Review Article

Brief Overview of a Decade of Genome-Wide Association Studies on Primary Hypertension

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Academic Editor: Raffaele Pezzani

Primary hypertension is widely believed to be a complex polygenic disorder with the manifestation influenced by the interactions of genomic and environmental factors making identification of susceptibility genes a major challenge. With major advancement in high-throughput genotyping technology, genome-wide association study (GWAS) has become a powerful tool for researchers studying genetically complex diseases. GWASs work through revealing links between DNA sequence variation and a disease or trait with biomedical importance. The human genome is a very long DNA sequence which consists of billions of nucleotides arranged in a unique way. A single base-pair change in the DNA sequence is known as a single nucleotide polymorphism (SNP). With the help of modern genotyping techniques such as chip-based genotyping arrays, thousands of SNPs can be genotyped easily. Large-scale GWASs, in which more than half a million of common SNPs are genotyped and analyzed for disease association in hundreds of thousands of cases and controls, have been broadly successful in identifying SNPs associated with heart diseases, diabetes, autoimmune diseases, and psychiatric disorders. It is however still debatable whether GWAS is the best approach for hypertension. The following is a brief overview on the outcomes of a decade of GWASs on primary hypertension.

1. Introduction

Hypertension is highly prevalent globally. The estimated number of people with uncontrolled hypertension is nearly 1 billion (around 15% of the world population), with the number predicted to increase to 1.56 billion by the year 2025 [1]. Due to its high prevalence, hypertension is the leading risk factor for cardiovascular disease, stroke, and end-stage kidney diseases. The increased risk of cardiovascular mortality and morbidity has led to the estimation that hypertension causes 13% of all deaths (around 7.5 million deaths worldwide) [2]. Patients are considered to have hypertension when their systolic blood pressure is ≥140 mmHg and/or their diastolic blood pressure is ≥90 mmHg [3]. However, raised blood pressure, even within the normal range, is positively and continuously related to mortality and morbidity—each increment of 20 (systolic)/10 (diastolic) mmHg of blood pressure doubles the risk of cardiovascular diseases

[2]. Hence, the number of people at risk is higher as the prevalence of raised blood pressure for adults (aged ≥25 years) is around 40% [2].

The majority of hypertension in the general population occur idiopathically with no apparent causes and therefore are categorized as primary hypertension. The remaining hypertensive cases (about 5%) are categorized as secondary hypertension as the raised blood pressure occur secondary to other causes/diseases, for example, hypertension due to aldosteronism, pheochromocytoma, renovascular diseases, or even Mendelian forms of hypertension [4, 5]. However, despite being classified as having no apparent cause, studies of familial aggregation on primary hypertensive patients have found associations of blood pressure among siblings and between parents and children, indicating that genetic factors contribute to the high blood pressure among primary hypertensive patients. Genetic factors have been estimated to explain 30–50% of the interindividual variation in blood

pressure which significantly predisposes family (siblings/children) of primary hypertensive patients to hypertension [6]. These heritable genetic factors, in addition to environment and demographic factors, play a major role in interindividual variation in blood pressure [7]. Therefore, extensive genetic research has been conducted over the years, including genome-wide association studies (GWASs), to help elucidate primary hypertension's heritability.

2. Outcomes of Genome-Wide Association Studies on Primary Hypertension

GWASs have identified over three hundred plus SNPs/loci associated with blood pressure and/or primary hypertension over the past decade (Table 1). Meta-analyses of GWASs have made the biggest contribution as they allowed for larger sample sizes and more extensive imputation panels. Despite these advancements, genetic variation identified so far only explains ~3–6% of the variance for blood pressure, approximately 1 mmHg per allele systolic blood pressure or 0.5 mmHg per allele diastolic blood pressure [8–12]. Further, the vast majority of GWASs were performed predominantly in Caucasian populations with only a few studies assessing or replicating in other populations even though high blood pressure burden risk is ranked number one in Southeast Asia, Central Asia, North Africa, and Middle East [13–40]. This suggests the existence of many more undiscovered SNPs/loci or at the very least SNPs unique to other populations that are not of Caucasian ancestry. For example, one meta-analysis on Oriental populations found five Oriental-specific loci near CAPZA1, FIGN, ENPEP, NPR3, and PTPN11 (near C12orf51) associated with hypertension [22]. Either the differences in environmental exposures/lifestyle factors or genetic background can explain why ethnic/racial susceptibility loci exist. Nevertheless, as even a small increase in blood pressure can increase the risk of cardiovascular diseases, the biological pathways identified by these SNPs would still be useful in resolving many of the open questions regarding blood pressure pathophysiology.

3. Biological Pathways Involved with Blood Pressure Pathophysiology

Mendelian forms of hypertension and germline mutations causing early-onset hypertension have highlighted biological pathways that involve renal salt handling (WNK1, WNK4, KLHL3, and CUL3), ion transport (CACNA1D, CACNA1H, KCNJ5, SCNN1B, and SCNN1G), corticosteroidogenesis (CYP11B2, HSD11B2, NR3C2, CYP11B1, and CYP17A1), and vascular tone (PDE3A) to regulate blood [41–44]. Thus, not surprisingly, GWASs have identified SNPs in or near to genes involved with these biological pathways associated with primary hypertension. In fact, one of the first few high-throughput genotyping was performed on only genes underlying monogenic hypertension and hypotension (not genome-wide) which found two renal sodium regulatory genes (KCNJ1 and NR3C2) to have SNPs associated with blood pressure in the general population [45].

3.1. Renal Salt Handling. One interesting SNP putatively involving renal salt-handling pathway was only linked to hypertension in an extreme case-control GWAS design [25]. This SNP, rs13333226, on chromosome 16 is in the $5'$ region of UMOD (combined P value of 3.6×10^{-11}). The minor G allele of this SNP had an OR of 0.87 (95% CI: 0.84–0.91) for hypertension, with the subject having the minor G allele having decreased urinary uromodulin and better renal function. The exclusive expression of uromodulin, the protein encoded by UMOD, in the thick portion of the ascending limb of Henle suggests that the SNP exerts its effect through sodium homeostasis [25]. Also based on renal expression, SNPs in or near to PAPPA2 and ADAMTS7 (rs61823001 and rs62011052, resp., [8]) are expected to play a role in the renal salt-handling pathway. Interestingly in regard to the protein encoded by ADAMTS7, angiotensin II stimulation induced renal expression of the protein [46]. Similarly, renal cortex expression of PAPPA2 in Dahl salt-sensitive rats responded to changes of salt diet supporting a role of the SNP in the renal salt-handing pathway [47]. SNPs in FAM186B and ARHGAP24 on the other hand are postulated to play a role in renal function based on involvement with kidney diseases. Combining whole exome sequencing and homozygosity mapping in consanguineous families, FAM186B was identified as a novel candidate gene for monogenic, recessive nephronophthisis-related ciliopathies [48]. ARHGAP24 on the other hand is thought to play a role in renal cell carcinoma and focal segmental glomerulosclerosis most likely through RhoA and Rac1 signaling pathways [49, 50].

3.2. Ion Transport. Several SNPs in genes involved with ion transport have been associated with blood pressure (e.g., ATP2B1, CACNA1D, CACNA2D2, CACNB2, KCNK3, SLC4A7, and SLC39A8; Table 1). Of these, the one most studied and replicated are SNPs in ATP2B1 [9, 18, 22, 51]. Confirming the role of ATP2B1 in blood pressure regulation is the vascular smooth muscle cell-specific knockout of ATP2B1 mice which had higher systolic blood pressure and significantly increased phenylephrine-induced vasoconstrictions [52]. Similarly, silencing of ATP2B1 through injection of an SiRNA complex into mouse tail veins led to an increase in blood pressure and an increase in contractile response to phenylephrine [53]. These results support that ATP2B1 genetic variants are the causative gene for the association with blood pressure seen in GWASs. The other gene encoding an ion channel with significant supporting evidence is CACNA1D. This is because gain of function mutations in CACNA1D have been found to be causal for primary aldosteronism and for aldosterone-producing cell clusters [42, 54, 55]. As aldosterone is a key regulator of blood pressure, even small changes which may not pass the clinical threshold for primary aldosteronism may be causal for increase in blood pressure. Elevation of aldosterone may also be the mechanism of action for the other ion channels associated with primary hypertension as mutations in the ATPase Na^+/K^+ transporting subunit alpha 1 and G protein-activated inward rectifier K^+ channel 4 have also been found causal for primary aldosteronism and aldosterone-producing cell clusters [55, 56].

Table 1: Loci associated with blood pressure and/or hypertension that have been identified through large-scale studies in the past decade.

Locus name	SNP	Chr ID	Chr position	Coded allele	Best trait	Effect size of best trait (OR beta)	Coded allele frequency	Reporting article
2q36.3	rs2972146	2	226,235,982	T	DBP	0.17	0.19	Surendran et al. [29]
7q32.1	rs4728142	7	128,933,913	A	SBP	−0.224	0.29	Surendran et al. [29]
ABHD17C	rs35199222	15	80,720,696	A	SBP	0.322	0.18	Hoffmann et al. [8], Warren et al. [26]
ABHD17C	rs11634851	15	80,736,624	G	SBP	0.316	0.461	Wain et al. [27]
ABLIM3-SH3TC2	rs9687065	5	149,011,577	A	DBP	0.26	0.16	Kato et al. [20]
ACE	rs4308	17	63,482,264	A	DBP	0.213	0.24	Hoffmann et al. [8], Warren et al. [26]
ACOX1	rs2467099	17	75,952,964	T	SBP	−0.307	0.18	Hoffmann et al. [8], Warren et al. [26]
ADAMTS7-MORF4L1	rs62012628	15	78,777,658	T	DBP	−0.238	0.34	Hoffmann et al. [8], Warren et al. [26]
ADAMTS7-MORF4L1	rs62011052	15	79,156,983	C	PP	−0.28	0.14	Hoffmann et al. [8]
ADAMTS8	rs11222084	11	130,403,335	T	PP	0.337	0.21	Wain et al. [19]
ADAMTS9	rs918466	3	64,724,577	A	DBP	−0.204	0.35	Ehret et al. [12]
ADCY3	rs55701159	2	24,916,727	T	DBP	0.285	0.1	Warren et al. [26]
ADM	rs360157	11	9,732,674	T	SBP	0.413	0.44	Ehret et al. [12]
ADM	rs7129220	11	10,350,538	A	SBP	−0.619	0.058	Ehret et al. [18]
ADM	rs7129220	11	10,350,538	A	DBP	−0.299	0.058	Ehret et al. [18]
ADO	rs10995311	10	62,805,174	G	DPB	−0.20	0.38	Liu et al. [23], Surendran et al. [29]
ADRB1	rs2782980	10	114,021,768	T	PP	−0.338	0.28	Wain et al. [19]
ADRB1-RNU6-709P	rs10787517	10	114,055,047	A	SBP	0.442	0.616	Wain et al. [27]
AGT	rs2004776	1	230,712,956	T	SBP	0.42	0.41	Johnson et al. [30]
AKT2	rs9710247	19	40,254,542	G	DBP	0.252	0.44	Wain et al. [27]
AMH-SF3A2	rs740406	19	2,232,222	A	PP	−0.55	0.21	Kato et al. [20]
ARHGAP12	rs10826995	10	31,793,730	T	PP	−0.212	0.3	Hoffmann et al. [8], Warren et al. [26]
ARHGAP24	rs2014912	4	85,794,517	T	SBP	0.62	0.19	Kato et al. [20]
ARNTL	rs900145	11	13,272,358	G	DBP	−0.25	0.43	Liu et al. [23]
ARVCF	rs12628032	22	19,980,457	T	PP	0.24	0.27	Hoffmann et al. [8], Warren et al. [26]
ARVCF	rs4819852	22	20,000,644	A	PP	0.261	0.29	Wain et al. [27]
ATP2B1	rs2681472	12	89,615,182	A	DBP	0.5	0.83	Levy et al. [9]
ATP2B1	rs2681492	12	89,619,312	T	SBP	1.26	0.21	Levy et al. [9]
ATP2B1	rs17249754	12	89,666,809	A	BP	0.8	0.35	Kelly et al. [31]
BAT2-BAT5	rs805303	6	31,648,589	G	SBP	0.376	0.44	Johnson et al. [30]
BDNF	rs11030119	11	27,706,555	A	DBP	−0.163	0.26	Hoffmann et al. [8], Warren et al. [26]
BLK-GATA4	rs2898290	8	11,576,400	C	SBP	NA	0.38	Ho et al. [33]
C10orf107	rs4590817	10	61,707,795	C	DBP	0.436	0.16	Wain et al. [27]
C10orf107	rs1530440	10	61,764,833	T	DBP	0.19	0.15	Newton-Cheh et al. [10]
C10orf32, C10orf32-ASMT	rs4409766	10	102,856,906	T	SBP	1.24	0.71	Lu et al. [51]
C17orf82-TBX2	rs2240736	17	61,408,032	T	MAP	0.35	0.35	Kato et al. [20]
C20orf187	rs1887320	20	10,985,350	A	SBP	0.78	0.53	Lu et al. [51]
C2orf43	rs2289081	2	20,682,080	C	PP	−0.223	0.31	Hoffmann et al. [8], Warren et al. [26]
C5orf56	rs2188962	5	132,435,113	T	DBP	−0.2	0.14	Liu et al. [23], Surendran et al. [29]

TABLE 1: Continued.

Locus name	SNP	Chr ID	Chr position	Coded allele	Best trait	Effect size of best trait (OR beta)	Coded allele frequency	Reporting article
CACNA1D	rs9810888	3	53,601,568	G	DBP	0.39	0.39	Lu et al. [51]
CACNA2D2	rs743757	3	50,438,947	C	DBP	0.245	0.36	Hoffmann et al. [8], Warren et al. [26]
CACNB2	rs1813353	10	18,418,519	C	DBP	0.332	0.34	Wain et al. [27]
CACNB2	rs11014166	10	18,419,869	A	DBP	0.46	0.21	Levy et al. [9]
CAMKV-ACTBP13	rs36022378	3	49,876,272	T	DBP	−0.202	0.11	Hoffmann et al. [8], Warren et al. [26]
CAPZA1	rs10745332	1	112,646,431	A	SBP	0.96	0.82	Lu et al. [51]
CASC15	rs6911827	6	22,130,372	T	SBP	0.296	0.30	Hoffmann et al. [8], Warren et al. [26]
CASZ1	rs880315	1	10,736,809	T	SBP	−0.475	0.39	Ehret et al. [12]
CCDC141	rs79146658	2	178,921,341	T	DBP	−0.311	0.03	Hoffmann et al. [8], Warren et al. [26]
CCDC41-CEP83-RN7SL483P	rs139236208	12	94,486,966	A	PP	−0.363	0.04	Hoffmann et al. [8], Warren et al. [26]
CCNE1	rs62104477	19	29,804,084	T	DBP	0.177	0.19	Hoffmann et al. [8], Warren et al. [26]
CD34	rs12731740	1	207,851,475	T	PP	−0.249	0.08	Warren et al. [26]
CDC42BPA	rs10916082	1	227,064,925	A	DBP	−0.177	0.27	Warren et al. [26]
CDH13	rs7500448	16	83,012,185	A	PP	0.329	0.17	Hoffmann et al. [8], Warren et al. [26]
CDH17	rs2446849	8	94,091,269	T	SBP	−0.63	0.22	Zhu et al. [32]
CELA2A	rs1042010	1	15,467,418	A	SBP	0.412	0.19	Hoffmann et al. [8], Warren et al. [26]
CELA2A	rs3820068	1	15,471,702	A	SBP	0.425	0.19	Wain et al. [27]
CEP164	rs8258	11	117,412,960	T	PP	0.236	0.47	Hoffmann et al. [8], Warren et al. [26]
CEP68	rs74181299	2	65,056,838	T	PP	0.23	0.46	Hoffmann et al. [8], Warren et al. [26]
CERS5	rs7302981	12	50,144,032	A	DBP	0.249	0.30	Liu et al. [23], Surendran et al. [29]
CFDP1	rs11643209	16	75,297,146	T	SBP	−0.339	0.47	Hoffmann et al. [8], Warren et al. [26]
CHIC2	rs871606	4	53,933,078	T	PP	0.429	0.21	Wain et al. [19]
chr15mb95	rs12906962	15	94,768,842	T	DBP	−0.221	0.42	Hoffmann et al. [8], Warren et al. [26]
chr1mb25	rs6686889	1	24,703,979	T	DBP	0.185	0.37	Warren et al. [26]
chr1mb9	rs9662255	1	9,381,890	A	PP	−0.207	0.41	Hoffmann et al. [8], Warren et al. [26]
CHST12-LFNG	rs2969070	7	2,472,910	A	DBP	−0.205	0.21	Ehret et al. [12]
CMIP	rs8059962	16	81,540,592	T	DBP	−0.170	0.45	Warren et al. [26]
CNNM2	rs11191548	10	103,086,421	C	SBP	1.082	0.09	Wain et al. [27]
COL21A1	rs1925153	6	56,237,982	T	PP	−0.21	0.44	Liu et al. [23]
CPEB4	rs72812846	5	173,950,633	A	DBP	−0.209	0.11	Hoffmann et al. [8], Warren et al. [26]
CRACR2B	rs7126805	11	828,916	A	PP	0.222	<0.01	Warren et al. [26]
CRK	rs12941318	17	1,430,304	T	SBP	−0.269	0.37	Hoffmann et al. [8], Warren et al. [26]
CRYAA-SIK1-RRP1B	rs12627651	21	43,340,723	A	SBP	0.503	0.19	Ehret et al. [12], Surendran et al. [29]

TABLE 1: Continued.

Locus name	SNP	Chr ID	Chr position	Coded allele	Best trait	Effect size of best trait (OR beta)	Coded allele frequency	Reporting article
CSK	rs1378942	15	74,785,026	A	DBP	0.371	0.65	Wain et al. [27]
CYB561-LOC342541	rs4459609	17	63,471,587	A	DBP	0.198	0.61	Wain et al. [27]
CYP17A1-NT5C2	rs1004467	10	102,834,750	A	SBP	1.2	0.16	Levy et al. [9], Newton-Cheh et al. [10]
CYP1A1-ULK3	rs6495122	15	74,833,304	A	DBP	0.45	0.29	Levy et al. [9], Newton-Cheh et al. [10]
CYP2C19	rs4494250	10	94,804,000	A	DPB	0.21	0.22	Liu et al. [23]
DBH	rs6271	9	133,657,152	T	DBP	−0.423	0.04	Ehret et al. [12]
DNM3	rs12405515	1	172,388,301	T	DBP	−0.165	0.47	Hoffmann et al. [8], Warren et al. [26]
DPEP1	rs1126464	16	89,637,957	C	DBP	0.275	0.26	Liu et al. [23], Surendran et al. [29]
EBF1	rs11953630	5	158,418,394	T	DBP	−0.281	0.18	Johnson et al. [30]
EBF2	rs6557876	8	26,043,159	T	SBP	−0.411	0.33	Wain et al. [27]
ENPEP	rs6825911	4	110,460,482	C	DBP	0.39	0.42	Kato et al. [22]
ESR1	rs13192976	6	151,991,280	A	PP	−0.332	0.21	Hoffmann et al. [8], Warren et al. [26]
FAF1	rs147696085	1	50,556,195	G	PP	0.298	0.06	Hoffmann et al. [8]
FAM186B	rs7977389	12	49,587,939	T	PP	0.237	0.18	Hoffmann et al. [8]
FAM208A	rs9827472	3	56,692,618	T	DBP	−0.177	0.46	Hoffmann et al. [8], Warren et al. [26]
FBLN5	rs2244643	14	91,892,678	A	PP	−0.213	0.29	Hoffmann et al. [8]
FBN2	rs6595838	5	128,532,506	A	SBP	0.344	0.41	Hoffmann et al. [8], Warren et al. [26]
FBXL19	rs72799341	16	30,925,422	A	DBP	0.185	0.27	Hoffmann et al. [8], Warren et al. [26]
FER1L5	rs7599598	2	96,686,103	A	DBP	−0.31	0.42	Ganesh et al. [34]
FERMT2	rs9888615	14	52,910,822	T	SBP	−0.318	0.36	Hoffmann et al. [8], Warren et al. [26]
FGD5	rs11128722	3	14,916,619	A	SBP	−0.383	0.41	Ehret et al. [12]
FGF5	rs16998073	4	80,263,187	T	DBP	0.21	0.23	Newton-Cheh et al. [10]
FGGY-HSD52	rs3889199	1	59,188,070	A	PP	0.351	0.14	Hoffmann et al. [8], Warren et al. [26]
FIGN-PRPS1P1	rs16849211	2	164,043,173	T	PP	0.364	0.23	Wain et al. [27]
FIGN-PRPS1P1	rs1446468	2	164,106,976	C	SBP	0.538	0.55	Wain et al. [27]
FIGN-GRB14	rs16849225	2	164,050,310	C	SBP	0.75	0.23	Ehret et al. [18], Kato et al. [22], Wain et al. [19]
FLJ32810-TMEM133	rs633185	11	100,722,807	G	SBP	−0.565	0.36	Johnson et al. [30]
FN1	rs1250259	2	215,435,759	A	PP	−0.314	0.23	Hoffmann et al. [8], Warren et al. [26]
FNDC1	rs449789	6	159,278,093	C	PP	0.359	0.15	Hoffmann et al. [8], Warren et al. [26]
FOSL2	rs7562	2	28,412,873	T	SBP	0.263	0.50	Warren et al. [26]
FRMD3	rs115795127	9	83,378,986	T	BP	NA	NR	Liang et al. [35]
FURIN-FES	rs2521501	15	90,894,158	T	SBP	0.65	0.21	Johnson et al. [30]
GATA2	rs62270945	3	128,483,046	T	PP	0.607	0.01	Hoffmann et al. [8], Warren et al. [26]
GJA1	rs11154027	6	121,460,244	T	PP	0.207	0.38	Warren et al. [26]
GNAS-EDN3	rs6015450	20	59,176,062	G	SBP	0.896	0.10	Johnson et al. [30]
GOSR2	rs17608766	17	46,935,905	T	SBP	−0.556	0.05	Johnson et al. [30]

TABLE 1: Continued.

Locus name	SNP	Chr ID	Chr position	Coded allele	Best trait	Effect size of best trait (OR beta)	Coded allele frequency	Reporting article
GPAT2-FAHD2CP	rs2579519	2	96,009,418	T	DBP	−0.197	0.41	Warren et al. [26]
GPATCH2	rs12408022	1	217,545,447	T	DBP	0.198	0.26	Hoffmann et al. [8], Warren et al. [26]
GPR20	rs34591516	8	141,356,987	T	SBP	0.323	0.05	Surendran et al. [29]
GPR20	rs78192203	8	141,364,973	T	BP	NA	NR	Liang et al. [35]
GPR98/ARRDC3	rs10474346	5	91,268,322	C	DBP	1.1	0.31	Fox et al. [36]
GTF2B	rs10922502	1	88,894,475	A	SBP	−0.382	0.34	Hoffmann et al. [8], Warren et al. [26]
GUCY1A3	rs13143871	4	155,698,052	T	SBP	0.96	0.80	Lu et al. [51]
GUCY1A3-GUCY1B3	rs13139571	4	155,724,361	C	DBP	0.26	0.21	Johnson et al. [30]
GYPA_HHIP	rs4292285	4	144,350,802	T	DBP	0.177	0.41	Hoffmann et al. [8]
HAAO-RNU6-242P-AC016735.1	rs13403122	2	42,851,618	C	DBP	0.226	0.20	Hoffmann et al. [8], Warren et al. [26]
HDAC9	rs2107595	7	19,009,765	A	PP	0.31	0.25	Kato et al. [20]
HFE	rs1799945	6	26,090,951	G	DBP	0.457	0.09	Johnson et al. [30]
HFE	rs1800562	6	26,092,913	A	DBP	0.394	0.06	Wain et al. [27]
HIPK2	rs1011018	7	139,763,465	A	SBP	−0.329	0.35	Warren et al. [26]
HIVEP3	rs7515635	1	41,942,399	T	SBP	0.336	0.47	Ehret et al. [12]
HM13-ID1	rs6060114	20	31,581,870	T	DBP	0.267	0.27	Hoffmann et al. [8]
HNF4G-RNU2-54P	rs1449544	8	75,679,645	A	PP	0.183	0.41	Hoffmann et al. [8]
HOTTIP	rs1859168	7	27,202,740	C	DBP	0.436	0.92	Wain et al. [27]
HOXA3	rs6969780	7	27,119,517	C	BP	NA	NR	Liang et al. [35]
HOXA-EVX1	rs17428471	7	27,298,248	T	SBP	1.2	0.08	Franceschini et al. [24]
HOXB7	rs7406910	17	48,610,894	T	SBP	−0.456	0.12	Surendran et al. [29]
HRCT1	rs76452347	9	35,906,474	T	DBP	−0.25	0.15	Liu et al. [23]
HSD52-LOC105378756	rs10889130	1	59,148,708	A	PP	0.288	0.33	Wain et al. [27]
HSPB7	rs1048238	1	16,015,154	T	SBP	0.366	0.02	Wain et al. [27]
IGFBP3	rs11977526	7	45,968,511	A	DBP	0.3	0.44	Zhu et al. [32], Liu et al. [23]
INPP5B	rs871524	1	37,945,773	A	PP	0.228	0.33	Wain et al. [27]
INSR	rs7248104	19	7,224,420	A	PP	−0.20	0.35	Liu et al. [23]
INSR	rs36047283	19	7,255,690	G	SBP	0.801	0.11	Wain et al. [27]
ITGA11	rs1563894	15	68,343,437	A	SBP	−0.093	0.18	Parmar et al. [37]
JAG1	rs1327235	20	10,988,382	G	DBP	0.302	0.46	Johnson et al. [30]
JAG1-LOC101929395	rs6040076	20	10,678,234	C	PP	0.285	0.49	Wain et al. [27]
KCNH4-HSD17B1	rs79089478	17	42,165,223	T	PP	0.584	0.01	Warren et al. [26]
KCNK3	rs1275988	2	26,691,496	T	SBP	−0.6	0.41	Ganesh et al. [34]
KIAA0753	rs7226020	17	6,570,508	T	PP	−0.256	0.38	Hoffmann et al. [8], Warren et al. [26]
KIAA1462	rs9337951	10	30,028,144	A	PP	0.28	0.26	Hoffmann et al. [8], Warren et al. [26]
L3MBTL4	rs403814	18	6,282,594	A	BP	1.15	NR	Liu et al. [23]
LHFPL2	rs10057188	5	78,541,966	A	PP	−0.205	0.24	Hoffmann et al. [8], Warren et al. [26]
LINC01615-THBS2	rs1322639	6	169,187,008	A	PP	0.316	0.33	Hoffmann et al. [8], Warren et al. [26]
LMO1	rs110419	11	8,231,306	A	DBP	0.159	0.43	Surendran et al. [29]
LOC101928278	rs10932679	2	216,787,868	T	PP	0.226	0.19	Wain et al. [27]
LOC102723446	rs10260816	7	45,970,501	G	PP	0.298	0.43	Wain et al. [27]

Table 1: Continued.

Locus name	SNP	Chr ID	Chr position	Coded allele	Best trait	Effect size of best trait (OR beta)	Coded allele frequency	Reporting article
LOC105369687-LOC105369688	rs73075659	12	20,220,607	G	SBP	0.357	0.31	Wain et al. [27]
LOC105370003	rs11067763	12	115,760,536	A	DBP	0.51	0.62	Lu et al. [51]
LOC105371811-LOC105371812	rs79917357	17	48,747,312	A	SBP	0.342	0.17	Wain et al. [27]
LOC105374567-LOC102723854	rs72876037	2	42,967,456	T	SBP	0.534	0.12	Wain et al. [27]
LOC105379231	rs9693857	8	9,409,607	T	SBP	0.337	0.45	Wain et al. [27]
LOC107986913-LOC105379224	rs7826238	8	8,529,585	T	SBP	0.335	0.47	Wain et al. [27]
LOC283335	rs73099903	12	53,046,995	T	SBP	0.768	0.06	Wain et al. [27]
LRP12/ZFPM2	rs35783704	8	104,954,030	A	SBP	−0.609	0.03	Wain et al. [27]
LRRC10B-SYT7	rs751984	11	61,510,774	T	MAP	0.33	0.27	Kato et al. [20], Ehret et al. [12]
LSP1-TNNT3	rs661348	11	1,884,062	T	MAP	−0.65	0.42	Johnson et al. [30]
MAP4	rs319690	3	47,885,994	T	DBP	0.282	0.41	Wain et al. [19]
MAPK4-MRO	rs36010659	18	50,757,579	T	PP	0.25	0.12	Hoffmann et al. [8], Warren et al. [26]
MCF2L	rs9549328	13	112,981,842	T	SBP	0.318	0.22	Hoffmann et al. [8], Warren et al. [26]
MECOM	rs419076	3	169,383,098	T	SBP	0.409	0.42	Johnson et al. [30]
METTL21A-AC079767.3	rs55780018	2	207,661,416	T	SBP	−0.391	0.35	Hoffmann et al. [8], Warren et al. [26]
MIR1263	rs16833934	3	164,019,462	G	DBP	−1.63	0.31	Simino et al. [38]
MKLN1	rs13238550	7	131,374,297	A	SBP	0.331	0.33	Warren et al. [26]
MOV10	rs12129649	1	112,688,881	T	DBP	0.548	0.06	Wain et al. [27]
MRAS	rs2306374	3	138,401,110	T	DBP	−0.184	0.08	Hoffmann et al. [8], Warren et al. [26]
MRC2	rs740698	17	62,689,790	T	PP	−0.228	0.41	Warren et al. [26]
MSRA	rs11249992	8	10,362,902	A	SBP	0.293	0.38	Wain et al. [27]
MTAP	rs4364717	9	21,801,531	A	DBP	−0.175	0.43	Warren et al. [26]
MTF1-SF3A3	rs4360494	1	37,990,219	C	PP	0.278	0.38	Hoffmann et al. [8], Warren et al. [26]
MTHFR	rs17367504	1	11,802,721	G	DBP	0.526	0.15	Wain et al. [27]
MTHFR-NPPB	rs4846049	1	11,790,308	T	DBP	−0.55	0.37	Johnson et al. [30]
MYEOV	rs67330701	11	69,312,240	T	DBP	−0.367	0.12	Hoffmann et al. [8], Warren et al. [26]
MYH6	rs452036	14	23,396,676	A	PP	−0.282	0.34	Liu et al. [23], Surendran et al. [29]
NADK-CPSF3L	rs139385870	1	1,754,504	D	SBP	−0.352	0.33	Hoffmann et al. [8], Warren et al. [26]
NFKBIA	rs8904	14	35,402,011	A	SBP	0.377	0.40	Wain et al. [27]
NME7	rs7519279	1	169,238,123	G	PP	0.218	0.13	Hoffmann et al. [8]
NOS3	rs3918226	7	150,993,088	T	DBP	0.83	0.03	Johnson et al. [30]
NOTCH3	rs10418305	19	15,167,997	C	PP	−0.282	0.13	Hoffmann et al. [8]
NOV	rs2071518	8	119,423,572	T	PP	0.312	0.32	Wain et al. [19]
NOX4	rs2289125	11	89,491,285	A	PP	−0.377	0.32	Hoffmann et al. [8], Warren et al. [26]
NPNT	rs13112725	4	105,990,585	C	SBP	0.435	0.34	Hoffmann et al. [8], Warren et al. [26]
NPPA-AS1, NPPA	rs12744757	1	11,846,764	T	SBP	0.695	0.06	Wain et al. [27]

TABLE 1: Continued.

Locus name	SNP	Chr ID	Chr position	Coded allele	Best trait	Effect size of best trait (OR beta)	Coded allele frequency	Reporting article
NPR1	rs35479618	1	153,689,947	A	SBP	1.34	0.01	Liu et al. [23]
NPR3-C5orf23	rs1173771	5	32,814,922	C	SBP	0.63	0.34	Johnson et al. [30], Kato et al. [22]
OBFC1	rs4387287	10	103,918,139	A	SBP	0.338	0.32	Surendran et al. [29]
OR5B12	rs11229457	11	58,439,730	T	SBP	−0.312	0.22	Surendran et al. [29]
OSR1	rs1344653	2	19,531,084	A	PP	−0.27	0.38	Kato et al. [20]
PABPC4	rs4660293	1	39,562,508	G	DBP	0.27	0.10	Liu et al. [23]
PALLD-chr4mb174	rs1566497	4	168,795,997	A	PP	0.236	0.23	Hoffmann et al. [8], Warren et al. [26]
PAPPA2	rs61823001	1	176,664,440	G	PP	0.31	0.03	Hoffmann et al. [8]
PAX2	rs112184198	10	100,844,757	A	SBP	−0.659	0.05	Hoffmann et al. [8], Warren et al. [26]
PDE10A	rs147212971	6	165,764,963	T	DBP	−0.360	0.13	Hoffmann et al. [8], Warren et al. [26]
PDE3A	rs12579720	12	20,020,830	C	DBP	−0.32	0.46	Kato et al. [20]
PDE5A	rs66887589	4	119,588,124	T	DBP	−0.215	0.50	Hoffmann et al. [8], Warren et al. [26]
PHACTR1	rs9349379	6	12,903,725	A	SBP	0.289	0.38	Surendran et al. [29]
PHIP	rs10943605	6	78,945,760	A	DBP	0.18	0.49	Liu et al. [23]
PIK3CG	rs17477177	7	106,771,412	T	PP	−0.418	0.17	Wain et al. [19]
PKHD1	rs13205180	6	51,967,696	T	DBP	0.168	0.34	Hoffmann et al. [8], Warren et al. [26]
PKN2-AS1	rs61767086	1	88,600,899	G	PP	0.413	0.14	Wain et al. [27]
PLCB1	rs6108168	20	8,645,624	A	DBP	−0.211	0.38	Warren et al. [26]
PLCD3	rs12946454	17	45,130,754	T	SBP	0.28	0.21	Newton-Cheh et al. [10]
PLCE1	rs932764	10	94,136,183	G	SBP	0.484	0.43	Johnson et al. [30]
PLCE1	rs932764	10	94,136,183	G	SBP	0.484	0.44	Ehret et al. [18]
PLEKHA7	rs177542	11	16,901,107	A	DBP	0.243	0.50	Wain et al. [27]
PLEKHA7-NUCB2	rs381815	11	16,880,721	T	SBP	0.84	0.21	Levy et al. [9]
PLEKHG1	rs17080102	6	150,683,634	C	DBP	−0.74	0.12	Franceschini et al. [24]
PNPT1	rs1975487	2	55,581,918	A	DBP	−0.217	0.32	Ehret et al. [12]
POC5-SV2C	rs10078021	5	75,742,606	T	DBP	−0.164	0.46	Hoffmann et al. [8], Warren et al. [26]
PPL	rs12921187	16	4,893,018	T	DBP	−0.174	0.41	Hoffmann et al. [8], Warren et al. [26]
PPP2R5E	rs8016306	14	63,461,828	A	SBP	0.335	0.41	Warren et al. [26]
PRDM11	rs11442819	11	45,186,590	I	PP	−0.279	0.13	Hoffmann et al. [8], Warren et al. [26]
PRDM16	rs2493292	1	3,412,095	T	SBP	0.42	0.13	Liu et al. [23]
PRDM6-SUMO1P5	rs337100	5	123,210,816	A	PP	0.277	0.40	Wain et al. [27]
PRDM6-CSNK1G3	rs13359291	5	123,140,763	A	SBP	0.53	0.28	Kato et al. [20]
PRDM8-FGF5	rs1902859	4	80,236,549	C	SBP	1.34	0.41	Lu et al. [51]
PRDM8-FGF5	rs1458038	4	80,243,569	T	DBP	0.403	0.30	Wain et al. [27]
PREX1	rs6095241	20	48,692,260	A	DBP	−0.168	0.46	Surendran et al. [29]
PRKAG1	rs1126930	12	49,005,349	C	PP	0.5	0.02	Surendran et al. [29]
PRKCE	rs11690961	2	46,136,197	A	PP	0.34	0.04	Hoffmann et al. [8], Warren et al. [26]
PRKD3	rs13420463	2	37,290,423	A	SBP	0.356	0.49	Hoffmann et al. [8], Warren et al. [26]
PROCR	rs867186	20	35,176,751	A	DBP	0.265	0.11	Surendran et al. [29]

TABLE 1: Continued.

Locus name	SNP	Chr ID	Chr position	Coded allele	Best trait	Effect size of best trait (OR beta)	Coded allele frequency	Reporting article
PRRC2A-BAG6	rs151168737	6	31,638,615	A	DBP	0.249	0.46	Wain et al. [27]
PSMD5	rs10760117	9	120,824,459	T	SBP	0.334	0.42	Ehret et al. [12], Liu et al. [23]
PYY	rs62080325	17	43,983,263	A	PP	−0.186	0.21	Warren et al. [26]
RABGAP1	rs10818775	9	122,993,292	C	PP	0.254	0.30	Hoffmann et al. [8]
RAPSN, PSMC3, SLC39A13	rs7103648	11	47,440,232	A	DBP	−0.203	0.33	Ehret et al. [12]
RBM47	rs35529250	4	40,426,074	T	SBP	−1.537	<0.01	Surendran et al. [29]
RCOR2	rs4980532	11	63,913,247	T	PP	0.301	0.56	Wain et al. [27]
RGL3	rs167479	19	11,416,089	T	DBP	−0.33	0.49	Liu et al. [23], Surendran et al. [29]
RNF207	rs709209	1	6,218,354	A	PP	0.199	0.36	Surendran et al. [29]
RP11-273G15.2	rs62524579	8	142,979,538	A	DBP	−0.175	0.48	Hoffmann et al. [8], Warren et al. [26]
RP11-321F6.1	rs7178615	15	66,576,734	A	DBP	−0.179	0.36	Warren et al. [26]
RP11-435J9.2-TLN2	rs956006	15	62,516,340	C	PP	0.188	0.23	Hoffmann et al. [8]
RP11-439C8.2	rs143112823	3	154,990,178	A	DBP	−0.403	0.06	Hoffmann et al. [8], Warren et al. [26]
RP11-61O1.1	rs9323988	14	98,121,293	T	PP	−0.212	0.29	Hoffmann et al. [8], Warren et al. [26]
RP4-710M16.1-PPAP2B-PLPP3	rs112557609	1	56,111,252	A	PP	0.227	0.22	Hoffmann et al. [8], Warren et al. [26]
RPL34P18-CDH17	rs7006531	8	94,098,516	G	BP	NA	NR	Liang et al. [35]
RPL35P4-LOC107986733	rs10279895	7	27,288,591	G	DBP	0.7553	NR	Liang et al. [35]
RPL35P4-LOC107986733	rs11563582	7	27,312,031	A	BP	NA	NR	Liang et al. [35]
RPL6-PTPN11-ALDH2	rs11066280	12	112,379,979	T	DBP	1.01	0.04	Kato et al. [22]
RPS29P9-LOC102724714	rs3845811	2	207,656,788	G	SBP	0.284	0.43	Wain et al. [27]
RRAS	rs61760904	19	49,636,675	T	SBP	1.499	<0.01	Surendran et al. [29]
RSPO3	rs13209747	6	126,794,309	T	DBP	0.56	0.35	Franceschini et al. [24]
RYK	rs9859176	3	134,281,183	T	SBP	0.322	0.25	Hoffmann et al. [8], Warren et al. [26]
SBNO1	rs1060105	12	123,321,672	T	DBP	−0.182	0.18	Surendran et al. [29]
SCAI-PPP6C	rs72765298	9	125,138,717	T	PP	−0.374	0.06	Hoffmann et al. [8], Warren et al. [26]
SDCCAG8	rs953492	1	243,307,890	A	DBP	0.22	0.49	Hoffmann et al. [8], Warren et al. [26]
SENP2	rs12374077	3	185,599,886	C	DBP	0.163	0.42	Hoffmann et al. [8], Warren et al. [26]
SEPT9	rs57927100	17	77,321,218	G	SBP	−0.489	0.01	Wain et al. [27]
SETBP1	rs12958173	18	44,562,012	A	SBP	0.386	0.25	Ehret et al. [12]
SH2B3	rs3184504	12	111,446,804	T	SBP	0.75	0.33	Levy et al. [9], Newton-Cheh et al. [10]
SLC12A9	rs7801190	7	100,860,471	C	BP	1.31	0.72	Lettre et al. [39]
SLC14A2	rs7236548	18	45,517,785	A	PP	0.352	0.3	Hoffmann et al. [8], Warren et al. [26]
SLC20A2	rs2978456	8	42,467,247	T	PP	−0.188	0.45	Hoffmann et al. [8], Warren et al. [26]
SLC24A3	rs6081613	20	19,485,263	A	PP	0.263	0.31	Hoffmann et al. [8], Warren et al. [26]
SLC35F1	rs9372498	6	118,251,323	A	DBP	0.334	0.07	Hoffmann et al. [8], Warren et al. [26]

Table 1: Continued.

Locus name	SNP	Chr ID	Chr position	Coded allele	Best trait	Effect size of best trait (OR beta)	Coded allele frequency	Reporting article
SLC39A8	rs13107325	4	102,267,552	T	DBP	−0.684	0	Johnson et al. [30]
SLC4A7	rs11716531	3	27,415,717	A	DBP	0.213	0.237	Wain et al. [27]
SLC4A7	rs13082711	3	27,496,418	T	DBP	−0.238	0.12	Johnson et al. [30]
SLC8A1	rs4952611	2	40,340,603	T	DBP	−0.157	0.34	Warren et al. [26]
SMARCA2-VLDLR	rs872256	9	2,496,480	T	SBP	0.096	0.43	Parmar et al. [37]
SNORD32B	rs926552	6	29,580,312	T	DBP	−0.31	0.07	Liu et al. [23]
SNX31	rs2978098	8	100,664,447	A	DBP	0.165	0.34	Warren et al. [26]
SOX6	rs4757391	11	16,281,393	C	DBP	0.49	0.28	Lu et al. [51]
SSPN	rs6487543	12	26,285,256	A	SBP	0.3	0.46	Warren et al. [26]
ST7L-CAPZA1-MOV10	rs2932538	1	112,673,921	G	DBP	0.24	0.17	Johnson et al. [30]
STK39	rs6749447	2	168,184,876	G	SBP	3	0.48	Wang et al. [40]
SUGCT	rs76206723	7	40,408,372	A	PP	−0.346	0.18	Hoffmann et al. [8], Warren et al. [26]
SULT1C3	rs6722745	2	108,258,788	C	SBP	0.28	0.4	Liu et al. [23]
SVEP1	rs111245230	9	110,407,495	C	SBP	0.94	0.03	Liu et al. [23]
SWAP70	rs2649044	11	9,742,422	T	DBP	0.2	0.547	Wain et al. [27]
TBC1D1-FLJ13197	rs2291435	4	38,385,774	T	SBP	−0.378	0.4	Ehret et al. [12]
TBX5-TBX3	rs2384550	12	114,914,926	A	DBP	−0.35	0.29	Levy et al. [9], Kato et al. [22]
TCF7L1	rs11689667	2	85,264,242	T	PP	0.176	0.28	Hoffmann et al. [8], Warren et al. [26]
TCF7L2	rs34872471	10	112,994,312	T	PP	−0.226	0.24	Hoffmann et al. [8]
TEX41	rs1438896	2	144,888,505	T	DBP	0.234	0.3	Hoffmann et al. [8], Warren et al. [26]
TEX41	rs55944332	2	144,969,054	G	DBP	0.267	0.24	Wain et al. [27]
TFAP2D	rs78648104	6	50,715,296	T	SBP	−0.481	0.09	Warren et al. [26]
TM6SF1	rs2034618	15	83,130,880	C	DBP	0.21	0.22	Hoffmann et al. [8]
TMEM161B	rs10059921	5	88,218,698	T	SBP	−0.526	0.06	Hoffmann et al. [8], Warren et al. [26]
TMEM194B-NEMP2-NAB1	rs7592578	2	190,574,865	T	DBP	−0.240	0.18	Hoffmann et al. [8], Warren et al. [26]
TNRC6A	rs11639856	16	24,777,324	A	SBP	−0.37	0.17	Liu et al. [23]
TNRC6B	rs470113	22	40,333,610	A	PP	−0.253	0.21	Surendran et al. [29]
TNS1	rs1063281	2	217,804,009	T	DBP	−0.200	0.43	Hoffmann et al. [8], Warren et al. [26]
TNXB	rs2021783	6	32,077,074	C	DBP	0.49	0.79	Lu et al. [51]
TNXB	rs185819	6	32,082,290	C	SBP	0.365	0.513	Wain et al. [27]
TP53-SLC2A4	rs78378222	17	7,668,434	T	PP	0.904	0	Hoffmann et al. [8], Warren et al. [26]
TRAPPC9	rs4288356	8	140,045,627	A	PP	0.224	0.615	Wain et al. [27]
TRAPPC9	rs4454254	8	140,049,929	A	PP	−0.261	0.45	Warren et al. [26]
TRIM36	rs10077885	5	115,054,424	A	DBP	−0.194	0.42	Ehret et al. [12]
UBA52P4-LOC105377005	rs820430	3	27,507,409	A	SBP	0.76	0.32	Lu et al. [51]
ULK4	rs7651190	3	41,724,463	G	BP	NA	NR	Liang et al. [35]
ULK4	rs9815354	3	41,912,651	A	DBP	0.6	0.17	Levy et al. [9]
ULK4	rs7372217	3	41,948,630	G	BP	NA	NR	Liang et al. [35]
UMOD	rs13333226	16	20,354,332	NA	HTN	NA	0.24	Padmanabhan et al. [25]
VAC14	rs117006983	16	70,721,707	A	PP	0.986	0	Warren et al. [26]
WNT3A	rs2760061	1	228,003,374	A	DBP	0.23	0.35	Hoffmann et al. [8], Warren et al. [26]

TABLE 1: Continued.

Locus name	SNP	Chr ID	Chr position	Coded allele	Best trait	Effect size of best trait (OR beta)	Coded allele frequency	Reporting article
XKR6	rs10107145	8	10,900,703	G	SBP	0.361	0.528	Wain et al. [27]
XRCC6	rs73161324	22	41,642,782	T	PP	0.496	0.02	Warren et al. [26]
ZBTB38	rs16851397	3	141,415,976	A	DBP	−0.493	0.05	Surendran et al. [29]
ZC3HC1	rs11556924	7	130,023,656	T	DBP	−0.214	0.27	Ehret et al. [12]
ZFAT	rs894344	8	134,600,502	A	SBP	−0.258	0.47	Warren et al. [26]
ZNF101	rs2304130	19	19,678,719	A	DBP	−0.292	0.11	Surendran et al. [29]
ZNF318-ABCC10	rs10948071	6	43,312,975	T	PP	−0.38	0.43	Ganesh et al. [34]
ZNF385B	rs13407401	2	179,850,979	A	SBP	0.434	0.291	Wain et al. [27]
ZNF638	rs3771371	2	71,400,409	T	PP	−0.160	0.37	Hoffmann et al. [8], Warren et al. [26]
ZNF652	rs12940887	17	49,325,445	T	DBP	0.26	0.374	Wain et al. [27]
ZNF652	rs16948048	17	49,363,104	G	DBP	0.39	0.29	Newton-Cheh et al. [10]
ZNRF3	rs4823006	22	29,055,683	G	SBP	−0.33	0.45	Liu et al. [23]

SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; HTN: hypertension; NR: not recorded; NA: not available.

3.3. Corticosteroidogenesis. Surprisingly in the sense that corticosteroids can highly affect blood pressure, only 2 cytochrome P450 enzyme genes involved with corticosteroidogenesis have been linked to hypertension by GWASs—CYP17A1 and CYP21A2. And of that, only SNPs in the CYP17A1 gene have been replicated, though even then with inconsistent results. CYP17A1 encodes 17α-hydroxylase which is essential to the synthesis of cortisol precursors. Therefore, alteration of this gene can cause a deficiency in 17α-hydroxylase and thus cortisol, which affects blood pressure [57]. Supporting the role of CYP17A1 in blood pressure regulation is the SNP rs11191548, a SNP near the CYP17A1 gene that has been consistently associated with blood pressure in both East Asian cohorts and Caucasian cohorts [10, 17, 18, 58–60]. Patients harboring the risky C allele had lower PRA and K+ levels similar to patients with 17α-hydroxylase deficiency, suggesting that the SNP (which is actually in the noncoding region of the gene CNNM2) has an effect on the enzymatic activity of CYP17A1 [58]. One hypothesis as to why inconsistent results occur with GWAS is if the association found between the lead SNP is indirect whereby the signal produced is actually caused by a synthetically linked rarer variant in linkage disequilibrium with the identified tag SNP. This could be the case with the lead SNP rs1004467 which was identified from the CHARGE + Global BPgen meta-analysis [9]. In an Oriental cohort (from Korea), rs1004467 was found to have a modest association with hypertension in prediabetic subjects and a significant association with augmentation index in diabetic subjects [61]. However, in another Oriental cohort with similar ethnic background (from China), rs1004467 association with hypertension/blood pressure was not found in children [62]. As such, perhaps the causal SNP is not rs1004467 as identified by the initial GWAS meta-analysis but a tag SNP with poor penetrance. Interestingly, rs1004467 is in linkage disequilibrium with rs138009835, a functional SNP located 1800 bases upstream of the transcription site of CYP17A1. In vitro gene reporter gene assays and clinical functional experiments found the minor alleles to have reduced mRNA expression of CYP17A1 and reduced aldosterone excretion [63]. To note, both rs1004467 and rs11191548 are associated with a reduction in both visceral and subcutaneous fat mass in Japanese women [64].

3.4. Vascular Tone. Interestingly, although only one of the fifteen monogenic hypertension genes is postulated to mediate an effect through the vasculature, SNPs associated with blood pressure and primary hypertension are enriched in genes that are expressing their proteins in vascular smooth muscle and endothelial cells [11, 12, 65–67]. This is consistent with vascular tone playing a primary role in blood pressure regulation. Many of these genes, however, may have been reported as the causal genes due to their proximity to the SNP in question and their likelihood of playing a role in blood pressure regulation rather than due to real functional data [68]. For example, the reported gene for rs7129220, a SNP downstream to the ADM gene in the noncoding RNA CAND1.11 gene, was the ADM gene as adrenomedullin the protein encoded by ADM plays a role in vasodilation [69]. Oppositely, the reported genes for rs633185 are FLJ32810-TMEM133, even though the SNP is within the intron of ARHGAP42 (Table 1). As a candidate gene for blood pressure regulation, ARHGAP42 has many functional evidence to be the causal gene as reduced expression of ARHGAP42 in mice elevated blood pressure [70]. To note, rs633185 is in high linkage disequilibrium with rs604723, another SNP in the intron of ARHGAP42, and the minor T allele is a functional variant that increases ARHGAP42 expression by promoting serum response factor binding to a smooth muscle-selective regulatory element [71]. Based on this strong functional data, rs604723 is most likely the causative SNP at this locus. rs6271 in exon 11 of the DBH gene on the other hand is one of the rare times where GWASs had managed to directly identify a missense variant which is probably damaging to the protein dopamine β-hydroxylase according to PolyPhen-2 prediction [72]. Concurrently, severe orthostatic

syndrome (postural hypotension) were found to be caused by truncating, splice site, or missense mutations in the *DBH* gene [73].

4. Conclusion

Although some of the SNPs identified by GWAS on primary hypertension associates with similar biological pathways as Mendelian or early-onset forms of hypertension (validating the study approach), none of the SNPs identified had a large size effect (≤1 mmHg) to be of significance to an individual patient. The ultimate goals of performing these GWASs are to determine the genetic factors regulating blood pressure that can be used to make predictions about who is at risk of developing hypertension and to identify the biological pathways of the disease allowing for identification of novel targets for treatment or even prevention strategies. As currently no direct clinical application of these GWAS findings can be made, it is still debatable whether GWAS is the best approach to identify the biological underpinnings of primary hypertension. Even though yet-to-be-discovered Oriental-specific loci or rare SNPs that might have larger effect size may increase the variance for blood pressure that can be explained by genetic variation, information on epigenetic modulation (e.g., DNA methylation, posttranslational modifications of proteins, or even gut microbiota [20, 74–78]) may still be needed to explain the total heritability of raised blood pressure which cannot be captured by GWASs.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

References

[1] P. Kearney, M. Whelton, K. Reynolds, P. Muntner, P. Whelton, and J. He, "Global burden of hypertension: analysis of world-wide data," *The Lancet*, vol. 365, no. 9455, pp. 217–223, 2005.

[2] Global Health Observatory (GHO) data, "Raised blood pressure: situation and trends," http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en.

[3] Clinical Practice Guidelines, *Management of Hypertension*, Ministry of Health, Malaysia, 4th edition, 2013.

[4] O. A. Carretero and S. Oparil, "Essential hypertension: part I: definition and etiology," *Circulation*, vol. 101, no. 3, pp. 329–335, 2000.

[5] J. B. Meigs, A. K. Manning, C. S. Fox et al., "Genome-wide association with diabetes-related traits in the Framingham Heart Study," *BMC Medical Genetics*, vol. 8, article S16, Supplement 1, 2007.

[6] M. O. M. Tanira and K. A. Al Balushi, "Genetic variations related to hypertension: a review," *Journal of Human Hypertension*, vol. 19, no. 1, pp. 7–19, 2005.

[7] R. P. Lifton, "Molecular genetics of human blood pressure variation," *Science*, vol. 272, no. 5262, pp. 676–680, 1996.

[8] T. J. Hoffmann, G. B. Ehret, P. Nandakumar et al., "Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation," *Nature Genetics*, vol. 49, no. 1, pp. 54–64, 2017.

[9] D. Levy, G. B. Ehret, K. Rice et al., "Genome-wide association study of blood pressure and hypertension," *Nature Genetics*, vol. 41, no. 6, pp. 677–687, 2009.

[10] C. Newton-Cheh, T. Johnson, V. Gateva et al., "Eight blood pressure loci identified by genome-wide association study of 34,433 people of European ancestry," *Nature Genetics*, vol. 41, no. 6, pp. 666–676, 2009.

[11] G. B. Ehret, "Genetics of hypertension," in *Hypertension: A Companion to Braunwald's Heart Disease E-Book*, p. pp. 52–59, Elsevier, USA, 2017.

[12] G. B. Ehret, T. Ferreira, D. I. Chasman et al., "The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals," *Nature Genetics*, vol. 48, no. 10, pp. 1171–1184, 2016.

[13] G. L. Hong, X. Z. Chen, Y. Liu et al., "Genetic variations in *MOV10* and *CACNB2* are associated with hypertension in a Chinese Han population," *Genetics and Molecular Research*, vol. 12, no. 4, pp. 6220–6227, 2013.

[14] A. R. Hong, J. H. Kim, Y. S. Song et al., "Genetics of aldosterone-producing adenoma in Korean patients," *PLoS One*, vol. 11, no. 1, article e0147590, 2016.

[15] F. Takeuchi, M. Isono, T. Katsuya et al., "Blood pressure and hypertension are associated with 7 loci in the Japanese population," *Hypertension*, vol. 121, no. 21, pp. 2302–2309, 2010.

[16] C. Liu, H. Li, Q. Qi et al., "Common variants in or near FGF5, CYP17A1 and MTHFR genes are associated with blood pressure and hypertension in Chinese Hans," *Journal of Hypertension*, vol. 29, no. 1, pp. 70–75, 2011.

[17] B. Xi, Y. Shen, K. H. Reilly, X. Wang, and J. Mi, "Recapitulation of four hypertension susceptibility genes (*CSK*, *CYP17A1*, *MTHFR*, and *FGF5*) in East Asians," *Metabolism*, vol. 62, no. 2, pp. 196–203, 2013.

[18] International Consortium for Blood Pressure Genome-Wide Association Studies, G. B. Ehret, P. B. Munroe et al., "Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk," *Nature*, vol. 478, no. 7367, pp. 103–109, 2011.

[19] L. V. Wain, G. C. Verwoert, P. F. O'Reilly et al., "Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure," *Nature Genetics*, vol. 43, no. 10, pp. 1005–1011, 2011.

[20] N. Kato, M. Loh, F. Takeuchi et al., "Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation," *Nature Genetics*, vol. 47, no. 11, pp. 1282–1293, 2015.

[21] X. Lu, L. Wang, X. Lin et al., "Genome-wide association study in Chinese identifies novel loci for blood pressure and hypertension," *Human Molecular Genetics*, vol. 24, no. 3, pp. 865–874, 2015.

[22] N. Kato, F. Takeuchi, Y. Tabara et al., "Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians," *Nature Genetics*, vol. 43, no. 6, pp. 531–538, 2011.

[23] X. Liu, C. Hu, M. Bao et al., "Genome wide association study identifies *L3MBTL4* as a novel susceptibility gene for hypertension," *Scientific Reports*, vol. 6, no. 1, article 30811, 2016.

[24] N. Franceschini, E. Fox, Z. Zhang et al., "Genome-wide association analysis of blood-pressure traits in African-ancestry individuals reveals common associated genes in African and non-African populations," *The American Journal of Human Genetics*, vol. 93, no. 3, pp. 545–554, 2013.

[25] S. Padmanabhan, O. Melander, T. Johnson et al., "Genome-wide association study of blood pressure extremes identifies variant near *UMOD* associated with hypertension," *PLoS Genetics*, vol. 6, no. 10, article e1001177, 2010.

[26] H. R. Warren, E. Evangelou, C. P. Cabrera et al., "Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk," *Nature Genetics*, vol. 49, no. 3, pp. 403–415, 2017.

[27] L. V. Wain, A. Vaez, R. Jansen et al., "Novel blood pressure locus and gene discovery using genome-wide association study and expression data sets from blood and the kidney," *Hypertension*, vol. 70, no. 3, pp. e4–e19, 2017.

[28] S. S. Lim, T. Vos, A. D. Flaxman et al., "A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010," *The Lancet*, vol. 380, no. 9859, pp. 2224–2260, 2012.

[29] P. Surendran, F. Drenos, R. Young et al., "Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension," *Nature Genetics*, vol. 48, no. 10, pp. 1151–1161, 2016.

[30] A. D. Johnson, C. Newton-Cheh, D. I. Chasman et al., "Association of hypertension drug target genes with blood pressure and hypertension in 86 588 individuals," *Hypertension*, vol. 57, no. 5, pp. 903–910, 2011.

[31] T. N. Kelly, F. Takeuchi, Y. Tabara et al., "Genome-wide association study meta-analysis reveals transethnic replication of mean arterial and pulse pressure loci," *Hypertension*, vol. 62, no. 5, pp. 853–859, 2013.

[32] X. Zhu, T. Feng, B. O. Tayo et al., "Meta-analysis of correlated traits via summary statistics from GWASs with an application in hypertension," *The American Journal of Human Genetics*, vol. 96, no. 1, pp. 21–36, 2015.

[33] J. E. Ho, L. Daniel, R. Lynda, A. D. Johnson, P. M. Ridker, and D. I. Chasman, "Discovery and replication of novel blood pressure genetic loci in the Women's Genome Health Study," *Journal of Hypertension*, vol. 29, no. 1, pp. 62–69, 2011.

[34] S. K. Ganesh, D. I. Chasman, M. G. Larson et al., "Effects of long-term averaging of quantitative blood pressure traits on the detection of genetic associations," *The American Journal of Human Genetics*, vol. 95, no. 1, pp. 49–65, 2014.

[35] J. Liang, T. H. Le, D. R. V. Edwards et al., "Single-trait and multi-trait genome-wide association analyses identify novel loci for blood pressure in African-ancestry populations," *PLoS Genetics*, vol. 13, no. 5, article e1006728, 2017.

[36] E. R. Fox, J. H. Young, Y. Li et al., "Association of genetic variation with systolic and diastolic blood pressure among African Americans: the Candidate Gene Association Resource study," *Human Molecular Genetics*, vol. 20, no. 11, pp. 2273–2284, 2011.

[37] P. G. Parmar, H. R. Taal, N. J. Timpson et al., "International Genome-Wide Association Study consortium identifies novel loci associated with blood pressure in children and adolescents," *Circulation: Cardiovascular Genetics*, vol. 9, no. 3, pp. 266–278, 2016.

[38] J. Simino, G. Shi, J. C. Bis et al., "Gene-age interactions in blood pressure regulation: a large-scale investigation with the CHARGE, Global BPgen, and ICBP Consortia," *The American Journal of Human Genetics*, vol. 95, no. 1, pp. 24–38, 2014.

[39] G. Lettre, C. D. Palmer, T. Young et al., "Genome-wide association study of coronary heart disease and its risk factors in 8,090 African Americans: the NHLBI CARe Project," *PLoS Genetics*, vol. 7, no. 2, article e1001300, 2011.

[40] Y. Wang, J. R. O'Connell, P. F. McArdle et al., "Whole-genome association study identifies *STK39* as a hypertension susceptibility gene," *Proceedings of the National Academy of Sciences*, vol. 106, no. 1, pp. 226–231, 2009.

[41] G. B. Ehret and M. J. Caulfield, "Genes for blood pressure: an opportunity to understand hypertension," *European Heart Journal*, vol. 34, no. 13, pp. 951–961, 2013.

[42] E. A. B. Azizan, H. Poulsen, P. Tuluc et al., "Somatic mutations in *ATP1A1* and *CACNA1D* underlie a common subtype of adrenal hypertension," *Nature Genetics*, vol. 45, no. 9, pp. 1055–1060, 2013.

[43] P. G. Maass, A. Aydin, F. C. Luft et al., "*PDE3A* mutations cause autosomal dominant hypertension with brachydactyly," *Nature Genetics*, vol. 47, no. 6, pp. 647–653, 2015.

[44] U. I. Scholl, G. Stölting, C. Nelson-Williams et al., "Recurrent gain of function mutation in calcium channel *CACNA1H* causes early-onset hypertension with primary aldosteronism," *eLife*, vol. 4, article e06315, 2015.

[45] M. D. Tobin, M. Tomaszewski, P. S. Braund et al., "Common variants in genes underlying monogenic hypertension and hypotension and blood pressure in the general population," *Hypertension*, vol. 51, no. 6, pp. 1658–1664, 2008.

[46] Y. X. Gao, C. A. Yu, J. H. Lu et al., "ADAMTS-7 expression increases in the early stage of angiotensin II-induced renal injury in elderly mice," *Kidney & Blood Pressure Research*, vol. 38, no. 1, pp. 121–131, 2013.

[47] A. W. Cowley Jr., C. Yang, V. Kumar et al., "Pappa2 is linked to salt-sensitive hypertension in Dahl S rats," *Physiological Genomics*, vol. 48, no. 1, pp. 62–72, 2016.

[48] D. A. Braun, M. Schueler, J. Halbritter et al., "Whole exome sequencing identifies causative mutations in the majority of consanguineous or familial cases with childhood-onset increased renal echogenicity," *Kidney International*, vol. 89, no. 2, pp. 468–475, 2016.

[49] G. Xu, X. Lu, T. Huang, and J. Fan, "ARHGAP24 inhibits cell cycle progression, induces apoptosis and suppresses invasion in renal cell carcinoma," *Oncotarget*, vol. 7, no. 32, pp. 51829–51839, 2016.

[50] S. Akilesh, H. Suleiman, H. Yu et al., "Arhgap24 inactivates Rac1 in mouse podocytes, and a mutant form is associated with familial focal segmental glomerulosclerosis," *The Journal of Clinical Investigation*, vol. 121, no. 10, pp. 4127–4137, 2011.

[51] L. X, L. Wang, S. Chen et al., "Genome-wide association study in Han Chinese identifies four new susceptibility loci

for coronary artery disease," *Nature Genetics*, vol. 44, no. 8, pp. 890–894, 2014.

[52] Y. Kobayashi, N. Hirawa, Y. Tabara et al., "Mice lacking hypertension candidate gene ATP2B1 in vascular smooth muscle cells show significant blood pressure elevation," *Hypertension*, vol. 59, no. 4, pp. 854–860, 2012.

[53] Y. B. Shin, J. E. Lim, S. M. Ji et al., "Silencing of Atp2b1 increases blood pressure through vasoconstriction," *Journal of Hypertension*, vol. 31, no. 8, pp. 1575–1583, 2013.

[54] U. I. Scholl, G. Goh, G. Stölting et al., "Somatic and germline *CACNA1D* calcium channel mutations in aldosterone-producing adenomas and primary aldosteronism," *Nature Genetics*, vol. 45, no. 9, pp. 1050–1054, 2013.

[55] K. Nishimoto, S. A. Tomlins, R. Kuick et al., "Aldosterone-stimulating somatic gene mutations are common in normal adrenal glands," *Proceedings of the National Academy of Sciences*, vol. 112, no. 33, pp. E4591–E4599, 2015.

[56] E. A. B. Azizan, M. Murthy, M. Stowasser et al., "Somatic mutations affecting the selectivity filter of KCNJ5 are frequent in 2 large unselected collections of adrenal aldosteronomas," *Hypertension*, vol. 59, no. 3, pp. 587–591, 2012.

[57] M. Huber, S. Lezius, R. Reibis et al., "A single nucleotide polymorphism near the *CYP17A1* gene is associated with left ventricular mass in hypertensive patients under pharmacotherapy," *International Journal of Molecular Sciences*, vol. 16, no. 8, pp. 17456–17468, 2015.

[58] X. Li, Y. Ling, D. Lu et al., "Common polymorphism rs11191548 near the CYP17A1 gene is associated with hypertension and systolic blood pressure in the Han Chinese population," *American Journal of Hypertension*, vol. 26, no. 4, pp. 465–472, 2013.

[59] K. Miyaki, N. C. Htun, Y. Song, S. Ikeda, M. Muramatsu, and T. Shimbo, "The combined impact of 12 common variants on hypertension in Japanese men, considering GWAS results," *Journal of Human Hypertension*, vol. 26, no. 7, pp. 430–436, 2012.

[60] Y. Lin, X. Lai, B. Chen et al., "Genetic variations in CYP17A1, CACNB2 and PLEKHA7 are associated with blood pressure and/or hypertension in She ethnic minority of China," *Atherosclerosis*, vol. 219, no. 2, pp. 709–714, 2011.

[61] S. J. Yang, S. T. Lee, W. J. Kim et al., "Genetic variation in CYP17A1 is associated with arterial stiffness in diabetic subjects," *Experimental Diabetes Research*, vol. 2012, Article ID 827172, pp. 1–8, 2012.

[62] B. Xi, Y. Shen, X. Zhao et al., "Association of common variants in/near six genes (*ATP2B1*, *CSK*, *MTHFR*, *CYP17A1*, *STK39* and *FGF5*) with blood pressure/hypertension risk in Chinese children," *Journal of Human Hypertension*, vol. 28, no. 1, pp. 32–36, 2014.

[63] L. A. Diver, S. M. MacKenzie, R. Fraser et al., "Common polymorphisms at the *CYP17A1* locus associate with steroid phenotype," *Hypertension*, vol. 67, no. 4, pp. 724–732, 2016.

[64] K. Hotta, A. Kitamoto, T. Kitamoto et al., "Genetic variations in the *CYP17A1* and *NT5C2* genes are associated with a reduction in visceral and subcutaneous fat areas in Japanese women," *Journal of Human Genetics*, vol. 57, no. 1, pp. 46–51, 2012.

[65] D. L. Mattson and M. Liang, "Hypertension: from GWAS to functional genomics-based precision medicine," *Nature Reviews Nephrology*, vol. 13, no. 4, pp. 195-196, 2017.

[66] M. Sano, N. Kuroi, T. Nakayama et al., "Association study of calcitonin-receptor-like receptor gene in essential hypertension," *American Journal of Hypertension*, vol. 18, no. 3, pp. 403–408, 2005.

[67] C. Lofqvist, J. Chen, K. M. Connor et al., "IGFBP3 suppresses retinopathy through suppression of oxygen-induced vessel loss and promotion of vascular regrowth," *Proceedings of the National Academy of Sciences*, vol. 104, no. 25, pp. 10589–10594, 2007.

[68] G. B. Ehret, "Genome-wide association studies: contribution of genomics to understanding blood pressure and essential hypertension," *Current Hypertension Reports*, vol. 12, no. 1, pp. 17–25, 2010.

[69] T. Shindo, T. Sakurai, A. Kamiyoshi et al., "Regulation of adrenomedullin and its family peptide by RAMP system – lessons from genetically engineered mice," *Current Protein & Peptide Science*, vol. 14, no. 5, pp. 347–357, 2013.

[70] X. Bai, K. C. Lenhart, K. E. Bird et al., "The smooth muscle-selective RhoGAP GRAF3 is a critical regulator of vascular tone and hypertension," *Nature Communications*, vol. 4, p. 2910, 2013.

[71] X. Bai, K. D. Mangum, R. A. Dee et al., "Blood pressure–associated polymorphism controls ARHGAP42 expression via serum response factor DNA binding," *The Journal of Clinical Investigation*, vol. 127, no. 2, pp. 670–680, 2017.

[72] I. A. Adzhubei, S. Schmidt, L. Peshkin et al., "A method and server for predicting damaging missense mutations," *Nature Methods*, vol. 7, no. 4, pp. 248-249, 2010.

[73] J. Deinum, G. C. Steenbergen-Spanjers, M. Jansen et al., "*DBH* gene variants that cause low plasma dopamine β hydroxylase with or without a severe orthostatic syndrome," *Journal of Medical Genetics*, vol. 41, no. 4, article e38, 2004.

[74] V. V. Lima, F. R. C. Giachini, H. Choi et al., "Impaired vasodilator activity in deoxycorticosterone acetate-salt hypertension is associated with increased protein O-GlcNAcylation," *Hypertension*, vol. 53, no. 2, pp. 166–174, 2009.

[75] V. V. Lima, C. S. Rigsby, D. M. Hardy, R. C. Webb, and R. C. Tostes, "O-GlcNAcylation: a novel post-translational mechanism to alter vascular cellular signaling in health and disease: focus on hypertension," *Journal of the American Society of Hypertension*, vol. 3, no. 6, pp. 374–387, 2009.

[76] F. Z. Marques, C. R. Mackay, and D. M. Kaye, "Beyond gut feelings: how the gut microbiota regulates blood pressure," *Nature Reviews Cardiology*, vol. 15, no. 1, pp. 20–32, 2017.

[77] J. Li, F. Zhao, Y. Wang et al., "Gut microbiota dysbiosis contributes to the development of hypertension," *Microbiome*, vol. 5, no. 1, p. 14, 2017.

[78] R. Fan, S.-Q. Mao, T.-L. Gu et al., "Preliminary analysis of the association between methylation of the ACE2 promoter and essential hypertension," *Molecular Medicine Reports*, vol. 15, no. 6, pp. 3905–3911, 2017.