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Progress and Future Aspects in Genetics of Human Hypertension

Qi Zhao, MD, PhD, **Tanika N. Kelly, PhD, MPH**, **Changwei Li, MD, MPH**, and **Jiang He, MD, PhD**

Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine

Qi Zhao: qizhao@tulane.edu; Tanika N. Kelly: tkelly@tulane.edu; Changwei Li: cli8@tulane.edu

Abstract

Hypertension has become a major global health burden due to its high prevalence and associated increase in risk of cardiovascular disease and premature death. It is well established that hypertension is determined by both genetic and environmental factors and their complex interactions. Recent large-scale meta-analyses of genome-wide association studies (GWAS) have successfully identified a total of 38 loci which achieved genome-wide significance ($P < 5\times10^{-8}$) for their association with blood pressure (BP). Although the heritability of BP explained by these loci is very limited, GWAS meta-analyses have elicited renewed optimism in hypertension genomics research, highlighting novel pathways influencing BP and elucidating genetic mechanisms underlying BP regulation. This review summarizes evolving progress in the rapidly moving field of hypertension genetics and highlights several promising approaches for dissecting the remaining heritability of BP. It also discusses the future translation of genetic findings to hypertension treatment and prevention.

Keywords

Blood pressure; Genetic association studies; Genetic linkage; Genome-wide association study; Hypertension; Rare variants; Sequencing; Risk prediction

Introduction

Elevated blood pressure (BP) is a major global health challenge due to its high prevalence and associated increased risk of cardiovascular disease (CVD) and premature death [1–4]. An estimated 978 million adults, or 28% of the world's adult population, had uncontrolled hypertension in 2008 [2]. More alarming, conservative estimates indicate that the global burden of hypertension will increase to more than 1.5 billion by 2025 [4]. As the most

Corresponding author: Jiang He, MD, PhD, Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, 1440 Canal Street, Suite 2000, New Orleans, LA 70112, Phone: 504-988-5165, Fax: 504-988-7448, jhe@tulane.edu.

Conflict of Interest

Qi Zhao, Tanika N. Kelly, Changwei Li, and Jiang He declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

important modifiable risk factor for CVD and all-cause mortality, elevated BP was responsible for approximately 7.6 million deaths globally, or 13.5% of all deaths, in 2001 [1, 3].

BP is influenced by both genomic and environmental factors, as well as their interactions. Although BP was established early on as an inheritable trait, with many monogenic forms of BP dysregulation clearly described, our understanding of the genomic architecture of the complex BP phenotype was initially slow to progress [5]. Early genome-wide linkage analyses, candidate gene studies, and genome-wide association studies (GWAS) were relatively unsuccessful in identifying reproducible loci related to BP [6–12]. However, increased methodological stringency and the recent formation of large BP consortia have enabled important breakthroughs in hypertension genomic research. Through GWAS meta-analyses, numerous loci have now been robustly associated with BP in populations of European and Asian ancestries [5, 13–16]. Although much of the heritability of BP still remains unexplained, there is renewed optimism as we turn our attention towards next-generation approaches for the discovery of novel genomic determinants of this complex trait.

Genetics of Hypertension in the Pre-GWAS Era

Monogenic forms of hypertension

Some of the earliest advancements in human BP genomics research involved the identification of the genes responsible for severe inherited forms of hypertension and hypotension. Although many physiological processes are responsible for the regulation of BP, the vast majority of genes identified for monogenic BP disorders play key roles in renal-sodium handling [17–23]. Many such genes have been shown to exert their effects by directly or indirectly influencing sodium and water reabsorption in the nephron’s distal tubule, leading to changes in plasma volume, cardiac output, and BP [24]. A number of reports have provided systematic reviews of a variety of types of monogenetic forms of hypertension and their related causal mutations [25–29].

Identification of genes responsible for monogenic hypertension and hypotension disorders has provided valuable insights into the genomic mechanisms and biological pathways underlying BP regulation. Furthermore, such research has also provided important clues to investigators of the complex essential hypertension phenotype. For example, in comparison to the rare variants in genes responsible for monogenic BP disorders, investigators have postulated that common genetic variation in these genes may have more modest effects, contributing to the inter-individual variation in the complex BP phenotype [30]. As such, these genes have been the target of myriad candidate gene studies of BP and hypertension [31], and are considered very promising targets for follow-up when present at GWAS-identified loci [13].

Heritability of essential hypertension

Blood pressure has long been established as an inheritable trait, suggesting a significant contribution of genetic factors to this complex phenotype [32–34]. The heritability of BP has been shown to range from about 30–60% in pedigree data to as high as 70% in twin studies

[35–44]. Longitudinal data from the Framingham Heart Study showed that 57% and 56% of inter-individual variability in systolic (SBP) and diastolic BP (DBP), respectively, was due to genetic factors [34]. Data from Nigerian families suggest heritabilities of 34% to 45% and 29% to 43% for SBP and DBP, respectively [43, 44]. Similarly, in the Chinese population, Gu et al estimated significant heritabilities of 31% and 32% for SBP and DBP, respectively [36].

Linkage and Candidate studies

Given the widespread success of genome-wide linkage analyses in the identification of genes for Mendelian disorders, investigators were initially optimistic about using this approach to localize genomic regions harboring susceptibility loci for the complex BP phenotype. Numerous genome-wide linkage scans of SBP, DBP, or hypertension were subsequently conducted, but with somewhat disappointing results. For example, among approximately 34 quantitative trait loci (QTLs) for SBP, DBP, and hypertension phenotypes which achieved a LOD score of 3.0 or higher [34, 45–53], only one locus has been replicated in independent samples. Hsueh and colleagues linked 2q31–2q34 to DBP among Old Order Amish families [45], while Morrison and colleagues linked 2q34 to hypertension among African-American families [46]. The failure of linkage analyses highlights the complexity of the genomic mechanisms underlying BP regulation. In addition, it has spurred a general shift away from this approach in favor of more powerful association methods.

To date**,** over 1,500 genes have been related to BP in human populations, with the vast majority derived from candidate gene association studies [54]. Based on a priori knowledge of biologic function, candidate gene studies offer a powerful approach for detecting genetic variants which influence common complex traits like BP. Despite their popularity, early candidate gene studies of BP were hampered by inconsistent findings, which to some extent may have reflected methodological limitations, including small sample sizes, poor phenotype measurement, inappropriate correction for multiple testing, and lack of verification in independent samples. Some investigators, however, have continued to support the use of candidate gene studies, noting that biologically relevant loci may be missed by GWAS which use very stringent alpha-thresholds for determining statistical significance [55]. Some of the more recent candidate gene studies have successfully identified genetic associations that are reproducible in independent samples [55–57]. Such successes are likely the results of the employment of large sample sizes and appropriate correction for multiple testing. Furthermore, more recent candidate gene studies have taken advantage of advances in high-throughput genotyping technology to identify gene variants related to BP utilizing gene-centric arrays which interrogate large numbers of variants in a multitude of genes and biological pathways [57, 58]. Using the HumanCVD BeadChip, which genotypes approximately 50,000 single nucleotide polymorphisms (SNPs) from 2,000 genes demonstrated to associate with CVD-related traits, Johnson and colleagues identified BP-related SNPs in the *LSP1/TNNT3*, *MTHFR-NPPB*, *AGT*, *ATP2B1*, *NPR3*, *HFE*, *NOS3* and *SOX6* genes among a discovery-stage sample of 25,118 participants and replication study of 59,349 participants [58]. In summary, these findings demonstrate that despite their tarnished reputation, candidate gene studies may still play a role in our quest to discover variants related to BP.

Progress in the GWAS Era

By interrogating a dense panel of SNPs covering the entire genome, GWAS represent an agnostic and powerful approach for the discovery of susceptibility loci for common complex traits. As such, there was initial enthusiasm at the prospect of using GWAS to identify novel BP-related variants. However, in contrast to GWAS for other CVD-related phenotypes [6, 59, 60], early GWAS failed to identify any associations with BP at a level of genome-wide significance ($P < 5\times10^{-8}$) [6, 8–11]. For example, in the Wellcome Trust Case Control Consortium (WTCCC), investigators used a 500K Affymetrix SNP chip to compare approximately 2,000 cases for each of 7 common diseases, including hypertension, to 3,000 shared controls. In this study, a total of 24 independent association signals were identified for 6 diseases with the exception of hypertension. There were no signals that achieved even a suggestive association of $P<5\times10^{-7}$ with hypertension [6]. While a couple of the more recent GWAS have identified BP loci that meet conventional significance thresholds with evidence of replication [61, 62], the failure of early GWAS created an impetus for the formation of consortia with the purpose of conducting GWAS meta-analyses in very large samples capable of detecting the modest effects of BP loci [5, 13–16].

In June 2009, two consortia, CHARGE and Global Blood Pressure Genetics (Global BPgen), reported findings of their large-scale GWAS meta-analyses. With discovery-stage sample sizes of 29,136 and 34,133 participants in CHARGE and Global BPgen, respectively, they together identified 13 independent loci associated with BP at a level of genome-wide significance ($P < 5\times10^{-8}$) [13, 14]. These findings represented an important advance in BP genomics research, providing some of the first robust evidence of genetic association for the BP phenotype. Since the 2009 publications, four additional large BP GWAS meta-analyses have been conducted in European and East Asian populations. These include two from the International Consortium of BP (ICBP), which is the largest GWAS meta-analysis of BP to date, with a discovery-stage sample of approximately 70,000 participants [5, 16]; one from the HYPERGENES Project, with a smaller sample size of 1,865 hypertension cases and 1,750 controls [63]; and one from the Asian Genetic Epidemiology Network (AGEN), with GWAS data from nearly 20,000 East Asian participants and follow-up genotyping in an additional 30,000 [15]. In total, these studies have identified 38 loci robustly associated with BP traits (Table 1).

Although inference of causal genes and variants based on GWAS signals alone is difficult due to regional linkage disequilibrium (LD) structure, findings from these large GWAS meta-analyses have provided robust association evidence for some biological candidate genes previously suspected to influence BP. For example, meta-analysis of CHARGE and Global BPgen findings revealed an association of SBP with intronic marker rs1004467 ($P=1.28\times10^{-13}$) of the *CYP17A1* gene, which is responsible for a monogenic form of hypertension [14, 64]. Similarly, in the GWAS meta-analysis by Global BPgen, Newton-Cheh and colleagues identified a strong signal for SBP at 1p36. The most significant SNP at that locus was rs17367504 ($P=7\times10^{-24}$), an intronic variant of the *MTHFR* gene, which has been implicated in BP due to its role in regulating homocysteine, a biomarker linked to endothelial dysfunction and hypertension [65]. Several other relevant biological candidates are also present at this locus, including *NPPA* and *NPPB*, which encode natriuretic peptides,

renin-angiotensinogen-aldosterone system (RAAS) component *AGTRAP*, and ion channel *CLCN6* [13].

While GWAS meta-analyses results have provided association evidence for some genes with known biologic relevance, the majority of loci identified had not been previously implicated in studies of BP regulation in human populations. For example, the *ATP2B1* gene at the 12q21 locus achieved genome-wide significance for SBP, DBP, and mean arterial pressure (MAP) in GWAS meta-analyses conducted by CHARGE, Global BPgen, and ICBP [5, 13, 14, 16], but has never been linked with BP regulation. The post hoc investigation into the potential biologic plausibility of *ATP2B1* revealed a previous experiment demonstrating increased mRNA expression in the spontaneously hypertensive rat [66]. While some genes at implicated loci, like that of *ATP2B1*, have demonstrated plausibility for association with BP based on our current knowledge, other loci discovered by GWAS meta-analyses have provided completely novel insights into BP regulation. For example, the *SH2B3* locus achieved genome-wide significance for SBP, DBP, and MAP in GWAS meta-analyses by CHARGE, Global BPgen, and ICBP [5, 13, 14, 16]. *SH2B3* had been shown previously to exert an effect on cytokine sensitivity in studies of knockout mice and was associated with autoimmune conditions in human populations [14]. Based on these studies, Levy and colleagues speculated that immune response pathways may influence BP by mechanisms not previously appreciated [14].

As the largest consortium of GWAS conducted in the East Asian population, the AGEN Hypertension meta-analysis replicated 7 of the 13 loci that had been identified previously by the CHARGE and Global BPgen consortia, including 4 at a level of genome-wide significance [15]. Of particular importance, the AGEN meta-analysis identified 5 novel loci which achieved $P < 5\times10^{-8}$ for association with BP phenotypes [15]. These findings indicate that the physiologic effects of many common polymorphisms may be generalizable across populations with diverse genetic backgrounds. On the other hand, the success of AGEN also suggests that genomic mechanisms may be discovered in unique populations due to differences in allele frequencies or factors that interact with genes to influence BP. Thus, the investigation of genomic factors influencing BP in populations with differing genetic backgrounds should continue to be pursued. Findings from these studies will be essential to enhancing our understanding of the molecular mechanisms underlying BP regulation.

Promising Approaches for Dissecting the Missing Heritability of Hypertension

To date, most identified genetic variants have displayed modest effect sizes. It was estimated that the currently identified common variants explain only about 0.9% of the variability of BP, leaving a large proportion of heritability unexplained [5]. As we look towards the future, new approaches are being sought to help explain the “missing heritability” of BP. On the horizon are global GWAS meta-analyses, research of gene-gene and gene-environment interactions (including epigenetic studies), and, as we move beyond GWAS, next-generation sequencing studies. While setbacks are likely to occur as we continue to move forward,

there is optimism that such work will make headway in our quest to better understand the genomic architecture of BP.

Global GWAS meta-analyses

In the ICBP GWAS meta-analysis, Ehret and colleagues estimated that up to 2.2% of inter-individual variation in BP would eventually be explained by approximately 116 common genetic variants theorized to associate with BP (compared to 0.9% of variation explained by 29 currently identified SNPs) [5]. However, they showed that very large sample sizes would be required to detect these remaining SNPs [5]. Mega-consortia are now being formed that include genetically diverse samples from around the world. By substantially increasing sample sizes, these studies will have power to detect additional BP loci [67, 68]. Furthermore, such research will present an outstanding opportunity to refine genomic signals in the search for causal variants by leveraging LD structure across populations [67, 68]. In undertaking these studies, investigators will likely encounter new challenges, such as how to appropriately account for the genetic heterogeneity that exists between ethnically diverse samples while maximizing study power [67, 68]. However, novel insights into other phenotypes, such as serum proteins, have already been identified by global GWAS meta-analysis approaches [69]. It is likely that BP will soon follow suit.

Gene-gene and gene-environment interactions

Given the commonly accepted belief that complex traits like BP are influenced by the interaction of genetic and environmental factors, it has been suggested that research of such interactions could help explain some of the missing heritability of these traits [30, 70, 71]. Still, there is a paucity of data from GWAS examining how genes interact with each other and with environmental factors to influence BP. Since current methods for detecting interactions have been shown to lack power, investigators may be hesitant to undertake such analyses, especially in light of the early difficulties of BP GWAS in identifying simple single-marker associations [72]. However, before moving completely beyond GWAS, it may be worthwhile to leverage data from existing large consortia to explore the interactions between genes and environmental factors on BP.

Epigenetics

Epigenetics is the study of heritable alterations in phenotypes and gene expression that occur without changes in the DNA sequence [73]. The epigenetic control of gene expression is critical for many cell functions, such as tissue specificity, germline specificity, imprinting, and X-chromosome inactivation [74]. Epigenetic processes include nucleic acid methylation, histone modification, nucleosome positioning, transcription control with DNA-binding proteins and noncoding RNAs, and translation control with microRNAs and RNA-binding proteins. Epigenetic mechanisms have been involved in the pathogenesis of CVD, including hypertension, [73, 75] and suggested as a potential mechanism for explaining a part of missing heritability of these complex diseases [74]. Studies have already shown a loss of global genomic methylation content among hypertension patients, as well as hypermethylation of the *HSD11B2* gene [76, 77]. To reveal epigenetic biomarkers implicated in hypertension etiology, progression, and prevention, the National Heart, Lung,

and Blood Institute convened a working group of multidisciplinary experts to identify urgently needed studies and resources and the future direction of epigenetic research of hypertension [74]. A better understanding of epigenetic changes in response to environmental and genetic stresses is needed to clarify the factors that act together to determine an individual's BP.

Rare variants and sequencing studies

Cohen and colleagues achieved early success identifying rare variants with large influence on lipid phenotypes by sequencing extremes of the population distribution, prompting investigators to turn their attention towards clarifying the role of rare genetic variants in the complex BP phenotype [78–80]. There is already some suggestion that rare variants could help explain the missing heritability of BP. For example, Ji and colleagues reported that carriers of rare functional mutations in three renal salt-handling genes (*SLC12A3*, *SLC12A1*, and *KCNJ1*) had significantly reduced BP compared to non-carriers [81]. Similarly, Rao et al resequenced a locus of the *CHGA* gene and discovered a Gly364Ser amino-acid substitution that decreased DBP by approximately 5 mmHg [82]. While these previous studies have sequenced a limited number of genes, the advent of next-generation sequencing technology has made it plausible to deeply sequence large stretches of DNA, whole exomes, or even the entire genome in large population-based studies [83]. As such, the National Heart, Lung, and Blood Institute sponsored an initiative to identify low-frequency and rare variants which may contribute to heart, lung, and blood disorders by conducting whole-exome sequencing in ongoing population-based studies [84]. With much of the sequencing completed and catalogued in the database of Genotypes and Phenotypes (dbGaP), results from the BP working group are eagerly anticipated [85].

Prospects for Translation of Genetic Findings

Development of novel drugs for hypertension treatment

Recent large-scale genetic studies have implicated novel biological pathways in BP regulation, providing potential targets for the treatment of hypertension and the prevention of CVD. However, the translation of genetic findings from GWAS into the clinic remains limited and a topic of intense debate. It takes a considerable length of time to move from a gene target identified by association study to an approved marketed drug, and most GWAS results have become available only in the past few years. In addition, the effect sizes of GWAS-identified BP variants are relatively small (ranging from 0.2–1.0 mm Hg per risk allele) [5], and the merit of their utilization in clinical practice is not clear. Nevertheless, the case for statins in the treatment of high low-density lipoprotein (LDL)-cholesterol provides optimism for the potential use of GWAS-identified BP genes as pharmaceutical targets for antihypertensive drug development [86]. Although statins were developed in the last century, a recent GWAS identified that the gene (*HMGCR*) encoding the statins' target protein, 3-hydroxy-3-methylglutaryl coenzyme A reductase, was associated with plasma LDL-cholesterol levels (P for rs12654264 = 1×10^{-20}) [87]. Despite an effect size of only 2.7 mg/dl per allele of the rs12654264 variant [87], the statin drug can lower LDL-cholesterol by 40–60% [88].

Although the development of novel drugs based on GWAS findings will take some time, Sanseau and collaborators have suggested a potential shortcut for using emerging genomics research to assuage human disease. In an analysis conducted using data from the National Human Genome Research Institute's repository of GWAS data and Informa Healthcare's Pharmaprojects database of drug development projects [89], they found that out of 155 genes that could be mapped to GWAS traits and were also targeted by available drugs, 92 genes were associated with drugs that had indications for diseases that differed from their mapped GWAS traits. These findings suggest that GWAS data may help us identify novel uses for existing drugs, leading to immediate translational opportunities for GWAS findings.

Hypertension risk prediction

Improving risk prediction is a key objective in genomic studies of human diseases and is an important component of "personalized medicine," including risk stratification, targeted prevention, and therapeutic interventions. However, GWAS-identified variants that have been robustly associated with BP and hypertension have relatively small effect sizes. In addition, most GWAS have used cross-sectional data, and the predictive values of variants identified by such studies need validation in prospective cohorts. Fortunately, investigators have begun to implement large-scale longitudinal cohorts to confirm the associations between GWAS-identified BP variants and both hypertension incidence and BP change over time. For example, Fava and colleagues recently validated a genetic risk score (GRS) with aggregate genetic information from 29 GWAS-BP SNPs. These variants were cumulatively and independently associated with hypertension incidence and BP changes over approximately 23 years' follow-up among more than 17,000 Swedes [90]. However, their analyses did not show an improvement in the prediction of incident hypertension beyond traditional risk factors. Indeed, the magnitude of association of the GRS with hypertension incidence is substantially lower than that of obesity and prehypertension status, but comparable to that of either positive family history of hypertension or the presence of diabetes. These results suggest that it is still too early to consider GWAS findings in the prediction of hypertension. In the future, however, knowledge of additional BP-related genomic variants and their complex interactions with both genetic and environmental factors could substantially improve the GRS and lead to its translation to the clinical setting.

Antihypertensive pharmacogenomics

Another promising area of genomic research is its application in the prediction of individual response and side effects to antihypertensive therapies. Although this is still far away from clinical application, the past decade has seen substantial growth in the literature surrounding hypertension pharmacogenomics. Most of the studies have been focused on candidate genes, primarily direct protein targets of a drug or involved in the physiological or pharmacological signaling pathways relevant to a drug's action. For example, genetic variants of several genes from the RAAS (*ACE*, *AGT*, *AGTR1*, *AGTR2*, and *REN*) have been widely investigated for their associations with BP response to angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers [91]. Variants of β1-adrenergic receptor (*ADRB1*) from the sympathetic nervous system and its associated regulatory protein (*GRK4*) have shown significant interaction effects with β-blocker on BP lowering [92–94]. In addition, renal sodium absorption-regulating genes *ADD1*, *WNK1*, and *NEDD4L* have

influenced BP response to diuretics in an interactive manner [95]. With the advent of GWAS, Turner et al published the first GWAS of antihypertensive pharmacogenomics [96], in which theyhey identified and validated a region on chromosome 12 that was associated with DBP response to hydrochlorothiazide. This region includes *LYZ*, *YEATS*, and *FRS2* genes that had not been previously implicated in hypertension or response to diuretics. The study highlights the potential power of the GWAS approach in antihypertensive pharmacogenomics. Other groups are conducting ongoing pharmacogenomics studies that will also utilize GWAS [97].

Although there have been significant advances in hypertension pharmacogenomics research, most of the studies were not sufficiently powered, with relatively small sample size and lack of replication samples. Thus, collaboration among investigators to allow large-scale joint analyses and replication will be essential in advancing this field. Ethnic differences have also been noted in response to the BP-lowering effects of antihypertensive medications, as seen with β-blockers and diuretics [98]. This not only supports the role of genetic factors in determining individuals' response to antihypertensive medications, but it also highlights the necessity and importance of utilizing multiple ethnicities to identify genetic variants responsible for varied BP response to treatment.

Conclusions

Although the genomic mechanisms underlying BP regulation have yet to be fully elucidated, there have been important advances in the field. Initially slow to progress, genetic association studies seem to have finally delivered on their promise to identify common polymorphisms associated with this trait. While it is true that much of the heritability of BP remains unexplained, the variants robustly identified by previous GWAS meta-analyses already show non-negligible associations with BP and its comorbid conditions. Furthermore, with the formation of global GWAS meta-analysis consortia, the emergence of epigenetics, and the advent of next-generation sequencing technology, the future for BP genomics research is bright. Investigators are optimistic that the coming years will offer a clearer picture of the genomic architecture of BP. Eventually, such insights could be used to identify individuals at high risk for hypertension who may benefit most from primary prevention efforts, and could provide new biological targets for developing more effective hypertension treatment methods. In addition, advances in pharmacogenomics of antihypertensive drugs may be used to develop novel personalized treatments for hypertension. Advancements in all of these areas will have important public health and clinical implications that will help to curb the growing cardiovascular disease epidemic at national and global levels.

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Table 1

Genetic variants which achieved $P < 5\times10^{-8}$ in previous GWAS meta-analyses, according to their one mega-base position.

Chr Region	Lead SNP	Position	Nearest Gene	Functional Relevance	Associated Phenotype(s)	Identifying Consortium
1p36	rs880315	10719453	*CASZ1*[1]	Intron	DBP	AGEN
	rs17367504	11785365	*MTHFR*[1]	Intron	SBP, DBP, HTN, MAP	Global BPgen, AGEN, ICBP[2,3]
1p13	rs17030613	112971190	*CAPZA1*[1]	Intron	DBP	AGEN
	rs2932538	113018066	*MOV10*	Near Promoter	SBP, DBP	ICBP[2]
2q24	rs16849225	164615066	*FIGN*	Intergenic	SBP	AGEN
	rs13002573	164623454	*FIGN*	Intergenic	PP	ICBP[3]
	rs1446468	164671732	*FIGN*	Intergenic	SBP, DBP, MAP	ICBP[3]
3p24	rs13082711	27512913	*SLC4A7*	Intergenic	DBP. MAP	ICBP[2,3]
3p22	rs3774372	41852418	*ULK4*[1]	Missense	DBP	ICBP[2]
	rs9815354	41887655	*ULK4*[1]	Intron	DBP	CHARGE, AGEN
3p21	rs319690	47902488	*MAP4*[1]	Intron	SBP, DBP, MAP	ICBP[3]
3q26	rs419076	170583580	*MECOM*[1]	Intron	SBP, DBP, MAP	ICBP[2,3]
	rs1343040	170668987	*MECOM*[1]	Intron	MAP	ICBP[3]
4q12	rs871606	54494002	*CHIC2*	Intergenic	PP	ICBP[3]
4q21	rs13149993	81377569	*FGF5*	Intergenic	MAP	ICBP[3]
	rs1458038	81383747	*FGF5*	Intergenic	SBP, DBP, MAP	ICBP[2,3]
	rs16998073	81403365	*FGF5*	Intergenic	SBP, DBP, HTN, MAP	Global BPgen, AGEN, ICBP[3]
4q24	rs13107325	103407732	*SLC39A8*[1]	Missense	SBP, DBP, MAP	ICBP[2,3]
4q25	rs6825911	111601087	*ENPEP*	Intergenic	DBP	AGEN
4q32	rs13139571	156864963	*GUCY1A3*[1]	Intron	DBP	ICBP[2,3]

Chr Region	Lead SNP	Position	Nearest Gene	Functional Relevance	Associated Phenotype(s)	Identifying Consortium
5p13	rs1173756	32825609	*NPR3*[1]	3′ UTR	PP	ICBP[3]
	rs1173766	32840285	*NPR3*	Intergenic	SBP	AGEN
	rs1173771	32850785	*NPR3*	Intergenic	SBP, DBP, HTN. MAP, PP	ICBP[2,3]
5q33	rs9313772	157737035	*EBF1*	Intergenic	MAP	ICBP[3]
	rs11953630	157777980	*EBF1*	Intergenic	MAP, SBP, DBP	ICBP[2,3]
6p22	rs1799945	26199158	*HFE*[1]	Missense	MAP, SBP, DBP, HTN	ICBP[2,3]
	rs198846	26215442	*HIST1H1T*	Near 3′UTR	MAP	ICBP[3]
6p21	rs805303	31724345	*BAG6*[1]	Intron	SBP, DBP, HTN	ICBP[2]
7q22	rs17477177	106199094	*PIK3CG*	Intergenic	PP, SBP	ICBP[3]
7q36	rs3918226	150321109	*NOS3*	Near Promoter	HTN	HYPERGENES
8q24	rs2071518	120504993	*NOV*[1]	3′ UTR	PP	ICBP[3]
10p12	rs4373814	18459978	*CACNB2*[1]	Intron	SBP, DBP	ICBP[2]
	rs1813353	18747454	*CACNB2*[1]	Intron	MAP, SBP, DBP, HTN	ICBP[2,3]
	rs11014166	18748804	*CACNB2*[1]	Intron	MAP, DBP	CHARGE, AGEN, ICBP[3]
	rs12258967	18767965	*CACNB2*[1]	Intron	MAP	ICBP[3]
10q21	rs4590817	63137559	*C10orf107*[1]	Intron	MAP, SBP, DBP, HTN	ICBP[2,3]
	rs1530440	63194597	*C10orf107*[1]	Intron	MAP, DBP	Global BPgen, AGEN, ICBP[3]
10q23	rs9663362	95885167	*PLCE1*[1]	Intron	PP	ICBP[3]
	rs932764	95885930	*PLCE1*[1]	Intron	SBP, HTN	ICBP[2,3]
10q24	rs1004467	104584497	*CYP17A1*[1]	Intron	PP, MAP, SBP	CHARGE, ICBP[3]
	rs3824755	104585839	*CYP17A1*[1]	Intron	PP	ICBP[3]
	rs11191548	104836168	*NT5C2*	Intergenic	PP, MAP, SBP, DBP, HTN	Global BPgen, AGEN, ICBP[2,3]

Chr Region	Lead SNP	Position	Nearest Gene	Functional Relevance	Associated Phenotype(s)	Identifying Consortium
	rs11191593	104929205	*NT5C2*[1]	Intron	MAP	ICBP[3]
10q25	rs2782980	115771517	*ADRB1*	Intergenic	MAP	ICBP[3]
11p15	rs7129220	10307114	*ADM*	Intergenic	SBP	ICBP[2,3]
11p15	rs381815	16858844	*PLEKHA7*[1]	Intron	MAP, SBP, DBP	CHARGE, AGEN, ICBP[2,3]
11q22	rs633185	100098748	*ARHGAP42*[1]	Intron	MAP, SBP, DBP, HTN	ICBP[2,3]
	rs604723	100115756	*ARHGAP42*[1]	Intron	MAP	ICBP[3]
11q24	rs11222084	129778440	*ADAMTS-8*	Intergenic	PP	ICBP[3]
12q21	rs4842666	88465680	*POC1B*	Intergenic	SBP	CHARGE
	rs11105328	88466521	*POC1B*	Intergenic	SBP	CHARGE
	rs2681472	88533090	*ATP2B1*[1]	Intron	PP, MAP, SBP, DBP, HTN	CHARGE, AGEN, ICBP[3]
	rs2681492	88537220	*ATP2B1*[1]	Intron	PP, MAP, SBP, DBP	CHARGE, ICBP[3]
	rs11105354	88550654	*ATP2B1*[1]	Intron	SBP, HTN	CHARGE
	rs12579302	88574634	*ATP2B1*	Near Promoter	SBP, HTN	CHARGE
	rs17249754	88584717	*ATP2B1*	Intergenic	PP, MAP, SBP, DBP, HTN	CHARGE, AGEN, ICBP[3]
	rs11105364	88593407	*ATP2B1*	Intergenic	SBP, HTN	CHARGE
	rs11105368	88598572	*ATP2B1*	Intergenic	SBP, HTN	CHARGE
	rs11105378	88614872	*ATP2B1*	Intergenic	SBP, HTN	CHARGE
	rs12230074	88614998	*ATP2B1*	Intergenic	SBP, HTN	CHARGE
12q24	rs3184504	110368991	*SH2B3*[1]	Missense	MAP, SBP, DBP	CHARGE, ICBP[2,3]
	rs4766578	110388754	*ATXN*[1]	Intron	DBP	CHARGE
	rs10774625	110394602	*ATXN*[1]	Intron	DBP	CHARGE
	rs653178	110492139	*ATXN2*[1]	Intron	MAP, DBP	CHARGE, Global Bpgen, ICBP[3]
	rs671	110726149	*ALDH2*[1]	Missense	SBP, DBP	AGEN
	rs11066132	110952589	*NAA25*[1]	Intron	SBP, DBP	AGEN
	rs2074356	111129784	*HECTD4*[1]	Intron	SBP, DBP	AGEN

Chr Region	Lead SNP	Position	Nearest Gene	Functional Relevance	Associated Phenotype(s)	Identifying Consortium
	rs11066280	111302166	*HECTD4*[1]	Intron	SBP, DBP	AGEN
12q24	rs2384550	113837114	*TBX3*	Intergenic	DBP	CHARGE, AGEN
	rs10850411	113872179	*TBX3*	Intergenic	DBP	ICBP[2,3]
	rs35444	114036820	*TBX3*	Intergenic	DBP	AGEN
15q24	rs1378942	72864420	*CSK*[1]	Intron	MAP, SBP, DBP, HTN	Global BPgen, AGEN, ICBP[2,3]
	rs6495122	72912698	*ULK3*[1]	Intron	MAP, DBP	CHARGE, ICBP[3]
15q26	rs2521501	89238392	*FES*[1]	Intron	MAP, SBP, DBP	ICBP[2,3]
17q21	rs12946454	40563647	*ACBD4*	Near Promoter	SBP	Global Bpgen, AGEN
17q21	rs8069437	42261948	*WNT3*	Intergenic	PP	ICBP[3]
	rs17608766	42368270	*GOSR2*[1]	Intron	PP, SBP	ICBP[2,3]
17q21	rs12940887	44757806	*ZNF652*[1]	Intron	SBP, DBP	ICBP[2,3]
	rs16948048	44795465	*ZNF652*	Near Promoter	DBP	Global Bpgen, AGEN
18p11	rs8096897	13428905	*c18orf1*[1]	Intron	SBP	CHARGE
20p12	rs1327235	10917030	*JAG1*	Intergenic	MAP, SBP, DBP	ICBP[2,3]
20q13	rs6026748	57179210	*ZNF831*	Intergenic	MAP	ICBP[3]
	rs6015450	57184512	*ZNF831*	Intergenic	MAP, SBP, DBP, HTN	ICBP[2,3]

AGEN=Asian Genetic Epidemiology Network; CHARGE=Cohorts for Hearts and Aging Research in Genomic Epidemiology; Chr=Chromosome; DBP=Diastolic blood pressure; Global Bpgen=Global Blood Pressure Genetics; HTN=Hypertension; ICBP=International Consortium of Blood Pressure; MAP=Mean arterial pressure; PP=Pulse pressure; SBP=Systolic blood pressure.

[1]Corresponding variant is located within this gene;

[2]ICBP publication by Ehret and colleagues [5];

[3]ICBP publication by Wain and colleagues [16].