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Mapping blood pressure loci in (A/J × B6)F2 mice

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Submitted 27 February 2003; accepted in final form 15 September 2003

Woo, David D. L., and Ira Kurtz. Mapping blood pressure loci in (A/J × B6)F2 mice. *Physiol Genomics* 15: 236–242, 2003; 10.1152/physiolgenomics.00027.2003.—Although the genetics of rare, monogenic, forms of human hypertension are fairly well defined, the genetics of the common polygenic form of human essential hypertension is only emerging. With the ability to control environmental variables, animal models have provided valuable tools with which to study blood pressure (BP) homeostasis. We have now studied BP genetics in a model consisting of 1,521 F2 mice from a series of (A/J × B6) intercrosses kept under standardized conditions. Using whole genome quantitative trait loci (QTL) mapping, we have identified four novel significant BP loci. These included *Abbp1* on mouse chromosome MMU1 [maximum LOD score (MLS) at ~35 cM = 6.8], *Abbp2* on MMU4 (MLS at ~25 cM = 9.8), *Abbp3* on MMU7 (MLS at ~25 cM = 5.4), and *Abbp4* on MMU11 (MLS at ~58 cM = 6.3). Compared with A/J homozygotes, homozygosity for the B6 alleles of *Abbp1*, *Abbp2*, or *Abbp4* is independently associated with a 7–12 mmHg increase in BP. In contrast *Abbp3* interacts epistatically with a locus on MMU17 (near *D17Mit180*) to modulate BPs in female (A/J × B6)F2 mice. Interestingly, *Abbp4* on MMU11 is homologous to a major confirmed BP locus, *BPI1*, on rat chromosome 10 and to a major confirmed BP locus, *HYT1*, on human chromosome 17. Defining the molecular differences between the A/J and the B6 alleles at these novel loci with major influences on the BP phenotype will contribute to our understanding of the complex genetics of BP control.

quantitative trait loci; genome scan

ESSENTIAL HYPERTENSION AFFECTS about 20–30% of adults in the United States and is defined as the presence of a chronic state of abnormally high blood pressure (BP) not associated with a recognizable predisposing condition. Although chronic hypertension, in itself, is an otherwise symptom-free disease state, the cardiovascular and renovascular consequences of chronic hypertension are often serious and life threatening. Cardiac and cerebral infarction, cerebral hemorrhage, and cardiac and renal failure resulting from hypertension account for a major portion of morbidity and death.

Twin studies, population studies and epidemiological studies have long suggested etiologic roles for genetic factors in the pathogenesis of essential hypertension. Although recent progress has been made in identifying rare mutations that cause Mendelian forms of

altered BP control in affected families (15, 16), unfortunately, the genetic components of the common form of essential hypertension have proved less tractable. Encouragingly, several novel human hypertension loci have recently been identified. These include *HYT1* [Online Mendelian Inheritance in Man (OMIM) ID 603918] on human chromosome 17q21–22 (3, 12), *HYT2* (OMIM 604329) on human chromosome 15q (33, 34), and *HYT3* (OMIM 607329) on human chromosome 2p25–24 (2, 36). However, the genetic complexity of human populations and the variable environmental influences on human essential hypertension imposed significant experimental challenges in identifying the causative gene(s) of human essential hypertension. Development of suitable animal models of these human essential hypertension loci may provide the necessary tools to help define the nature of the genetic alterations underlying human essential hypertension.

Capitalizing on the well-developed genetic and genomic tools available for laboratory strains of inbred mice and on the ability to vigorously control diet and environmental conditions, we have developed and characterized a new F2 intercross model of differential BP regulation in mice. Whole genome quantitative trait loci (QTL) mapping studies of these mice have led us to identify a set of novel genetic loci that are significantly involved in BP regulation in young adult mice fed a normal diet. Interestingly, one of these mouse BP controlling loci is located in a genomic region homologous to the human genomic interval containing *HYT1*, a major confirmed human hypertension locus (3, 12).

METHODS

Mice. Seven inbred mouse strains were obtained from the Jackson Laboratory (Bar Harbor, ME). These were A/J, C57BL/6 (abbreviated as B6), DBA/2, BALB/c, CBA, C3H, and AKR. In addition, (A/J × B6)F1 mice were also obtained from the Jackson Laboratory. All mice were housed under specific pathogen-free conditions and were provided free access to water and a standardized diet (NIH31 diet; Harlan 7013). Mice were acquainted to the handling and restraint associated with BP measurement procedure by placing a 50-ml plastic centrifuge tube, open at both ends, in their cages for 4–7 weeks and by daily mock BP measurements for 5 days prior to actual BP measurements.

Phenotyping. Systolic BPs were measured using a validated tail-cuff BP measuring system (model 229; IITC, Woodland Hills, CA). Tail-cuff BP measurement in trained mice has been shown to be reproducible and to correlate well with mean arterial pressures in unrestrained, unanesthetized mice (13). A set of training and measurement protocols were developed and strictly followed to ensure reliable and reproducible tail-cuff BP measurements.

Article published online before print. See web site for date of publication (<http://physiolgenomics.physiology.org>).

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Table 1. Tail-cuff systolic blood pressure in 7 inbred mouse strains

Strain	Blood Pressure, mmHg	
	Male	Female
A/J	104 ± 6	111 ± 6
AKR	119 ± 11	104 ± 6
BALB/c	145 ± 11	120 ± 1
C3H	113 ± 8	105 ± 3
C57BL/6	132 ± 12	132 ± 9
CBA	126 ± 11	113 ± 16
DBA/2	118 ± 6	112 ± 2

Values are means ± SD.

In preliminary studies, we compared the tail-cuff BP of A/J and B6 mice measured at 31°C (the minimal temperature necessary to establish a constant blood flow through the mouse tail) and at 38°C. Our results indicated that the BPs of A/J mice at 31°C and 38°C were 103 ± 6 and 100 ± 10 mmHg, respectively (not significant). In contrast, the BPs of B6 mice at 31°C and 38°C were 134 ± 10 and 115 ± 10 mmHg, respectively ($P < 0.02$). These results demonstrate that the BP of B6 mice is significantly dependent on the animal's core temperature. To minimize the effect of heat stress, mice were warmed in their own uncovered cage within a constant 31°C temperature chamber for a period of 15–25 min before and during the BP measurement. To minimize the diurnal variation in BP measurements, all mice were kept under a strict 6 AM/6 PM, 12:12-h light/dark cycle, and all BP measurements were acquired between 1 PM and 5 PM. To minimize age-related variations, BPs were obtained from mice that were between 10 and 14 wk of age. To minimize operator-dependent measurement errors, each mouse's BPs were measured on two separate days by two different individuals blinded to each other's results. When these two separate measurements did not agree within <5 mmHg, additional independent measurements were obtained.

With suitably trained and cooperative mice, successive BP readings were reproducible to within 2 mmHg. Of all the mice studied, the BPs of 28 mice still did not agree within 7 mmHg after 4 or 5 additional measurements. Data from these mice were not used. All animal protocols were approved by UCLA's Chancellor's Animal Research Committee.

Genotyping. Genomic DNA were prepared using a standard proteinase-K-SDS digestion, ethanol precipitation procedure. DNA were adjusted to 25 µg/ml in 10 mM Tris, pH 8.0. All genotyping were carried out at the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Mammalian Genotyping Service at the Marshfield Clinic. Genotyping was carried out with a set of 111 microsatellite markers selected from the MIT mouse genome map (6). These markers span the mouse genome at an average distance of ~15 cM. The markers used were *D1Mit211*, 303, 49, 217, 102, 36, 165, 362; *D2Mit81*, 296, 192, 75, 274, 285, 266; *D3Mit151*, 212, 215, 45; *D4Mit149*, 1, 111, 166, 203, 251; *D5Mit267*, 113, 10, 240, 136, 30, 223; *D6Mit86*, 223, 188, 149, 15; *D7Mit74*, 228, 232, 37, 329, 44, 259; *D8Mit64*, 205, 249, 112, 245; *D9Mit206*, 207, 196, 182, 82; *D10Mit123*, 183, 198, 42, 150, 14; *D11Mit227*, 231, 242, 212, 124, 180, 214; *D12Mit182*, 153, 172, 158, 194, 134; *D13Mit16*, 198, 139, 202, 213, 78; *D14Mit44*, 141, 203, 194, 165, *D15Mit175*, 85, 63, 107, 35; *D16Mit132*, 154, 4, 71; *D17Mit164*, 52, 180, 93, 155; *D17Mit164*, 52, 180, 93, 155; *D18Mit19*, 60, 152, 162, *D19Mit68*, 40, 91, 71 and *DXMit124*, 141, 119, 79, and 135.

Statistical analyses. QTL mapping was carried out using MapManager QTX version b17. ANOVA and other statistical

analyses were carried using Statview 5.0 and GraphPad Prism 3.0.

RESULTS

Blood pressure differences in inbred mouse strains. The systolic BP of six male and six females of each mouse strain using tail-cuff method were obtained. Significant and reproducible differences in BPs were observed among the different inbred mouse strains. Although systolic BPs of each animal were reproducible to less than 5 mmHg, BPs among different individuals of the same inbred strain sometime differ by more than 5 mmHg. These differences are reflected in the larger standard deviations in some of the strains. These results are summarized in Table 1 and are comparable with previously reported values for these mice (24, 26).

Because male and female A/J mice have the lowest systolic BP of the seven inbred strains studied and male and female B6 mice have the highest BPs of the seven inbred strains studied, we chose A/J and B6 as the two parental strains to generate a model of polygenic BP regulation in a F2 intercross study design.

Blood pressure in (A/J × B6)F1 mice. At 10 wk of age, the BPs of male and female (A/J × B6)F1 are 103 ± 10 and 108 ± 5 mmHg, respectively. These results showed that the BP of (A/J × B6)F1 mice resembled A/J more than B6 mice.

Blood pressure in (A/J × B6)F2 mice. The systolic BPs of mice in an $n = 763$ (A/J × B6)F2 intercross is shown in Fig. 1 and summarized in Table 2. We found that the BP phenotypes in the (A/J × B6)F2 intercross can differ by as much as 70 mmHg among the F2 progeny mice. This variability in the systolic BP phenotype is consistent with the notion that BP is a polygenic trait. The polygenic nature of systolic BP phenotype in (A/J × B6)F2 cross is also supported by the fact that the F2 BPs did not segregated into A/J-like and B6-like bimodal distributions. Finally, we observed that the BP variation is similar between male and female F2 progenies. These results were confirmed in a

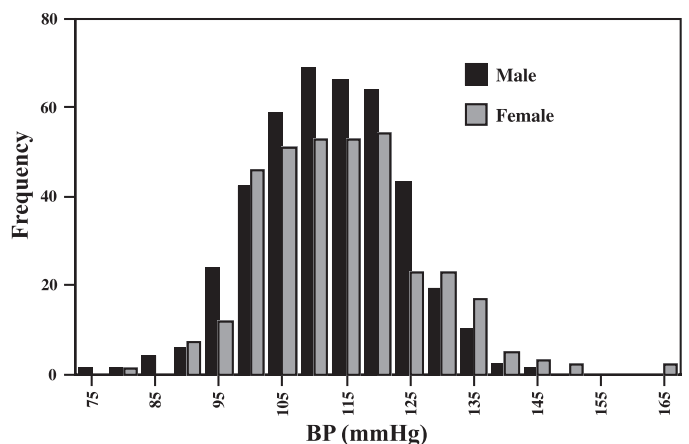


Fig. 1. Range and distribution in 763 (A/J × B6)F2 mice. BP, blood pressure.

Table 2. Summary statistics of blood pressure in (A/J × B6)F2 mice (cross 1, n = 763; cross 2, n = 758)

	Cross 1		Cross 2	
	Male	Female	Male	Female
Minimum BP, mmHg	75	70	88	90
Maximum BP, mmHg	148	162	157	159
Range (Max – Min), mmHg	73	92	69	69
Mean BP, mmHg	114	115	117	117
SD	11	13	11	11
Variance, mmHg	123	157	111	120
n	411	352	332	426

BP, blood pressure.

second n = 758 (A/J × B6)F2 intercrosses (Table 2 and Fig. 2).

Selective genotyping of mice with significantly increased or decreased blood pressure. Lander and Botstein (14) have formally shown that when the distribution of a quantitative trait is normal, individuals with phenotype more than one standard deviation (SD) from the mean (~33% of the total population) will contribute ~81% of the total linkage information. It has been shown that genotyping only the individuals from both the upper and the lower 25% tails of the phenotypic distribution (50% of the population) is practically the same as genotyping the entire phenotypic distribution (5). In addition, it has been shown that selective genotyping of more than 40–50% of the population does not decrease the confidence interval of a given detected QTL (5). We therefore selectively genotyped all F2 progenies with BP more than 1 SD from the mean BP of our crosses. Of the 1,521 F2 mice, there were 233 mice with BP higher than 127 mmHg (1 SD above the mean BP) and there were 232 mice with BP less than 103 mmHg (1 SD below the mean BP). Thus there was at least a 24 mmHg difference in BP between the high BP samples and the low BP samples that were chosen for genotyping. This approach also minimized the effect of any potential minor errors in BP measurements on the detected BP loci. Experimentally, the selective genotyping were conducted separately for the two (A/J × B6)F2 crosses.

For the first cross consisting of 763 (A/J × B6)F2s, 107 mice with BP >127 mmHg and 118 mice with BP <103 mmHg were genotyped with a set of 110 markers spanning the mouse genome at ~15-cM intervals. Whole genome QTL analyses of the genotype data using the MapManager QTX program (17, 18) identified one significant BP QTL on MMU7 (LOD = 3.9) and at least four suggestive BP QTLs (2.3 < LOD < 3.3) on MMU1 (LOD = 2.7), MMU4 (LOD = 2.4), MMU9 (LOD = 2.7), and MMU11 (LOD = 3.2).

For the second cross consisting of 758 (A/J × B6)F2 mice, 126 mice with BP >128 mmHg and 114 mice with BP <106 mmHg were genotyped with the same set of 110 markers. The genotype data from this second set of samples were combined with the genotype data from the first set and analyzed with MapManager QTX. By increasing the number of sample genotyped from 225 to 465, the statistical power of our sample

was increased. As a result, the significant QTL on MMU7 was independently confirmed with an LOD score of 5.4. The suggestive QTLs on MMU1, MMU4, and MMU11 were also confirmed with highly significant LOD scores of 6.8, 9.8, and 6.3, respectively. However, the suggestive QTL on MMU9 failed to be confirmed. We named the BP QTLs on MMU1, MMU4, MMU7, and MMU11 as *Abbp1*, *Abbp2*, *Abbp3*, and *Abbp4*. The LOD score plots of these BP loci are shown in Fig. 3.

Although *Abbp1*, *Abbp2*, and *Abbp4* were significantly associated with BP variations in both male and female mice, *Abbp3* was significantly associated with BP variations in female mice only. No significant male-specific BP QTL was detected.

Using the interaction feature of MapManager QTX and the recommended $1.0e^{-5}$ threshold for detecting interacting loci, we detected a pair of interacting BP QTLs involving *D7Mit228* (*Abbp3*) and *D17Mit180* with a likelihood ratio statistic (LRS) of 38.3. By itself *D7Mit228* had an LRS of 16.7, and by itself *D17Mit180* had an LRS score of 4.3. Permutation analyses of the data indicated that 95% genome-wide significant threshold for a pair of interacting QTLs is achieved at LRS = 37.

No interacting loci were detected for *Abbp1*, *Abbp2*, and *Abbp4*, indicating that these three BP loci act independently to exert their effect on BP and their individual effects are not subjected to epistatic genetic interactions from other loci. These findings are important for future attempts to physically refine these loci to identify the underlying genes. This is because phenotypes of primary acting loci will continue to breed true, whereas the phenotypes of epistatic loci may be lost upon segregating the epistatically interacting alleles into separate congenic and subcongenic strains.

Phenotypic effects of Abbps. The contributions to the BP phenotype of the A/J and the B6 alleles of each *Abbp* were determined by the ANOVA statistics test using the Statview 5.0 Program. From the results illustrated in Fig. 4, it can be seen that homozygosity

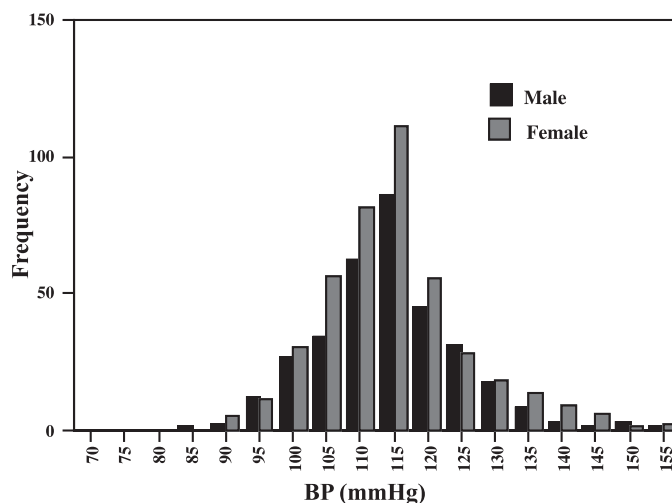


Fig. 2. Range and distribution in 758 additional (A/J × B6)F2 mice.

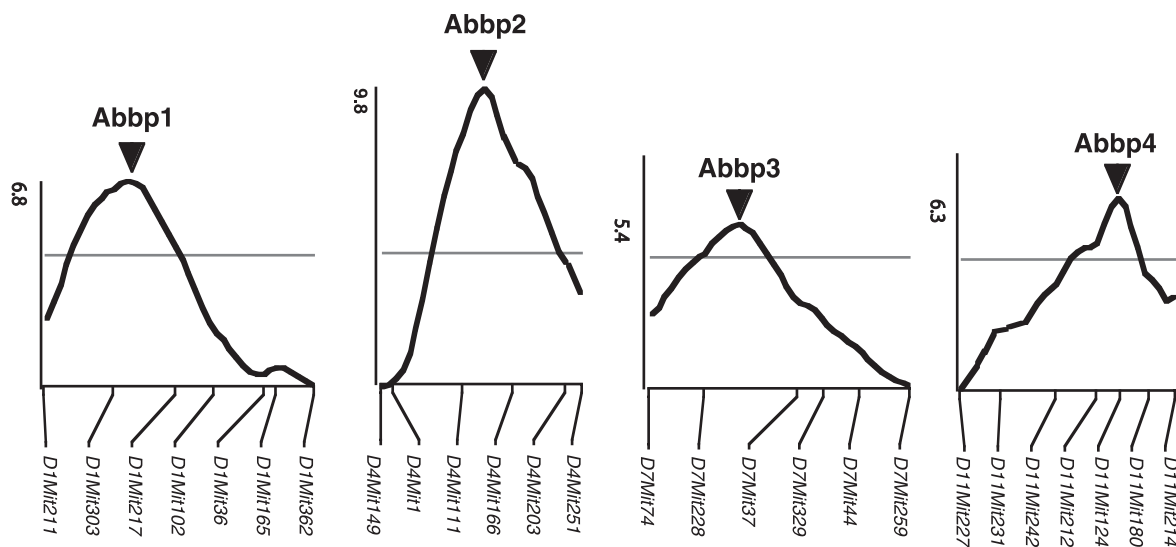


Fig. 3. LOD score plot of four BP quantitative trait loci (QTL). Maximum LOD score is shown by the number on the y-axis, and LOD = 4.3 is represented by the horizontal line.

for the B6 alleles of *Abbp1*, *Abbp2*, and *Abbp4* are associated with an increase of 7–12 mmHg in BP relative to homozygosity for the A/J alleles of these loci. In contrast, homozygosity for the B6 alleles of *Abbp3* is associated with a decrease of 15 mmHg in BP relative to homozygosity for the A/J alleles of these loci. The fact that most of the B6 alleles of the *Abbps* are associated with increases in the BP phenotypes is consistent with the observation that B6 mice have higher BP than A/J mice.

The BPs of animals heterozygous for *Abbp1* are intermediate between animals homozygous for the A/J or B6 alleles of *Abbp1*. This suggests that A/J and B6 alleles of *Abbp1* act additively to control the BP phenotype. The BPs of animals heterozygous for *Abbp3* are intermediate between animals homozygous for the A/J or B6 alleles of *Abbp3*. This suggests that A/J and B6 alleles of *Abbp3* also act additively to control the BP phenotype. The BPs of animals heterozygous for *Abbp2* are the same as the BPs of animals homozygous for the A/J allele of *Abbp2*. This finding suggests that the A/J alleles of *Abbp2* are dominant over the B6 alleles of *Abbp2*. The BPs of animals heterozygous for *Abbp4* are the same as the BP of animals homozygous for the A/J allele of *Abbp4*. This finding suggests that the A/J

alleles of *Abbp4* are dominant over the B6 alleles of *Abbp4*. The fact that most of the A/J alleles of the *Abbps* are dominantly associated with a lower BP phenotype is consistent with our observation that the BP phenotype in (A/J × B6)F1 mice resembled A/J mice more than B6.

Using comparative genomics tools from both the Mouse Genome Database (MGD) web site (<http://www.informatics.jax.org>), from the Rat Genomic Database web site (<http://rgd.mcw.edu>), and from the Human/Mouse homology web site (<http://www.ncbi.nlm.nih.gov/Homology/>), we have determined the most likely rat (RNO) and human (HSA) genomic region that is homologous to the ~20–25 cM genomic interval containing the peak LOD score for each of the *Abbps*. These results are tabulated in Table 3.

The human syntenic region of *Abbp1*, *Abbp2*, and *Abbp4* involved only a single chromosomal region. These are 2q33–34 for *Abbp1*, 9q31–32 for *Abbp2*, and 17q12–23 for *Abbp4*. In contrast the human syntenic region of *Abbp3* contained chromosomal regions from human chromosome 11, 15, and 19. Determining the exact human genomic region that is syntenic to *Abbp* will require refining the *Abbp3* interval using congenic approaches. In addition, *Abbp3* is syntenic with a re-

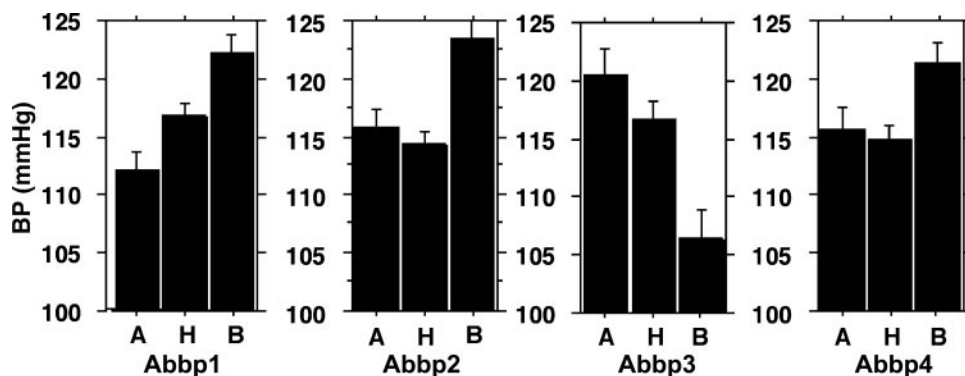


Fig. 4. Phenotypic effect of allele combinations of *Abbps*. H = heterozygous; A = homozygous A/J; and B = homozygous B6.

Table 3. Homologous genomic regions of *Abbp1* through *Abbp4* in mouse (MMU), rat (RNO), and human (HSA)

<i>Abbp1</i>	MMU1; 35 cM	RNO9; 566 cR	HSA2; 2q33-34
<i>Abbp2</i>	MMU4; 25 cM	RNO5; 400 cR	HSA9; 9q31-32
<i>Abbp3</i>	MMU7; 26 cM	RNO1; 580 cR	HSA15; 15q11-14 HSA19; 19q13.3 HSA11; 11p15
<i>Abbp4</i>	MMU11; 58 cM	RNO10; 990 cR	HSA17; 17q12-23

gion on RNO1 that also has strong evidence for BP QTLs (28). The human syntenic locations of these four *Abbp* loci do not overlap with the locations of a recently published list of 150 known BP-related genes (7, 8), suggesting that the genes underlying these *Abbp* loci may represent novel BP controlling genes. Interestingly, *Abbp4* on distal MMU11 is syntenic to a major BP QTL on RNO10 (9, 11) and to a major human hypertension locus, *HYT1* (OMIM 603918), on HSA 17q (3, 12). This genomic region is also contained in a hypertension locus mapped to human chromosome 17p11-q21 by Mansfield et al. (19).

Genomic intervals for the *Abbps*. Lander and Botstein (14) proposed that the region within 1 LOD score unit of the maximum LOD can be used to represent the 96.8% confidence interval for strong QTL. Using this criteria, the LOD score plot for *Abbp1* in Fig. 3 indicated that the peak LOD score is located at 35 cM on MMU1 and that the 1 LOD confidence interval for *Abbp1* spanned ~25 cM from 23 cM to 48 cM on MMU1. By placing *Aox1*, a marker gene mapped to 23 cM on MMU1 and *Ncl*, a marker gene located at 48 cM on MMU1 from the MGD mouse genetic map onto the February 2002 release of the public mouse genome sequence (<http://genome.cse.ucsc.edu/>), this 25-cM interval is estimated to be ~28 Mbp in length and contains ~120 known genes. Similarly, the 1 LOD confidence interval for *Abbp2* spanned ~12 cM on MMU4, is ~15 Mbp long, and contains ~55 known genes. The 1 LOD confidence interval for *Abbp3* spanned 20 cM on MMU7, is ~40 Mbp in length, and contains ~190 known genes. The 1 LOD confidence interval for *Abbp4* spanned 10 cM on MMU11, is ~14 Mbp in length, and contains ~200 known genes.

DISCUSSION

Although it is well known that there are definitive genetic influences in the development of human essential hypertension, the identification of human essential hypertension genes remains a significant scientific challenge. Genetic studies of Mendelian mouse models of human disease and human physiology have provided substantial contributions to our understanding of these conditions. More recently, genetic dissections of common, quantitative traits such as diabetes, obesity, and hypertension in rodent models have provided novel insights to understand the genetics of these important human disease traits. For example, from a total of 67 QTLs mapped for 39 blood pressure traits collected from published results of seven F2 rat intercross stud-

ies of genetic hypertension, Stoll et al. (28) used comparative genomics to predict 26 chromosomal regions in the human genome that are very likely to harbor hypertension genes. Four of these 67 predicted human BP genomic intervals have known significant or suggestive linkage in genome scans for hypertension in humans (28).

Numerous transgenic and gene-targeted mice have demonstrated the utility of the laboratory mouse in studying the role of defined single gene alterations on the BP phenotype (27). However, compared with the established role of the rat in studies of polygenic BP controls, only a few polygenic mouse models of differential BP controls have been reported. Sugiyama et al. (30) detected two significant BP loci on MMU15 and MMU7 in a (BALB/cJ × CBA/CaJ) F2 intercross involving 207 males. The two parental strains studied had BPs differing by only 8 mmHg. In contrast, BPs in F2 mice ranged from 80 mmHg to 124 mmHg, a difference of 44 mmHg. This study illustrated that genetic loci with substantial effects on normal BP homeostasis can be uncovered by studying progenies from inbred mouse strains with similar BPs.

In a salt-induced hypertension model involving 250 male backcross offspring from F1 mice produced from the salt-sensitive B6 and the non-salt-sensitive A/J inbred mouse strain, Sugiyama et al. (29) detected six significant salt-induced hypertension loci. Five of these loci are concordant with hypertension loci in rats, and four of these loci were concordant with hypertension loci in humans.

Using an eight-way cross design involving the inbred LP/J, SJJ/J, BALB/cJ, C57BL/6J, 129/J, CBA/J, RF/J, and BDP/J mouse strains and nearly 50 generations of inbreeding, Schlager and Sides (25) developed and characterized several inbred mouse strains with either spontaneously elevated or decreased systolic BPs. Genetic mapping studies using these unique hypertensive mouse strains identified major significant systolic BP loci on MMU10 and on MMU13 in addition to suggestive systolic BP loci on MMU2, MMU6, MMU8, and MMU18 (32).

To develop a predominantly genetic model of differential BP regulation in mice, we have carried out a series of initial exploratory and subsequent confirmatory genetic mapping studies of BP-regulating loci in a F2 population produced from intercrossing F1 mice from mating the A/J and B6 inbred mouse strains. In our studies, all mice were kept under standard conditions and fed a standard diet containing 6% fat. In addition, all mice were phenotyped between 10–14 wk of age. Thus the variations in the BP phenotype in these F2 mice are primarily due to differences in the genomic composition they inherited from their A/J or B6 grandparents. As a result, the BP loci detected in these studies reflect loci that are associated with genetic differences between the A/J and B6 mouse strains with environmental influences experimentally controlled to a minimum.

Blood pressure is a complex trait that is determined by the combined influences of genetic and environmen-

tal factors. It is not unreasonable to speculate that the phenotypes of BP loci detected in genetic studies can be modulated by environmental factors. Thus it will be important to determine how or whether the likely candidate-environmental factors such as diet and age will interact with these *Abbp* loci to modulate BP. However, it is interesting to note that *Abbp1* on MMU1 and *Abbp2* on MMU4 mapped to the same 20–25 cM genomic intervals as the recently reported salt-induced hypertension loci *Bpq1* and *Bpq3*, respectively (29). *Bpq1* and *Bpq3* were detected in a male only B6.A/J F1 × B6 backcross design in which the animals were fed a high-salt diet (29).

Abbp4 on MMU11 is of particular interest because this genomic interval is syntenic to confirmed BP loci in human (3, 12) and rat (9, 11). Inspection of the *Abbp4* genomic interval in the draft mouse genome sequence (31) revealed the following candidate genes which could potentially play important roles in BP modulation. These include *Slc4a1*, anion exchanger 1 (*AE1*) (1); *CA-RP X*, carbonic anhydrase related protein 10 (21); *Cacnb1*, β 1-subunit of a L-type voltage-dependent calcium channel (23); *Psa*, puromycin-sensitive aminopeptidase (10); and *Igfbp4*, insulin-like growth factor binding protein 4 (35).

Whole genome quantitative trait mapping studies produce statistical evidences for the presence of and for the approximate genomic location of genetic factors associated with the trait under investigation (4). To physically confirm these statistical results and to provide physical specimens to carry out additional genetic studies to refine the mapped loci, the creation of specific congenic mouse strains carrying the respective genomic interval are required (22). The construction of a panel of consomic mouse strains in which each of the 20 chromosomes from the parental inbred B6 mice was replaced with the corresponding chromosome from the A/J mice has been described (20). We have obtained and established local breeding colonies of B6.A/J strains consomic for A/J chromosomes 1, 4, 7, 11, and 17. Preliminary tail-cuff BP measurements confirmed the BP lowering effects of the donor A/J chromosomes 1, 4, and 11 (data not shown). These consomic mouse strains will allow us to investigate whether diet and age will have any effects on the BP phenotype associated with replacing each of the *Abbp1*-, *Abbp2*-, or *Abbp4*-containing B6 chromosomes with the corresponding chromosome from A/J. In addition, these consomic mouse strains will serve as the ideal starting strains for refining the genomic intervals of *Abbp1*, *Abbp2*, and *Abbp4* to less than 1 cM by serial backcrossing to inbred B6 mice. With the available and soon to be completed genomic sequences, single nucleotide polymorphism (SNP) resources for both B6 and for A/J mice and with whole genome expression profiling tools, it should be feasible to identify the genes and to elucidate the nature of the allelic differences responsible for the 7–15 mmHg differential BP associated with the B6 vs. the A/J alleles of the *Abbps* identified in this study.

GRANTS

This work is funded in part by American Heart Association Grant 50756Y. D. D. L. Woo is supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Grant DK-60514; I. Kurtz is supported by NIDDK Grants DK-58563 and DK-63125, by the Max Factor Family Foundation, and by the Richard and Hinda Rosenthal Foundation.

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