Review Article

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

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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 environmental 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, SCN1B, and SCN11G), 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-handling 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 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 ID  | 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       | rs6201268 | 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               | rs1122084 | 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]               |
| 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            | DBP        | 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] |
| ARVCDF                | rs419852  | 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]          |
| C10orf52, C10orf52-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]                 |
| C2orf43               | rs2289081 | 2      | 20,682,080   | C            | PP         | −0.223                             | 0.31                   | Lu et al. [51]                   |
| C5orf56               | rs2188862 | 5      | 132,435,113  | T            | DBP        | −0.2                               | 0.14                   | Liu et al. [23], Surendran et al. [29] |
| Locus name | SNP     | Chr pos | Coded allele | Best trait | Effect size of best trait (OR beta) | Coded allele frequency | Reporting article |
|------------|---------|---------|--------------|------------|-------------------------------------|-----------------------|-------------------|
| CACNA1D    | rs9810888 | 3       | G            | DBP        | 0.39                                | 0.39                  | Lu et al. [51]    |
| CACNA2D2   | rs743757  | 3       | C            | DBP        | 0.245                               | 0.36                  | Hoffmann et al. [8], Warren et al. [26] |
| CACNB2     | rs1811353 | 10      | C            | DBP        | 0.332                               | 0.34                  | Wain et al. [27]  |
| CACNB2     | rs11014166| 10      | A            | DBP        | 0.46                                | 0.21                  | Levy et al. [9]   |
| CAMKV-ACTBP13 | rs36022378 | 3       | T            | DBP        | −0.202                              | 0.11                  | Hoffmann et al. [8], Warren et al. [26] |
| CAPZA1     | rs10745332| 1       | A            | SBP        | 0.96                                | 0.82                  | Lu et al. [51]    |
| CASC15     | rs6911827 | 6       | T            | SBP        | 0.296                               | 0.30                  | Hoffmann et al. [8], Warren et al. [26] |
| CASZ1      | rs880315  | 1       | T            | SBP        | −0.475                              | 0.39                  | Ehret et al. [12] |
| CCDC141    | rs79146658| 2       | T            | DBP        | −0.311                              | 0.03                  | Hoffmann et al. [8], Warren et al. [26] |
| CCDC41-CEP83-RN7SL483 | rs139236208 | 12      | A            | PP         | −0.363                              | 0.04                  | Hoffmann et al. [8], Warren et al. [26] |
| CCNE1      | rs62104477| 19      | T            | DBP        | 0.177                               | 0.19                  | Hoffmann et al. [8], Warren et al. [26] |
| CD34       | rs12731740| 1       | T            | SBP        | −0.249                              | 0.08                  | Warren et al. [26] |
| CDC42BPA   | rs10916082| 1       | A            | DBP        | −0.177                              | 0.27                  | Warren et al. [26] |
| CDH13      | rs7500448 | 16      | A            | PP         | 0.329                               | 0.17                  | Hoffmann et al. [8], Warren et al. [26] |
| CDH17      | rs2446849 | 8       | T            | SBP        | −0.63                               | 0.22                  | Zhu et al. [32]   |
| CELA2A     | rs1042010 | 1       | A            | SBP        | 0.412                               | 0.19                  | Hoffmann et al. [8], Warren et al. [26] |
| CELA2A     | rs3800068 | 1       | A            | SBP        | 0.425                               | 0.19                  | Wain et al. [27]  |
| CEP164     | rs8258    | 11      | T            | PP         | 0.236                               | 0.47                  | Hoffmann et al. [8], Warren et al. [26] |
| CEP68      | rs74181299| 2       | T            | PP         | 0.23                                | 0.46                  | Hoffmann et al. [8], Warren et al. [26] |
| CERS5      | rs7302981 | 12      | A            | DBP        | 0.249                               | 0.30                  | Liu et al. [23], Surendran et al. [29] |
| CFDP1      | rs11643209| 16      | T            | SBP        | −0.339                              | 0.47                  | Hoffmann et al. [8], Warren et al. [26] |
| CHIC2      | rs871606  | 4       | T            | SBP        | 0.429                               | 0.21                  | Wain et al. [19]  |
| chr15mb95  | rs12906962| 15      | T            | DBP        | −0.221                              | 0.42                  | Hoffmann et al. [8], Warren et al. [26] |
| chr1mb25   | rs6686889 | 1       | T            | DBP        | 0.185                               | 0.37                  | Warren et al. [26] |
| chr1mb9    | rs9662255 | 1       | A            | PP         | −0.207                              | 0.41                  | Hoffmann et al. [8], Warren et al. [26] |
| CHST12-LFNG| rs2969070 | 7       | A            | DBP        | −0.205                              | 0.21                  | Ehret et al. [12] |
| CMIP        | rs8059962 | 16      | T            | DBP        | −0.170                              | 0.45                  | Warren et al. [26] |
| CNNM2      | rs11191548| 10      | C            | SBP        | 1.082                               | 0.09                  | Wain et al. [27]  |
| COL21A1    | rs1925153 | 6       | T            | PP         | −0.21                               | 0.44                  | Liu et al. [23]   |
| CPEB4      | rs72812846| 5       | A            | DBP        | −0.209                              | 0.11                  | Hoffmann et al. [8], Warren et al. [26] |
| CRACR2B    | rs72812846| 5       | A            | DBP        | 0.222                               | <0.01                 | Warren et al. [26] |
| CRK        | rs12941318| 17      | T            | SBP        | −0.269                              | 0.37                  | Hoffmann et al. [8], Warren et al. [26] |
| CRYAA-SIK1-RRP1B | rs12672651 | 21      | A            | SBP        | 0.503                               | 0.19                  | Ehret et al. [12], Surendran et al. [29] |
| 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            | DBP        | 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        | −0.423                                | 0.04                   | Hoffmann et al. [8]                |
| 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] |
| EAF1          | 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            | SBP        | −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] |
| FG5D          | rs11128722 | 3      | 14,916,619    | A            | SBP        | −0.383                                | 0.41                   | Ehret et al. [12]                  |
| FGF5          | rs16998073 | 4      | 80,263,187    | T            | SBP        | 0.21                                  | 0.23                   | Newton-Cheh et al. [10]            |
| FGFY-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. [12], Kato et al. [22], Wain et al. [19] |
| FJ32810-TMEM133 | rs633185  | 11     | 100,722,807   | G            | SBP        | −0.565                                | 0.36                   | Johnson et al. [30]                |
| FNI           | 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] |
| FOSS12        | rs7562     | 2      | 28,412,873    | T            | SBP        | 0.263                                 | 0.50                   | Warren et al. [26]                |
| FRMD3         | rs115795127| 9      | 83,378,986    | T            | NA         | NR                                    | 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]                |
| 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                 | rs3143871 | 4      | 155,698,052  | T            | DBP        | 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]                 |
| GYP_AHHHP               | rs4292285 | 4      | 144,350,802  | T            | DBP        | 1.1                                 | 0.31                   | Hoffmann et al. [8]                 |
| HAAO-RNU6-242P-AC016735.1 | rs13403122 | 2   | 42,851,618   | T            | 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   | T            | SBP        | 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  | T            | 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   | A            | SBP        | 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]                 |
| HOTTP                   | rs1859168 | 7      | 27,202,740   | C            | DBP        | 0.436                               | 0.92                   | Wain et al. [27]                    |
| HOXA3                   | rs9696970 | 3      | 27,119,517   | C            | BP         | NA                                  | NR                     | Liang et al. [35]                   |
| HOXA-EXV1               | rs1742871 | 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            | SBP        | −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     | 10,988,328   | 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            | SBP        | 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] |
| LINCO01615-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]               |
| LOC10192827             | rs10932679| 2      | 216,787,868  | T            | SBP        | 0.226                               | 0.19                   | Wain et al. [27]                    |
| LOC102723446            | rs10260816| 7      | 45,970,501   | G            | PP         | 0.298                               | 0.43                   | Wain et al. [27]                    |
| 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]  |
| LRPI2/ZFPM2                | rs35783704 | 8      | 104,954,030  | A            | SBP        | −0.609                              | 0.03                   | Wain et al. [27]  |
| 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] |
| OBF1             | 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] |
| OS1              | 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            | SBP        | -0.312                             | 0.22                   | 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        | 0.31                               | 0.49                   | Liu et al. [23]   |
| PHIP             | rs10943605   | 6      | 78,945,760   | A            | DBP        | 0.236                              | 0.23                   | Hoffmann et al. [8] |
| PIK3CG           | rs17477177   | 7      | 103,918,139  | A            | SBP        | -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   | 15     | 45,130,754   | T            | DBP        | 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]   |
| PLEKKG1          | rs17080102   | 6      | 150,683,634  | C            | SBP        | -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] |
| PPPR25E          | 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] |
| Locus name               | SNP      | Chr ID   | Chr position | Coded allele | 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]                    |                        |                                    |
| **RAPS, 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]                     |                        |                                    |
| **RP11-435F9.2-TLN2**    | rs956006   | 15       | 62,516,340   | C            | PP           | 0.188        | 0.23       | Hoffmann et al. [8]                    |                        |                                    |
| **RP11-399C8.2**         | rs143112823| 3        | 154,990,178  | A            | DBP          | −0.403       | 0.06       | Hoffmann et al. [8], Warren et al. [26]|                        |                                    |
| **RP11-6101.1**          | rs9323988  | 14       | 98,121,293   | T            | PP           | −0.212       | 0.29       | Hoffmann et al. [8], Warren et al. [26]|                        |                                    |
| **RP4-710M16.1-PPAP2B-PLP3**| 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       |           | Liang et al. [35]                      |                        |                                    |
| **RPL35P4-LOC107986733** | rs11563582 | 7        | 27,312,031   | A            | DBP          | 0.188        |           | 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       | Hoffmann et al. [8], Warren et al. [26]|                        |                                    |
| **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   | 2        | 243,307,890  | A            | DBP          | 0.22         | 0.49       | Hoffmann et al. [8], Warren et al. [26]|                        |                                    |
| **SEN2**                 | 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]|                        |                                    |
| 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]     |
| SPPN       | 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            | DBP        | 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            | DBP        | −0.378                              | 0.4                    | Ehet 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] |
| TRAPP9     | rs4288356 | 8      | 140,045,627  | A            | PP         | 0.224                               | 0.615                  | Wain et al. [27]   |
| TRAPP9     | rs4454254 | 8      | 140,049,929  | A            | PP         | −0.261                              | 0.45                   | Warren et al. [26] |
| TRIM36     | rs10077885 | 5      | 115,054,244  | A            | DBP        | −0.194                              | 0.42                   | Ehet 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] |
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 vasoconstriction [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]. Concurringy, severe orthostatic

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### 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]  |
| XRC6       | 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]|
| ZNF1001    | 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    | rs13470401 | 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     | rs16968048 | 17     | 49,363,104   | G            | DBP        | 0.39                                | 0.29                  | Newton-Cheh et al. [10]|
| ZNRF3      | rs4823006  | 22     | 29,005,683   | 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.
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 need 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.

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