulating genes. The interactions between adducin subunits are modest but relevant regarding the dimeric structure of the protein.

Discussion

In the present work, we analyzed a large cohort of (MHS × MNS) F2 animals to apply stringent statistical criteria that are indicative of the presence of a QTL. BP phenotype was measured both directly with an intracarotid catheter and indirectly with tail-cuff plethysmography. The 2 measurements had a relatively weak correlation in our F2 population (r=0.24). Our genome scanning revealed suggestive QTLs for direct SBP on chrs 1 and 14 and for indirect SBP on chr 20, indicating a QTL for indirect SBP on chr 10. Different methods of BP measurement may shed light on different components of the final phenotype that can be modulated independently and influenced, at least in part, by different genetic loci. In our F2 rats, BP measurements were carried out at 3 to 4 months of age, and therefore the separate QTLs identified for the 2 phenotypes should not reflect an age dependency.

The linkage study of the rat chr 14 confirmed the presence of a QTL for direct SBP with a maximum LOD score of 3.2 on the Add1 locus. We had already demonstrated that compared with the MNS, the rat hypertensive variant of α-adducin differently modulates actin assembly and increases the surface expression and the activity of the Na+/K+ pump when transfected in rat kidney cells, and in a cell-free system, it stimulates the Na+/K+ pump at significant lower concentration. Moreover, a new compound (PST2238), which is able to selectively interfere with the biochemical cellular events triggered by the Add1 hypertensive variant, exhibits a selective antihypertensive activity in MHS rats. A functional mutation in the ADD1 locus has been shown to be associated with human essential hypertension in 3 independent studies, whereas others failed to confirm these findings. However, the absence of association in a given population does not exclude the involvement of ADD1 polymorphism in the regulation of renal sodium handling and BP. We recently studied 2 independent populations from northern Italy and Sardinia. In the former, a positive association between the ADD1 locus and hypertension was present, whereas in the latter, this association was absent.

The hypertensives of both populations with the ADD1 "hypertensive" variant display lower levels of plasma renin in basal condition and a greater fall in BP on long-term treatment with diuretics. The pharmacological approach is of particular biological significance in assessment of the involvement of adducin in the regulation of renal sodium handling and BP.

### Table 3. Summary of (MHS × MNS) F2 QTLs for Blood Pressure

<table>
<thead>
<tr>
<th>Locus</th>
<th>chr 1</th>
<th>chr 10</th>
<th>chr 14</th>
<th>chr 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>D1Rat121</td>
<td>D10Rat33</td>
<td>Add1</td>
<td>D20Rat40</td>
</tr>
<tr>
<td>Max LOD</td>
<td>Direct SBP</td>
<td>Indirect SBP</td>
<td>Direct SBP</td>
<td>Indirect SBP</td>
</tr>
<tr>
<td>NN</td>
<td>144.8±1.4</td>
<td>149.1±0.8</td>
<td>143.5±1.3</td>
<td>154.1±1.0</td>
</tr>
<tr>
<td>NH</td>
<td>147.3±1.1</td>
<td>151.1±0.7</td>
<td>149.8±1.0</td>
<td>151.2±0.6</td>
</tr>
<tr>
<td>HH</td>
<td>152.4±1.3</td>
<td>155.4±1.1</td>
<td>150.5±1.6</td>
<td>149.4±0.8</td>
</tr>
<tr>
<td>% Vp*</td>
<td>6</td>
<td>9</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>ANOVA P†</td>
<td>0.0006</td>
<td>0.0001</td>
<td>0.0009</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Percentage of phenotypic variance explained with the single QTL. Blood pressure values are expressed in mean±SEM mm Hg.
†P value obtained with 1-way ANOVA.

### Table 4. Two-Way ANOVA Interactions Between Blood Pressure QTLs and Other Markers

<table>
<thead>
<tr>
<th>Locus*</th>
<th>Marker</th>
<th>Phenotype</th>
<th>F Test†</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add1</td>
<td>Add2</td>
<td>Direct SBP</td>
<td>2.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Add1</td>
<td>Add3</td>
<td>Direct SBP</td>
<td>2.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Add1</td>
<td>D4Rat2</td>
<td>Direct SBP</td>
<td>3.5</td>
<td>0.009</td>
</tr>
<tr>
<td>D10Rat33</td>
<td>D6Rat46</td>
<td>Indirect SBP</td>
<td>3.4</td>
<td>0.009</td>
</tr>
<tr>
<td>D10Rat33</td>
<td>D12Rat43</td>
<td>Indirect SBP</td>
<td>4.2</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Representative loci in the QTL regions identified in Figure 1.
†F test and P obtained with 2-way ANOVA.
The QTL found in the short arm of chr 1 with the peak on D1Rat121 marker (LOD=3.3) differs from those already described.32–35 The causative candidate gene of our identified QTL remains to be elucidated, but comparative mapping analysis5,4 indicates that D1Rat121 maps near to D1Rat9 in a region syntenic to human chr 5p15.3. In this region, in both rats and humans, a member of the Na+/H+ exchanger (SLC9A3, Na+/H+ exchanger, isoform A3 NHE3) was located, and at present, there is a rather large body of literature that describes alterations in the different Na+/H+ exchanger isoforms in human and rat genetic hypertension.36,37

The indirect SBP analysis detected QTLs in a broad region on chr 10, with a major peak on D10Rat33 marker (LOD=5.0) and minor peaks: 1 within D10Rat81 and D10Rat116 (LOD score = 3.3), 1 within D10Wox12(Abp) and D10Wox13(Syb2) (LOD score = 3.3), and 1 within D10Rat59 and D10Wox5 (LOD score = 3.0). Several studies in other rat crosses described QTLs on chr 10 in Ngf/Pepc region or near the Aby locus.35,38,39 Only recently, QTLs for sodium-loaded indirect SBP were detected on rat chr 10 in regions corresponding to D10Rat33 and D10Rat59.40

Rat chr 10 is syntenic to human chr 16, 5, and 17.41 The region of the maximum LOD score in our cross is syntenic with human chr 5q31.1-5q33.4 In the human 5q31.1 region, some interleukin (IL) genes have been mapped (IL-5, IL-4, IL-3, IL-12B, and IL-13). It was suggested that cytokines modulate NO generation via inducible NO synthase.42 In the human 5q33 region, the ADRA1B (a2-adrenergic receptor), a G protein–coupled receptor that participates in the control of vascular tone, has been mapped and found to be associated with BP.43,44 Moreover, the lack of this receptor determines a decrease in BP.45 Our results and others, with work on different crosses, suggested that rat chr 10q24-pter contains ≥1 QTLs for SBP (Aby, D10Rat59/D10Wox5, Ace). Comparative maps demonstrated that the region is homologous to human chr 17.41 Two linkage studies in humans indicated that chr 17q could contain a susceptibility locus for human essential hypertension.46,47 We are now analyzing recombinant strains within different congenic intervals for chr 10 to identify the chromosomal region or regions that account for the phenotypic variation.

Statistical analysis revealed potential interactions between the QTLs identified and chromosomal regions apparently not linked to SBP. Even if modest, the interactions among Add loci (Table 4) are consistent with the notion that the cellular biological activity of the protein is displayed only by the assembled heterodimer. The modulating effect of Add2 on Add1 polymorphisms in actin polymerization and Na+/K+ pump activity has been previously demonstrated.8,9 At the present, we are analyzing single and double congenic strains for adducins to clarify either statistical and biological evidence of Add loci on BP regulation and intermediate phenotypes. Additional interactions were detected between the QTLs identified and other chromosomal regions that would be otherwise ignored. Among them, the region surrounding D4Rat2 is of particular interest because in an interval of 6 CM that includes IL-6 and Cd36 loci, QTLs for multiple cardiovascular risk factors have been identified.48–50

Although the statistical analysis of interactions is admittedly somewhat arbitrary, epistatic interactions between ≥2 loci that harbor genes that code for proteins with a plausible biochemical–physiological interaction is certainly one of the strongest arguments in favor of their role in BP regulation. Unfortunately, at the present, no obvious candidate genes for hypertension are known to lie around the loci listed in Table 4.

To conclude, despite the relatively modest degree of polymorphism (28.7%) in the (MHS×MNS) cross and the mild BP difference between parental strains, QTLs for SBP have been detected and their interactions are reported here. The relevance of these findings to human hypertension relies on previous results that show the involvement of a-adducin variants in renal sodium handling and BP regulation of both rat and human hypertension. It is reasonable to hope that the new QTLs and their interactions will also offer new hints to unravel the genetic basis of human hypertension, particularly for the subgroup of patients who show pathophysiological similarities to MHS rats.5

Acknowledgments

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References


Genetic Mapping of Blood Pressure Quantitative Trait Loci in Milan Hypertensive Rats
Laura Zagato, Rossana Modica, Monica Florio, Lucia Torielli, Marie-Thérèse Bihoreau, Giuseppe Bianchi and Grazia Tripodi

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