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TOWARDS PRECISION MEDICINE FOR HYPERTENSION: A REVIEW OF GENOMIC, EPIGENOMIC, AND MICROBIOMIC EFFECTS ON BLOOD PRESSURE IN EXPERIMENTAL RAT MODELS AND HUMANS

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Padmanabhan S, Joe B. Towards Precision Medicine for Hypertension: A Review of Genomic, Epigenomic, and Microbiomic Effects on Blood Pressure in Experimental Rat Models and Humans. *Physiol Rev* 97: 1469–1528, 2017. Published September 20, 2017; doi:10.1152/physrev.00035.2016.—Compelling evidence for the inherited nature of essential hypertension has led to extensive research in rats and humans. Rats have served as the primary model for research on the genetics of hypertension resulting in identification of genomic regions that are causally associated with hypertension. In more recent times, genome-wide studies in humans have also begun to improve our understanding of the inheritance of polygenic forms of hypertension. Based on the chronological progression of research into the genetics of hypertension as the "structural backbone," this review catalogs and discusses the rat and human genetic elements mapped and implicated in blood pressure regulation. Furthermore, the knowledge gained from these genetic studies that provide evidence to suggest that much of the genetic influence on hypertension residing within noncoding elements of our DNA and operating through pervasive epistasis or gene-gene interactions is highlighted. Lastly, perspectives on current thinking that the more complex "triad" of the genome, epigenome, and the microbiome operating to influence the inheritance of hypertension, is documented. Overall, the collective knowledge gained from rats and humans is disappointing in the sense that major hypertension-causing genes as targets for clinical management of essential hypertension may not be a clinical reality. On the other hand, the realization that the polygenic nature of hypertension prevents any single locus from being a relevant clinical target for all humans directs future studies on the genetics of hypertension towards an individualized genomic approach.

I. BLOOD PRESSURE AS A COMPLEX POLYGENIC TRAIT

The focus on the role of arterial blood pressure as an important reporter of cardiovascular health has deep historical roots dating back to the 18th century. In 1733, the British clergyman Stephen Hales is documented to have made the first published measurement of blood pressure in several animals by inserting fine tubes into arteries and measuring the height to which the column of blood went up (86, 88, 215). In 1836, Richard Bright found an association between renal disease and left ventricular hypertrophy (23). He suggested that left ventricular hypertrophy could be a consequence of high blood pressure. Clinical features of essential hypertension were studied by T. C. Allbutt (6), who then went on to coin the term *hyperpiesis* to describe

essential hypertension, but the term was not popular. Eberhard Frank is believed to have replaced it with the term *Essentielle Hypertonie*, the English translation of which is Essential Hypertension, i.e., elevated high blood pressure for no known causes (189). Despite these documented observations on the very nature of essential hypertension being noticeable in humans, the clinical significance of hypertension was, interestingly, a discovery attributed to keen observations of individuals from a nonscientific background. As early as in 1906, long before the clinical concept of hypertension as a risk factor became accepted, several insurance companies required medical examiners to document applicants' blood pressures (44, 190). The extent of blood pressure being a good predictor of serious illness from stroke, heart failure, or renal disease was first recognized by L.I. Dublin and A. J. Lotka, who were demographers working for a life insurance firm in the United States (71, 72). Soon thereafter, the medical community followed with evidence from the studies in populations such as the Framingham study to conclude that essential hypertension is a condition qualitatively distinct from normotension and that elevated blood pressure was not just in those able to afford life insurance (189). There was however the question of whether there was a "dividing line" between normal blood pressure and hypertension. Further clarification that arterial blood pressure did not have a dividing line between normal blood pressure and hypertension was provided by Pickering and co-workers (273, 280, 281) who studied larger populations to study the frequency distributions of arterial blood pressure in populations and emphasized that there is a continuous relationship between arterial pressure and mortality over a full range of arterial pressure. This definition changed the perception of hypertension being a qualitatively different feature from normal blood pressure to a "quantitative" feature, i.e., a trait that varies continually from low to high in a population. The recognition of this feature was in itself a milestone in the understanding of hypertension, but many questions remained as to what caused this variation in populations.

II. EVIDENCE FOR INHERITANCE

Pickering and co-workers (125–127, 283) were among the first to recognize familial correlation of blood pressure (BP). They collected BP data from large groups of normotensive and hypertensive subjects along with their relatives and plotted frequency distribution curves after adjustment for age and gender. BP of relatives of hypertensive subjects were significantly higher than that of the relatives of normotensives (127). There was a linear relationship between the level of BP of individual subjects with their relatives (282). This led to the important conclusion that what was inherited was not only hypertension, but the level of BP regardless of whether it was high or normal. To provide some perspective, this study was published in 1954, which is over half a century after Mendel's ideas on inheritance were applied to medicine by Archibald Garrod (110). Beginning in 1902, Garrod had studied alkaptonuria, cystinuria, and albinism in relatives of patients and found that genetics explained these inborn errors of metabolism as Mendelian heritable traits, but he also speculated that genetics may play a role in common diseases (110–114).

More precise evidence for genetic factors to influence BP came from correlative observations of a history of hypertension in parents of hypertensive subjects in various populations in Europe and North America (158, 251, 333, 334, 378). Additional evidence was obtained through population studies wherein a greater concordance of blood pressure was observed within families than between families (226), but such studies also raised the question of additional shared nongenetic, environmental factors such as food habits within a family that could influence blood pressure. Twin studies wherein a greater similarity of blood pressures was documented with monozygotic than dizygotic twins (87, 207) suggested that genetic factors strongly influenced the incidence of hypertension. Other studies suggest that genetic effects on BP are evident early in life by demonstrating a significant sib-pair and maternal-children correlation of BP in infants (133, 212) and in children between 2 and 14 yr of age (409). However, a clarification on environmental factors overriding the genetic factors was inferred based on studies of BP variance in a Montreal adoption study of French-Canadian families with both adopted and natural children (8, 9, 19, 20, 252). The study pointed to the highest correlations of BP within children in a shared household environment, regardless of whether they were adopted or not. This correlation between the children was more significant than correlations between the BP of parents and their natural children, leading to the inference that nongenetic, environmental factors contribute more than genetic factors to the extent of BP; however, the identities of both genetic and environmental factors remained enigmatic. Another metric that is used to measure familial resemblance of a trait and hence its genetic component is heritability. The higher the heritability, the stronger is the correlation between phenotype and genotype. From twins and family studies, the heritability of BP ranges from 15 to 40% for the office BP and around 51–69% for night time blood pressure obtained from ambulatory BP monitoring (131, 192, 207). In general, low heritability estimates indicate that genetic mapping would be difficult for that phenotype.

III. WHY AND HOW TO STUDY THE GENETICS OF BLOOD PRESSURE CONTROL

Hypertension being inherited in families serves as an important clue for the presence of susceptibility factors on our genomes that predispose some of us but not others to develop high BP. It is interesting to note that most of the above-mentioned correlative observations were made in the

first half of the 20th century well ahead of 1953, the year in which Watson and Crick made the landmark discovery of the molecular structure of DNA (376, 377). This discovery marked the dawn of the era of Molecular Biology and paved the way for a series of monumental discoveries to follow that gave fundamental insights into key concepts that sealed our current understanding of DNA as the genetic material that is inherited. DNA was therefore accepted as the "molecule of life," and the following three decades since 1953 revolutionized our understanding of the structure-function relationship between the inheritance of DNA and the role it plays in determining the structure of proteins. While the definitions of what constitutes a "gene" were being worked on in the 1950s to the 1980s by molecular biologists, during the same period, physiologists interested in the etiology of hypertension began looking into dietary factors such as the components of the Kempner rice diet influencing the extent of hypertension (186, 375, 383). Salt being an important component influencing BP was inferred by studying various populations around the globe (55). It was apparent that dietary salt intake was directly proportional to the extent of BP observed (55).

IV. RATS AS MODELS TO STUDY THE GENETICS OF HYPERTENSION

To further address the question of whether salt was responsible for the development of hypertension, Lewis Kitchener Dahl et al. (56) conducted experiments with a population of Sprague-Dawley rats, wherein BP of the rats was recorded following their dietary intake of a high salt (8% NaCl) diet. If a high dietary salt intake caused an elevation in BP, all the rats should have developed higher BP. However, this was not the case. Only a subset of rats developed higher BP in response to dietary salt. The fundamental factor driving some but not all rats in the population to develop hypertension in response to dietary salt is now interpretable as genetic susceptibility. By selectively breeding rats with hypertension in response to a high salt intake, not only was further evidence obtained for the inheritance of hypertension, but also the model that ensued came to be known as the Dahl salt-sensitive (S) rat (56, 57), the inbred version of which continues to be one of the most popular models used to study the genetics of hypertension to date. In addition to this model developed in the United States, there are several other models of genetically hypertensive rats that were developed in other regions of the world. These include the spontaneously hypertensive rat (SHR) (272) and the spontaneously hypertensive rats stroke prone (SHRSP) from Japan (261, 272), DOCA salt-sensitive (SBH) rat from Israel (13), Fawn-hooded hypertensive (FHH) rat from The Netherlands (204), Lyon hypertensive (LH) rat from France (75), Milan hypertensive strain (MHS) from Italy (15), Prague hypertensive rat (PHR) from the Czech Republic (132), genetically hypertensive (GH) rat and the albino surgery (AS) rat from New Zealand (141, 343), and inherited stress-induced arterial hypertension (ISIAH) rat from Russia (236). The origins of these models are described in greater detail in a review by Rapp (298). These inbred rats served as models to test the hypothesis that there are regions, referred to as quantitative trait loci (QTLs), on the genome that cause an elevation in BP of these inbred rats.

To identify such genomic regions, comparisons of inbred hypertensive strains had to be made at the genomic DNA level with that of inbred normotensive strains. However, there was a significant roadblock to study genomic DNA, because during the 1970s and early 1980s there were few genetic markers and the technology for genotyping by amplification of DNA through the polymerase chain reaction (PCR) had not yet been developed. The experimental design used to find DNA regions related to BP was to breed hypertensive rats to their normotensive counterparts to generate filial generation 1 (F1) rats. The F1 rats were intercrossed to obtain a filial generation 2 (F2) population. The BP of F2 rats were recorded. Initially, Mendelian genetic markers were used to detect differences between regions of the genomes of hypertensive and normotensive rats. Such polymorphisms were used to track the cosegregation of marker genes with BP. The first example of this marker gene approach was demonstrated in 1972 by Yamori et al. (391) using an electrophoretic protein polymorphism within the renal esterase gene as a genetic marker to study the cosegregation of BP in populations derived from SHR and Wistar-Mishima rats. In the same year, another cosegregation study of BP with a Mendelian polymorphism in adrenal steroid biosynthesis was reported using the Dahl rats (302). In this case the genetic marker turned out to be due to variants in the gene actually causing the BP changes (see sect. IV*A*). A DNA restriction fragment length polymorphism (RFLP) was also exploited as a marker to demonstrate cosegregation of a segment of rat chromosome 13 containing the renin gene with hypertension in the Dahl rats (311).

During the mid 1980s, largely driven by the discovery of the PCR technology, methods were quickly evolving to improve the detection of DNA polymorphisms on the genome. RFLP was soon replaced by the relatively more efficient method of using polymorphic microsatellite markers at the scale of the entire genome for BP linkage analysis. Such experiments were first reported in 1991 by Jacob et al. (163) and Hilbert et al. (142). A major BP QTL on rat chromosome 10 was thus identified by both these groups (142, 163, 298). This method called as "linkage mapping" or "linkage analysis" and the subsequent method called "substitution mapping" were extensively applied to the study of inheritance of hypertension in rat genetic models (298). The results obtained through these efforts were that specific regions on the rat genome were identified as BP QTLs, meaning regions that were flanked by specific microsatellite markers (genotyped using PCR), were linked to the inheri-

tance of BP in segregating populations (usually F2). Following the studies in 1991–92, when the first such mapping studies were reported using rats (78, 142, 163), several such BP QTLs were either identified solely by linkage analysis or further validated by substitution mapping using congenic or consomic strains. Previous review articles by Rapp (298) and Cowley Jr (45) are highly recommended for a detailed understanding of linkage analysis and substitution mapping as applied to the study of the inheritance of BP using rat models of hypertension. For a quick review on the technique to make congenic strains, which are used for substitution mapping, see Rapp (298). The following section provides an update to these mapping efforts of rat BP QTLs, which are important and significant given the rapid rise in sequencing technology since the review by Rapp in 2000 (298).

The dawn of the 21st Century ushered in the new era of whole genome sequencing, which served as the next wave of opportunity to query genomes in further detail. Following the sequencing of the human genome, the rat genome was sequenced in 2004 (116). The genome sequence obtained was from the Brown Norway (BN) rat, which is a relatively normotensive strain compared with the hypertensive S rat or the SHR. The BN rat strain is highly polymorphic, implying that there are a large number of sequence variants of this strain compared with any other rat strain. While the sequence of this strain served as a general reference for comparison with the sequence data of other rat strains, nonavailability of whole genome sequences of other, especially, genetically hypertensive strains, was an impediment. However, the availability of an assembled, complete rat genome sequence served several purposes: *1*) provided the means to define BP loci on the physical map of the rat genome, whereby BP QTLs could be represented in physical locations on a chromosome in kilobases or megabases as units as opposed to genetic distances calculated using recombinations with centimorgans as units; *2*) served to improve the resolutions of the already identified BP loci because with the genome sequence, additional markers could be located. For example, additional polymorphic microsatellite markers (which are tandemly repeated nucleotide sequences that range in length from two to five nucleotides repeated in different numbers in different rat strains) could be located and exploited to further delimit the genomic region encompassing a BP locus. *3*) Sequences of candidate genes within the BP QTL could be determined in any strain by designing primers to amplify genome DNA of any chromosome.

These enhanced features resulted in high-resolution mapping of the identified BP QTL. A summary of all linkage mapping studies, which identified large rat genomic regions of interest is provided in **TABLE 1**. The main points to note from these linkage analyses are as follows:

1. All rat chromosomes harbor BP QTLs, implying that BP causal genes are not limited to any particular chromosome and that the overall genetic control of BP could be facilitated by a large number of randomly distributed genetic elements.
2. Some of the BP QTLs, for example, on rat chromosomes 1, 2, and 10 are consistently and recurrently detected in multiple genetic linkage studies conducted despite the differences in the hypertensive strains used for the studies. The density of QTLs is not proportional to the size of the chromosomes. Chromosomes 1 and 2 are the longest, but chromosome 10 is among the shorter rat chromosomes.
3. The context of genetic background wherein the QTL alleles are presented in a segregating population has an important effect on whether a given QTL will be detected. For example, a BP QTL was detected on RNO7 in the backcross population generated with the Dahl S rat, but not in an F2 population.
4. BP QTLs are not always gender independent. Some are gender specific.
5. BP QTLs are not always salt sensitive.

Some but not all of the linkage mapped regions were corroborated with substitution mapping studies. The substitution mapping studies are tabulated and schematically represented in **TABLE 2** and **FIGURE 1**, respectively, and discussed previously (166, 167, 298). As products of such substitution mapping studies, several genes have been prioritized as positional candidates for BP regulation. The genes identified as a result of these mapping efforts are discussed below through section VIII.

A. Cyp11b1

With the use of the mapping approach, the first locus to be deduced as a bona fide rat BP QTL was the gene *Cyp11b1*, which codes for both 18- and 11β-hydroxylation of adrenal steroids. The premise for this locus to be tested as a BP QTL was the observation of a striking difference in adrenal steroidogenesis between Dahl S and R rats. Compared with R rats, S rats had an increased ability to 18-hydroxylate 11-deoxycorticosterone (DOC) to form 18 hydroxy-11-deoxycorticosterone (18OH-DOC) and a reduced ability to 11β-hydroxylate DOC to form corticosterone (300–302, 304). These biochemical changes resulted in higher circulating levels of the weak mineralocorticoid 18OH-DOC in S rats (309), which was interpreted to cause increased BP especially on a high-salt diet (304). These steroid profiles were shown to be due to a single genetic locus (302) and the enzyme responsible (Cyp11b1) was identified in 1976 based on strain differences in Warburg's partition constant [inhibition by carbon monoxide (CO)] (303). Further genetic proof was obtained through the characterization of a congenic strain constructed by introgressing ~22 centimorgans (cM) of rat chromosome 7 including the *Cyp11b1* gene

Table 1. *Summary of BP QTL linkage mapping studies conducted using the rat as a model organism*

RNO	Hypertensive Model	Linkage Analysis	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
1	FHH	F1 (FHH X ACI) X FHH	Not mentioned	M	I	N	D1Mit17	D1Mit5	133,795,442	215,712,024	Brown et al. (24)
1	FHH	F2 (FHH X ACI)	Not mentioned	M	I	N	D1Wox6	Mt1pa	137,787,261	197,963,072	Shiozawa et al. (337)
1	HTG	F2 (HTG X LEW)	LS	B	D	N	D1Rat171	D1Mgh12	166,577,232	263,271,840	Ueno et al. (363)
1	MHS	F2 (MHS X MNS)	Not mentioned	B	B	N	D1Rat5	D1Mit9	10,259,237	49,547,474	Zagato et al. (398)
1	MHS	F2 (MHS X MNS)	Not mentioned	B	B	N	D1Rat76	D1Mit14	244,992,467	280,632,620	Zagato et al. (398)
1	MWF /Fub*	F1 (MWF/Fub X LEW/Fub) X MWF/Fub	LS	M	I	N	D1Rat136		43,579,208	Unmapped	Schulz et al. (328)
1	SBH	F2 (SBH X SBN)	LS	M	I	N	D1Mgh2	D1Mit11	23,406,428	108,057,505	Yagil et al. (389)
1	SBH	F2 (SBH X SBN)	IS	B	I	N	D1Mit2	D1Mgh8	140,953,686	163,796,432	Yagil et al (389),
1	SHR	F2 (SHR X WKY)	Not mentioned	M	I	N	Sa		189,514,503		Iwai et al. (161)
1	SHR	F2 (SHR X WKY)	LS	M	B	N	Sa	Mt1pa	189,514,503	197,963,072	Samani et al. (323)
1	SHR	RI- SHR X BN	LS	M	D	N	KAL		100,133,276		Pravenec et al. (290)
1	SHR	F1 (SHR X F344) X SHR	LS	B	I	Y	D1Rat43	D1Mgh11	144,634,295	221,753,518	Ohno et al. (271)
1	SHR	F1 (S X SHR) X S	LS	M	I	N	D1Rat189	D1Rat158	90,804,143	161,321,256	Garrett et al. (100)
1	SHR	F2 (S X SHR)	HS	M	I	N	D1Rat1	D1Rat335	10,065,314	67,227,947	Siegel et al. (339)
1	SHR/Mol	F1 (SHR/Mol X BB/OK) X SHR/Mol, F1 (SHR/Mol X BB/OK) X BB/OK	LS	B	I	N	Igf2	D1Mgh12	215,828,102	263,271,840	Kovacs et al. (197)
1	SHRSP	F2 (W.S.1O X SHRSP)	IS	B	D	N	Scnn1b		191,829,555		Kreutz et al. (200)
1	SHRSP/izm	F2 (SHRSP/Izm x WKY/Izm)	IS	M	I	N	D1Wox29	Mt1pa	130,779,148	197,963,072	Mashimo et al. (237)
1	SHRSP/izm	F2 (SHRSP/Izm x WKY/Izm)	IS	B	I	N	D1Mgh5	Mt1pa	79,689,548	197,963,072	Kato et al. (178)
1	SHRSP/izm	F1 (SHRSP/Izm x WKY/Izm) X SHRS/Izm	% not found	M	I	N	D1Wox29	D1Wox10	130,779,148	236,763,528	Kato et al. (178)
1	SS/Jr	F2 (S X LEW)	HS	M	I	N	D1Wox1	Igf2	50,508,884	215,828,102	Garrett et al. (101)
1	SS/Jr	F1 (S X SHR) X S	LS	M	I	N	D1Rat189	D1Rat158	90,804,143	161,321,256	Garrett et al. (100)
1	SS/JrHSDMCwi	F2 (S X BN)	HS	F	D	N	D1Rat295	D1Rat301	227,107,736	249,206,417	Moreno et al. (255)
1	SS/JrHSDMCwi	F2 (S X BN)	HS	F	D	N	D1Rat265	D1Rat183	94,364,073	137,084,126	Moreno et al. (255)
1	SS/Rkb	F2 (S X SHR)	HS	M	I	N	D1Rat1	D1Rat335	10,065,314	67,227,947	Siegel et al (339)
1	LH	F2 (LH X LN)	LS	M	D	N	D1Rat278		175,980,731		Bilusic et al. (17)
1	LH	F2 (LH X LN)	LS	M	D	N	D1Rat278		175,980,731		Bilusic et al. (17)
1	ISIAH	F2(ISIAHXWAG)	Not mentioned	M	I	N	D1Rat54	D1Rat81	174,905,700	264,802,994	Redina et al. (313)
1	ISIAH	F2(ISIAHXWAG)	Not mentioned	M	I	N	D1Rat54	D1Rat117	174,905,700	233,490,237	Redina et al. (313)
1	ISIAH	F2 (ISAH X WAG)	Not mentioned	M	I	N	D1Rat168	D1Rat76	217,372,257	244,992,610	Redina et al. (314)
1	ISIAH	F2 (ISAH X WAG)	Not mentioned	M	I	N	D1Rat54	D1Rat168	174,905,700	217,372,467	Redina et al. (314)
1	SS/Rkb	F2 (S X SHR)	HS	M	I	N	D1Rat1	D1Rat335	10,065,314	67,227,947	Siegel et al. (339)

Continued

Table 1.—*Continued*

RNO	Hypertensive Model	Linkage Analysis	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	To base pair #	References
1	SS/Hsd	F2 (S x R)	HS	B	D		D1Rat45		153,834,077		Herrera et al. (139)
1	SS/Hsd	F2 (S x R)	HS	M	D		D1Mgh11		221,753,409		Herrera et al. (139)
2	AS	F2 (S X AS)	HS	M	I	N	D2Uia17	D2Mco25	12,666,921	33,718,888	Garrett et al. (102)
2	GH	F2 (GH X BN)	LS	B	B	N	Gca		189,840,403		Harris et al. (130)
2	LH	F2 (LH X LN)	LS	M	D	N	D2Rat270		54,436,698		Bilusic et al. (17)
2	LH	F1 (LH X LN) X LH	LS	M	D	N	D2Mit5	D2Wox20	66,828,049	188,448,205	Vincent et al. (365)
2	SHR	F2 (SHR X WKY)	LS	M	I	N	D2Wox24	D2Mgh12	189,854,122	217,498,710	Samani et al. (322)
2	SHR	F2 (SHR X BN)	IS	Not mentioned	D	Y	Mt1pb	Gca	11,261,631	189,856,090	Schork et al. (327)
2	SHR	RI- SHR X BN	LS	M	D	N	D2N35		153,799,585		Pravenec et al. (287)
2	SHR/Mol	F1 (SHR X Wild) X SHR	Not mentioned	B	I	N	Fgg		181,987,217		Kloting et al. (185)
2	SHRSP/Glasgow	F2 (SHRSP X WKY)	IS	B	D	N	D2Mit5	Cpb	66,828,049	105,089,659	Clark et al. (42),
2	SHRSP/Heidelberg	F2 (SHRSP X WKY)	IS	B	D	Y	Gca		189,840,403		Jacob et al. (163)
2	SS/Hsd	F2 (S X R)	HS	M	D	N	D2Mit10	D2Mit14	157,914,311	204,585,731	Herrera et al. (140)
2	SS/Jr	F2 (S X LEW)	HS	M	I	N	D2Mit1	D2Mit6	3,127,441	78,466,260	Garrett et al. (101)
2	SS/Jr	F2 (S X MNS)	HS	M	I	N	Fgg	Camk2d	181,987,217	231,132,039	Deng et al. (69), Deng et al. (65)
2	SS/Jr	F2 (S X WKY)	HS	M	I	N	Fgg	Camk2d	181,987,217	231,132,039	Deng et al (69), Deng et al. (65)
2	BN	F2 (BN X GH)	HS	M	B	Y	D2Mgh7	D2Mgh11	158,159,186	204,022,555	Bilusic et al. (18)
2	SS/Hsd	F2 (SS/Hsd x R)	HS	F	D		EA4		Unmapped		Herrera et al. (139)
2	SS/Hsd	F2 (SS/Hsd x R)	HS	F	D		D2Rat143		106,156,724		Herrera et al. (139)
2	Ss/Hsd	F2 (SS/Hsd x R)	HS	M	D		D2Mgh11		204,022,334		Herrera et al. (139)
2	SS/Jr	F2 (S X AS)	HS	M	I	N	D2Uia17	D2Mco25	12,666,921	33,718,888	Garrett et al. (102)
3	hHTg	F2 (hHTg X BN)	LS	M	D	N	D3Rat126		125,753,279		Klimes et al. (184)
3	HTG	F2 (HTG X LEW)	LS	B	D	N	D3Wox3	D3Rat17	30,846,101	127,023,997	Ueno et al. (363)
3	SHR	F2 (S X SHR)	HS	M	I	N	D3Rat53	D3Rat45	13,126,914	41,510,346	Garrett et al. (108)
3	SHR	F2 (S X SHR)	HS	M	I	N	D3Mgh9	D3Rat75	3,285,929	55,279,027	Siegel et al. (339)
3	SHRSP/Glasgow	F2 (SHRSP X WKY)	IS	B	D	N	D3Mit10	D3Wox2	13,152,311	50,533,259	Clark et al. (42)
3	SHRSP/Izm	F2 (SHRSP/Izm x WKY/Izm)	IS	M	I	N	D3Mgh16	D3Mgh8	6,000,748	26,684,263	Mashimo et al. (237)
3	SHRSP/Izm	F2 (SHRSP/Izm x WKY/Izm)	IS	B	I	N	D3Mgh8	D3Wox10	6,363,336	51,821,835	Kato et al. (177)
3	SHRSP/Izm	F1(SHRSP x WKY) x SHRSP	LS	M	I	N	D3Mit9		34,394,121		Kato et al. (178)
3	SS/Hsd	F2 (SS/Hsd X R)	HS	M	I	Y	D3Rat18	D3Rat6	124,580,247	153,412,619	Herrera et al. (135)
3	SS/Jr	F2 (S X LEW)	HS	M	I	N	D3Wox3	D3Mco21	30,846,101	72,672,468	Garrett et al. (101)
3	SS/Jr	F2 (S X BN)	HS	M	I	N	D3Wox20	D3Wox1	129,787,213	174,632,112	Kato et al. (176)
3	SS/Jr	F1 (S X R) X S	HS	B	I	N	D3Mco16	D3Rat100	25,633,106	39,248,617	Cicila et al. (37)

Continued

Table 1.—*Continued*

RNO	Hypertensive Model	Linkage Analysis	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
3	SS/Rkb	F2 (S X SHR)	HS	M	I	N	D3Mgh9	D3Rat75	3,285,929	55,279,027	Siegel et al. (339)
4	AS	F2 (S X AS)	HS	M	I	N	D4Uia1	D4Rat160	119,130,374	Unmapped	Garrett et al. (102)
4	MHS	F2 (MHS X MNS)	Not mentioned	B	B	N	Add2		117,743,710		Bianchi et al. (16)
4	MWF /Fub	F1 (MWF/Fub X LEW/Fub) X MWF/Fub	LS	M	I	N	D4Rat41		97,758,884		Schulz et al. (328)
4	SHR	F2 (SHR X WKY)	LS	B	D	N	Npy		79,573,998		Katsuya et al. (181)
4	SHR	F2 (SHR X BN)	IS	Not mentioned	D	Y	Npy		79,573,998		Schork et al. (327)
4	SHR	RI- SHR X BN	LS	M	D	N	Il6		3,043,231		Pravenec et al. (287)
4	SHR/Mol	F1 (SHR X BB/OK) X BB/OK	LS	M	I	N	D4Mit2	D4Mit24	55,791,564	79,575,658	Kovacs et al. (196)
4	SHR/Sankyo	F2(SHR x WKY)	LS	B	D	N	Npy		78		Takami et al. (352)
4	SHRSP/Izm	F2 (SHRSP/Izm x WKY/Izm)	IS	M	I	N	D4Mit2	Spr	55,791,564	116,916,236	Mashimo et al. (237)
4	SHRSP/Izm	F2 (SHRSP/Izm x WKY/Izm)	IS	B	I	N	D4Mgh7	Try1	136,351,734	70,779,249	Kato et al. (177)
4	SS/Jr	F2 (S X AS)	HS	M	I	N	D4Rat160	D4Uia1	Unmapped	119,130,374	Garrett et al. (102)
5	hHTg	F2(hHTg x BN)	LS	M	D	N	D5Mgh9		172,402,477		Klimes et al. (184)
5	HTG	F2 (HTG X LEW)	LS	B	D	N	D5Rat77	D5Rat105	75,995,687	154,794,907	Ueno et al. (363)
5	MWF /Fub*	F1 (MWF/Fub X LEW/Fub) X MWF/Fub	LS	M	I	N	D5Rat41		155,051,873		Schulz et al. (328)
5	SHR	F2 (SHR X WKY)	LS	B	D	N	D5Mgh14		149,568,795		Zhang et al. (401)
5	SHR	F2 (SHR X WKY)	LS	B	D	N	D5Mgh5	D5Rat180	44,404,276	165,718,386	Ye P et al. (395)
5	SHR/Mol	F1 (SHR X Wild) X SHR	Not mentioned	B	I	N	Slc2a1	D5Mgh9	138,154,673	172,402,610	Kloting et al. (185)
5	SHR/NCrlBr	F2 (SHR X BN)	IS	B	D	N	D5Rjr1		134,502,121		Stec et al. (348)
5	SHRSP/izm	F2 (SHRSP/Izm x WKY/Izm)	IS	B	I	N	D5Mgh2	D5Rat4	17,064,231	48,722,188	Kato et al. (177)
5	SS/Jr	F2 (S X LEW)	HS	M	I	N	D5Mit5	D5Mco2	108,092,659	147,641,079	Garrett et al. (101)
5	BN	F2 (BN X SHR)	IS		D	N	R589		Unmapped		Soler et al. (345)
5	SS/Hsd	F2 (S x R)	HS	F	D		D5Rat106		156,443,753		Herrera et al. (139)
5	Ss/Hsd	F2 (S x R)	HS	F	D		D5Rat23		105,924,457		Herrera et al. (139)
6	SHR	F2 (SHR X LEW)	LS	B	I	Y	D6Mit4		60,606,186		Ramos et al. (297)
6	SHR	RI-SHR X BN, BN X SHR	Not mentioned	Not mentioned	D	N	D6Rat46	D6Rat84	13,122,958	33,259,316	Jaworskiet al (164)
6	SHR	F1 (S X SHR) X S	LS	M	I	N	D6Rat180	D6Mit3	174,130	75,623,393	Garrett et al. (100)
6	SHR	F2 (S X SHR)	HS	M	I	N	D6Rat80	D6Rat108	1,120,393	16,100,257	Siegel et al. (338)
6	SS/Jr	F1 (S X SHR) X S	LS	M	I	N	D6Rat180	D6Mit3	174,130	75,623,393	Garrett et al. (100)
6	SS/Rkb	F2 (S X SHR)	HS	M	I	N	D6Rat80	D6Rat108	1,120,393	16,100,257	Siegel et al. (338)
6	BN	BN.GH	HS	M	B	Y	D6Mit12	D6Mit3	Unmapped (2,916,444 on RNOr_5.0)	75,623,393	Bilusic et al. (18)

Continued

Table 1.—*Continued*

RNO	Hypertensive Model	Linkage Analysis	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
7	SHR/Mol	F1 (SHR X Wild) X SHR	Not mentioned	B	I	N	*Igf1*		28,412,198	28,486,609	Kloting et al. (185)
7	SS/Jr	F1 (S X R) X S	HS	B	I	N	*Cyp11b1*		112,977,395		Cicila et al. (41)
8	AS	F2 (S X AS)	HS	M	I	N	D8Mgh9	D8Mgh4	38,202,434	89,058,369	Garrett et al. (102)
8	HTG	F2 (HTG X LEW)	LS	B	D	N	D8Rat37	D8Rat117	55,435,004	125,428,828	Ueno et al. (363)
8	SHR	F2 (SHR X BN)	IS	Not mentioned	D	Y	D5Mit3	D5Mit5	83,646,702	108,092,802	Schork et al. (327)
8	SHR	F2 (SHR X WKY)	HS	B	D	N	D8Mgh10				Takami et al. (352)
8	SHR	F2 (S X SHR)	HS	M	I	N	D8Rat36	D8Rat133	58,425,510	96,998,640	Garrett et al. (108)
8	SHR	RI-SHR X BN, BN X SHR	Not mentioned	Not mentioned	D	N	D8Mit6	D8Rat40	11,373,267	50,708,951	Jaworski et al. (164)
8	SHRSP/izm	F2 (SHRSP/Izm x WKY/Izm)	LS	B	I	N	D8Mit1	Acaa	95,349,621	128,036,236	Kato et al. (177)
8	SS/Iwai	F2 (S/Iwai X WKY)	HS	B	D	N	D8Mgh10				Takami et al. (352)
8	SS/Jr	F2 (S X LEW)	HS	M	I	N	D8Mgh9	D8Wox2	38,202,434	62,427,969	Garrett et al. (101)
8	SS/Jr	F2 (S X SHR)	HS	M	I	N	D8Rat36	D8Rat133	58,425,510	96,998,640	Garrett et al. (108)
8	SS/Jr	F2 (S X AS)	HS	M	I	N	D8Mgh9	D8Mgh4	38,202,434	89,058,369	Garrett et al. (102)
8	SHR	F2(SHRXBN)	Not mentioned	M	D	N	Apoa02	R830 (D8Mit12)	Unmapped	59,087,488	Silva et al. (340)
9	SHR	F2 (SHR X WKY)	HS	B	D	N	D9Mit2		71,771,288		Takami et al. (352)
9	SHR	F2 (S X SHR)	HS	M	I	N	D9Mit3	D9Rat5	63,269,904	93,442,944	Siegel et al. (339)
9	SHR	F2 (S X SHR)	HS	M	I	N	D9Uia10	D9Rat92	31,001,440	54,885,226	Garrett et al. (108)
9	SHRSP/izm	F2 (SHRSP/Izm x WKY/Izm)	LS	B	I	N	D9Wox18	D9Mit2	25,692,373	71,771,476	Kato et al. (178)
9	SS/Jr	F2 (S X R)	HS	B	I	N	D9Rat12	D9Rat4	73,334,111	98,606,834	Rapp et al. (305)
9	SS/Jr	F2 (S X SHR)	HS	M	I	N	D9Uia10	D9Rat92	31,001,440	54,885,226	Garrett et al. (108)
9	SS/Rkb	F2 (S X SHR)	HS	M	I	N	D9Mit3	D9Rat5	63,269,904	93,442,944	Siegel et al. (339)
9	SS/Jr	F2(SS.SHR(9)X8A X SS)	IS	M	B	N	D9Mco72	D9Mco93	52,686,874	98,164,303	Toland et al. (356)
10	GH	F2 (GH X BN)	LS	B	B	N	*Ace*		94,170,766		Harris et al. (130)
10	ISIAH	F2 (ISAH X WAG)	Not mentioned	Not mentioned	D	N	D10Wox16		83,390,674		Redina et al. (312)
10	MHS	F2 (MHS X MNS)	Not mentioned	B	B	N	D10Rat82	D10Rat73	32,942,229	46,449,947	Zagato et al. (398)
10	SHR	F2 (SHR X WKY)	LS	B	D	N	*Ace*		94,170,766		Zhang et al. (400)
10	SHR/Mol	F2 (SHR/Mol X BB/OK)	LS	B	I	N	*Abp*	*Ppy*	56,219,861	90,042,877	Kovacs et al. (197)
10	SHRSP//HD	F2 (SHRSP//HD X WKY/HD-O)	LS	B	D	N	*Chrnb1*		56,390,671	56,403,188	Kreutz et al. (199)
10	SHRSP//HD	F2 (SHRSP//HD X WKY/HD-O)	LS	B	D	N	*Ace*		94,170,766		Kreutz et al. (199)
10	SHRSP/Heidelberg	F2 (SHRSP X WKY)	IS	B	D	Y	*Ace*		94,170,766		Jacob et al. (163)
10	SHRSP/izm	F2 (SHRSP/Izm x WKY/Izm)	IS	M	I	N	*Gh1*	D10Mgh1	94,486,205	102,748,839	Mashimo et al. (237)
10	SS/Jr	F2 (S X BN)	HS	M	I	N	D10Mit4		36,584,373		Kato et al. (176)
10	SS/Jr	F2 (S X WKY)	HS	M	I	N	D10Mgh6		64,648,175		Kato et al. (176), Deng et al. (68)
10	SS/Jr	F2 (S X MNS)	HS	M	I	N	D10Wox11	D10Wox6	53,637,485	Unmapped	Kato et al. (176), Deng et al. (68)
10	SS/Jr	F2 (S X LEW)	HS	M	I	N	D10Mco30	D10Mco15	76,420,583	97,308,569	Garrett et al. (101)

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Table 1.—*Continued*

RNO	Hypertensive Model	Linkage Analysis	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
10	SS/Jr	F1 (S X SHR) X S	LS	M	I	N	D10Rat38	D10Mco66	31,643,957	81,202,850	Garrett et al. (100)
10	TGRm*Ren*2-27 SD	F1 (F344 X LEW) X TGRmRen2-27	Not mentioned	B	I	Y	D10Wox3	D10Mit4	18,246,394	36,584,560	Kantachuvesiri et al. (174)
11	SHR/Mol	F1 (SHR X Wild) X SHR	Not mentioned	B	I	N	D11Mgh4	D11Wox6	62,653,194	86,714,647	Kloting et al. (185)
11	SS/Jr	F1 (S X SHR) X S	IS	M	I	N	D11Rat67	D11Rat50	47,263,866	86,994,795	Garrett et al. (103)
11	SS/Hsd	F2 (S x R)	HS	M	D		D11Mgh5		44,444,112		Herrera et al. (139)
12	SHR	F2 (SHR X LEW)	LS	B	I	Y	D12Mit3		24,294,687		Ramos et al. (297)
12	SS/Jr	F2 (S X WKY)	HS	M	I	N	D12Wox16	D12Wox8	30,641,840	44,098,244	Kato et al. (176)
12	R	F2 (R X SS)	HS	F	D		D12Mit6		14,419,775		Herrera et al. (139)
13	SHR	F2 (SHR X WKY)	LS	M	I	N	D13Wox5	D13Mit3	55,560,677	80,285,772	Samani et al. (322)
13	SHR	F2 (SHR X WKY)	LS	B	B	N	*Ren*		50,502,724	50,514,151	Sun et al. (351)
13	SHR	F2 (SHR X WKY)	Not mentioned	B	B	N	*Ren*		50,502,724	50,514,151	Yu et al. (397)
13	SHR	F2 (SHR X LEW)	LS	B	I	N	*Ren*		50,502,724	50,514,151	Kurtz et al. (208)
13	SHR/Mol	F1 (SHR X BB/OK) X BB/OK	LS	M	I	N	D13Uwm1		55,560,677	55,560,862	Kovacs et al. (196)
13	SHR/Ola	RI- SHR X BN	LS	M	D	N	*Ren*		50,502,724	50,514,151	Pravenec et al. (292)
13	SHRSP/izm	F2 (SHRSP/Izm x WKY/Izm)	LS	B	I	N	D13Mgh4	D13Mgh7	42,310,744	67,207,219	Kato et al. (177)
13	SS/Jr	F2 (S X R)	HS	B	I	N	D13Mgh3	D13Mit3	39,372,926	80,285,772	Zhang et al. (402)
13	SS/Jr	F2 (S X R) X S	HS	B	I	N	*Ren*		50,502,724	50,514,151	Rapp et al. (310)
13	SS/JrHSDMCwi	F2 (S X BN)	HS	F	D	N	D12Rat22		51,955,573	51,955,754	Moreno et al. (255)
13	LH	F2 (LH X LN)	LS	M	D	N	D13Rat120		49,549,739	49,549,883	Bilusic et al (17)
14	MHS	F2 (MHS X MNS)	Not mentioned	B	B	N	D14Rat90	D14Rat94	73,391,467	88,870,994	Zagato et al. (398)
14	SS/JrHSDMCwi	F2 (S X BN)	LS	F	D	N	D14Rat12		61,783,047		Moreno et al. (255)
15	SHRSP/izm	F2 (SHRSP/Izm x WKY/Izm)	LS	B	I	N	*Ednrb*	D15Mgh6	88,006,977	104,003,672	Kato et al. (177)
15	SS/JrHSDMCwi	F2 (S X BN)	HS	F	D	N	D15Rat106		106,550,444		Moreno et al. (255)
16	SHR	F2 (SHR X BN)	IS	Not mentioned	D	Y	D16Mi2	D16Mit5	5,013,802	16,482,677	Schork et al. (327)
16	SS/Jr	F2 (S X LEW)	HS	M	I	N	D16Wox11	D16Mit3	19,398,181	47,346,612	Garrett et al. (101)
17	FHH	F2 (FHH X ACI)	Not mentioned	M	I	N	D17Rat54		18,538,334		Shiozawa et al. (337)2000
17	LH	F2 (LH X LN)	LS	M	D	N	D17Rat98		64,047,700		Bilusic et al. (17)
17	SBH	F2 (SBH X SBN)	IS	B	I	N	D17Mgh3	D17Mit4	43,677,641	63,994,435	Yagil et al. (389)
17	SS/Jr	F2 (S X LEW)	HS	M	I	N	D17Mit2	D17Mco3	33,303,627	64,946,465	Garrett et al. (101)
17	TGRm*Ren*2-27 SD	F1 (F344 X LEW) X TGRmRen2-27	Not mentioned	B	I	Y	D17Mit2		33,303,627		Kantachuvesiri et al (174)
17	LH	F2 (LH X LN)	LS	M	D	N	D17Rat32		61,036,503		Bilusic et al (17)
18	SHR/Mol	F2 (SHR/Mol X BB/OK)	LS	B	I	N	Ttr	D18Mit9	15,532,963	80,696,375	Kovacs et al. (197)
18	SHRSP/Heidelberg	F2 (SHRSP X WKY)	IS	B	D	Y	D18Mit7		12,597,179		Jacob et al. (163)

Continued

Table 1.—*Continued*

RNO	Hypertensive Model	Linkage Analysis	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
18	SS/Jr	F2 (S X LEW)	HS	M	I	N	D18Mit1	D18Mco3	15,539,427	29,530,769	Garrett et al. (101)
18	SS/JrHSDMCwi	F2 (S X BN)	HS	M	D	N	D18Mit1	D18Mit8	15,539,427	61,985,812	Cowley et al. (49)
18	BN	F2 (BN X GH)	HS	M	B	Y	D18Mgh2	D18Mgh4	61,901,172	79,948,741	Bilusic et al. (18)
19	SHR	F2 (SHR X WKY)	IS	M	D	N	*Agt*		57,321,640		Lodwick et al. (225)
19	SHR	RI- SHR X BN	LS	M	D	N	D19Mit7		47,318,201		Pravenec et al. (287)
20	GH	F2 (GH X BN)	Not mentioned	B	B	N	Tnf		4,855,829		Harris et al. (129)
20	MHS	F2 (MHS X MNS)	Not mentioned	B	B	N	D20Rat44	D20Rat38	32,469,646	45,719,230	Zagato et al. (398)
20	SHR	RI- SHR X BN	LS	M	D	N	D20Mgh4		5,875,339		Pravenec et al. (288)
20	SHRSP/Izm	F1(SHRSP x WKY) x SHRSP	LS	M	I	N	D20Mgh1		51,892,390		Kato et al. (178)
20	R	F2 (R X SS)	HS	M	D	N	D20Rat37		Unmapped		Herrera et al. (139)
X	SBH	F2 (SBH X SBN)	IS	B	I	N	DXRat4	DXRat15	12,370,136	65,347,605	Yagil C et al. (390)
X	SHR	F2 (SHR X WKY)	IS	B	D	N	DXMgh5	DXMit4	23,143,255	61,398,097	Hilbert et al. (142)
Y	SHR	F2 (SHR X WKY) and reciprocal F1 crosses	Not mentioned	B	I	N	Entire Y	Entire Y	Entire Y	Entire Y	Ely et al. (84),
Y	SHRSP	F2 (SHRSP X WKY), reciprocal crosses	IS	B	B	N	Entire Y	Entire Y	Entire Y	Entire Y	Davidson et al. (59)

Bp QTLs that are reported in the literature are curated by their location on the rat genome and organized by chromosome. For details on strain names, please refer to the Rat Genome Database (www.rgd.mcw.edu). LS, low-salt diet (≤1% NaCl); IS, intermediate-salt diet (1% to <2% NaCl); HS, high-salt diet (≥2% to 8% NaCl); M, male; F, female; B, both genders; I, indirect tail-cuff method for BP measurement; D, direct, telemetry method for BP measurement; B, both tail-cuff method and telemetry for BP measurement. Blank spaces in all columns represent data that are insufficient or not provided in the original publications.

Table 2. *Summary of BP QTL identified using rat congenic strains*

RNO #	Letter Designated in Figure 1	Hypertensive Model	Congenic Strain	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
1	a	SS/Jr	S.LEW	HS	M	D	N	D1Rat211	D1Rat12	33,667,777	36,129,328	Joe et al. (168)
1	b	SS/Jr	S.LEW/NCrIBR	IS	M	I	N	D1Mgh7	D1Mco36	113,593,576	129,209,407	Saad et al. (319)
1	c	SS/Jr	S.LEW/NCrIBR	IS	M	I	N	D1Rat35	D1Rat131	130,917,121	152,871,103	Saad et al. (319)
1	d	SHR	SHR.WKY-Sa	LS	M	I and D	N	D1Wox34	D1Rat55	175,447,029	Unmapped (184,481,458 on Rnor_5.0)	Frantz et al. (96)
1	e	SHR	SHR.WKY-Sa	LS	M	I and D	N	D1Rat56	D1Rat111	184,419,946	215,097,919	Frantz S et al. (96)
1	f	SBH	SBH.SBN	HS	B	I and D	N	D1Rat10	D1Rat24	85,706,847	78,434,672	Yagil et al. (388)
1	g	SBH	SBH.SBN	HS	B	I and D	N	D1Rat27	D1Rat74	94,201,400	241,482,368	Yagil et al. (388)
1	h	SHRSP	WKY-1.SHRSP	IS	Not mentioned	D	N	D1Rat29	D1Rat57	108,986,301	188,794,576	Hubner et al. (155)
1	i	SHR	SHR.BN	IS	M	D	N	D1Rat68	D1Rat71	205,603,081	230,420,772	St Lezin et al. (346)
1	j	SHRSP/Izm	SHRSP/Izm.WKY.Izm	LS	B	D	N	Klk1	D1Wox10	100,059,967	236,763,528	Kato et al. (178)
1	k	SHRSP/Izm	.WKY.Izm/ SHRSP/Izm	Not mentioned	M	D	N	D1Wox18	D1Smu11	100,133,276	184,185,332	Cui et al. (54)
1	l	SHRSP	WKY.SHRSP	LS	M	D	Y (with RNO10)	D1Rat29	D1Rat57	108,986,301	188,794,576	Monti et al. (253)
1	m	SS/Jr	S.LEW	HS	M	D	Y	*Serac-1*	D1Rat19	46,942,192	49,578,693	Deng et al. (64)
1	n	SS/Jr	S.LEW	HS	M	D	Y	D1Uia4	D1Rat320	64,588,516	125,875,986	Deng et al. (64)
1	o	SS/Jr	S.LEW	HS	M	D	Y	*D1Rat320*	D1Mgn32	125,875,986	Unmapped (mentioned as 269,689,xxx in the article)	Deng et al. (64)
1	p	SS/Jr	S.LEW/NCrIBR	IS	M	I	N	D1Uia8	D1Rat18	49,454,221	49,454,378	Saad et al. (319)
1	q	SHRSP/izm	WKY.SHRSP	Not mentioned	M	D	N	D1Wox29	D1Arb21	130,779,148	199,254,774	Cui et al. (53)
1	r	SHRSP/izm	WKY/Izm.SHRSP/Izm	Not mentioned	M	D	Y	D1Smu13	D1Arb21	166,884,926	199,254,774	Xiao et al. (387)
1	s	SHRSP/izm	SHRSP/Izm.WKY/Izm	Not mentioned	M	D	Y	Apbb1	D1Arb21	170,387,609	199,254,774	Xiao et al. (387)
1	t	SS/Jr	S.LEW/NCrIBR	IS	M	D	N	D1Mco55	D1Mco101	134,089,429	129,209,407	Mell et al. (244)
1	u	SS/Jr	S.LEW/NCrIBR	IS	M	D	N	D1Rat200	D1Mco136	133,076,978	133,164,521	Mell et al. (244)
1	v	SS/Jr	S.LEW/NCrIBR	IS	M	D	N	D1Muo1	D1Muo28	34,894,063	35,664,727	Joe et al. (170)
2	a	SS/Jr	S.LEW	HS	M	D	N	D2Rat35	D2Wox18	150,211,243	181,987,474	Garrett et al. (106)
2	b	SS/Jr	S.LEW	HS	M	D	N	D2Wox18	D2Wox25	181,987,474	200,585,297	Garrett et al. (106)
2	c	SS/Jr	S.LEW	HS	M	D	N	D2Wox25	D2Rat259	200,585,297	210,251,018	Garrett et al. (106)
2	d	SS/Jr	S.MNS	HS	M	D	N	D2Rat166	D2Mgh10	145,903,536	200,453,484	Dutil et al. (76)
2	e	SHR/Ij	WKY.SHR	LS and HS	M	D	N	D2Rat21	D2Rat27	75,687,495	96,556,765	Alemayehu et al. (5)
2	f	SHR/Ij	WKY.SHR	LS and HS	M	D	N	D2Mgh10	D2Rat62	200,453,324	236,318,668	Alemayehu et al. (5)
2	g	SHR/Ij	SHR.WKY	LS and HS	M	D	N	D2Rat40	D2Rat50	169,852,670	207,612,467	Alemayehu et al. (5)

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Table 2.—*Continued*

RNO #	Letter Designated in Figure 1	Hypertensive Model	Congenic Strain	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
2	h	SHR/Ij	SHR.WKY	LS and HS	M	D	N	D2Rat161	D2Mgh10	118,446,646	200,453,484	Alemayehu et al. (5)
2	i	SHR	SHR.BN	LS	M	D	N	D2Rat171	D2Arb24	116,075,644	228,737,869	Pravenec et al. (293)
2	j	SHRSP	SHRSP.WKY	LS	M	D	N	D2Rat43	D2Mgh12	Unmapped (199,443, 778 on Rnor_5.0)	217,498,710	McBride et al. (241)
2	k	SS/Hsd	S.R	HS	B	D	N	D2Rat352	SNP2786652	180,909,971	187,195,159	Herrera et al. (137)
2	l	SHRSP	SHRSP.WKY	IS	M	D	Y (with RNO3)	D2Rat13	D2Rat157	37,861,479	241,761,983	Koh-Tan et al. (187)
2	m	SHR	SHR.BN	IS	M	D	N	D2Rat226	D2Rat294	177,680,772	243,901,375	Aneas et al. (7)
2	n	SHR	SHR.BN	IS	M	D	N	D2Rat114	D2Rat123	36,245,223	112,175,725	Aneas et al. (7)
2	o	SS/Jr	S.LEW	IS	M	D	N	D2Chm277	Prlr	56,736,401	60,325,692	Eliopoulos et al. (83)
2	p	SS/Jr	S.LEW	IS	M	D	N	D2Rat199	D2Mco17	41,179,255	42,776,280	Charron et al. (30),
3	a	SS/Jr	S.R	HS	B	I	N	D3Mco19	D3Mco24	153,325,515	172,890,235	Cicila et al. (37)
3	b	SS/Jr	S.LEW	HS	M	D	Y	D3Rat52	D3Rat130	14,090,411	48,662,146	Palijan et al. (277)
3	c	SS/Jr	S.LEW	HS	M	D	Y	D3Chm63	D3Rat26	55,245,276	95,176,874	Palijan et al. (277)
3	d	SS/Jr	S.R	HS	M	I	Y	D3Mco81	D3Mco75	Unmapped (128,986, 468 from Rat genome database)	173,986,468	Lee et al. (211)
3	e	SS/Jr	F2(SREdn3XS)	HS	M	I	Y	D3Mco39	D3Mco36	176,305,697	177,366,660	Lee et al. (211)
3	f	SHRSP	SHRSP.WKY	IS	M	D	Y	D3Mgh16	D3Wox28	6,000,748	156,575,096	Koh-Tan et al. (187)
3	g	SS/Jr	S.R	HS	B	I	N	D3Rat61	D3Rat59	153,381,237	170,534,769	Cicila et al. (37)
4	a	SHR	SHR.BN-Il6/Npy	IS	M	B	N	D4Rat247	SNP2788971 (labeled as 17.37Mb)	4,780,787	Unmapped	Pravenec et al (286)
4	b	SHR	SHR.BN	IS	M	D	N	D4Rat33	D4Rat54	81,874,073	119,546,974	Aneas et al. (7)
5	a	SS/Jr	S.LEW/NCrlBR	IS	M	I	Y	D5Uwm31	D5Rjr1	47,842,131	134,502,294	Garrett et al. (107)
5	b	SS/Jr	S.LEW/NCrlBR	IS	M	I	Y	D5Rat154	D5Wox39/ Lepr	Not mapped (closest marker is D5Mit5 at 108,092, 659)	124,025,214	Garrett et al. (107)
5	c	SHR	SHR.BN	LS	M	D	N	D5Wox20	D5Rat63	107,316,809	145,726,262	Pravenec et al. (289)
5	d	SS/Hsd	S.R	HS	F	D	N	SNP2791496	SNP2791569	Unmapped (labeled as 134,909, 988)	Unmapped (labeled as 141,744, 732)	Herrera et al. (136)

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Table 2.—*Continued*

RNO #	Letter Designated in Figure 1	Hypertensive Model	Congenic Strain	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
5	e	SS/Jr	S.LEW/NCrlBR	IS	M	B	Y	D5Mco58	D5Mco41	Unmapped (mentioned as 131, 853,815)	Unmapped (mentioned as 124, 085,611)	Pillai et al. (284).
5	f	SS/Jr	S.LEW/NCrlBR	IS	M	B	Y	D5Mco42	D5Mco47	Unmapped (mentioned as 122,070, 175)	Unmapped (mentioned as 117,894,038)	Pillai et al. (284)
7	a	SS/Jr	S.R	HS	M	D	N	D7Mco19	D7Mco7	115,922,628	Unmapped (116,060,096 on Rnor_5.0)	Garrett et al. (105)
7	b	SS/Hsd	S.LEW	IS	M	D	N	D7Chm6	D7Mgh1	Unmapped (nearest marker D7Rat73 is at 61,047,589)	Unmapped (nearest marker D7Rat128 is at 124, 246,733	Crespo et al. (51)
8	a	SHR	SHR.BN-Lx	LS	M	D	N	D8Mit6	Rbp2	11,373,509	106,506,834	Kren et al. (198)
8	b	SS/Hsd	S.LEW	IS	M	D	N	D8Chm14	D8Rat16	51,844,002	101,305,168	Ariyarajah et al. (10)
8	c	SS/Hsd	S.LEW	IS	F	D	N	D8Rat51	D8Rat55	30,918,112	7,238,999	Deng et al. (67)
8	d	S	S.LEW	IS	M	D	N	D8Rat56	D8Rat51	9531047	30918267	Ariyarajah et al. (10)
9	a	SS/Jr	S.R	HS	M	D	N	D9Mco14	D9Uia6	82,356,030	83,686,404	Meng et al. (247)
9	b	SS/Jr	S.R	IS	M	B	N	D9Mco95	D9Mco98	81,100,315	81,180,041	Gopalakrishnan et al. (122)
9	c	SS/Jr	S.R	IS	M	D	N	D9Mco14	D9Mco61	82,356,030	89,338,443	Garrett et al. (104)
9	d	SS/Jr	S.R	IS	M	D	N	D9Mco14	Resp18-Intron2	82,356,030	82,477,136	Garrett et al. (104)
9	e	SS/Jr	S.SHR	IS	M	D	N	D9Mco113	D9Mco124	95,430,880	97,679,852	Nie et al. (267),
10	a	SS/Jr	S.MNS and S.LEW	HS	M	D	N	D10Mco1	D10Wox23	691,236,03	836,536,98	Garrett et al. (109)
10	b	SS/Jr	S.MNS	HS	M	D	N	D10Mit1	D10Mco6	94,178,327	101,482,600	Garrett et al. (109)
10	c	SS/Jr	S.LEW	HS	M	D	N	D10M11Mit119	D10Rat27	Unmapped (nearest marker D10Wox51 is at 70,428,844	75,983,805	Palijan et al. (278)
10	d	SS/Jr	S.LEW	HS	M	D	N	D10Rat204	D10Rat9	93,622,786	Unmapped (99,588, 446 on RGSC_v3.4)	Palijan et al. (278)
10	e	SS/Jr	S.LEW	HS	M	D	N	D10Rat27	D10Rat93	75,983,662	80,946,110	Palijan et al. (278)
10	f	SHRSP	WKY.SHRSP	LS	M	D	N	Myhse	D10Mit11	53,621,375	100,759,938	Monti et al. (254)

Continued

Table 2.—*Continued*

RNO #	Letter Designated in Figure 1	Hypertensive Model	Congenic Strain	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
10	g	SHRSP	WKY.SHRSP	LS	M	D	Y	Myh3	Aldoc	53,621,375	65,590,126	Monti et al. (253)
10	h	SS/Jr	S.LEW	IS	M	D	Y	D10Mgh6	D10Mgh1	64,648,175	102,748,839	Crespo et al. (52)
10	i	SS/Jr	S.LEW	IS	M	D	Y	D10Chm169	D10Chm147	69,808,793	70,581,793	Charron et al. (29)
10	j	SS/Jr	S.LEW	IS	M	D	Y	D10Chm212	D10Chm29	73,727,917	75,099,909	Charron et al (29)
10	k	SS/Jr	S.LEW	IS	M	D	Y	D10Got92	D10Rat127	77,055,741	86,419,171	Charron et al. (29)
10	l	SS/Jr	S.MNS	IS	M	B	N	D10Mco88	D10Mco89	70,647,089	71,727,943	Saad et al. (318)
10	m	SS/Jr	S.LEW	IS	M	B	N	D10Mco129	D10Mco147	69,910,996	Unmapped (71,100, 513)	Saad et al. (320)
10	n	SS/Jr	S.LEW	IS	M	B	N	D10Rat58	D10Mco43	70,202,084	70,610,989	Saad et al. (320)
10	n	SS/Jr	S.LEW	IS	M	B	N	D10Got88	D10Mco62	70,800,238	Unmapped (70,763, 527 on Rnor_5.0)	Saad et al. (320)
10	o	SS/Jr	S.LEW	HS	M	B	N	SNP marker	SNP marker	71,028,112	71,070,581	Gopalakrishnan et al. (121)
11	a	SS/Jr	S.SHR	IS	M	I	N	D11Rat31	D11Rat50	6,673,351	86,994,795	Garrett et al. (103)
13	a	SS/MCW	SS.BN	HS	M	D	N	Consomic (whole chromosome)	Consomic (whole chromosome)	1	114,033,958	Cowley et al. (48)
13	b	SS/MCW	SS.BN	HS	B	D	N	D13Rat7	D13Rat60	14,279,081	26,919,398	Moreno et al. (257)
13	c	SS/MCW	SS.BN	HS	B	D	N	D13Rat111	D13Rat101	35,301,263	53,264,877	Moreno et al. (257)
13	d	SS/MCW	SS.BN	HS	F	D	N	D13Rat88	D13Rat91	53,264,698	50,799,665	Moreno et al. (257)
13	e	SS/MCW	SS.BN	HS	F	D	N	D13Rat178	D13Got51	62,788,897	75,026,713	Moreno et al. (257)
13	f	SS/MCW	SS.BN	HS	B	D	N	D13Rat111	D13Rat88	35,301,263	46,444,796	Moreno et al. (257)
13	g	SS/MCW	SS.BN	HS	B	D	N	D13Rat39	D13Mit2	37,352,631	65,008,446	Moreno et al. (257)
13	h	SS/MCW	SS.BN	HS	B	D	N	D13Rat91	D13Got45	50,799,478	72,031,708	Moreno et al. (257)
13	i	SS/MCW	SS.BN	HS	B	D	N	D13Rat101	D13Got45	53,264,877	72,031,708	Moreno et al. (257)
13	j	SS/MCW	SS.BN	HS	M	D	N	D13Rat7	D13Rat20	14,279,081	42,155,682	Moreno et al. (257)
13	k	SS/MCW	SS.BN	HS	M	D	N	D13Rat7	D13Rat101	14,279,081	53,264,877	Moreno et al. (257)
13	l	SS/MCW	SS.BN	HS	M	D	N	D13Rat111	D13Rat101	35,301,263	53,264,877	Moreno et al. (257)
13	m	SS/MCW	SS.BN	HS	M	D	N	D13Rat115	D13Rat101	39,639,775	53,264,877	Moreno et al. (257)
13	n	SS/MCW	SS.BN	HS	M	D	N	D13Rat88	D13Rat91	46,444,570	53,264,877	Moreno et al. (257)
13	o	SS/MCW	SS.BN	HS	M	D	N	D13Rat88	D13Got51	46,444,570	75,026,713	Moreno et al. (257)
13	p	SS/MCW	SS.BN	HS	M	D	N	D13Rat178	D13Got51	62,788,897	75,026,713	Moreno et al. (257)
13	q	SS/MCW	SS.BN	HS	M	D	N	D13Rat20	D13Hmgc98	42,155,543	44,730,157	Moreno et al. (258)
13	r	SS/MCW	SS.BN	HS	M	D	N	D13Hmgc755	D13Hmgc5 885	76,000,378	77,381,370	Cowley et al. (46)
13	s	SS/MCW	SS.BN	HS	M	D	N	D13Hmgc10 48	D13Hmgc10 50	Unmapped (mentioned as 81,011kb in the article)	Unmapped (mentioned as 81,717 kb in the article)	Cowley et al. (50)

Continued

Table 2.—*Continued*

RNO #	Letter Designated in Figure 1	Hypertensive Model	Congenic Strain	Diet	Sex	BP Method	Epistatic Interaction	From Marker	To Marker	QTL Location (on Rnor 6.0) From base pair #	QTL Location (on Rnor 6.0) To base pair #	References
14	a	MHS	MNS.MHS	LS	M	D	Y	D14Rat43	D14Wox15	78,446,303	81,093,349	Tripodi et al. (360)
16	a	SS/Jr	S.LEW	HS	M	D	N	D16Rat88	D16Rat21	1,550,330	Unmapped (11,086,530 on Rnor_5.0)	Moujahidine et al. (258a)
16	b	SS/Jr	S.LEW	HS	M	D	N	D16Chm48	D16Chm60	2,471,921	3,525,217	Crespo et al. (52a)
16	c	SHR	SHR.BN	IS	M	D	N	D16Rat87	D16Mgh1	4,136,355	45,905,331	Aneas et al. (7)
16	d	SS/Jr	S.LEW	HS	M	D	N	D16Rat12	D16Chm66	1,090,164	3,439,525	Moujahidine et al. (258b)
17	a	SS/Jr	S.LEW	IS	M	D	N	D17Rat181	D17Rat97	33,209,117	58,467,778	Grondin et al. (123a)
18	a	SHR	SHR.BN	IS	M	D	N	D18Rat113	D18Rat99	3,719,547	32,487,870	Johnson et al. (170a)
18	b	SHR	SHR.BN	IS	M	D	N	D18Rat40	D18Rat82	61,499,531	73,016,546	Johnson et al. (170a)
18	c	SS/Jr	S.LEW	IS	M	D	Y	D18Wox7	D18Rat101	15,539,551	27,743,236	Charron et al. (30)
18	d	SS/Jr	S.LEW	IS	M	D	Y	D18Rat101	D18Chm56	27,743,024	48,499,517	Charron et al. (30)
18	e	SS/Jr	S.LEW	IS	M	D	Y	D18Rat55	D18S481	54,108,375	Unmapped	Charron et al. (30)
19	a	SHR/Ola	SHR.BN-Agt	LS	M	D	N	D19Mit7	D19Rat57	47,318,314	60,220,451	St Lezin et al. (346a)
20	a	SHR	SHR.BN	LS	M	D	N	D20Cebr215s7	D20Rat23	Unmapped (nearest mentioned Tnfα maps to 4,857,203)	21,569,567	Pausova et al. (279a)
X	a	SHR	SHR.BB/OK	unknown	B	I	N	*Ar-Mysc-Pfkb1*	DXMgh3	17,823,554 (location of *Mysc*)	11,969,489	Klöting et al. (185a)
Y	a	SHR	SHR.BN	IS	M	D	N	Consomic (entire chromosome)	Consomic (entire chromosome)	1	3,310,458	Kren et al. (198a)
Y	b	SHRSP	SHRSP.WKY and WKY.SHRSP	IS	M	D	N	Consomic (entire chromosome)	Consomic (entire chromosome)	1	3,310,458	Negrin et al. (236a)

BP QTLs that are reported in the literature are curated by their location on the rat genome and organized by chromosome. For details on strain names, please refer to the Rat Genome Database (www.rgd.mcw.edu). LS, low-salt diet (≤1% NaCl); IS, intermediate-salt diet (1% to <2% NaCl); HS, high-salt diet (≥2% to 8% NaCl); M, male; F, female; B, both genders; I, indirect tail-cuff method for BP measurement; D, direct, telemetry method for BP measurement; B, both tail-cuff method and telemerty for BP measurement.

from the R rat into the S rat. The resultant congenic strain had a significantly lower BP and increased survival compared with the S rats (38). This locus was defined by further substitution mapping to be within 177 kb (**FIGURE 1**, RNO7) (105). Five S and R allelic single nucleotide polymorphisms (SNPs) were identified within the coding region of *Cyp11b1*, all of which were nonsynonymous substitutions (41, 238). Further specific evidence was obtained through site-directed mutagenesis and experiments conducted with artificially constructed chimeric genes of S and R rats to demonstrate that the strain-specific steroid patterns were due to the substitutions in exon 7 coding for amino acid residues 381 and 384 which probably alters the structure of the steroid binding site of the Cyb11b1 enzyme (238, 269).

Mutations in the *CYP11B1* human gene are known to cause rare monogenic forms of inherited hypertension (381, 382). In a limited study of essential hypertension with 160 subjects (12), eight novel missense heterozygous mutations were identified in the *CYP11B1* gene that alters the encoded amino acids: R43Q, L83S, H125R, P135S, F139L, L158P, L186V, and T196A. None of these mutations accounted for hypertension; however, in vitro testing indicated that the variants L158P and L83S severely impaired while R43Q, F139L, P135S, and T196A increased the enzymatic activity of 11β-hydroxylase, suggesting the importance of these affected residues to enzyme function (12), which may point to lack of power for detecting associations. Further evidence for the association of *CYP11B1* in humans, albeit modest, was obtained through a resequencing approach in 560 individuals with extreme systolic BP belonging to the GenNet cohort with European American and African American ancestry (266). Association of *CYP11B1* was detectable only after pooling all coding and noncoding variants at evolutionarily conserved sites (266). An interesting relationship between CYP11B1 and the neighboring gene CYP11B2, encoding aldosterone synthase, was discovered by haplotypic analysis. The pattern of variation across the entire CYP11B locus was determined by sequencing 26 normotensive subjects homozygous for the −344 and intron conversion variants within CYP11B2. Four common haplotypes with 83 variants associated with −344 and intron conversion were identified confirming strong linkage disequilibrium across the region. Two novel CYP11B1 polymorphisms upstream of the coding region (−1889 G/T and −1859 A/G) were identified as contributing to the common haplotypes. Hypertensive subjects (n = 512) from the British Genetics of Hypertension Study population were genotyped for these polymorphisms, and the study strongly suggested that the impaired 11β-hydroxylase efficiency associated previously with the CYP11B2 −344 and intron conversion variants was due to linkage with these polymorphisms in CYP11B1 (12). Overall, the data from all these studies points to both coding and noncoding variants of CYP11B1 as imparting a modest but significant effect (average allelic effect <1 mmHg, P = 0.005), on BP regulation via regulation of steroidogenesis in humans.

V. BEYOND HIGH-RESOLUTION MAPPING: POSITIONAL CLONING OF INHERITED LOCI FOR BLOOD PRESSURE REGULATION

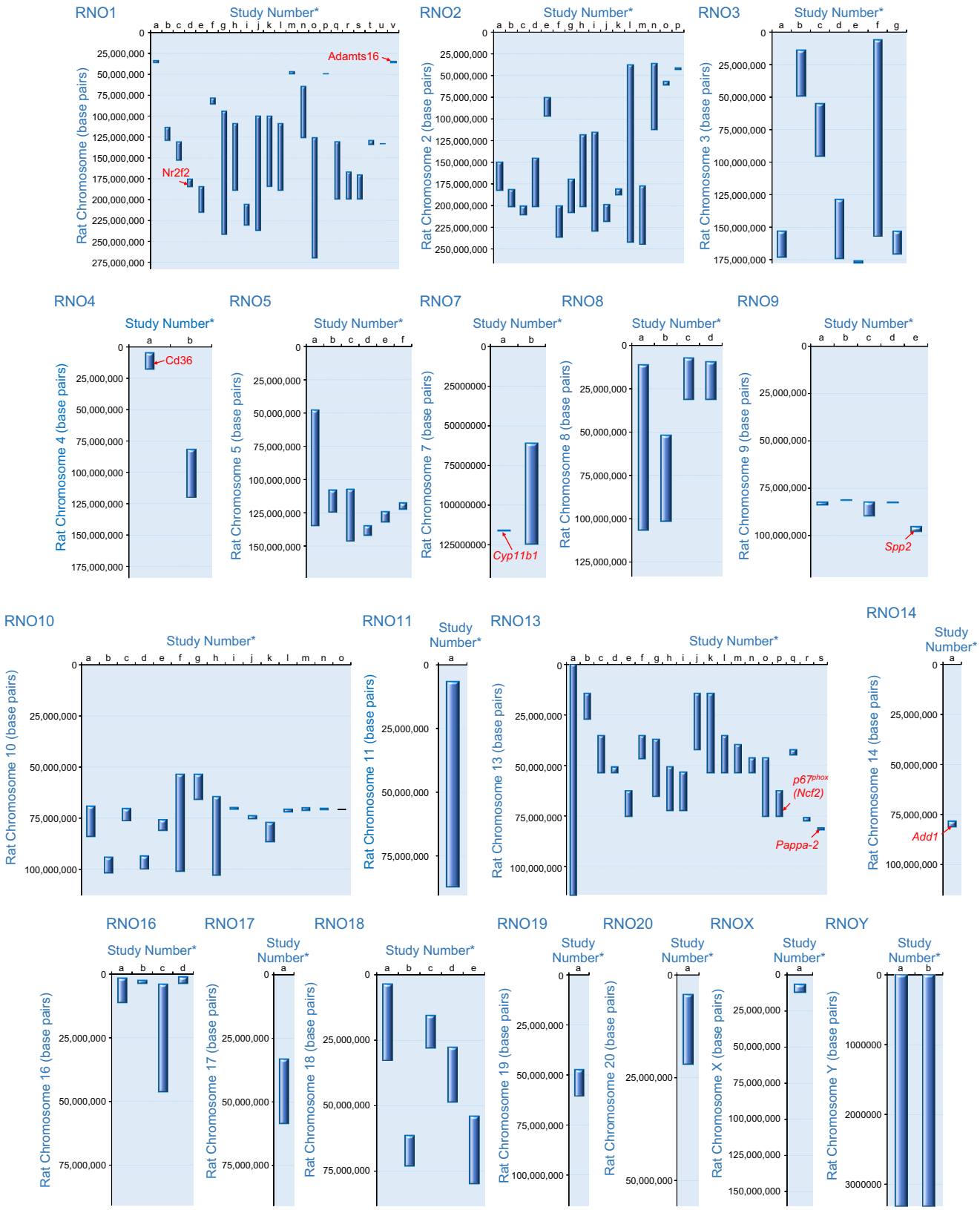
Substitution mapping using congenic strains has been highly successful to resolve BP QTLs from large intervals of a few megabases to, in some cases, very short intervals encompassing less than a megabase or in some cases, a few kilobases (104, 105, 120, 122, 268, 318). However, there are hundreds of variations presenting as candidate quantitative trait nucleotides within each of these highly resolved loci. Further substitution mapping alone is highly unlikely to uncover the precise genetic elements imparting the change in BP because substitution mapping relies on naturally occurring meiotic recombinations, the frequency of occurrence of which is inversely proportional to the size of the genomic segment. In other words, the shorter the congenic interval, the rarer it is for recombinations to occur within that interval. Given this impediment, other complimentary approaches were needed to move the field forward from mapping to positional cloning of BP QTLs.

VI. IDENTIFICATION OF MAPPED BP QTLs WITH COMPLIMENTARY APPROACHES

A. Transcriptome Analysis

Soon after the sequencing of the human genome, prompted by the availability of the microarray technology for quantitatively evaluating gene expression on a large scale, transcriptomic analyses were superimposed with the substitution mapping approach to assess whether candidate genes

FIGURE 1. Regions on the rat genome mapped using substitution mapping. *The letters on the *x*-axis are studies listed with the same alphabet in **TABLE 2**. The *y*-axis of each panel in this figure represents the length of a single rat chromosome. Bars represent the locations of BP QTLs. These locations were determined by searching the Ensembl data (www.ensembl.org) and the rat genome data (www.rgd.mcw.edu) for the rat genome version 6.0. In cases where the locations of the end markers were not available on the rat genome version 6.0, other closest markers or other versions of the rat database were used. Red arrows with names of genes indicate locations on congenic strains where the evidence for the actual gene accounting for the QTL is "strong." Data with mapping ambiguity for positioning markers on the rat genome map are not featured in this diagram.



with QTLs were differentially expressed between a parental strain and a congenic strain. Although this method did not directly test the genomic variation within the QTL segment causing the BP effect, the hypothesis for such studies was that variation within the QTL segment within regulatory regions such as promoters or enhancers could influence the level of expression of a BP QTL gene. The contemplation of applying this technology was prompted by the application of such studies at that time to studies on yeast mutants (349), in mice (79, 175), and in rats (3). With the use of the combinatorial approach of mapping and microarrays, complement factor was identified as a susceptibility locus in a murine model of allergic asthma, *Cr2* as a susceptibility locus for murine systemic lupus erythematosus, and *Cd36* as a locus causing defective fatty acid and glucose metabolism in the SHR (3, 79, 175).

One of the first genes identified using a combinatorial approach of mapping and microarray analyses is a fatty acid transporter called Cd36. Aitman et al. (3) were mapping genes for metabolic syndrome using the SHR rat. They used congenic strains with genomic segments introgressed from the normotensive Brown Norway rat into the SHR background and observed partially reduced insulin resistance of the SHR. The QTL interval affecting glucose and fatty acid metabolism was thereby located to a genomic segment spanning 36 cM on rat chromosome 4 with *Cd36* as a candidate gene at the peak of the QTL (3). The SHR rat had lower expression of *Cd36* and a functional fatty acid transporter deficiency in both adipose tissue and heart. The lower expression of *Cd36* in SHR rats was traced to a genomic deletion within the 3′-untranslated region, the only region represented on the microarray. Congenic substitution of chromosome 4 (including *Cd36*) from the Brown Norway (BN) rat onto the SHR also caused reductions in BP and ameliorated dietary-induced glucose intolerance, hyperinsulinemia, and hypertriglyceridemia. These results demonstrated that a single chromosome region could influence a broad spectrum of cardiovascular risk factors including hypertension and metabolic syndrome. The interpretation that Cd36 was a genetic determinant of BP was thwarted by the analysis of Cd36 genotypes in the stroke-prone SHR strain, which, despite being hypertensive, did not inherit the deletion variant of *Cd36* carried by the SHR. So, for a while, it was inferred that the deletion polymorphism of *Cd36* was not important to the hypertensive phenotype of the SHR (294).

Later however, definitive proof for *Cd36* as a BP QTL was obtained by focusing on the renal expression of *Cd36*. With the use of an integrated renal whole transcriptome profiling experiment coupled with linkage analysis in a BXH/HXB panel of rat recombinant inbred strains developed from SHR and BN rats, *Cd36* was identified as a potential expression QTL (eQTL) linked to BP (156). This evidence was strengthened by the observation that the renal quantitative expression of *Cd36* correlated inversely with arterial BP in these recombinant inbred strains (286). Furthermore, another SHR.BN congenic strain (SHR-Chr.4a subline) with a shorter introgressed segment carrying the wild-type allele for *Cd36* also demonstrated a decrease in BP (**FIGURE 1**, RNO4) (286). To investigate whether selective lack of wild-type *Cd36* in the kidney is sufficient to promote increased BP, renal transplantation experiments were conducted using donor kidneys from either the SHR progenitor that lacks wild-type *Cd36* or from a SHR-TG19 transgenic strain with robust renal expression of wild-type *Cd36* into recipient SHR.BN congenic rats. Rats receiving kidneys from SHR (with mutant Cd36) had significantly higher BP compared with rats that received kidneys from SHR-TG19 transgenic strain (expressing wild-type *Cd36*) (286). These data provided compelling evidence for *Cd36* as a genetic determinant of BP. This conclusion with rat models is also supported with data from *Cd36* knockout mice, which develop hypertension (188). It is to be noted that humans with CD36 deficiency exist, with prevalence of 2–3% reported in Asian and African populations (143, 209). BP of Japanese individuals with CD36 deficiency was reported to be elevated compared with BP in age-matched controls (250). SNPs of CD36 are also reported to be associated with essential hypertension (222) and ischemic stroke (404) among Chinese populations.

CD36 is referred to as a scavenger receptor, but has been demonstrated to transport fatty acids and facilitate the uptake of long-chain fatty acids and oxidized lipids (43, 182, 210). Although the findings from molecular genetic studies clearly demonstrate that a primary defect in fatty acid transport can promote disordered carbohydrate metabolism in the SHR (291) and evidence is mounting (36, 117) for the involvement of CD36 in metabolic dysfunction via signaling pathways such as the c-Jun N-terminal kinase (JNK) activation and Toll-like receptors (182), association of CD36 with endothelial dysfunction (335), and the recognition of Cd36 as a multifunctional immune-metabolic receptor with many ligands (2), the critical question of the precise molecular mechanism impacted by CD36 in the kidney, heart, or blood vessels, to regulate BP, remains unknown.

B. Targeted Gene-Editing Approaches

In 2003, a set of guidelines was suggested (1) to confirm candidates within QTLs beyond the fine-mapping stage to be recognized as bona fide quantitative trait genes (QTGs). Mentioned among these guidelines is the use of knockout and knock-in models (1). While knockout (or null alleles) of a candidate QTL can be used for deficiency-complementation testing, knock-ins can serve the purpose of direct testing of replacement of one allele with another at the candidate QTL to alter BP. Prior to 2009, on one hand, fine-mapping of BP QTLs was steadily progressing, but on the

other hand, specific gene-targeting technology was lagging in the rat (162). In 2009, a major breakthrough was achieved by the creation of the world's first targeted knockout rat using zinc-finger nucleases (115). This discovery paved the way for the assessment of several prioritized genes within fine-mapped BP QTLs to be further examined for their effect on BP in targeted gene deletion models. Although not directly a candidate gene for a BP QTL, as a proof-of-principle for this method to work, renin, a major gene involved in BP regulation, was targeted using the zinc-finger nuclease system and the resultant $Ren^{-/-}$ rats, which had a 10-bp deletion in exon 5, resulting in a frameshift mutation, were demonstrated to have almost 50 mmHg lower BP compared with the heterozygous $Ren^{+/-}$ rats (256).

These studies were conducted by researchers in the Medical College of Wisconsin using the SS/MCW rat. Since then, it is important to point out that the Medical College of Wisconsin led a program for creating knockout genes on the background of the SS/MCW rat. The SS/MCW rat originated from the Dahl S rat and was rederived from (genetically contaminated) SS/JrHsd rats originally obtained as a congenic control strain from Dr. T. Kurtz (University of California-San Francisco) in 1991 (257). At the genomic level, SS/MCW is different from the original colony of inbred Dahl SS/Jr rats maintained at the University of Toledo by ~1,353,492 base pairs (**FIGURE 2A** obtained from the Rat Genome Database, www.rgd.mcw.edu). To assess whether these genetic differences had any effect on BP, BP readings from SS/MCW and SS/Jr rats were both measured under identical housing and dietary conditions in experiments conducted at the University of Toledo. The data presented in **FIGURE 2B** illustrate that these genetic differences cause the systolic BP of SS/MCW rat to be 40 mmHg lower than that of the authentic inbred SS/Jr rat. The situation is particularly unfortunate since in general larger effects of any genetic or environmental manipulations to alter BP in the rat are best accomplished on a very permissive genetic background. The SS/MCW rat is relatively less permissive compared with the SS/Jr based on its BP level. So obviously one has to be careful about choosing "control" strains for genetically engineered SS rats. To be specific, a targeted gene-edited model (disruption, knockout, or knock-in strain) made in the SS/MCW rat should not be compared with SS/Jr rats but only to SS/MCW and a targeted gene-edited model made in the SS/Jr rat should not be compared with SS/MCW rats.

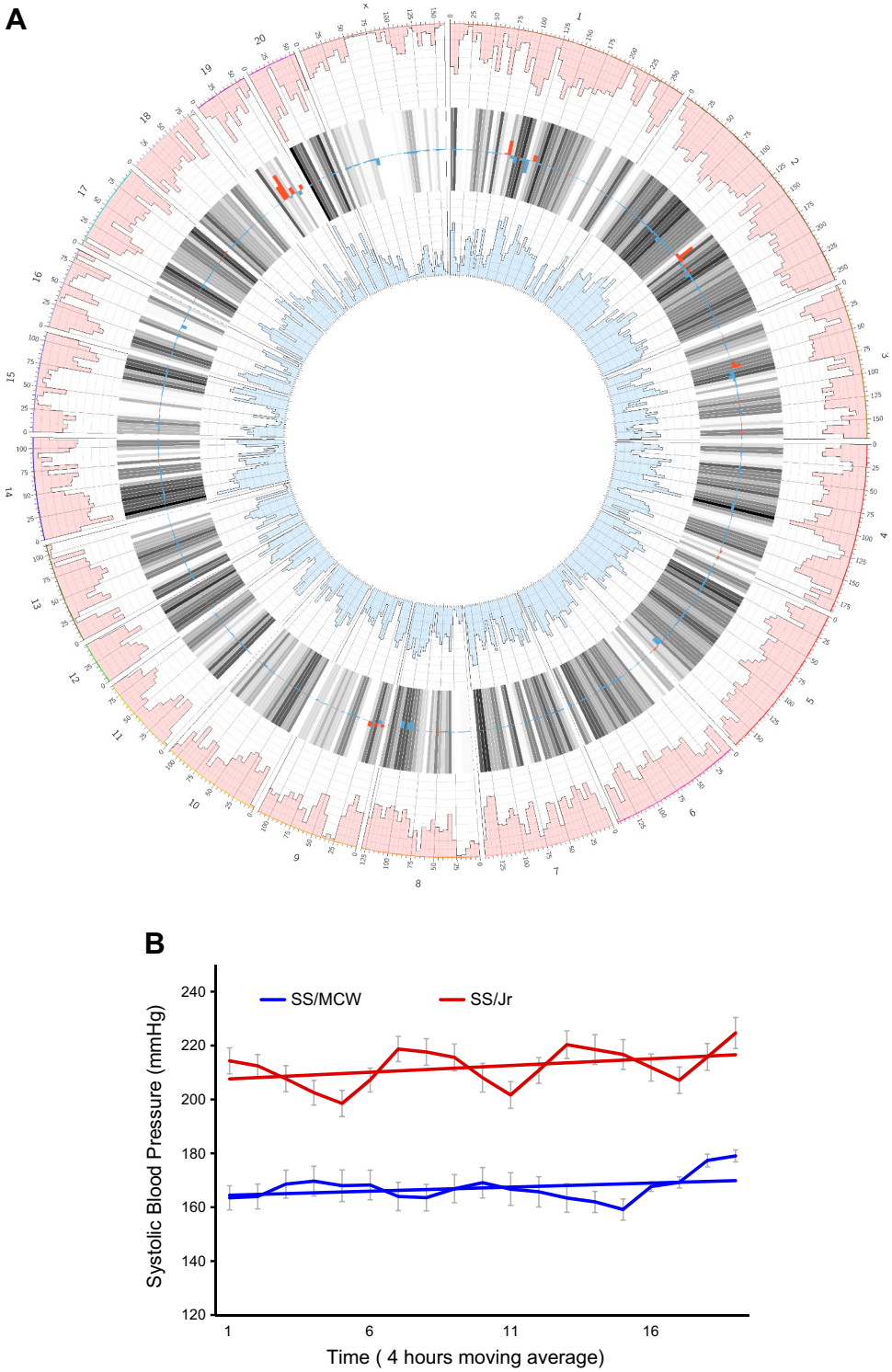
1. A disintegrin-like metalloproteinase with thrombospondin motifs 16 (Adamts16)

The first reported application of the use of the ZFN method for tracking down a BP QTL candidate gene was for the gene *Adamts16* (118). *Adamts16* was a primary candidate gene within a BP QTL located on rat chromosome 1. The QTL was initially detected through a linkage analysis of an F2 population derived from SS/Jr (or S) and normotensive LEW rats (101). By substitution mapping, linkage was confirmed and demonstrated to be due to three independent BP QTLs named QTL1a, QTL1b, and QTL2 (170, 319) (**FIGURE 1**, RNO1). QTL2 was further mapped in multiple iterations and located within 804.6 kb. The primary congenic strain [labeled as S.LEW (D1Mco4) in Ref. 319] had a BP lowering effect of −30 mmHg and the final two congenic strains (labeled as D1Mco4x1x3Bx1 and D1Mco4x1x3Bx2), both spanning 804.6 kb, had BP lowering effects of −14 and −18 mmHg. These strains contained two genes, one of which was *Adamts16,* which harbored two nonsynonymous variants and five synonymous variants (170). *Adamts16* was therefore prioritized as a candidate BP QTL and tested using the ZFN gene-targeting approach. The *Adamts16* gene-edited S rat contained a 17-bp deletion in the first exon, which introduced a stop codon in the transcript. The BP of this $Adamts16^{-/-}$ S rat was significantly lower than that of the S rat, providing additional evidence for the involvement of *Adamts16* in BP regulation (118). Other physiological observations pointed to the vasculature as a potential site of action of *Adamts16* to lower BP. $Adamts16^{-/-}$ rats exhibited significantly lower aortic pulse wave velocity and vascular media thickness compared with S rats. The mechanosensory cilia of vascular endothelial cells from the $Adamts16^{-/-}$ rats were longer than that of the S rats. Furthermore, $Adamts16^{-/-}$ rats survived longer when compared with the S rats. Further studies will be required for a deeper molecular mechanistic understanding of how *Adamts16* impacts BP. The translational significance of this locus as a BP QTL was indicated by the detection of linkage to BP in the Quebec Family Study of a region on human chromosome 5 encompassing ADAMTS16 under the QTL LOD plot (170). While ADAMTS16 was only one of several candidate genes in the linkage analysis, specific SNPs (rs2086310 in particular) within ADAMTS16 were tested and confirmed for association with BP not only in the Quebec Family Study, but also replicated in another cohort, GenNet (170).

2. $p67^{phox}$, a cytosolic subunit of NAD(P)H oxidase

Through mapping experiments conducted using the Dahl SS/MCW and BN rats, four independent genomic regions ranging from 4.5 to 16 Mega basepairs (Mb) were identified on chromosome 13 (257). Each of these BP QTL regions significantly lowered salt sensitivity in the SS/MCW rat (**TABLE 2 AND FIGURE 1**, RNO13) (46). The largest effect among these QTLs was found in a region that overlapped with the original renin gene region first mapped by Rapp (311). The largest region however, spanning 16 Mb, was mapped using a congenic strain $SS.13^{BN26}$, which was reported to be mapped to 12.2 Mb containing $p67^{phox}$, a cytosolic subunit of NAD(P)H oxidase, as a candidate gene. The mRNA expression of *p67phox* was significantly higher in the renal outer medulla of SS/MCW rats

compared with SS.13^{BN26} congenic rats (89). SS/MCW rats had a 204 bp deletion and 4 SNPs within the promoter region of *p67*^{phox} and the promoter activities tested through transfection and luciferase reporter studies in immortalized rat medullary thick ascending limb cells further supported these genetic variances in the promoter region to contribute to higher mRNA expression of *p67*^{phox} in the SS/MCW compared with SS.13^{BN26} (89). To further examine the functional relevance of *p67*^{phox} in salt-sensitive hypertension, a ZFN-based *p67phox* null mutant (*p67*$^{phox-/-}$) rat was generated and tested for BP along with the SS/MCW rat. The *p67*$^{phox-/-}$ rats had a 5 bp deletion in their genomic sequence. *p67phox* being a subunit of NADPH oxidase, an enzyme critical for macrophage respiratory burst activity, macrophage activation in response to phorbol myristate ac-



etate was examined. Respiratory burst activity was completely abolished in the *p67phox* null mutant ($p67^{phox-/-}$) rat compared with controls. Also, salt-sensitive hypertension renal oxidative stress and renal glomerular injury were significantly attenuated in the *p67phox* null mutant ($p67^{phox-/-}$) rat compared with SS/MCW rats (89). These phenotypes were associated with a significantly lower H_2O_2 concentrations in the medullary interstitial fluid of *p67phox* null mutant ($p67^{phox-/-}$) rats. Collectively, authors interpreted these data to suggest that *p67phox* plays a crucial role in the development of salt-sensitive hypertension, which at least in part is due to its effects noted in the kidney. From a mapping standpoint, the region containing *p67phox* is large and cannot be ignored for the presence of other genetic determinants of BP, but the data on *p67phox* are compelling to speculate that it is indeed a genetic determinant of BP. Validation studies will be required to assess the naturally occurring polymorphisms of $p67^{phox}$ as the precise quantitative nucleotide variants causing alterations in BP and renal phenotypes. Authors also indicate that SNPs in human $p67^{phox}$ have not been found in human genetic association studies, but suggest that stratification of populations based on salt sensitivity may serve as a better design to uncover any association of $p67^{phox}$ with human salt-sensitive hypertension.

VII. OTHER GENES PRIORITIZED THROUGH MAPPING STUDIES

A. Pappalysin-2 (Pappa2)

Also known as pregnancy-associated plasma protein-A2, *Pappa2* is a metalloproteinase in the metzincin superfamily. *Pappa2* was prioritized through substitution mapping on rat chromosome 13, using SS/MCW and BN rats (46, 50, 257). The highest resolution reported within which *Pappa2* is mapped is 0.71 Mb (chromosome 13, 81.01–81.72 Mb) containing two other annotations, a protein coding gene *Astn1* and a microRNA *miR-488* (50). BN alleles in this genomic segment lowered salt-sensitive mean arterial BP by 24 mmHg (50). Although no nonsynonymous variants were observed, eight SNPs, five insertions, and two deletion polymorphisms are reported within a 25 kb 5′ upstream sequence of *Pappa2*. Expression of *Pappa2* was eight times higher in the renal cortex of the SS/MCW.BN congenic strain compared with S. By the observation of immunocostaining of Pappa2 with a Na^+-K^+-Cl2 cotransporter (Nkcc2), Pappa2 was more precisely located in the cortical thick ascending limbs of renal proximal tubules (50). Exactly how the upregulation of Pappa2 in the congenic strain protected from elevated BP is not clear. The authors (50) point out that Pappa2 is known as a protease that can cleave Igfbp-5 (insulin-like growth factor binding protein 5) (274, 392) and thereby may regulate hydroxyapatite and insulin-like growth factor (IGF)-1 binding. Clinical associations between Pappa2, IGF-1, hypertension, and cardiovascular risk have also been reported (50, 173, 330, 385). To further support the candidacy of *Pappa2*, validation experiments with gene-edited models to assess the naturally occurring polymorphisms of *Pappa2* will be required.

B. Secreted Phosphoprotein 2 (Spp2)

Substitution mapping of BP QTLs on rat chromosome 9 (**FIGURE 1**, RNO9) led to the prioritization of Spp2 as the sole gene with a nonsynonymous variation. The QTL was mapped using congenic strains developed from the introgression of SHR alleles onto the genome of the S rat, which demonstrated significant lowering of BP and proteinuria (268). A nonsynonymous G/T polymorphism was detected in the Spp2 gene between the S and S.SHR congenic rats. Interestingly, the T allele was rare, being detected from among 45 rat strains, only in substrains of SHR and WKY. Importantly, this polymorphism was potentially pleiotropic, because, in addition to improved cardiovascular and

FIGURE 2. *A*: Circos plots of genomic variant densities between SS/Jr (or S/Jr) and SS/MCW strains of genetically hypertensive rat strains. The outermost ring of numbers 1–20 and X indicate rat chromosomes. The numbers beneath the outer ring that are labels of tick marks represent locations on each chromosome in megabases. The pink-colored outer circumference of Manhattan plots represents the histogram of variants of the SS/MCW strain compared with the rat reference sequence from Brown Norway rat. The blue innermost circumference of Manhattan plots is the histogram of variants of the SS/Jr strain compared with the rat reference sequence from Brown Norway rat. The histograms consist of 10 levels wherein each level represents 2,500 variants. The gray bars in between the 2 histograms (pink and blue) show the average of the 2 densities with darker bars for higher densities. The key data with regard to SS/MCW and SS/Jr strains in this plot are the overlaid red and blue bars over the gray bars. The density of variants is overlaid on the gray average bars with red bars for higher SS/MCW density and blue bars for higher SS/Jr density. The range of density difference from the bottom to the top of a gray bar is minus 12,500 to plus 12,500 variants. This Circos plot was drawn and based on the requested analysis conducted by the Rat Genome Database (www.rgd.mcw.edu). Comparisons of blood pressure (BP) readings from SS/MCW are lower than that of the SS/Jr rats (see **FIGURE 2*B***). Thus this genetic difference could be one of the reasons for this observed relatively lower BP reported for the SS/MCW strain compared with the BP of the SS/Jr strain. *B*: radiotelemetry measurements of systolic BP of male SS/Mcw and SS/Jr rats. Studies were conducted as per IACUC approved protocols at the University of Toledo. Rats were weaned at 28–30 days of age and fed a low-salt (0.3% NaCl) Harlan Teklad diet. At 40–42 days of age, all rats were placed on a 2% NaCl diet and maintained on this diet for 24 days. While on the high-salt diet, rats were surgically implanted with C40 BP radiotelemetry transmitters. Their BP was monitored on day 25 post the high-salt diet regimen by radiotelemetry. The average systolic BP data plotted in this graph were collected from 4 independent BP studies for SS/MCW (total n = 30) rats and 3 independent BP studies from SS/Jr rats (total n = 21). Data points are 4-h moving averages ± SE. The straight lines through the BP data are trend lines.

renal function, high salt fed congenic animals carrying the SHR T variant of Spp2 demonstrated a significantly lower bone mass and altered bone microarchitecture. In addition to Spp2, the mapped congenic segment contains two other genes, Arl4c and Trpm8, but neither of these genes had any nonsynonymous variants (268). The deduced inferences from the current observations on the candidacy of Spp2 are nevertheless translationally interesting because a GWAS study reports an association to systolic BP responses to cold pressor test (34, 243) and salt-sensitivity (243) on human chromosome 2q37 to a region close to SPP2 and TRPM8. An interesting feature to note is that the BP QTL containing Spp2 is mapped between a relatively salt-insensitive hypertensive rat, the SHR, and a salt-sensitive hypertensive strain, the S rat. To formally test these genes, further mapping and application of targeted gene-edited models will be required. If indeed Spp2 presents as a valid BP QTL, targeting this gene will require caution as the protective allele for BP has adverse effects on bone mass.

C. Adducin

A linkage analysis using an F2 population of Milan hypertensive and normotensive rats detected a BP QTL on rat chromosome 14 including the gene Adducin 1 (*Add1*) (398). Adducin is a heterodimer of α- and β-subunits that functions to promote the assembly of actin with spectrin. Milan hypertensive and normotensive rats harbor polymorphisms at the α-adducing locus wherein an A to T polymorphism results in a Y316F substitution and at the β-adducin locus wherein a G to A polymorphism results in a R529Q amino acid substitution in the Milan normotensive strain. These polymorphisms cosegregate with a significant increment in BP of the Milan hypertensive strain (16). Congenic strain analyses (**FIGURE 1**, RNO14) as well as human associations (14, 360) have confirmed that adducin is an important gene implicated in BP regulation. To assess mechanisms, renal function was studied. Polymorphisms of adducin affect the development of glomerular lesions by modulating the expression of podocyte proteins (90). In humans, three polymorphisms within the ADD genes [*ADD1* (Gly460Trp-rs4961), *ADD2* (C1797T-rs4984), and *ADD3* (IVS11+386A>G-rs3731566)] are reported to influence brachial arterial diameter, distensibility, and compliance (331). Physiological interaction between the ADD1 and WNK1-NEDD4L pathways influences the effects of variants in all of these genes on BP and renal sodium handling (234). There was also a strong correlation between endogenous ouabain levels, renal sodium handling in hypertension, and α-adducin polymorphisms (232, 235). Also, adducin polymorphisms in both rats and humans are demonstrated to affect renal cellular endocytosis and Na/K pump activity (359). Much research was since conducted by the Bianchi group (81) that has resulted in clinical trial for rostafuroxin, a selective inhibitor of Src-SH2 interaction with mutant adducin for sodium handling in hypertensives (347). Unfortunately, the results were not encouraging as rostafuroxin did not reduce BP at any dose (347). Polygenic nature of hypertension is perhaps not permissive enough for a single gene effect to be promising. A personalized therapeutic approach is proposed for future approaches to results from single candidate gene analysis for hypertension (233).

VIII. PRIORITIZING CANDIDATE GENES BASED ON HUMAN GENOME-WIDE ASSOCIATION STUDIES

Technological advancements in targeted gene-editing approaches in model organisms were not only useful to validate fine-mapped rat BP loci, but were also favored as an approach to validate genes that were prioritized through genome-wide association studies (GWAS) in humans. GWAS, wherein SNPs associated with disease are detected on a genome-wide scale, are different from linkage studies in that inheritance is not a consideration, because associations are reported among unrelated individuals. Nevertheless, GWAS came into prominence as the next step after the human genome sequence was deciphered. The first genome-wide association study for hypertension was reported in 2007 by the Wellcome Trust Case Control Consortium (WTCCC) (380). The study included ~2,000 cases of essential hypertensives and ~3,000 controls, which, at that time, represented the single largest human association study for hypertension. Surprisingly, no major association was detected with any SNP for hypertension. However, six single-nucleotide polymorphisms (SNPs) were reported as being associated with hypertension with marginal significance (380). Comparative mapping revealed that the homologous locations of four out of these six human SNPs (rs2820037, rs6997709, rs11110912, and rs2398162 on human chromosomes 1q43, 8q24, 12q23, and 15q26) map within regions of the rat genome identified as BP quantitative trait loci (QTL) on rat chromosomes 17, 7, 7, and 1, respectively (101). It is also interesting that among the many strain comparisons that were used for mapping BP QTLs, all four regions are reported as BP QTL containing regions originally identified from a single linkage analysis between the hypertensive Dahl Salt-sensitive (S) rat and the Lewis (LEW) rat (101).

A. Nuclear Receptor 2, Factor 2 (Nr2f2)

The human 15q26 region containing the gene *NR2F2* was tabulated in the supplementary data section of the first human GWAS conducted for hypertension, the WTCCC study (380). The homologous rat chromosome 1 region containing *Nr2f2* was identified as a BP QTL within a 13 Mb region (169, 319) (**FIGURE 1**, RNO1 and **TABLE 2**), whereby *Nr2f2* was also a positional candidate locus (one of many genes within the region) for BP control. The

candidacy of *NR2F2* in human hypertension was further corroborated in humans through a haplotypic analysis of the WTCCC data (26). All these different studies in both humans and rats collectively pointed to *Nr2f2* as a plausible BP QTL, but fell short of providing conclusive evidence. The targeted gene-editing approach was applied to address the question of whether disruption of *Nr2f2* impacts BP of the S rat (206). A ZFN-based *Nr2f2* mutant rat generated for this purpose had a 5-amino acid deletion (Δ amino acid residues159–163) in the hinge region of the Nr2f2 protein. BP of the Nr2f2 mutant rats were significantly lower than that of the S rats. An enhanced binding of the mutant Nr2f2 with the transcription factor Friend of GATA 2 (*Fog2*) was noted. Furthermore, by chromatin immunoprecipitation, an enhanced binding of the mutant form of Nr2f2 to the promotor of atrial natriuretic factor (*Anf*) was observed. *Anf* is a direct target gene influenced by the *Nr2f2-Fog2* interaction (157) and a vasorelaxant (183, 203). Mesenteric arteries from *Nr2f2* mutant rats relaxed better than the S rats. Conclusions from this study were that the extent of BP is inversely linked to the extent of interaction between Nr2f2 and Fog2 through the hinge region of Nr2f2 and through this interaction, transcription of *Anf*, is regulated.

B. Pleckstrin Homology Domain Containing Family A Member 7 (Plekha7)

Five independent GWAS in multiple populations associated the human SNP rs381815 in intron 1 of *Pleckha7* with systolic BP (93, 144, 145, 213, 220). To test this association, the rat Plekha7 gene was mutated by applying the ZFN approach in the SS/MCW rat (85). *Plekha7* mutant S rats had blunted hypertension and renal disease, which the authors attribute to improvements in vascular function because in vitro assays revealed enhanced endothelium-dependent and flow-mediated dilation in the mutant vessels compared with wild-type (WT) controls, which was associated with augmented intracellular calcium release in endothelial cells and an increased bioavailability of the vasodilator nitric oxide. Plekha7 encodes an adherens 84 junction protein (295) and is a cytoplasmic protein reported to stabilize cadherins and nectins at adhesion junctions (124, 193, 195, 279, 332). More recently, PLEKHA7 is reported to regulate cellular behavior via miRNAs by associating with the microprocessor complex at the apical zonula adherens (193, 194). Through a proteomic approach, proteins associating with PLEKHA7 were identified to be cytoskeletal-related and RNA-binding proteins. Loss of PLEKHA7 activates the actin regulator cofilin by regulating the levels and associating with PP1alpha, a phosphatase responsible for cofilin activation (193, 194). Interestingly, cofilin1 is involved in hypertension-induced renal damage (370). Therefore, it is possible that *Plekha7* affects hypertension-induced renal function in addition to the alterations in vascular function detailed in the *Plekha7* mutant SS/MCW rat.

C. Cd247

CD247 encodes the zeta chain of the T-cell receptor. T cells are increasingly being recognized as important in the etiology of salt-sensitive hypertension (60, 134, 366, 386). A large genome-wide human linkage analysis in the GenNet Network of the Family Blood Pressure Program (FBPP) identified a highly significant linkage peak on human chromosome 1q spanning a 100 cM region (354). By genotyping 1,569 SNPs within this linkage peak in 2,379 individuals, associations were found for both systolic and diastolic BP in or near 2 genes, *GPA33* and *CD247*. In *CD247,* a single-nucleotide polymorphism variant in intron 1 is associated with diastolic and systolic BP in hypertensive black and European American subjects (82). Given these associations, *Cd247* was tested as a candidate gene for hypertension through ZFN-mediated deletion of *Cd247* in the SS/MCW rat (316). These mutant *Cd247* rats had no functional T cells and demonstrated significantly lower hypertension, renal disease, and lower infiltration of T cells in to the kidneys in response to dietary high salt (316). Thus authors conclude that Cd247 is an important link between T cell biology and development of hypertension and renal disease (316).

D. Sh2b3

SH2B adaptor protein 3 also known as lymphocyte-specific adapter protein Lnk is a gene nominated as a candidate gene by GWAS of hypertension and renal disease (21, 150, 151, 213). Sh2b3 is an intracellular adaptor protein expressed in hematopoietic and endothelial cells. To test the contribution of Sh2b3 to hypertension in the Dahl SS/MCW rat, a ZFN mutant rat with a 6-bp deletion in the *Sh2b3* gene was generated (317, 408). As a result, the native proline-leucine-glutamic acid sequence is replaced with a single glutamine in the Sh2b3^{em1Mcwi} mutant rat, resulting in modification of the phosphotyrosine-peptide binding pocket of the SH2 domain. BP of the *Sh2b3* mutant Dahl SS/MCW rat was attenuated. Associated with the lowering of BP was reduced renal damage and blunted infiltration of immune cells into the kidney (317). Transplanting bone marrow from *Sh2b3*^{em1Mcwi} mutants to Dahl SS/MCW rats fed a high (2% NaCl) salt diet resulted in a significant decrease in mean arterial pressure and kidney injury (317). Although not proven to be an inherited factor for susceptibility to develop hypertension, studies in *Sh2b3*$^{-/-}$ mice also confirm these functions of Sh2b3, whereby Sh2b3 is recognized as a key gene implicated in the development of hypertension (58).

E. GWAS-Nominated Agtrap-Plod1 Locus

GWAS not only detect single gene associations, but also present with associations to multiple SNPs clustered by

proximity within multiple genes in linkage disequilibrium, thus depriving clarity on which of the closely linked genes are likely to be significant determinants of BP. An example of this in the case of a GWAS for BP in a genomic region on human chromosome 1:11,736,084–11947845bp, containing six genes, *Agtrap*, *Mthfr*, *Clcn6*, *Nppa*, *Nppb*, and *Plod1,* reported in 11 human studies (35, 98, 165, 171, 179, 213, 221, 264, 265, 357, 403). To overcome this limitation of GWAS and to determine the relative contributions of each of these genes to BP regulation, ZFN-based mutant rats were individually constructed and characterized on the Dahl S background (92). The results demonstrated that five of the six genes influence BP and/or renal function (92), indicating that multiple genes within a short genomic segment can individually modulate BP.

IX. HAS RAT GENETICS ADVANCED THE SEARCH FOR INHERITANCE OF HYPERTENSION IN HUMANS?

Taking a broad perspective, it is well to recognize that the fact that rats can be bred for hypertension and for susceptibility to salt-induced hypertension is a profound statement of what phenomena are also likely in human hypertension. While this is easily demonstrated in rats because of the freedom to breed and change the environment for the life of the rat, similar manipulation in humans is impossible. And of course the genetic and salt susceptibility data available from humans are compatible with what is unequivocal in rats. At the time the initial work in rats was done, such results were far from given.

This article began with documenting the quest for inherited factors for the development of hypertension and then cataloged a large number of BP QTLs on almost every chromosome of the rat. These BP QTLs have yielded only a handful of genes that have varied tiers of experimental proof to suggest that inheritance of allelic forms of these protein-coding genes impact BP. In other words, these genes are putative BP quantitative trait genes in rats and perhaps in humans as well. The number of loci mentioned above is relatively small and by no means representative of the entire blueprint of the genetic/inherited factors responsible for BP regulation. What are we missing? Observations made during the course of the mapping studies that are beyond the discovery of SNPs within protein-coding genes are worth noting as they support the reasoning that much remains to be discovered. These observations are listed below.

1. The numbers of BP QTLs identified in either rats or humans far exceeds the number of causative genes identified in these QTLs to date (listed in **TABLE 1**).
2. Variants within protein-coding genes are not the sole variants present within positionally mapped BP QTLs. There are a larger number of variants within any mapped segment that are outside of protein-coding genes or other annotations. These may have unknown effects.
3. Further mapping of BP QTLs that were originally identified as single LOD peaks have demonstrated that underneath each of these single LOD peaks is a cluster of independently operating BP QTLs.
4. Many BP QTLs have also been detected which do not operate independently, but require allelic interactions with other QTLs to impart a change in BP. These observations are mainly in rat genetic studies and provide important clues to the genomic architecture governing the pathophysiology of hypertension in humans. They suggest that inheritance of the level of BP of an individual attributed to major effects of a small number of genes is perhaps a gross underestimation.
5. Ideally the discovery of new genetic inputs to BP control in the rat would lead to new therapies for hypertension in humans. The fact that the work on Adducin did not result in a successful treatment for hypertension (347) does not abrogate the desirability for further work to truly understand the complex genetics of hypertension. In addition, if the same result turns out to be true for all the genes found to be causative for hypertension in the rat on a very permissive (artificially constructed by selective breeding) genetic background, then we need to know that therapeutic targeting of singe genes on a nonpermissive outbred genetic background is an unworkable approach. If that turns out to be true for the genes found using the rat models, then the same situation is likely to be true for any causative genes for hypertension discovered by GWAS in humans.

X. EPISTASIS OF BP QTLs

Epistasis or gene-gene interactions occur when the effect of alleles at one locus depends on the alleles at another locus. In the context of BP studied in rats, such interactions can be discovered in segregating populations by comparing the effect on BP of genotypes at one marker versus the effect on BP of genotypes at another marker. This is done by a two-way factorial analysis of variance and finding a significant interaction term. Note that in an F2 population this analysis will include all three possible genotypes at each marker.

In working with congenic strains for BP QTL on the background of a given strain, epistasis can be defined as the nonadditive effect (positive or negative) when combining two congenic strains into a new double congenic strain. In this case it is important to appreciate that only homozygous genotypes are being compared at the two QTLs involved. The BP of four strains (the background strain, two congenic strains, and the double congenic strain) is required. The analysis of BP again involves a two-way factorial analysis of variance on the genotypes at the QTLs being tested (306). Epistasis is present if this analysis yields a significant interaction term.

One of the early reports of such an epistasis between two BP QTLs was weak statistical evidence for epistasis between two BP QTLs on rat chromosomes 2 and 10 (69). Subsequently, separate congenic strains were constructed on the S background for the appropriate regions of Chr 2 (D2Mit5-D2Mit8) or 10 (D10Mco1-D10Mco6) introgressed from a normotensive strain (66, 73). Evidence for individual effects of these two segments was obtained by the observation that each congenic strain had lower BP than the S rats. However, when a double congenic strain was constructed containing low BP QTL alleles from both chromosomes 2 and 10 and tested for BP, the sum effect of the two regions was smaller than the additive effects of decreasing BP relative to S. This provided definitive evidence for a strong epistatic interaction on BP of the QTL on chromosomes 2 and 10. At that time, this was the only documentation of an interaction on a quantitative trait in a mammalian system (306). Unfortunately, the identities of the two genes in epistasis remain unknown as there are no further reports of mapping of the QTLs involved. Epistasis has been reported for a number of other BP QTLs (29–31, 33, 39, 63, 77, 187, 253, 277, 284, 326, 355). Furthermore, a theoretical modeling study of epistasis of BP QTLs through analysis of data obtained by substitution mapping using congenic rats is reported by Rapp (299). In the case of human hypertension, detections of epistatic relationships are largely limited with the current approach of querying for individual loci that are associated with BP.

In working with Dahl rats in particular, the usual practice is to make congenic strains introgressing QTL segments of chromosome from the normotensive strain into the S-rat genetic background. There is a good reason for this. It is simply that in early work the S-rat genetic background was found to be permissive for finding genetic effects but the R-rat genetic background was not (40, 41, 310). The same is true for the LEW rat background. In this case the LEW background has been studied extensively using congenic strains, by introgressing S rat QTL chromosomal segments (associated with increasing BP) on the LEW background. No or minimal effects on BP were observed (30, 51, 52) even when multiple S rat QTL chromosomal segments were introgressed into the same congenic strain (52). Additional work suggests that a segment on rat chromosome 18 may be important in maintaining low BP in the LEW rat (52). The result of this is that one should not expect the relatively large observable effects of introgressed chromosomal segments on the S genetic background to translate into effects on other genetic backgrounds. Such a profound influence of genetic background is presumably due to epistatic effects.

An attempt has been made to place interacting pairs of QTLs into two "epistatic modules" wherein pairs of QTLs within a module show epistatic effects but pairs of QTLs from different modules show only additive effects (32). Whether such modules are actually a valid concept has been questioned on the basis of biased sampling and lack of a statistical analysis to establish their existence (307). Such objections could be overcome by the systematic collection of further data, but for now the concept, albeit interesting, remains to be adequately supported.

There are some interesting effects of epistasis on dominance in comparing Dahl S rats to LEW rats. An F1 cross between S and LEW has a BP equal to LEW (52), that is, the LEW phenotype is dominant. Interestingly, the LEW alleles at 9 out of 10 BP QTL when studied individually on the S background were dominant to the S alleles (74). This strong dominance is lost in an F2 population derived from S and LEW (101), suggesting that dominance of LEW QTL alleles is highly dependent on genetic background.

When repeated backcrosses of LEW were made to S, it took three backcrosses (after making the initial F1 cross) for the BP of the backcross population to increase only modestly (52), and it was still well below that of S rats. After backcross 3, the population would be expected to have only 6.25% of LEW alleles. This again demonstrates the powerful effect of the LEW background to lower BP. This is surprising because the inbred LEW rats used were never selectively bred for low BP.

The focus on genetic interactions between pairs of QTL is an oversimplification because: 1) a given gene may interact pairwise with several other genes; and 2) higher order interactions exist (128, 353) but have not been addressed in hypertensive rats. A study on higher order QTL interactions involving insulin-like growth factor-1 in mice (128) is especially interesting because the three-locus and four-locus interactions were considerably larger than the component two-locus interactions. One can speculate that S rats might accumulate QTL alleles leading to higher-order interactions increasing BP during selective breeding while the LEW rat would not accumulate (by chance) QTL alleles leading to higher-order interactions decreasing BP because inbred LEW rats were never selectively bred for BP. Thus substitution of a LEW allele on the S background at a QTL that was part of a haplotype creating a higher-order interaction would be expected to disrupt the higher-order interaction and show a disproportionately large effect. In contrast, the reciprocal substitution of an S allele on the LEW background at one of the QTLs in such a complex would not disrupt a higher order interaction that did not exist and would, therefore, be expected to have a lesser effect.

It is anticipated that the genes underlying BP QTL exist in metabolic pathways which eventually impinge on BP and that any given pair is either in series or in parallel. A model for pairwise QTL interactions using congenic strains has been constructed assuming the QTL act like switches that can be either on or off (299). The switches themselves are not imaginary, but are based on the basic biochemical con-

struct of binding curves between two molecules of any type. The binding curves (and therefore the switches) have allelic and metabolic inputs.

FIGURE 3 gives actual data from the literature showing epistatic patterns. It is often convenient in this work to express the effect of a congenic strain as the deviation from the S strain. Thus S rat BP is always at zero, and if a congenic strain decreases (or increases) BP compared with S, the deviation is negative (or positive). This convention is used in **FIGURE 3**, but the reader is advised that sometimes the double congenic is used as a baseline in the literature. This results in a purely technical artifact causing what looks like positive epistasis in one frame of reference to look like negative epistasis in the other, and vice versa (299).

The data in **FIGURE 3*A*** (284) are identical to the pattern predicted if two QTL switches are in parallel, and in both congenic strains the S allelic switch (an on switch) is replaced by a LEW allelic switch (an off switch). The data in **FIGURE 3*B*** (32) are identical to the pattern predicted if two QTL switches are in series, and in both congenic strains the S allelic switch (an on switch) is replaced by a LEW allelic switch (an off switch). Other more common patterns can be simulated by assigning leak properties to the switches under certain logical constraints, but such patterns do not always result in a unique solution as to the relative position of the QTL in metabolic pathways, possibly because most of the QTL involved are not due to a single genetic factor. The point is, however, that the epistatic patterns vary and contain information that can be extracted (299).

Note in **FIGURE 3*A*** that the congenic strains are both on the same chromosome (chromosome 5) and that individually they would be undetectable. The complex was of course found when a QTL on chromosome 5 was dissected by construction of nested congenic substrains from either end of the original congenic segment, resulting in the finding that the effect of the original QTL disappeared when its components were separated (107). The structure and its epistatic effect have been confirmed and the location of the components better defined with the component QTL separated by ~2 Mb (284). If two such subcomponents, each without a BP effect of its own, were on different chromosomes, they could only be discovered by testing genetic markers for interactions throughout the genome in a segre-

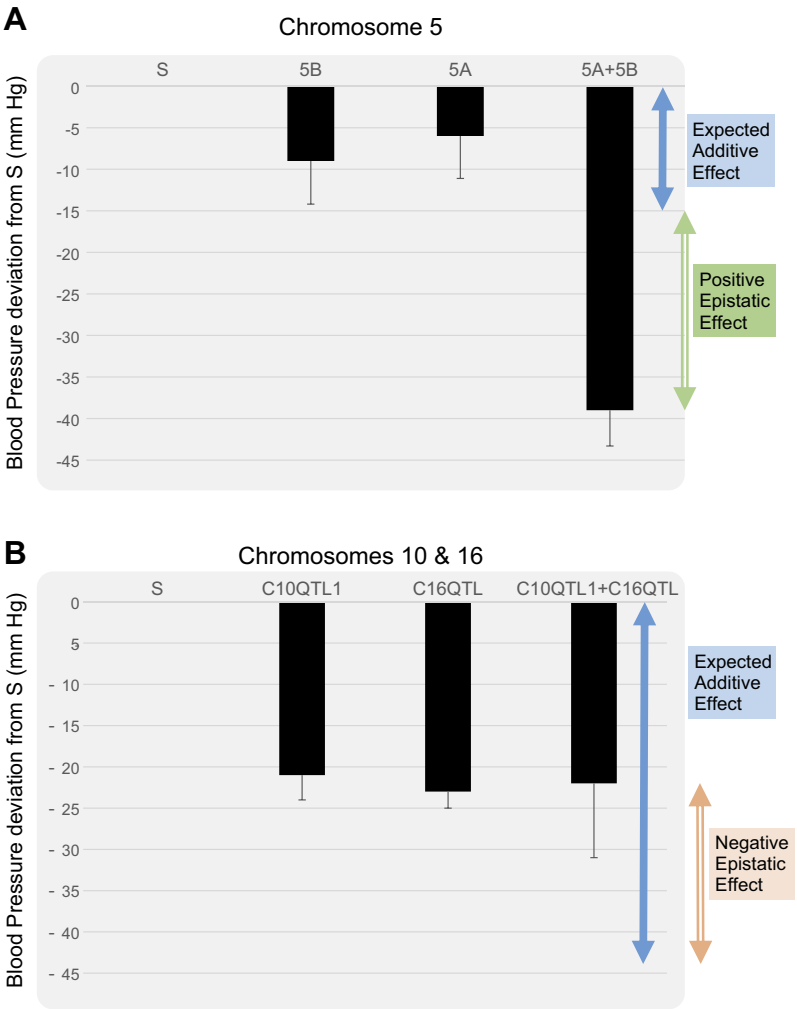


FIGURE 3. Epistatis in rat models. The data in *A* are redrawn from Pillai et al. (284), and the data in *B* are redrawn from Figure 1*D* of Chauvet et al. (39). In each panel BP is given for two congenic strains each for a different QTL and for a double congenic strain which has the introgressed chromosomal segments from both of the original congenic strains. All congenic strains are on the Dahl S genetic background. BP of each congenic strain is expressed as a deviation from Dahl S rats which is defined as the zero point. Blue arrows on the right of the figures show the effect expected if the two QTL effects were additive, and the red arrows show the difference between expected and observed. In both panels the epistatic effects were reported to be significant ($P < 0.05$). The pattern in *A* is compatible with two QTL in parallel metabolic pathways, and the pattern in *B* is compatible with two QTL in series in the same metabolic pathway (299).

gating population. As an aside, the merits of dissecting QTL using nested or contiguous congenic strains has been discussed (308).

Another property of the QTL switches is that one of the inputs is the concentration of one of the ligands, and this of course can vary. This lends itself to inputs subject to metabolic changes induced by environmental challenges or, for example, by sex hormones. The quintessential environmental factor is of course dietary sodium chloride and the changes it induces in the renin-angiotensin-aldosterone system. Dietary salt does increase rat [Na^+] in cerebrospinal fluid (153). One example of a salt-sensitive QTL that alters BP, heart rate, and renal sympathetic nerve activity in response to changes in cerebrospinal fluid [Na^+] is on chromosome 10 (152). Dietary salt also markedly influences the mRNA for the strong candidate gene *Pappa2* on chromosome 13 noted above (50). Suppression of aldosterone by dietary salt is also necessary for the steroid changes resulting from the *Cyp11b1* polymorphism between S and R rats to be effective (304). Dietary factors other than salt are also known to influence BP in the Dahl S rat (239, 240), and sex-dependent QTL are also known in the this model (67, 138, 139).

One thing that has not been done intensively enough in work with hypertensive rats is to look systematically for two-way interactions between genetic markers throughout the genome, similar to studies in other model organisms (154, 229, 358), although the techniques used in some model organisms are not always applicable to the rat. Higher order interactions on BP in the rat also need to be sought. In the original study of an F2 population derived from S and LEW, several QTL interactions were found by testing markers against each other, but this was not extensive enough to uncover larger scale networks of interactions (101). Programs for this that would be applicable to the rat have been developed (329, 362), and one was used successfully in a time study of urinary albumin excretion (UAE) using a backcross population F1(SxSHR)xS. In this study 11 pairwise interactions were observed, most of which were age dependent (100). Viewed in the context of variable environmental and metabolic inputs into the statistical existence and presumed associated functional importance of QTL, the expression of QTL and interaction networks can be viewed as somewhat ephemeral.

Most of the QTL in the Dahl S rat that have been extensively dissected by substitution mapping using congenic strains have (as predicted) turned out to be compound (contain multiple loci harboring alleles with both positive, negative, and interactive effects on BP). Having dissected the QTL into components, we now need to understand why clusters of interacting loci influencing BP (that is, the observable QTL) in a genome scan of a segregating population exist in the first place. It is interesting that it was relatively easy to obtain Dahl S rats with hypertension by only several generations of selection (56) in spite of the fact that many genes are involved. This implies, although it seems unlikely, that haplotypes favoring high (or low) BP in relatively few chromosomal segments (equates to already known compound QTL) should exist in the outbred Sprague-Dawley rats from which Dahl rats were selected. Or, more likely, it could be that compound QTL are in a sense an artifact of the selection process, during which highly interactive alleles for increased BP (in the case of the S rat) are assembled relatively quickly by chromosomal crossover events into hypertensive haplotypes where the loci involved happen to be loosely linked. This would explain why essentially all observable BP QTL turn out to be compound QTL. The same perspective could be applied to compound QTL found in studies by crossing any selectively inbred strains for any trait.

It hardly seems likely that an essential hypertensive human is genetically assembled by the chance association of alleles each with a BP effect of about +1 mmHg at 25 or more loci (as GWAS studies would lead us to contemplate) and that this could result in a 15–20% prevalence of hypertension in human populations. In any case it appears that we are missing some fundamental genetic phenomenon in rats and humans. That "missing something" is probably our lack of an adequate understanding of the complex architecture of genetic interactions.

Unlike in rat models, genetic background is not taken into consideration as a critical factor in human studies, so candidate genes in epistasis are not detected, let alone validated in any other species. The status of human research into finding loci linked or associated with hypertension is captured in the following sections describing studies conducted in humans that encompass investigations on monogenic forms of hypertension and more recent queries on a genome-wide scale for individual loci that are associated with BP.

XI. GENETIC STUDIES OF HUMAN HYPERTENSION AND HYPOTENSION

Diseases or traits can be broadly classified as common (complex, polygenic) or simple (Mendelian, monogenic). Simple traits are attributed to dysfunction of a single gene, whereas a complex interplay of genetic and environmental factors contribute to the pathogenesis of common diseases (sometimes referred to as multifactorial inheritance). Genetic variants with large effect sizes manifest as Mendelian or single-gene disorders, accounting for only a small fraction of cases in the population and manifest in infancy and early adulthood. Mendelian disease mutations are highly penetrant and under a very strong selection, which ensures lower frequencies in populations. Tracing patterns of genetic segregation in fam-

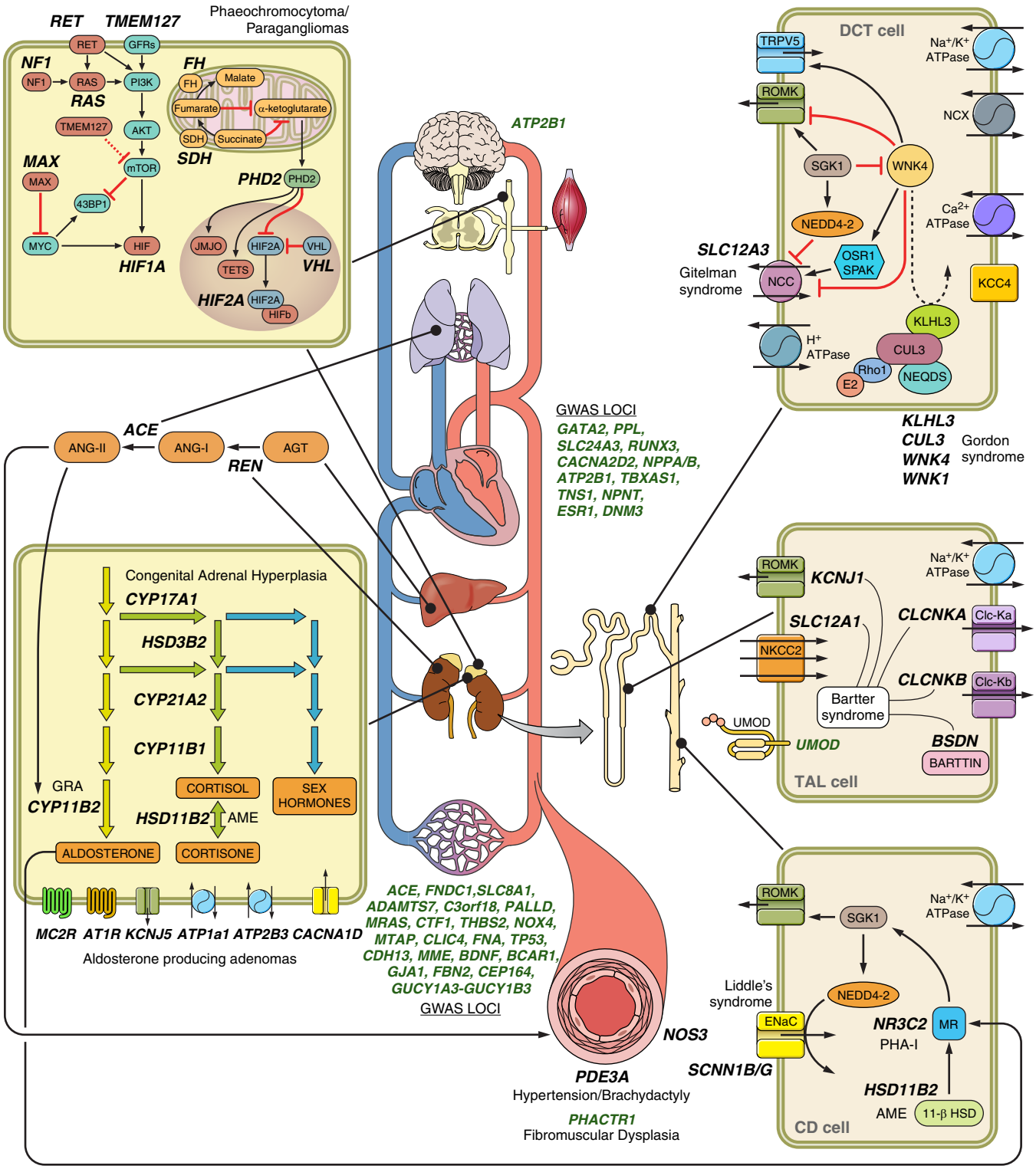


FIGURE 4. Mutations altering blood pressure in humans and GWAS loci linked to plausible genes. The figure shows the circulatory system and pathways that modulate blood pressure containing genes with known mutations that cause monogenic high or low blood pressure syndromes. In addition, plausible genes linked GWAS loci are shown based on multiple lines of evidence (eQTL or nonsynonymous SNPs or genome-wide 3D proximity maps) (374).

Table 3. *Monogenic disorders of blood pressure regulation with characteristic clinical features and treatment*

Syndrome	Subtypes	Inheritance	Locus	Gene	BP	Renin	Aldosterone	Serum K^+	Catecholamines	Treatment
Liddle's syndrome	MIM 177200	AD	16p12.2	*SCNN1B-SCNN1G*	↑↑	↓↓	↓↓	↓↓	—	Amiloride or triamterence.
Gitelman syndrome	MIM 263800	AR	16q13	*SLC12A3*	↓↓	↑↑	—	↓↓	—	Oral potassium and magnesium supplementation with adequate salt and water.
Bartter syndrome	Type 1 "antenatal" MIM 601678	AR	15q21.1	*SLC12A1*	↓↓	↑↑	↑↑	↓↓	—	Potassium supplementation and use of cyclooxygenase inhibitors, angiotensin converting enzyme (ACE) inhibitors, and potassium sparing diuretics.
	Type 2 "antenatal" MIM 241200	AR	11q24.3	*KCNJ1*						
	Type 3 "antenatal"	AR	1p36.13	*CLCNKB*						
	Type 4a MIM 602522	AR	1p32.3	*BSND*						
	Type 4b (digenic) MIM 613090	AR	1p36.13	*CLCNKA, CLCNKB*						
	Type 5 antenatal MIM 300971	AR	Xp11.21	*MAGED2, MAGED, BARTS5*						
Familial hyperaldosteronism (FH)	FH type 1, or glucocorticoid remediable aldosteronism MIM 103900	AD	8q24.3	*CYP11B1*	↑↑	↓↓	↑↑	↓	-	Dexamethasone
	FH type 2 MIM 605635	AD	7p22.3—7p22.1							
	FH type 3 MIM 613677	AD	11q24.3	*KCNJ5*						
Apparent mineralocorticoid excess (AME)	MIM 218030	AR	16q22.1	*HSD11B2*	↑↑	↓↓	↓↓	↓↓	—	Low sodium diet and spironolactone
Pseudohypoaldosteronism (PHA)	PHA1A MIM 177735	AD	4q31.2	*NR3C2*	↓↓	↑↑	↑↑	↑↑	—	Thiazide diuretics, prostaglandin inhibitors, alkalizing agents, and potassium-binding resins.
	PHA2B "Gordon syndrome" MIM 614491	AD	17q21.2	*WNK4*	↑↑	↓↓	↑	↑	—	
	PHA2C "Gordon syndrome" MIM 614492	AD	12p12.3	*WNK1*						
	PHA2D "Gordon syndrome" MIM 614495	AD/AR	5q31.2	*KLHL3*						
	PHA2E "Gordon syndrome" MIM 614496	AD	2q36.2	*CUL3*						

Continued

Table 3.—*Continued*

Syndrome	Subtypes	Inheritance	Locus	Gene	BP	Renin	Aldosterone	Serum K^+	Catecholamines	Treatment
Sporadic aldosterone-producing adenoma (APA), or primary aldosteronism		AD AD AD Xq28	11q24.3 1p31.1 3p21.3 *ATP2B3*	*KCNJ5* *ATP1A1* *CACNA1D*	↑↑	↓↓	↑↑	↓	—	Surgery, aldosterone antagonists.
Hypertension exacerbation in pregnancy	MIM 605115	AD	4q31.2	*NR3C2*	↑↑	↓↓	↓↓	↓	—	Spironolactone contraindicated; sodium chloride treatment.
11β-Hydroxylase	MIM 202010	AR	8q21	*CYP11B1*	↑↑	↓↓	↓↓	↓↓	—	Glucocorticoid therapy.
3β-Hydroxysteroid dehydrogenase	MIM 613890	AR	1p12	*HSD3B2*	↑↑	↓↓	↓↓	↓↓	—	Glucocorticoid therapy.
17α-Hydroxylase deficiency	MIM 202110	AR	10q24.3	*CYP17A1*	↑↑	↓↓	↓↓	↓↓	—	Glucocorticoid therapy, potassium sparing diuretics.
21-Hydroxylase deficiency	MIM 201910	AR		*CYP21A2*	↑↑	↓↓	↓↓	↓↓	—	Glucocorticoid therapy.
Hypertension and brachydactyly syndrome	Bilginturan syndrome MIM 112410	AD	12p12.2	*PDE3A*	↑↑	—	—	—	—	Possible role for PDE3 inhibition
Paragangliomas (PGL)	Paragangliomas 1 MIM 168000	AD	11q23.1	*SDHD*	↑↑	—	—	—	↑↑	Surgery, adrenergic blockers (alpha-blockade followed by beta-blockade).
	Paragangliomas 2 MIM 601650	AD	11q12.2	*SDHAF2*						
	Paragangliomas 3 MIM 605373	AD	1q23.3	*SDHC*						
	Paragangliomas 4 MIM 115310	AD	1p36.13	*SDHB*						
	Paragangliomas 5 MIM 614165	AD	5p15.3	*SDHA*						
von Hippel–Lindau syndrome	MIM 193300	AD	3p25.3	*VHL*	↑↑	—	—	—	↑↑	
Multiple endocrine neoplasia, type IIA	MIM 171400	AD	10q11.2	*RET*	↑↑	—	—	—	↑↑	
NOS3-pregnancy-induced hypertension	MIM 163729	AD	7q36.1	*NOS3*	↑↑	—	—	—	↑↑	

↑, Increase; ↓, decrease; —, no effect.

Table 4. *Summary of all GWAS results for BP and hypertension in different ancestries*

				Coded Allele Frequency			BP Effect			
Locus	SNP	Genotype	Coded Allele	European	Asian	African	European	Asian	African	Nearest Gene(s)
1p36.2	rs880315	C/T	C	0.35	0.59	0.16	↑	↑		*CASZ1*
1p36.22	rs17367504	A/G	G	0.17	0.10	0.06	↓	↓		*MTHFR, CLCN6, NPPA, NPPB*
	rs5068	C/T	C	0.07	0.00	0.01	↓			
1p13.2	rs2932538	C/T	C	0.73	0.80	0.85	↓			*SLC16A1, CAPZA1, ST7L, MOV10*
	rs17030613	A/C	C	0.19	0.45	0.05		↑		
	rs10745332	A/G	A	0.74	0.81	0.77		↑		
1q32.1	rs2169137	C/G	G	0.74	0.94	0.80	↑			*MDM4*
1q42.2	rs2004776	A/G	A	0.26	0.67	0.54	↑			*AGT*
2p23.2	rs1275988	A/G	A	0.60	0.23	0.08	↓			*KCNK3*
2q11.2	rs7599598	A/G	A	0.57	0.63	0.09	↓			*FER1L5*
2q24.3	rs1446468	A/G	A	0.53	0.47	0.96	↓			*FIGN*
	rs13002573	A/G	G	0.25	0.40	0.11	↓			*FIGN*
	rs16849225	C/T	C	0.75	0.59	0.94		↑		*FIGN*
	rs6749447	G/T	G	0.28	0.72	0.58	↑			*STK39*
2q32.1	rs16823124	A/G	A	0.23	0.51	0.10	↑			*PDE1A*
3p25.3	rs347591	G/T	G	0.33	0.23	0.51	↓			*HRH1-ATG7*
3p24.1	rs13082711	C/T	T	0.80	0.94	0.96	↓			*SLC4A*
	rs820430	C/T	T	0.64	0.40	1.00	↑			
3p22.1	rs9815354	A/G/T	A	0.23	0.12	0.17	↑	↑		*ULK4*
	rs3774372	C/T	T	0.77	0.87	0.81	↓			
	rs1717027	C/T	T	0.22	0.12	0.66	↑			
3p21.31	rs319690	A/G	A	0.51	0.75	0.41	↑			*MAP4*
	rs7651237	A/G	G	0.64	0.94	0.88	↑			
3p21.1	rs9810888	G/T	G	0.53	0.59	0.46		↑		*CACNA1D*
3q26.1	rs16833934	A/G	G	0.37	0.17	0.65	↓			*MIR1263*
3q26.2	rs419076	G/T	T	0.48	0.13	0.57	↑			*MECOM*
4q12	rs871606	A/G	A	0.87	0.78	0.76	↑	↑		*CHIC2*
4q21.21	rs16998073	A/T	T	0.19	0.30	0.05	↑	↑		*FGF5*
	rs1458038	A/G	A	0.27	0.34	0.05	↑			
4q24	rs13107325	A/C/T	T	0.10	0.00	0.00	↓			*SLC39A8*
4q25	rs6825911	C/T	C	0.20	0.48	0.54		↑		*ENPEP, PITX2*
4q32.1	rs13139571	A/C	C	0.74	0.68	0.88	↑			*GUCY1A3-GUCY1B3*
5p13.3	rs1173771	C/T	C	0.51	0.57	0.81	↑			*NPR3-C5orf23*
	rs7733331	C/T	T	0.50	0.42	0.42	↓			
	rs1173766	C/T	C	0.52	0.59	0.62		↑		
5q33.3	rs11953630	A/C/T	T	0.34	0.06	0.15	↓			*EBF1*
6p22.2	rs1799945	C/G	G	0.18	0.04	0.00	↑	↑		*HFE*
	rs198823	G/T	T	0.65	0.23	0.60	↓			
6p21.33	rs805303	C/T	C	0.70	0.57	0.30	↑			*BAG1*
	rs2021783	C/T	C	1.00	0.81	1.00		↑		*CYP21A2*
6p21.32	rs2854275	G/T	T	0.08	0.03	0.08	↓			*HLA-DQB1*
6p21.1	rs10948071	C/T	T	0.70	0.67	0.05	↓			*CRIP3*
6q22.33	rs13209747	C/G/T	T	0.45	0.48	0.12	↑	↑	↑	*RSPO3*
6q25.1	rs17080102	C/G	C	0.06	0.01	0.09	↓	↓	↓	*PLEKHG1*
7p15.2	rs17428471	G/T	T	0.08	0.05	0.14	↑	↑	↑	*EVX1-HOXA*
7p12.3	rs2949837	A/T	A	0.23	0.61	0.00	↑			*IGFBP3*
7q21.2	rs2282978	C/T	C	0.36	0.06	0.43	↑			*CDK6*

Continued

Table 4.—*Continued*

Locus	SNP	Genotype	Coded Allele	Coded Allele Frequency			BP Effect			Nearest Gene(s)
				European	Asian	African	European	Asian	African	
7q22.3	rs17477177	C/T	T	0.72	0.91	0.93	↓			*PIK3CG*
	rs12705390	A/G	G	0.72	0.91	0.93	↓			
7q36.1	rs3918226	C/T	T	0.10	0.00	0.00	↑			*NOS3*
8p23.1	rs4841569	A/G	G	0.57	1.00	0.89	↑			*BLK-GATA4*
	rs2898290	C/T	C	0.58	0.02	0.55	NR			
8q24.12	rs2071518	C/T	T	0.20	0.19	0.60	↑			*NOV*
10p12.31	rs11014166	A/T	A	0.63	0.97	0.89	↑	↓		*CACNB2*
	rs1813353	A/G	A	0.65	0.92	0.85	↑			
	rs4373814	C/G	G	0.63	0.53	0.43	↓			
	rs12258967	C/G	C	0.64	1.00	0.73	↑			
10q21.2	rs1530440	C/T	T	0.16	0.20	0.02	↓			*c10orf107*
	rs4590817	C/G	G	0.82	1.00	0.82	↑			
	rs12244842	G/T	T	0.25	0.19	0.35	↓			
	rs7070797	A/G	A	0.15	0.00	0.00	↓			
10q22.2	rs4746172	C/T	C	0.23	0.56	0.19	↑			*VCL*
10q23.33	rs932764	A/G	G	0.43	0.58	0.15	↑			*PLCE1*
10q24.32	rs1004467	C/T	T	0.92	0.67	0.81	↑			*CYP17A1-NT5C2*
	rs11191548	C/T	T	0.92	0.72	0.99	↑	↑		
	rs12413409	A/G	G	0.92	0.72	0.98		↑		
	rs4409766	C/T	T	0.93	0.78	0.82		↑		
	rs3824755	C/G	C	0.07	0.23	0.17	↓			
10q25.3	rs2782980	C/T	T	0.27	0.15	0.44	↓			*ADRB1*
	rs7076938	C/T	C	0.33	0.17	0.45	↓			
	rs1801253	C/G	G	0.32	0.15	0.41	↓			
11p15.5	rs661348	C/T	C	0.45	0.58	0.11	↑			*LSP1-TNNT3*
11p15.4	rs7129220	A/G	G	0.89	1.00	0.95	↓			*ADM*
11p15.1	rs381815	A/C/T	T	0.30	0.25	0.18	↑			*PLEKHA7*
	rs757081	C/G	G	0.63	0.66	1.00	↑			*PIK3C2A, NUCB2, NCR3LG1*
11p15.2	rs2014408	C/T	T	0.20	0.21	0.03	↑	↑	↑	*SOX6*
	rs4757391	C/T	C	0.18	0.17	0.23		↑		
11q13.1	rs4601790	A/G	G	0.25	0.42	0.07	↑			*EHBP1L1*
	rs3741378	A/G	A	0.15	0.38	0.36	↓			*RELA*
11q22.1	rs633185	C/G	G	0.68	0.55	0.82	↓			*FLJ32810-TMEM133*
11q24.3	rs11222084	A/T	T	0.40	0.07	0.26	↑			*ADAMTS8*
12q13.13	rs7297416	A/C	C	0.25	0.62	0.38	↓			*HOXC4*
12q21.33	rs11105354	A/G	G	0.12	0.42	0.11	↓			*ATP2B1*
	rs2681492	A/G	A	0.88	0.58	0.84	↑			
	rs2681472	C/T	T	0.88	0.58	0.89	↑	↑		
	rs17249754	A/G	G	0.88	0.59	0.84	↑	↑		
12q24.12	rs3184504	C/T	T	0.45	0.00	0.00	↑			*SH2B3*
	rs653178	A/G	A	0.56	1.00	1.00	↓			
12q24.13	rs11066280	A/T	T	1.00	0.75	1.00		↑		*RPL6-ALDH2*
12q24.21	rs35444	C/T	T	0.59	0.73	0.55	↑			*TBX5-TBX3*
	rs2384550	A/G	A	0.37	0.09	0.34	↓			
	rs10850411	C/T	T	0.72	0.46	0.66	↑			
	rs1991391	C/T	C	0.64	0.91	0.58	↑			
	rs11067763	A/G	A	0.89	0.61	0.65		↑		*MED13L*

Continued

Table 4.—*Continued*

Locus	SNP	Genotype	Coded Allele	Coded Allele Frequency			BP Effect			Nearest Gene(s)
				European	Asian	African	European	Asian	African	
15q21.1	rs1036477	A/G	G	0.10	0.42	0.61	↓			*FBN1*
15q24.1	rs6495122	A/C	A	0.38	0.78	0.78	↑			*CYP1A1-ULK3*
	rs1378942	G/T	G	0.32	0.79	1.00	↑			
15q24.2	rs11072518	C/T	T	0.34	0.42	0.44	↑			*COX5A*
	rs1133323	A/G	A	0.59	0.17	0.00	↓			
15q26.1	rs2521501	A/T	T	0.63	0.93	0.80	↑			*FURIN-FES*
16p12.3	rs13333226	A/G	G	0.18	0.05	0.38	↑			*UMOD*
16q22.1	rs33063	A/G	A	0.19	0.15	0.00	↑			*NFAT5*
17q21.31	rs12946454	C/T	T	0.71	0.62	0.80	↑			*PLCD3*
17q21.32	rs17608766	C/T	T	0.91	1.00	1.00	↓			*GOSR2*
17q21.33	rs12940887	C/T	T	0.41	0.09	0.03	↑			*ZNF652*
	rs16948048	A/G	G	0.42	0.09	0.42	↑			
20p12.2	rs1327235	A/G	G	0.52	0.48	0.53	↑			*JAG1*
	rs1887320	A/G	A	0.58	0.43	0.54		↑		
20q13.32	rs6015450	A/G	G	0.07	0.00	0.22	↑			*GNAS-EDN3*
	rs6092743	A/G	A	0.06	0.00	0.06	↑			*C20orf174*
	rs12244842	G/T	T	0.25	0.19	0.35	↓			
	rs7070797	A/G	A	0.15	0.00	0.00	↓			

BP, blood pressure; ↑, increase; ↓, decrease.

ilies have been used successfully in Mendelian diseases as exemplified by discoveries using linkage analysis.

Susceptibility variants involved in common (complex) diseases/traits, unlike monogenic traits, do not have high penetrance, are not under a strong selection, and present with lower allelic heterogeneity. Nevertheless, previous selection can be a factor in hypertension, which is a modern disease and could very well be an undesirable pleiotropic effect of a preserved genotype that was perhaps optimized for fitness in the ancient environment. Compared with populations of European ancestry, susceptibility to develop hypertension is higher in people of African ancestry (27). Ancestral sodium-conserving alleles are more prevalent in people of African origin, who also demonstrate increased rates of hypertension and sodium sensitivity (262, 379, 396). These variants may have exerted significant adaptive phenotypic effects in the past, for example, in the time of low salt intake, and now under changed environmental circumstances may have become maladaptive.

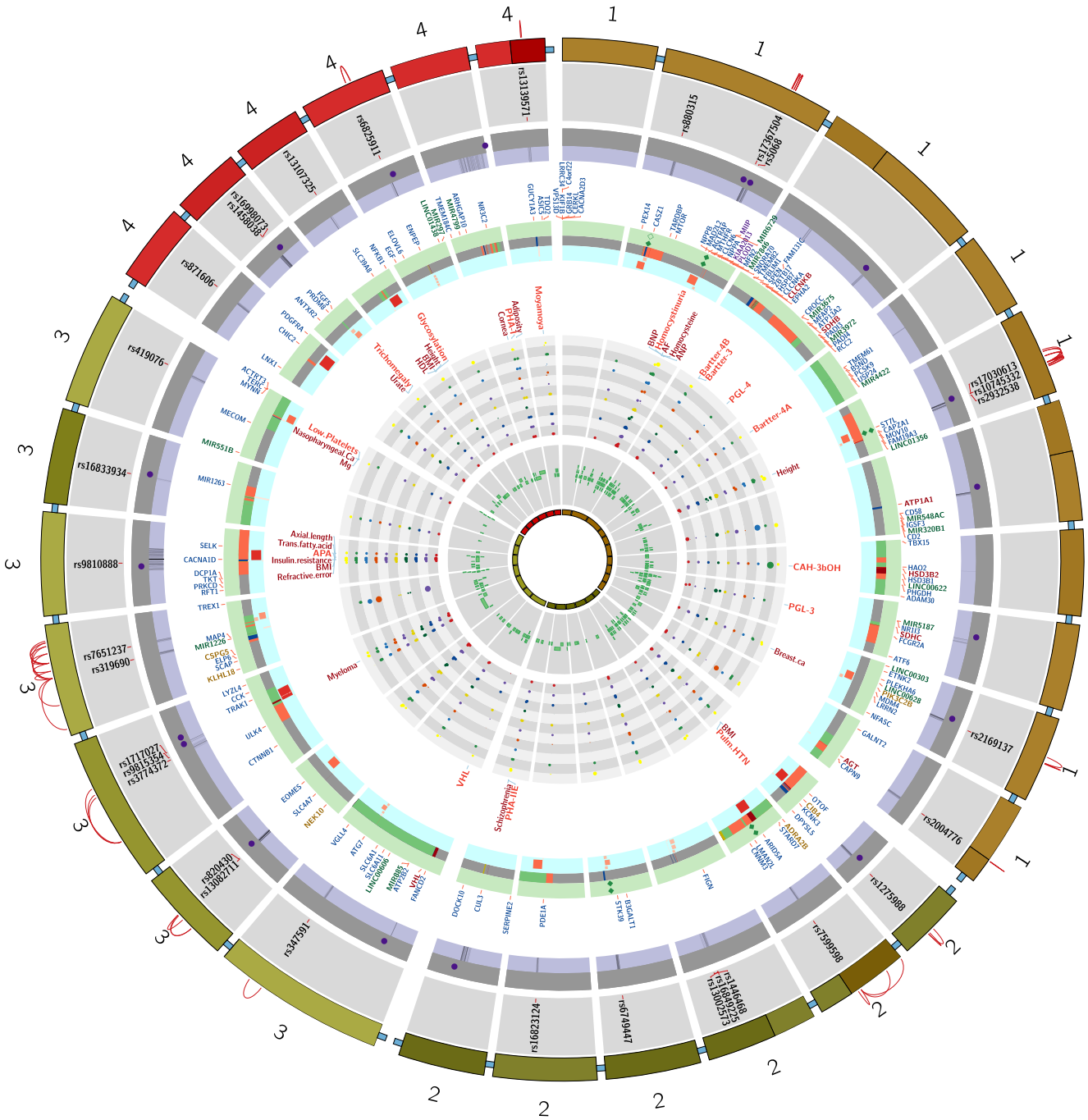
The role of genetics in human BP regulation and hypertension was established through family and twin studies which showed a significantly higher risk of hypertension among subjects with one or two hypertensive parents, and a greater correlation of BP levels in monozygotic twins compared with dizygotic twins (178, 281) (see sect. II). The distribution of BP in the population shows a normal unimodal pattern which supports a complex multifactorial basis of BP regulation. GWAS are the standard methods for genetic dissection of complex traits, which is based on the common disease/common variant hypothesis stated as follows: "the genetic variants underlying complex traits occur with a relatively high frequency (>1%), have undergone little or no selection in earlier populations and are likely to date back to >100,000 yr ago" (216). The spectrum of genetic variants and their target tissues that affect blood pressure regulation are summarized in **FIGURE 4**.

A. Monogenic Pathways of BP Regulation and Hypertension

Discovery of the monogenic Mendelian forms of hypertension has mainly been through positional cloning using large family pedigrees, with multiple members of the family showing a clear inheritance pattern. Patients with these types of disorders represent <1% of the hypertensive population and are considered to have secondary hypertension. Mutations causing monogenic hypertension are characterized by being rare with a major defect that usually disrupts a single pathway. Despite the complexity and the presence of several systems and physiological pathways that control BP, the majority of mapped monogenic hypertension syndromes are due to mutations in genes that play key roles in renal-sodium handling (228, 369), which have contributed enormously to our understanding of salt and water homeostasis and blood pressure regulation. **TABLE 3** summarizes the different forms of monogenic hypertension, their key features, and causal genes.

B. Polygenic Pathways of BP Regulation and Hypertension

Several GWAS have been conducted using BP as a quantitative trait, or by using a binary definition of hypertension. All the significant GWAS signals are summarized in **TABLE 4**, and additional unpublished efforts are ongoing to discover more common variants associated with BP using larger and larger population samples. The first GWAS was a case-control design from the WTCCC, published in 2007 (380). The study examined seven common complex diseases using 2,000 cases each and 3,000 shared controls. The study genotyped ~500,000 SNPs using the 500 K Affymetrix SNP chip and reported a total of 24 significant disease-SNP association signals ($P < 5.0 \times 10^{-7}$). Hypertension was the only trait without any significant association signal across the genome. Following this a series of large collaborative GWAS (95, 160, 180, 213, 214, 227, 276, 321, 367) with increasing sample sizes and in different ancestries resulted in the discovery of several common SNPs associated with BP and hypertension. The largest of these was the International Consortium for Blood Pressure genome-wide association studies (ICBP-GWAS) which conducted a GWAS meta-



analysis for systolic and diastolic BP in >69,899 European individuals, followed by validation in 132,000 individuals (160). The study identified 29 independent SNPs at 28 loci. Although the majority of SNPs identified by ICBP were intragenic, some loci were in gene desert regions or in genomic regions that has no gene encoding protein with a biological plausible effect on BP.

While most of the GWAS for BP have taken the quantitative route studying BP as a continuous variable, two studies analyzed hypertension as a binary trait (276, 321). These studies identified a novel locus located in the promoter region of Uromodulin gene (*UMOD)*, which is exclusively expressed in the kidney and may influence BP by a novel sodium homeostatic pathway (276) and another locus in the promoter region of *NOS3* (321) which codes for nitric oxide synthase 3 implicated in vascular smooth muscle relaxation, angiogenesis, and renal tubular response to salt loading.

GWAS for populations other than European descent were also performed with the aim of replicating the variants identified in European populations, and also finding new population-specific loci (95, 180, 227). The success of replicating the previously reported loci for European population in the other population suggests that the physiological effects of these loci may be generalized across populations with diverse genetic backgrounds. Yet, identifying novel loci also suggests that populations with different genetic background may have unique genetic factors as a result of differences in allele frequencies or population-specific factors that interact with genes to influence BP.

In contrast to monogenic syndromes, interpreting the signals from GWAS is not straight forward. The success of GWAS is dependent on three critical factors: *1*) sufficiently large sample size drawn from a population of appropriate genetic background, *2*) efficient genotyping panel that adequately covers variation within the whole genome, and *3*) powerful statistical methods that can reveal genuine association signals. A major drawback is the large number of statistical tests performed in GWAS which increases the chance of type I error. The penalty applied for multiple testing is to use a genome-wide significant P value threshold of 5×10^{-8} or lower which is the Bonferroni-corrected alpha of 0.05 for testing a million markers. As the design of GWAS chips are based on whole genome coverage using linkage disequilibrium, most of the significant SNPs reported by GWAS of all traits lie within noncoding regions. These SNPs are not the causal variant for the trait studied, but are likely to be in linkage disequilibrium with the causal variant nearby. While this approach has been extremely fruitful in discovering novel loci, several challenges exist in the interpretation of GWAS findings. For each SNP mapped by GWAS, it is likely that within ~100,000 bases of the locus, there exists a causal gene. The biggest challenge of GWAS is not the discovery of significant trait associated SNPs, but the need to understand for each GWAS SNP: *1*) the causal variant, *2*) the causal gene, *3*) the mechanism by which the variant affects the gene function, and *4*) the mechanism by which the gene function affects the phenotype. However, as most of the GWAS signals occur in the noncoding regions of the genome, they require complementary mechanistic studies to delineate the physiological mechanisms underlying their genetic association with BP. Around 85–90% of GWAS hits tag noncoding variants only and identifying causal regulatory variants and target gene require a combination of genetic fine mapping, epigenomic profiling, individual reporter assays, expression quantitative trait loci (eQTL) studies in appropriate tissues, or creating isogenic cellular models [e.g., via genome editing (80)]. The putative gene thus identified is then modulated in vitro in primary cell cul-

FIGURE 5. Chromosome 1-4: genetic landscape of monogenic and polygenic blood pressure/hypertension syndromes, causal genes, GWAS loci, and information used to prioritize functional genes and variants tagged by the GWAS SNPs (154). The Circos plot tracks from outside inward are as follows: *1*) chromosome ideogram; *2*) location and ID of GWAS SNPs for BP and hypertension; *3*) CpG islands: epigenetic markers such as methylation sites can mark transcriptional activity; *4*) DNAse I hypersensitivity sites are open chromatin sites and GWAS variants located in these sites have been shown to control distant genes; *5*) genes underlying GWAS SNPs or monogenic BP syndromes: genes in red are monogenic BP genes, while genes in blue are plausible candidate genes that may be causal for the GWAS SNP. For each SNP mapped by GWAS, it is likely that within ~100,000 bases of the locus, there exists a causal gene. This track just highlights a fraction of the genes present within the selected genetic loci that are most plausible candidates for BP, and the innermost track depicts all the genes that are present within each genetic loci from which the plausible candidates are selected. *6*) Regulatory polymorphisms from ORegAnno (Open Regulatory Annotation): location of regulatory regions, transcription factor binding sites, RNA binding sites, regulatory variants, haplotypes, and other regulatory elements from the Open Regulatory Annotation; *7*) structural variation (deletion = red, insertion = blue, duplication = yellow): location of structural variation where low frequency and rare variants with intermediate to large effect sizes may lie and require further targeted sequencing studies; *8*) multiple alignments of 100 vertebrate species and measurements of evolutionary conservation: highly conserved sites indicating possibly functional sites depicted by size and color intensity of the filled squares; *9*) monogenic BP syndromes and GWAS traits for the SNPs and monogenic genes in the outer 2 tracks; *10*) GTEX expression data of genes within the selected chromosomal segments: adipose, adrenal, aorta, artery, brain, left ventricle, kidney cortex, liver, muscle, and blood; *11*) genes within the chromosome segment. The loops on the top of the ideograms are representation of eQTL locations of GWAS SNPs. Expression quantitative trait loci (eQTL) mapping is performed to find statistical association between a genetic variant and the transcript level of a gene considered as a quantitative trait. eQTL studies can be used as a general method to help identify a set of target genes as many SNPs associated with GWAS traits were shown to be eQTLs.

ture or in vivo in animal models to identify its role in determining the original phenotype (259).

The success of GWAS in identifying a multitude of robust signals for BP is summarized in **TABLE 4** and illustrated in **FIGURES 5–8**, which present all the GWAS signals for BP and hypertension along with details of genomic features near the GWAS SNPS including proximate genes that may help identify the causal variant tagged by the GWAS SNP.

C. Specific Genetic Pathways of BP Regulation and Dysregulation

We now describe the genetic pathways the perturb BP regulation that manifest as clinical syndromes associated with high or low blood pressure in humans. While the majority of the pathways are rare monogenic syndromes **(TABLE 3)**, we also describe a novel pathway for BP regulation identified through GWAS.

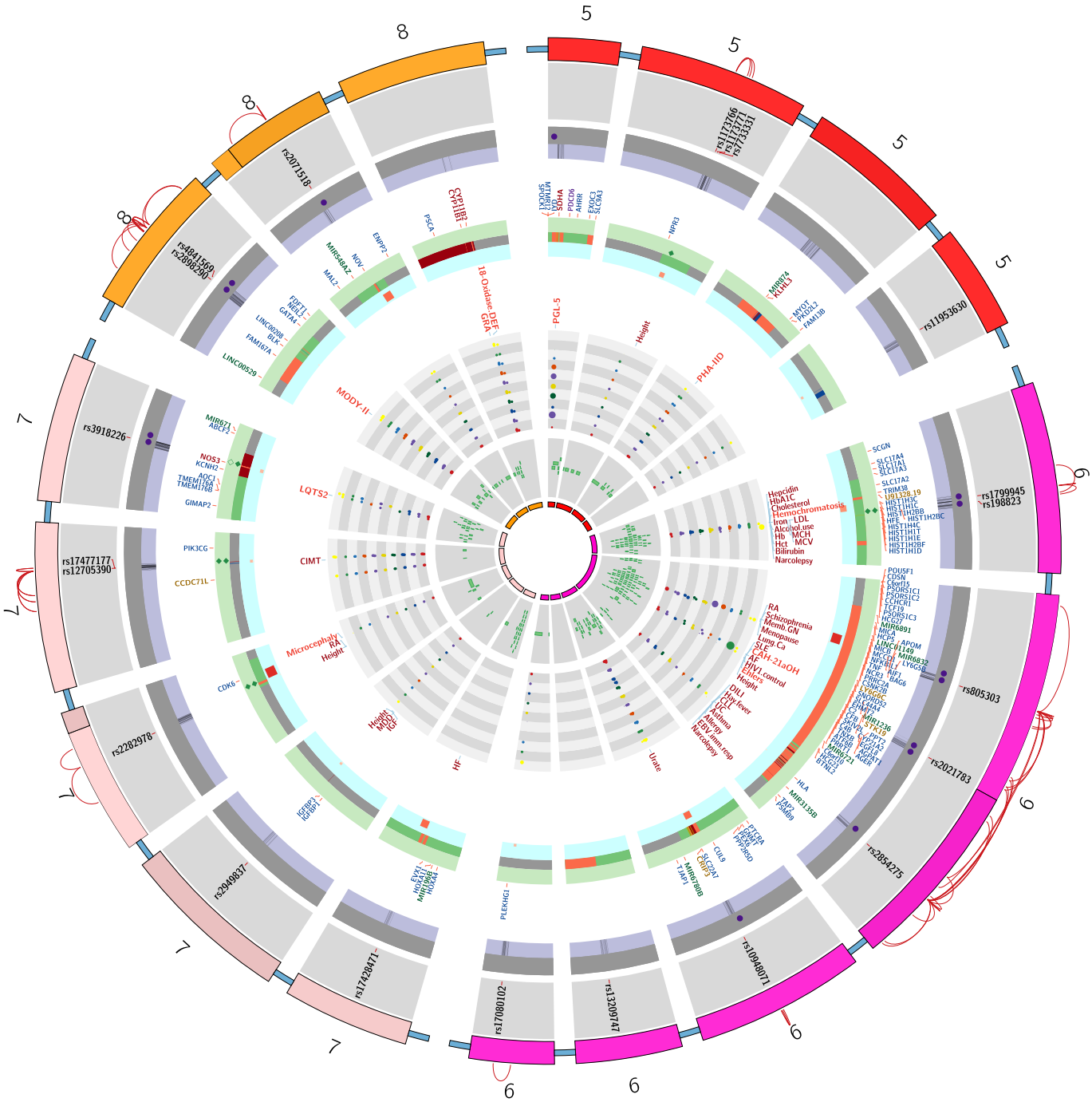


FIGURE 6. Chromosome 5-8: genetic landscape of monogenic and polygenic blood pressure/hypertension syndromes, causal genes, GWAS loci, and information used to prioritize functional genes and variants tagged by the GWAS SNPs (154). See legend to Figure 5 for Circos plot track details.

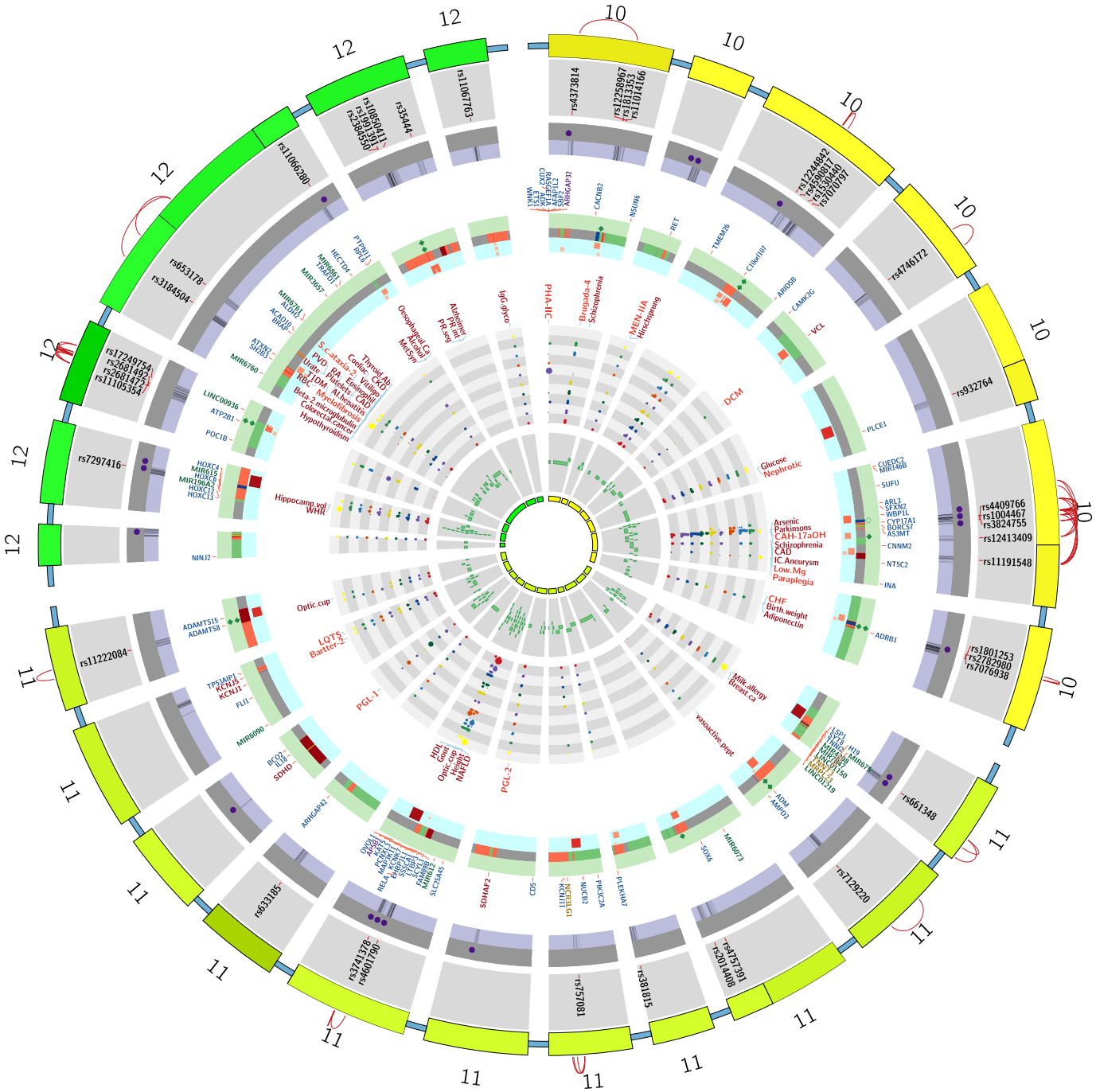


FIGURE 7. Chromosome 10-12: genetic landscape of monogenic and polygenic blood pressure/hypertension syndromes, causal genes, GWAS loci, and information used to prioritize functional genes and variants tagged by the GWAS SNPs (154). See legend to Figure 5 for Circos plot track details.

1. Glucocorticoid-remediable aldosteronism or familial hyperaldosteronism type 1

This is a rare autosomal dominant disorder characterized by early-onset hypertension, hyperaldosteronism, variable hypokalemia, low plasma renin activity (PRA), and abnormal production of 18-oxocortisol and 18-hydroxycortisol. This is attributed to a chimeric gene caused by the fusion of the 5′ regulatory sequences of 11β-hydroxylase [CYP11B1; which confers adrenocorticotropic hormone (ACTH) responsiveness] with the distal coding sequences of aldosterone synthase (CYP11B2). This leads to ACTH becoming the main controller of aldosterone secretion, rather than angiotensin II or potassium (218). Low-dose glucocorticoids to suppress ACTH secretion, or amiloride to directly block the epithelial sodium channel (ENaC), or spironolactone to block binding of aldosterone to the mineralocorticoid receptor (MCR) are the specific treatment options for hypertension in these individuals.

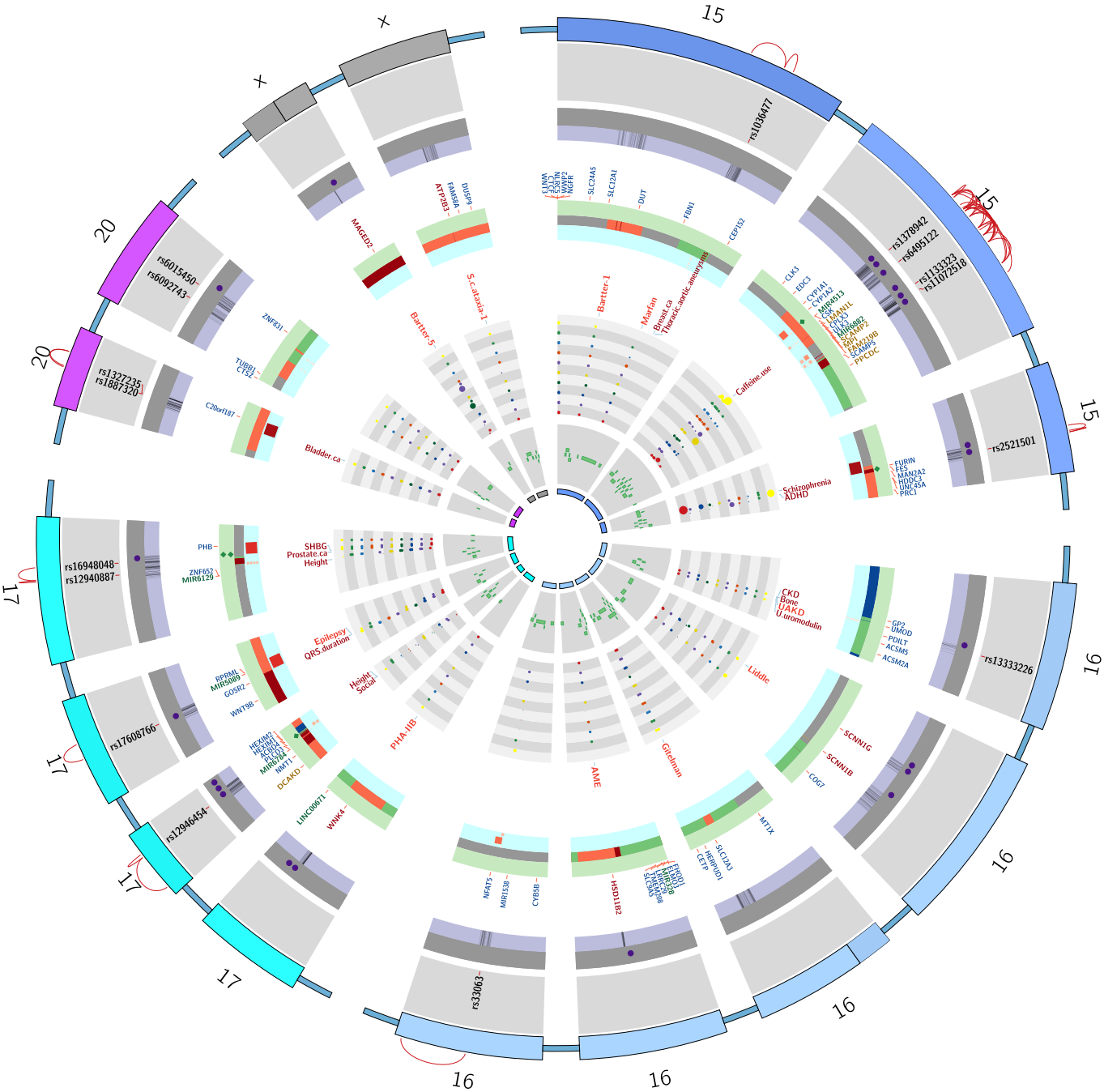


FIGURE 8. Chromosome 15-X: genetic landscape of monogenic and polygenic blood pressure/hypertension syndromes, causal genes, GWAS loci, and information used to prioritize functional genes and variants tagged by the GWAS SNPs (154). See legend to Figure 5 for Circos plot track details.

2. Apparent mineralocorticoid excess

Hypertension due to apparent mineralocorticoid excess (AME) ensues due to the absence or reduced activity of 11β-hydroxysteroid dehydrogenase (HSD11B2), an enzyme which metabolizes cortisol to prevent its binding to the mineralocorticoid receptor. Reduced activity of HSD11B2 results in cortisol to not be metabolized but acts as if it were a potent mineralocorticoid (28). Patients diagnosed with AME syndrome respond well to low-sodium diet and are treated with spironolactone, which blocks binding of both cortisol and aldosterone to mineralocorticoid receptors.

3. Pseudohypoaldosteronism type II (Gordon's syndrome)

This is a form of hypertension associated with hyperkalemia, non-anion gap metabolic acidosis, and increased salt reabsorption by the kidney. The WNK (with-no-lysine [K])

kinases play central roles in regulating mammalian BP by initiating a signaling pathway that controls the activity of critical ion cotransporters in the kidney NCC (Na^+/Cl^- ion cotransporter) and NKCC2 ($Na^+/K^+/2Cl^-$ cotransporter 2). Gordon's syndrome is caused by mutations in WNK1, WNK4, Kelch-like 3 (KLHL3), and Cullin 3 (CUL3) genes. CUL3 and KLHL3 mutations putatively inhibit the ubiquitylation of WNK4, and probably other WNK isoforms, resulting in the the overactivation of NCC/NKCC2 ion cotransporters, and consequently, increased salt retention and hypertension (22, 384). Treatment consists of either a low-salt diet or thiazide diuretics, aimed at decreasing chloride intake and blocking Na^+-Cl^- cotransporter activity, respectively.

4. Liddle's syndrome

Liddle's syndrome is an autosomal dominant condition presenting with hypertension and aldosterone excess, but associated with low renin and aldosterone levels. It is caused by mutations in the genes coding the β- or γ-subunits of ENaC, *SCNN1B* and *SCNN1G*. The mutations result in deletions of proline-rich regions of the protein products of these ENaC subunits, which are essential for binding of Nedd4–2 (NEDD4L), a regulatory repressor that promotes ENaC channel degradation (336). Increased rates of sodium reabsorption, volume expansion, and hypertension result due to lack of binding activity of β- and γ-subunits to Nedd4, which results in constitutive expression of sodium channels and prolongation of the half-life of ENaCs at the renal distal tubule apical cell surface. Patients with Liddle's syndrome are treated with amiloride or triamterene to lower BP and correct acidosis and hypokalemia.

5. Bartter's syndrome

This is a salt-losing condition characterized by hypokalemic metabolic alkalosis and normal or low BP with increased renin activity and high aldosterone levels. The defective mechanism is located in the thick ascending limb (TAL) of Henle's loop and comprises loss of function of NKCC2 or a group of other proteins which lead to secondary loss of function of NKCC2-ROMK channel, chloride channel Kb (ClC-Kb), Bartin, and calcium sensing receptor (CaSR) (341). Increased urine levels of prostaglandin E_2 (PGE_2) and diminished susceptibility to the pressor effect of ANG II and norepinephrine are features of Bartter's syndrome. Patients with Bartter's syndrome are more prone to volume depletion, diarrhea, spasm, fever, and dangerous hypokalemia, which are life-threatening complications, especially during the postnatal period. Chronic treatment of underlying abnormalities of Bartter's syndrome including features to treat increased prostaglandin synthesis and RAAS activity, which aggravate electrolyte and acid base disturbances, are potassium supplementation and use of cyclooxygenase inhibitors, angiotensin converting enzyme (ACE)-inhibitors, and potassium sparing diuretics.

6. Gitelman's syndrome

In Gitelman's syndrome, the defective mechanism is located in the distal convoluted tubule and comprises loss of function of the sodium-chloride cotransporter (NCC) (342) and is characterized by hypokalemic metabolic alkalosis along with significant hypomagnesemia, low urinary calcium excretion, and low blood pressure. The prevalence of Gitelman's syndrome is very low, estimated to be 1:40,000 in the general population and the prevalence of heterozygotes in the Caucasian population is ~1%. Chronic treatment of patients with Gitelman's syndrome comprises maintaining effective extracellular volume with adequate salt and water consumption along with oral potassium and magnesium supplementation. Indomethacin, amiloride, and eplerenone are also used to treat hypokalemia.

7. Primary aldosteronism

Individuals with primary aldosteronism constitutively produce aldosterone from the adrenal gland, resulting in hypertension with variable hypokalemia and a suppressed circulating renin. A gain-of-function somatic mutation in a K^+ channel, KCNJ5, which results in membrane depolarization and enhanced aldosterone production, is a common genetic defect noted for ~40% of aldosterone producing adenomas. Mutations in three other genes, encoding the α1-subunit of Na^+-K^+-ATPase itself; and ATP2B3, a plasma membrane Ca^{2+}-ATPase 3 homologous to the sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPases (SERCA); and CACNA1D, encoding an L-type Ca^{2+} channel CaV1.3, are observed in ~7% of the cases (399). Whereas APAs in adrenal zona glomerulosa cells harbor gain-of-function mutations in genes important for the regulation of Na^+ and Ca^{2+}, ATP1A1, and CACNA1D, respectively, KCNJ5 mutations are common in APAs resembling cortisol-secreting cells of the adrenal zona fasciculata (25). Adrenalectomy of the affected adrenal gland in APAs cures or ameliorates hypertension in the majority of patients.

8. Phaeochromocytomas and paragangliomas

Rare neuroendocrine tumors of the adrenal glands and the sympathetic and parasympathetic paraganglia are called phaeochromocytomas and paragangliomas, respectively. RET pro-to-oncogene mutations cause autosomal dominantly inherited phaeochromocytomas. Other susceptibility genes include genes that encode succinate dehydrogenase subunits A, B, C, and D (*SDHA*, *SDHB*, *SDHC*, and *SDHD*, respectively) with heterozy-

gous germline mutations of *SDHB*, *SDHC*, and *SDHD* causing familial pheochromocytoma-paraganglioma syndromes known, respectively, as paraganglioma 4, paraganglioma 3, and paraganglioma 1 and the tumor suppressor gene *VHL* observed in families with von Hippel-Lindau syndrome (91). Recently discovered predisposing genes for pheochromocytoma/paraganglioma include *KIF1Bbeta*, *PHD2*, and *SDHAF2* (91).

9. Uromodulin

A GWAS of BP extremes showed the minor G allele of a UMOD promoter SNP, rs13333226, was associated with a lower risk of hypertension and reduced urinary UMOD excretion (276). Uromodulin gene expression is exclusively localized to the thick ascending limb of the loop of Henle (TAL) in the kidney where 25% of the filtered sodium is reabsorbed. An increased localization of the salt-retaining NKCC2 (sodium-potassium-chloride cotransporter 2) in subapical vesicles of TAL cells with reduced phosphorylation, both resulting in reduced cotransporter activity was noted in UMOD knockout mice (260). The resulting effects noted are a greater sodium excretion as compared with wild-type mice, and a 20 mmHg lower BP in the knockout mice at baseline, as measured by radiotelemetry (123). Notably, this difference in BP was exacerbated with salt, whereby the knockout mice were resistant to the hypertensive effects of salt (123). Conversely, UMOD overexpression was associated with an increase in BP (361). The main sodium transporter in TAL is NKCC2, which is blocked by the commonly used loop-diuretic furosemide. Trudu et al. (361) showed furosemide treatment significantly enhanced natriuresis and reduced BP levels both in the transgenic mice and in the hypertensive individuals homozygous for the UMOD increasing allele. Thus GWAS has directed focus on a novel pathway of BP regulation involving altered expression of uromodulin which appear to influence sodium homeostasis and opens an avenue for translational studies to discover or repurpose drugs for treatment of hypertension.

10. Natriuretic peptide

Common SNPs in the chromosomal region containing NPPA and NPPB, the genes encoding the ANP and BNP propeptides, show consistently that alleles associated with increased circulating natriuretic peptide concentrations are also associated with lower systolic blood pressure (264, 265). The GWAS SNP rs5068 lies in the 3′-UTR of the *NPPA* gene which encodes the pro-peptide of ANP, NT-proANP. Healthy volunteers, which were homozygous for the risk allele of rs5068 showed lower NT-proANP expression possibly mediated through a microRNA miR-425 and provides a putative mechanism to explain how the risk allele reduces ANP level and consequently increases BP (11). The genetic effect of rs5068 on circulating NT-pro-ANP levels is comparable to the environmental change induced by switching from an extremely low-salt diet (230 mg/day) to a diet with salt content typical of a Western diet (4600 mg/day) (11).

XII. EMERGING CONCEPTS

A. Noncoding RNA, Epigenome, and the Inheritance of Hypertension

Variations within the protein-coding genome and epistatic interactions therein do not completely account for the heritability of hypertension. A vast majority of variants detected through human GWAS for hypertension are within noncoding genomic segments. These can be categorized into variants that are within regions that can generate noncoding RNA and variants that are within segments with no evidence of any annotation. Research on the latter is rather difficult and stagnant at this point; however, the hypothesis that variants within noncoding RNA molecules that can influence BP has gained some attention (201). In rat models of hypertension, various classes of noncoding RNAs have been profiled. With the ue of the Dahl SS/MCW rat and a consomic model (SS13.BN), wherein substitution of chromosome 13 of the Dahl SS/MCW rat with that of the BN rat lowered BP, a total of 377 microRNAs were profiled in the renal medulla under the conditions of a high-salt diet (224). In this study, five microRNAs are reported as differentially expressed between the SS/MCW and the SS13.BN strain (224). Of these two microRNAs, Mir214 and Mir29b are located on chromosome 13. miR-214 was readily detectable in the SS/MCW strain, but undetectable in the SS13.BN strain. miR-29b was expressed higher in the SS13.BN strain relative to the SS/MCW strain. The Dahl S rat demonstrates substantial renal medullary interstitial fibrosis, which was hypothesized as at least in part due to the upregulation of miR-29b, which was predicted to regulate genes encoding many proteins of the extracellular matrix. The observation that the expression of nine collagen genes and matrix metalloproteinase 2 (Mmp2), integrin β1 (*Itgb1*), and other genes related to the extracellular matrix were all downregulated in the renal medulla of SS13.BN provided further proof for the link between miR-29b and associated renal medullary interstitial fibrosis and hypertension. Further evidence was provided through luciferase construct assays wherein miR-29b suppressed the activity of luciferase when the reporter gene was linked to a 3′-untranslated segment of collagen genes *Col1a1*, *Col3a1*, *Col4a1*, *Col5a1*, *Col5a2*, *Col5a3*, *Col7a1*, *Col8a1*, *Mmp2*, or *Itgb1*. While miR-29b is an attractive candidate as an inherited element that may regulate BP, formal detection of variants within miR-29b or factors that influence its expression differentially would support its candidacy. For now, it appears to be an important mediator of renal fibrosis and related hypertension.

The second class of noncoding RNAs are the long noncoding RNAs. In rats, there are very few investigations that

have led to the prioritization of noncoding elements as inherited factors for the development of hypertension partly due to the fact that the rat genome annotation for noncoding RNA genes is limited. There are two reports of profiling for rat long noncoding RNAs (119, 368). These are important starting points for future investigations into the relationships between variants within long noncoding RNAs and hypertension. As far as inheritance of noncoding RNA variants as BP QTLs, there is indirect evidence provided by mapping of a BP QTL on rat chromosome 9 through the congenic approach by introgressing normotensive Dahl R rat alleles onto the genome of the Dahl S rat to a <81.8 kb segment (122). This relatively short genome segment has no protein-coding gene annotations within it, but the congenic strain demonstrated a strong BP lowering effect, thus providing evidence for variants within noncoding regions of the genome to influence BP. A second report is on an even shorter segment of <42.5 kb, which when replaced by LEW rat alleles on the genome of the S rat, accounts for a BP increasing effect. There is a single protein-coding gene within this region called rififylin, but the gene itself does not have coding-sequence variants between S and LEW (121). The expression of rififylin is higher in the congenic strain with the increased BP compared with the S rat, and this increased expression is demonstrated to cause a delay in cellular recycling, a molecular mechanism linked to the observation of not only increased BP, but also shorter QT intervals (121). The expression of rififylin to be higher in the congenic strain is circumstantial to indicate that a variant or variants that are not responsible for coding for a protein are responsible for the observed BP effect. If these sequence variants are noncoding in the rat, it is of interest to note a parallel in humans wherein SNPs within noncoding regions around the rififilyin gene are also associated with aberrant, shorter QT intervals in humans (264).

B. Epigenetics and Hypertension

Epigenetics refers to molecular changes and associated phenotypes that are inherited, but do not involve variations in the DNA nucleotide sequence. Epigenetic mechanisms involve modification of DNA through methylation or histone modification or noncoding RNA, which then contribute to biological regulation by influencing the expression of protein-coding genes. Due to the feature that epigenetic marks such as methylation or histone modification are heritable and can be transmitted either through mitosis or meiosis even without altering the underlying DNA sequence, epigenetics is an inherited factor contributing to the genesis of hypertension. Epigenetic inheritance is an essential mechanism that accounts for the stable propagation of gene activity from one generation of cells to the next. Unlike genomic variants, epigenetic alterations can be difficult to study as they are often tissue or cell-type specific. There are very few studies reported that test the hypothesis that methylation of genomes at CpG sites is associated with hypertension. A study was conducted on a genome-wide scale using DNA from leukocytes from a small cohort of eight African-American hypertensive subjects and eight normotensive age-matched controls, but this initial study lacked power to detect any significant associations (371). Validations were conducted with additional subjects to demonstrate that higher methylation of at least one gene, the sulfatase 1 (*SULF1*) gene, was associated with hypertension (371). A recent study in humans was conducted using thin-layer chromatography to determine 5-methylcytosine (5mC) levels in blood DNA samples from 60 subjects with essential hypertension and 30 control subjects (344). Lower levels of 5mC were observed in DNA of patients with essential hypertension that correlated with the stage of hypertension (344). Among animal models, a similar approach of genome-wide methylation status analysis is reported using renal outer medullary tissue from the Dahl S hypertensive rat model and the SS.13^{BN26} congenic strain with a significantly attenuated salt-induced hypertension and renal injury. The SS.13^{BN26} congenic strain has a 12.9 Mbp segment introgressed from the BN rat. The specific methylations characterized were 5mC and 5-hydroxymethylcytosines (5hmC), both of which were mapped at single-base resolutions (223). The study also examined the effect of increased dietary salt intake and compared the SS rat with the congenic SS.13^{BN26} rat to investigate the effect of genomic segment substitution on 5mC and 5hmC and the association of 5mC and 5hmC with changes in the disease phenotypes. While there were no detectable alterations in DNA methylation as a result of the chromosome 13 substitution, there was a notable alteration in response to dietary salt in both the strains examined. Nearly 80% of the CpG islands that were differentially methylated in response to salt and associated with differential mRNA abundance were intragenic CpG islands.

Overall, it has become quite clear that a DNA sequence-based approach may only partially explain the involvement of our genome in the genesis of hypertension. Epigenetics is an attractive proposition for explaining some of the "missing heritability" (47, 97, 191, 216, 372, 373) for further studies, which are clearly needed to test and ascertain the causal implications of epigenetics in BP regulation.

C. Microbiome and the Inheritance of Hypertension

Beyond all the features presenting as genomic or epigenomic factors for the inheritance of hypertension, investigations into the realm of the microbiome have opened a new and previously unsuspected role of microbiota in regulating BP **(FIGURE 9)**. Early clues for the involvement of the genome in microbiotal influenced alterations in BP came from the reports on short-chain fatty acid (SCFA) receptor knockout mice (285). Circulating SCFAs originate largely from gut microbiota as they are the end products of bacte-

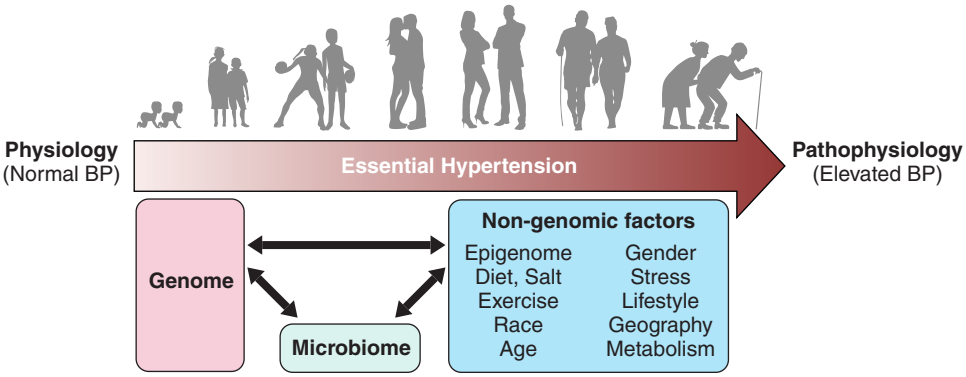


FIGURE 9. Cartoon representation of factors influencing the etiology of hypertension. The red double-sided arrow represents the interactions between the host genome and nongenomic factors that act in concert to influence the transition from normal physiology of BP regulation to the pathophysiological state of elevated BP.

rial fermentation, which are absorbed into the host circulation. The link between SCFAs produced by the gut microbiota and modulation of BP via these SCFA receptors was demonstrated by using antibiotics to reduce the biomass of the gut microbiota before monitoring BP in these SCFA receptor gene deletion models described below.

Olfactory receptor 78 and G protein-coupled receptor 41 are both receptors for short-chain fatty acids. Both *Gpr41* and *Olfr78* are expressed in smooth muscle cells. *Olfr78* is expressed in the renal arterioles and the juxtaglomerular apparatus. In the juxtaglomerular cells, *Olfr78* mediates renin secretion in response to short-chain fatty acids. Deletion of the Olfr gene in *Olfr78*$^{-/-}$ knockout mice resulted in lower BP associated with lower levels of plasma renin which was demonstrated to be due to modulation of short-chain fatty acid-mediated renin release from the juxtaglomerular cells. *Gpr41* is expressed in smooth muscle cells of small resistant blood vessels. Gpr41 contributes to the hypotensive effect of the short-chain fatty acid propionate. Furthermore, a relationship was demonstrated between these two receptors, whereby Olfr78 functions to raise BP and thereby antagonizes the contribution of Gpr41 to hypotensive effects of propionate (285). These studies provided some basic insights into the relationship between gut microbiota and previously unknown mechanisms leading to hypertension.

Soon thereafter, two studies were reported on the influence of microbiota on the development of inherited hypertension in rats. The first study was conducted to test the hypothesis that the extent of hypertension of the Dahl S rat can be determined by an alteration in its gut microbiotal composition (245). Gut microbiotal composition of the Dahl S rat was altered by transplantation of the relatively normotensive Dahl R rat microbiota. As a result of the transplantation, a significant increase in BP of the Dahl S rat was documented. The reciprocal transfer of S rat microbiota to the R rats did not alter the BP of the R rats. 16S RNA analysis of the microbiotal compositions combined with plasma short-chain fatty acid profiles revealed that microbiotal compositions were indeed altered and that the short-chain fatty acids acetate and heptanoate were higher in the S rats transplanted with microbiota from the R rats compared with the S rats given microbiota from the S rats (245). These data suggest that inherited levels of elevated BP can be further augmented by the type of gut microbiota. The second reported study is on the SHR rat (394). The gut microbiota of the hypertensive SHR was decreased in microbial richness, evenness, and diversity compared with the normotensive WKY rats (394). Administration of an antibiotic, minocycline, lowered BP of the SHR. The effect of this particular antibiotic is interesting because it crosses the blood-brain barrier and has neuronal effects on lowering BP. The microbiotal influence of minocycline was demonstrated through alterations in the 16S RNA composition of microbiota post minocycline treatment that was associated with a decrease in ANG II-induced BP as well as a reduction in the Firmicutes to Bacteriodetes (F/B) ratio and an increase in plasma butyrate, a short-chain fatty acid known to induce vasodilation. Cross-transplantation of microbiota from WKY to SHR and vice versa will be interesting, but has not yet been reported. Collectively, these data point to the importance of microbiota and their genomes, referred to as the microbiome in the pathogenesis of hypertension. The historical relevance of these studies is summarized in an editorial by Honor who draws attention to studies conducted in the late 1970s and early 1980s, which have suggested a role for the gut microbiome in the development of hypertension in rats and man (147). Early work conducted in humans and experimental rats (146, 148, 149) suggests that an increase in BP through the action of steroids was prevented by administration of antibiotics (146, 148). Studies in rats were conducted in Sprague-Dawley (SD) rats rendered hypertensive with corticosterone or by administration of ACTH. Hypertension was prevented by prior treatment of the rats with neomycin and to a lesser extent with vancomycin (146, 148). Neomycin also slowed the development of hypertension in the SHRSP rat (148). Since modern methods to detect microbiota through 16S sequencing was not available at that time, gut flora was examined with conventional techniques such as diluting of fecal samples that were then spread on agar plates enriched to selectively support growth of organisms. The findings were insufficiently detailed to assign links with steroid metabolism; however, the effect of neomycin on BP was re-

peated in the Florey Institute, Melbourne, Australia with rats given ACTH and corticosterone (159) and in the rat model of one clip, one kidney (CSK) hypertension (94). Three decades later, the two reports on the Dahl S rat and the SHR and their links to microbiota as a factor influencing development of hypertension (245, 394) has generated much excitement in the field as is evident from a number of review articles (4, 172, 242, 246, 263, 296, 324, 407) and a working group report from the National Heart, Lung, and Blood Institute of the National Institutes of Health, USA (270) related to the importance of salt, immunity, the microbiome and hypertension, or kidney disease.

Thus the microbiome now belongs to the long list of factors beyond inheritance of the host genome that influence the etiology of hypertension **(FIGURE 9)**. Admittedly the discoveries thus far, albeit associations, are in need of further studies for cause-effect relationships between the host genome and the microbiome to impact a change in BP. This could be challenging because unlike the single host genome, the microbiome consists of a group of genomes, which means that these groups of genomes will have collective transcriptomes that are influenced by the host genome and vice versa. However, the microbiome cannot explain inherited difference in blood pressure in human or animal studies. It serves as a complicating factor that obscures the influence of genetics on blood pressure regulation. Environmental factors such as, for example, dietary proteins, which are known to alter blood pressure, at least in the Dahl S model (61, 239), may do so via the microbiome or by altering the meta-transcriptome, epigenome, or the metabolome. Contemplation of these many possibilities is impossible unless one considers these host-microbiotal interactions in the context of a "holobiont," which is defined as an ecosystem consisting of a macro-organism (the host) with a group of microorganisms (microbiota). Galla et al. (99) provide a perspective leading to this concept along with an update on the status of research on microbiota in hypertension.

XIII. LOOKING AHEAD

In conclusion, research into the inherited susceptibility factors for BP, which perhaps began with the ambitious view of finding a handful of causal variants with major effects on BP, which could be used as targets for better clinical management of hypertension, has not proven to be the case. Instead, a small number of genes have been identified through positional mapping approaches, and a deeper understanding of additional mechanisms as being operational at the genomic level has emerged. These mechanisms are depicted in **FIGURE 10** as epistasis, epigenetics, chromosome conformations, and interactions with genomes of microbiota, all of which impact molecular pathways converging to causally influence BP regulation.

For the future of research on the genetics of hypertension, the following are a few considerations and anticipatory remarks.

A. Missing Heritability

Despite the identification of numerous SNPs associated with hypertension and BP traits, the proportion of phenotypic variance that is explained by all of these loci together is <2.5%. This phenomenon has been described as the problem of "missing heritability" and is not restricted to BP traits (230). For instance, a classic complex trait such as height, which has a very large heritability estimate from family studies (~80%), has <10% of the phenotypic variance explained from the SNPs identified using very large sample sizes (>180,000 individuals). A different way of estimating heritability using SNP data of unrelated individuals is the GCTA approach introduced by Yang et al. (h^2_{SNP}) (393). This is based on estimating the heritability from unrelated individuals using common SNPs with the assumption that heritability estimates in unrelated individuals is only attributable to the common SNPs, while the estimation in related individuals is attributed to the entire genome. Applying this method to systolic BP has shown that h^2_{SNP} was ~24%, which is ~50% of the heritability estimates from other twin studies, and ~80% of the same study heritability estimate (h^2 = 30%). Furthermore, the number of independent variants with similar effect size to those reported in the ICBP study was estimated to be 116 (95% CI: 57–174), which can collectively explain around 2.2% of the phenotypic variance for BP phenotypes, compared with only 0.9% explained by the 29 SNPs identified by ICBP (160). These findings indicate that a large proportion of the heritability of BP is "hidden" rather than "missing" because of a large number of common variants, each of which has too small an effect to be detected at the stringent genome-wide significance level using current sample sizes.

The search for missing heritability is one of the primary goals for research on hypertension and other complex conditions. Among the hypotheses contemplated to explain "missing heritability" of complex traits are overestimates of heritability, genomic regions that are unexplored, genetic variants that remain untested, rare genetic variants that are yet unknown or not associated, gene interactions or epistasis (230, 231), and more recently the underrecognized role of the host genomic interactions with the microbiome. Thus there is no question that the quest for genetic analysis of hypertension thus far has opened up more avenues to pursue. Appropriate experimental designs have to be employed that allow for investigations to be focused on causal relationships rather than mere associations. Determining the full extent to which each of these additional avenues contributes to the genotype-BP relationship is expected to im-

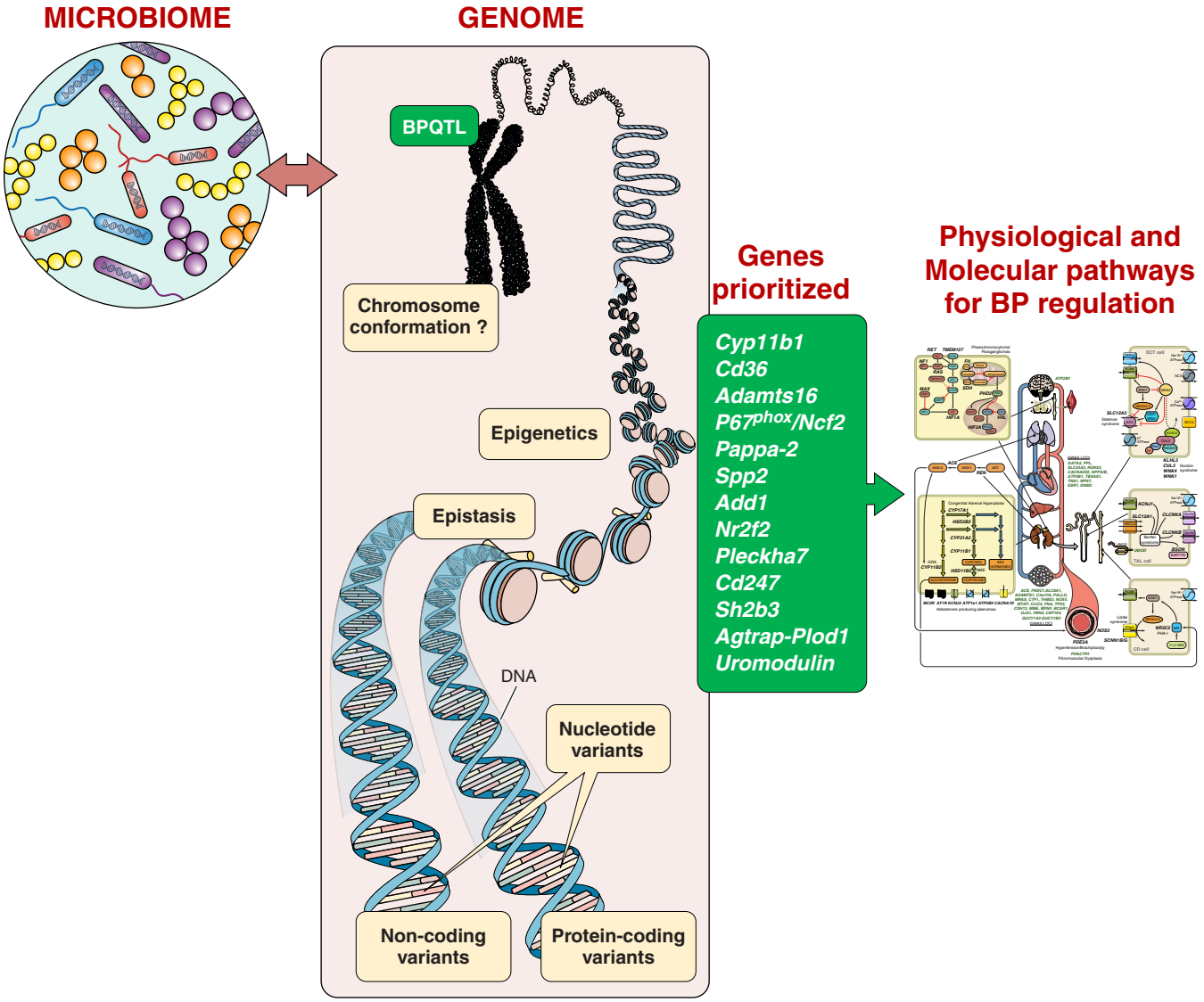


FIGURE 10. Current views on mechanisms by which DNA impacts blood pressure regulation. The genome of the host as well as the genome of microbiota, called microbiome, are depicted as known genomic factors influencing BP. The genes researched and found to be linked or associated with the inheritance of hypertension in rat models and/or in humans are listed on the right hand side of the diagram. Please see NOTE ADDED IN PROOF for *Rffl-lnc1* as an additional noncoding locus validated recently as a new BP QTL.

prove our understanding of the biological systems that underpin variation conferring susceptibility to the development of hypertension as well as increase the accuracy of individual risk prediction.

B. Emerging Insights From Other "Omics": Metabolomics

Other omics technologies such as metabolomics are potentially powerful tools to identify molecular pathways. They can capture both intrinsic and extrinsic factors, and their dynamic nature makes them ideal for measuring physiological response to external stimuli or the development of pathogenic processes. Metabolomics, which is the systematic study of small molecule metabolites, may have an important role in defining candidate systems/pathways in the pathogenesis of hypertension. Furthermore, metabolomic markers are closer to the phenotype of interest in contrast to the genotype which is static and unchanged throughout life. Metabolomic profiling of over 3,000 adult twins identified a putative novel pathway for BP regulation involving a dicarboxylic acid (hexadecanedioate) with a causal role supported by in vivo studies in rats (248). The role of hexadecanedioate in a vascular mechanism for hypertension is supported by evidence from a study of pulmonary hypertension, indicating a disruption of β-oxidation and an increase of ω-oxidation in this condition and pointing to a putative role in elevating pressure in both the systemic and the pulmonary circulations (405). The strongest genetic as-

sociation seen with hexadecanedioate maps to SLCO1B1, an association previously reported in a metabolome-wide genetic study in caucasians (350). Targeted metabolomics profiling in the European Prospective Investigation Into Cancer and Nutrition (EPIC)-Potsdam study showed higher concentrations of serine, glycine, and acyl-alkyl-phosphatidylcholines C42:4 and C44:3 tended to be associated with higher and diacyl-phosphatidylcholines C38:4 and C38:3 with lower predicted 10-yr hypertension-free survival (70). Other metabolite associations with incident hypertension and BP come from two US studies which found 4-hydroxyhippurate, a metabolic sex steroids pattern and 2 diacylglycerols 16:0/22:5 and 16:0/22:6 to be associated with BP and incident hypertension (205, 406). Finally, Menni et al. (249) showed 12 metabolites to be strongly associated with pulse wave velocity with uridine, phenylacetylglutamine, and serine appearing to strongly correlate with PWV in women.

C. Networks of Relationships and Pathways Influencing the Inheritance of Hypertension

Beyond the factors listed above, investigations into the genotype-phenotype relationship of BP regulation is expected to follow the genetic investigations conducted in lower order organisms such as yeast and *Drosophila*. **FIGURE 11** (154) is provided as an example to illustrate the point that quantitative traits studied extensively in *Drosophila* have revealed pervasive networks of epistatic interactions that recapitulate known as well as candidate genetic networks affecting complex traits (154). It is tempting to speculate that similar extensive networks of pathways govern the genotype-BP causality relationship. Others have also proposed similar regulatory networks operating within specific genomic contexts that interact with environmental factors such as dietary salt levels in the context of epigenomic contributions to salt-sensitive hypertension (216). Furthermore, a treelike paradigm has been proposed for understanding such pathway networks underlying the development of salt-sensitive hypertension (216). On one hand, reductionistic approaches of modeling single genes in suitable experimental designs for assessing causal effects on BP are expected to progress further, but on the other hand, it is also important to test the molecular network hypothesis on a genome-wide scale to fully assess the genetic contributions to the development of hypertension. Technological advances in machine-learning and other computational approaches will perhaps be required to test the molecular network hypothesis in the context of BP regulation. Mackay and Moore (230, 231) point out that "the most important short-term goal is to develop, evaluate and employ statistical and computational methods that embrace, rather than ignore, the complexity of the genotype to phenotype map." They predict as quoted below: "artificial intelligence is poised to have a big impact on the genetic analysis of complex traits by generating interesting and unexpected models of genotype to phenotype relationships" (230, 231).

D. Chromosome Conformations

Another emerging hypothesis for contributions from the genome to complex traits is that alterations in nuclear organization of DNA resulting in higher order structures such as folds of DNA within chromatin confer differential susceptibility. Fueled primarily by advances in chromosome conformation capture assay (3C) and sequencing-based chromosomal contact mapping (Hi-C, 5C and 4C-seq) that is applicable on a genome-wide scale (62, 217, 315, 325, 364), it is now technically feasible to detect such spatial organization of nuclear DNA. However, there is little known about how such folds affect the ways in which cells access, read, and interpret genetic information pertinent to BP regulation.

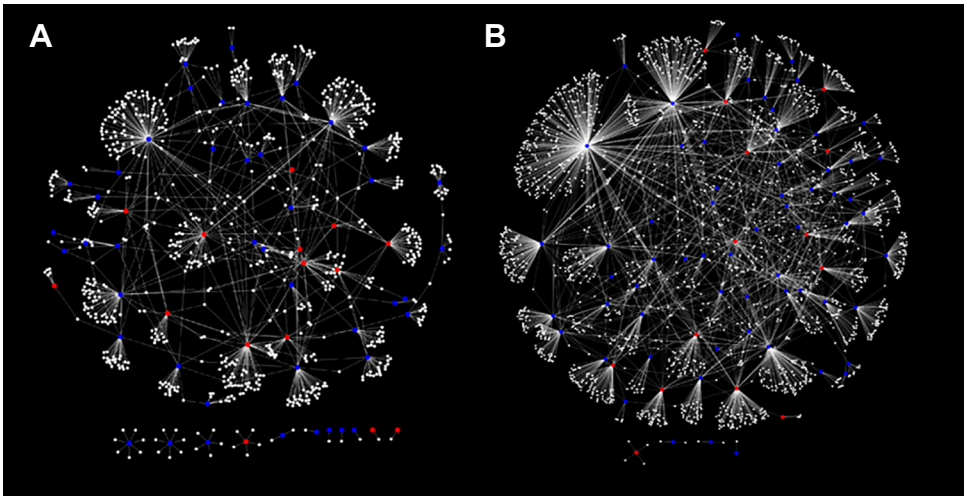


FIGURE 11. Networks of epistatic interactions. Interaction networks are depicted for starvation resistance (*A*) and chill coma recovery (*B*). Nodes depict genes, and edges significant interactions. Red nodes are genes containing significant SNPs from the Flyland analysis. Blue nodes are genes containing significant SNPs from DGRP analysis. [From Huang et al. (123), with permission from *Proceedings of the National Academy of Sciences USA*.]

XIV. CONCLUDING REMARKS

To conclude, advances in genomics have accelerated over the last decade leading to an unparalleled leap in our understanding of the genetic architecture of BP and hypertension. While the technological and analytic aspects of genomics have been very successful in discovering DNA sequence variants associated with BP and hypertension, the functional and biological significance of the vast number of these variants in the human genome are unknown. In the near future, integrated analyses of whole genome sequences along with other "-omics" is anticipated to mature and lead to better insights, which can then be accommodated into the decision-making tree of health care for every individual. The challenging task will be to identify variants or biomarkers or pathways that are disease-causing or disease-modifying or treatment-stratifying, and to develop strategies to prevent or treat hypertension while keeping the ethical and social implications constantly aligned with technical and clinical limitations of the diagnostic/therapeutic used.

NOTE ADDED IN PROOF

Since this article was accepted, a new study has been published (36a), wherein a precise 19 bp indel polymorphism was positionally cloned as quantitative trait nucleotides (QTNs) for blood pressure and short QT intervals. This study is a follow-up of the work presented in Table 2 on rat chromosome 10, study "o". The BP QTL was previously located within <45 kb of the rat genome (121). In the new study, using CRISPR/Cas9 technology, both targeted disruption and targeted knock-in rescue approaches were applied to validate the 19 bp of the DNA sequence variation between S and Lew rats as QTNs. The 19 bp sequence was discovered to be part of the genomic sequence which is transcribed into a long noncoding RNA called *Rffl-lnc1*. Secondary structural alterations of *Rffl-lnc1* were noted as a result of the 19 bp indel polymorphism. This study is not only the first to define genomic variation at the highest level of precision for mapping inherited elements that control a complex trait among mammalian models, but also the first to identify the inheritance of a variation within a long noncoding RNA as a causal factor for BP regulation.

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DISCLOSURES

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