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Recent Findings in the Genetics of Blood Pressure and Hypertension Traits

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Abstract

We provide an overview of ongoing discovery efforts in the genetics of blood pressure (BP) and hypertension (HTN) traits. Two large genome-wide association meta-analyses of individuals of European descent were recently published, revealing ~13 new loci for BP traits. Only two of these loci harbor genes in a pathway known to affect BP (*CYP17A1* and *NPPA/NPPB*). Functional variants in these loci are still unknown. Few genome-wide association studies (GWAS) of complex diseases have been published from non-European populations. The study of populations with different evolutionary history and linkage disequilibrium (LD) structure, such as individuals of African ancestry, may provide an opportunity to further narrow these regions to identify the causal gene(s). Several collaborative efforts toward discovery of low-frequency variants and copy number variation for BP traits are currently underway. As evidence for new loci for complex diseases accumulates the assessment of the epidemiologic architecture of these variants in populations assumes higher priority. The impact of public health–relevant contexts such as diet, physical activity, psychosocial factors, and aging has not been examined for most common variants associated with BP.

Keywords

blood pressure; genes; genome-wide association; hypertension

Hypertension (HTN) is a leading risk factor for cardiovascular disease morbidity and mortality, and renal disease.[1,2] HTN affects 24% of the US adult population,[3] with a disproportionate burden in minorities, particularly African Americans.[4] The regulation of blood pressure (BP) is complex and multiple genes likely interact to influence BP, modulated by environmental contexts such as diet, physical activity, psychosocial factors, and aging. Although some of the pathways of BP control have been well described in humans and experimental models,[5–8] identifying genes that contribute to the distribution of BP in populations and the underlying biology has proved challenging (reviewed in refs. 9,10).

The extensive and important work in functional variant discovery using genome-wide linkage and candidate gene approaches will not be reviewed here and is summarized elsewhere.[11,12] Recent discovery efforts have used hypothesis-free association scans of the

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genome (genome-wide association studies, GWAS) to identify new loci for HTN susceptibility and BP distribution. So far, two large meta-analyses of GWAS in individuals of European ancestry have been published.[13,14] Several collaborations to study BP traits are currently ongoing with expected publications of novel genetic findings in the next several months. Loci identified may provide new insights into the biology of BP regulation, and suggest targets for therapy and for population level risk reduction.

Here, we summarize the recent genetic findings of BP traits, while attempting to provide some perspective on the discovery efforts and impact on public health and clinical care. We review recently published GWAS of HTN and BP traits and outline other strategies of gene discovery focused on BP such as low-frequency variants and copy number variations. Finally, we discuss recent efforts toward generalization of these discoveries to individuals of different ancestry. Because the field is rapidly evolving, this review offers a snap shot of the current state of the knowledge of the genetics of BP traits.

OVERVIEW OF GENE DISCOVERY FOR BP TRAITS AND HTN

Common variants

GWAS findings in individuals of European ancestry—GWAS use dense sets of genetic markers to investigate associations of common single-nucleotide polymorphism (SNP) with complex traits. The analyses rely on the linkage disequilibrium (LD) or correlation patterns of typed (or imputed) SNPs with functional variants and, therefore, identified SNPs are usually proxies of untyped functional variants.[15] At a genome-wide level, >80% of common SNPs (defined as having a minor allele frequency of at least 5%) can be interrogated by genotyping in the range of 500,000 to 1 million SNPs, depending on the population. To adjust for multiple testing and to decrease type I error (false-positive rates) stringent *P* values are used. Consortia and collaborative studies have enabled meta-analyses of multiple GWAS based on large samples (usually in the range of tens of thousands to >100,000 individuals) and statistical power sufficient to identify new common variants. Most published studies to date have targeted individuals of European ancestry. GWAS strategy for discovery has been successful in identifying new genes and loci for complex traits, although these findings explain a small proportion of the trait variability.[16] Because this method relies on proxies of causal variants, the proportion of variation explained by common genetic variants is small, but may be underestimated.[16,17] The heritability of BP is estimated as 30–40% in populations,[9] but gene discovery has proved challenging for BP traits.[18,19]

Two large GWAS meta-analyses of individuals of European descent were recently published,[13,14] revealing ~13 new loci for BP traits (Tables 1 and 2). These analyses were cross-sectional, included cohort and case–control studies, and involved individuals with a broad range of age and HTN prevalence (Table 1). The main genetic analyses assessed systolic (SBP) and diastolic (DBP) BP as quantitative traits, for which statistical power is generally greater than categorical outcomes such as HTN. Minimal covariate adjustments were performed: age, sex, and body mass index. For individuals using BP-lowering medications, a constant was added to measured BP. The study by Levy *et al.* had a discovery sample of over 29,000 participants from the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE Consortium).[14] Replication was done in 34,000 individuals participants of the Global Blood Pressure Genetics (Global BPgen) Consortium. Global BPgen recruited 13 cohort studies and 4 nonhypertensive control groups from case–control studies for the discovery phase.[13] Global BPgen used the CHARGE Consortium samples and additional 70,000 samples of European individuals for *in silico* replication, and *de novo* genotyping was performed in 13,000 Asians (Table 1).

The main findings of these two meta-analyses are summarized in Table 2. CHARGE identified eight loci associated with SBP and DBP near or in *CYP17A1* (SBP), *PLEKHA7* (SBP), *ATP2B1* (SBP, DBP, HTN), *SH2B3-ATXN2* (SBP, DBP), *ULK4* (DBP), *TBX3-TBX5* (DBP), *CSK-ULK3* (DBP) and *CACNB2* (DBP) (Table 2). Global BPgen identified eight loci for BP in regions near or in *MTHFR-CLCN6-NPPA-NPPB* (SBP), *CNNM2-NT5C2-CYP17A1* (SBP), *PLCD3* (SBP), *FGF5* (DBP), *C10orf107* (DBP), *SH2B3-ATXN2* (DBP), *CSK* (DBP), and *ZNF652* (DBP). Three loci were identified in both meta-analyses: *CYP17A1*, *SH2B3-ATXN2* and *CSK-ULK3*.

As expected for common variants, the association effect sizes were small (<1 mm Hg) and explained a small proportion of the phenotypic variation. Studies identified the same regions for SBP and DBP. Although this is not surprising given the high correlation between SBP and DBP, it remains to be determined whether genetic predisposition applies to different types of HTN and those more common among certain demographic groups (e.g., isolated systolic HTN in older adults). Given complex and different regulatory mechanisms at play, alternative phenotypic traits may prove to be informative as strategies for investigation of BP genes, such as BP responses to stressors and responsiveness to dietary and pharmacologic interventions.[20]

Some of the BP-associated regions identified through GWAS extend over several genes. Because of the strong LD or local correlation between SNPs in Caucasians it is difficult to localize the causal gene(s) for some of these loci. For example, the 10q24 region identified for SBP spans ~430 kb and includes six genes.[13,14] The 3p22.1 and 12q24.21 loci similarly apply to regions with multiple genes.[14] The study of populations with different evolutionary history and LD structure may provide an opportunity to narrow such regions in efforts to identify the causal gene(s).

Of several identified loci only two regions, 1p36 and 10q24, harbor genes in a pathway known to affect BP (*CYP17A1* and *NPPA/NPPB*, respectively). Mutations in the *CYP17A1* gene, which encodes the cytochrome P450 enzyme CYP17A1, cause congenital adrenal hyperplasia and hypokalemic HTN.[21] Common variants in the *NPPA* and *NPPB* genes associated with natriuretic peptide concentrations have been previously shown to contribute to BP and HTN risk.[22] Even though candidate gene analysis have not been proven successful in revealing variants associated with BP, these findings suggest that common variants in these genes may indeed contribute to BP variation in the population at large. In fact, a recent study of *WKN1*, in which mutations lead to HTN and hyperkalemia of the Gordon syndrome, identified associations of both common and rare genetic variants in the *WKN1* gene with BP and potassium excretion. Such results indicate that targeted candidate gene sequencing efforts may provide informative discovery sets for both common and rare variants, in genes associated with known pathways of BP control including monogenic disorder of hypotension and HTN.

The 12q24 region associated with BP contains ~15 genes in addition to *SH2B3* and has been associated pleiotropically with multiple phenotypes. rs3184504 of *SH2B3* encodes an arginine to tryptophan substitution at amino acid 262 (R262W) in the lymphocyte-specific adapter protein (LNK). In addition to BP, the allele corresponding to the 262W variant has been associated with higher blood cell counts (hemoglobin/hematocrit, eosinophils, and platelets) as well as increased risk of autoimmune diseases (celiac disease and type 1 diabetes) and myocardial infarction.[23–26] Molecules that contain an SH2 domain in their structure, like LNK, regulate growth factor and cytokine receptor–mediated pathways implicated in hematopoiesis and immunity.[27,28] Cells isolated from individuals homozygous for the *SH2B3* risk allele display increased production of proinflammatory cytokines such as interleukin-1-β. There is a strong signal of positive selection at the *SH2B3* locus in

Europeans, which has been postulated as due to improved host defense against infections.[24,29] Consistent with the association of the *SH2B3* locus with myocardial infarction, LNK also may play a role in platelet activation and stabilization of a developing thrombus.[30] The relationship to BP physiology may be less apparent, though LNK has also been reported to regulate bone marrow–derived endothelial progenitor cell proliferation and mobilization[31] as well as cytokine-induced signaling nitric oxide synthase activity in human ECs.[32]

Gender differences in BP are well-documented in different populations[3,33,34] and have been largely attributed to sex hormone effects.[35] Sex-specific quantitative trait loci have been described for BP traits.[36,37] In contrast, BP-associated SNPs identified in recent GWAS by Global BPgen did not show evidence for sex-specific effects.[13] Potential interactions with important environmental determinants of BP, such as diet, body mass, physical activity, and behavioral factors,[38] have yet to be investigated systematically.

Findings from other GWAS of individuals of European ancestry are summarized in Table 3, as studies of smaller sample sizes, most of which contributed data to the above described meta-analyses. Currently, a joint meta-analysis of Global BPgen and CHARGE is underway, which may uncover additional loci with even smaller effects. In addition, studies using high-density custom arrays for fine mapping of regions identified in GWAS are in progress.[39]

GWAS discovery in individuals of non-European ancestry—Differences in allele frequency and LD patterns as well as in disease prevalence between populations of different ancestry may be helpful in identifying loci and functional variants for complex diseases.[40] Few GWAS of complex diseases in non-European populations have been published and only four studies are known to have investigated BP traits (Table 3). A study of Han Chinese (175 hypertensive cases and 175 normotensive controls) failed to identify genome-wide associated loci.[17] A GWAS of 1,526 Japanese individuals (403 cases and 452 controls) similarly did not reveal significant loci associated with HTN.[41] These studies had limited statistical power due to study size and the restricted focus on HTN. Interestingly, a study of over 16,000 Korean individuals identified a BP-associated SNP (rs17249754, $P = 1 \times 10^{-7}$ in combined meta-analysis) near the *ATP2B* gene, the region also identified in the CHARGE Consortium.[14,42]

Despite the high prevalence of HTN in African Americans, only one BP GWAS in individuals of African ancestry has been published to date. Included in the discovery sample were 509 hypertensives and 508 normotensive controls enrolled in Washington DC.[43] This study identified several loci for SBP and DBP but these findings did not replicate in independent samples comprising 980 unrelated nondiabetic West Africans enrolled in the Africa America Diabetes (AADM) study.[43] Additional GWAS involving larger number of US minority participants are currently underway, including the Women's Heath Initiative minority sample (WHI-SHARe) and the Candidate Gene Association Resource (CARe).[44]

Identification of BP genetic variants in African-American and other minority populations poses particular challenges. Foremost are the limited availability of large samples, a reduced coverage of common variants on current genotyping platforms, and a lack of well-validated genotype imputation methods in populations of mixed genetic ancestry. In addition, population stratification may lead to increased false positives but also may obscure true associations. Additional strategies for gene finding in populations of African ancestry include admixture models based on alleles that differ in frequency across populations of different ancestry and are thus suitable to the study of diseases, such as HTN, with disparities among racial/ethnic groups.[45,46]

Rare variants

Although GWAS have led to the discovery of new genes or genomic regions associated with BP traits, the functional variants underlying these associations remain largely unknown. It is therefore possible that the true functional variants, whether common or rare, have larger effect sizes than the proxy SNPs identified in GWAS. Localization or fine mapping of associated genomic regions will likely contribute to understanding the biological processes involved in BP regulation.

Contributions by low-frequency genetic variants to complex traits[47] including BP have been demonstrated.[48,49] Mutations in salt-handling genes have been identified in rare families with Mendelian forms of HTN or hypotension. In the community-based Framingham Heart Study, putatively functional rare variants in renal salt–handling genes originally identified in patients with Gitelman's or Bartter's syndrome (*SLC12A3*, *SLC12A1*, and *KCNJ1*) were shown to contribute to BP variation at the population level.[49] Different mutations within the same gene can lead to low or high BP depending on whether the mutation is associated with gain or loss of function of the encoded protein. Low-frequency variants (minor allele frequency <2–3%) may contribute to large variability of the trait in the aggregate, or may individually have a larger effect.

A recent Wellcome Trust Case Control Consortium (WTCCC) investigation used haplotype analyses to genome-wide association data to identify the contribution of rare genetic variants to several common complex diseases.[50] The study identified a novel locus for HTN (*ZFATI*), not tagged by SNPs, which replicated in an independent sample. However, the replication was not in the same block suggesting a role for multiple rare variants within the gene/region influencing the susceptibility to HTN.

Collectively, the rare and common variants identified to date explain <2% of population variation in BP. Because rare non-synonymous variants in salt-handling genes have had large effects on BP in the population,[49] it is possible that a multitude of highly penetrant, low-frequency alleles affecting a variety of pathways involved in BP regulation explain a substantial proportion of the remaining heritability.[47] An effective way to identify low-frequency genetic variants responsible for heritable disease–related traits is through DNA sequencing, which can directly identify disease mutations in the genome that are not tagged by GWAS panels of common SNPs. Advances in next-generation DNA technologies and the resultant substantial reductions in the cost of DNA sequencing have enabled direct sequencing of the entire genome (whole-genome sequencing). An alternative approach is whole-genome analysis of all coding sequences (exome sequencing), which focuses variant discovery on coding regions that are more likely to be functional. Such techniques are actively being pursued in novel variant discovery.[51] The 1,000 Genomes project, which is sequencing genomes from individuals of 10 different ethnicities (http://1000genomes.org/page.php?page=home), will provide a catalog of human variants to help in the identification of disease-causing variants. Whole-genome sequencing has been successfully applied to discover mutations in patients with rare Mendelian disorders[52] and efforts such as the National Heart, Lung, and Blood Institute–funded Exome Sequencing Project, apply exonic whole-genome sequencing to larger numbers of samples in populations and less highly penetrant, more complex phenotypes, such as BP. These studies allow for the identification of variants in a broad range of allele frequency by sequencing participants from the extreme tails of the distribution of traits such as BP, but also pose significant analytic challenges in the evaluation of very rare variants at reasonable statistical power.

Structural variations

Structural variants refer to DNA segments that differ in copy number between individuals and they include insertions–deletions (indels), inversions, duplications, and other copy number variations.[53] In addition to their association with rare Mendelian disorders, copy number variations may have an important role in genetic susceptibility to common diseases.[54,55] Recent efforts to map and validate structural variants have identified several challenges, including methodological limitations in approaches to capture the spectrum of genetic variations and in the quality of the data.[56] The WTCCC has performed a comprehensive analysis of copy number variation in Caucasians for eight common traits including HTN.[55] The study replicated three loci where copy number variations were associated with various diseases, but not for the trait HTN. Interestingly, several validated common copy number variations were well tagged by SNPs and therefore could be studied using GWAS data.[55] Conrad *et al.* recently showed that 474 of 1,521 polymorphic trait-associated SNPs identified in GWAS of individuals of European ancestry fell within a recombination hotspot interval that also contained a copy number variation with correlations of 0.5 or higher.[54] As mapping of structural variations continues to be refined, the impact of these variants in complex diseases may be more evident.

EPIDEMIOLOGIC ARCHITECTURE OF BP-ASSOCIATED GENETIC VARIANTS

As evidence for new loci for complex diseases accumulates, obvious logical next step is to assess the epidemiologic architecture of these variants in diverse populations. Although the functional variants underlying the risk are mostly unknown, the population impact of such variants is yet to be determined, particularly in public health–relevant environmental and behavioral contexts such as diet, physical activity, psychosocial factors, and age. Integration of individual-level and group-level (social, cultural, and behavioral) contexts into molecular/genetic analyses has been recently proposed.[57] Comparability in, and high quality of phenotypic characterization and of exposure data across studies will be essential to such efforts.

The degree to which associations with mature genetic variants can be generalized to populations of diverse ethnic/racial ancestry has not been explored sufficiently. A recent study attempted to validate findings of BP GWAS of European ancestry studies to Japanese subjects.[41] This study of 24,000 Japanese individuals from three cohort studies replicated associations with BP or HTN at 7 of 13 investigated loci including *MTHFR*, *FGF5*, *CYP17A1*, *ATP2B1*, *CSK-ULK3*, *ITGA9*, and *CASZ1*. The SNP in *SH2B3* was monomorphic in this study's samples. Interestingly, two SNPs, rs880315 (*CASZ1*) and rs16998073 (*FGF5*), showed significant interpopulation effect heterogeneity, with larger effect in Japanese than Europeans. A study of 8,512 Korean individuals replicated associations of BP with *ATP2B1*, *CSK-ULK3*, *CYP17A1*, and *PLEKHA7*.[58] In African Americans, Adeyemo *et al*. replicated associations with BP for SNPs in *STK39* and *CDH13*.[43]

The recently funded Population Architecture using Genomics and Epidemiology (PAGE) Study (www.pagestudy.org) proposes a comprehensive analysis of the association of genetic variants with complex traits. The PAGE consortium consists of four large ongoing NIH-funded population-based studies or consortia: the Women's Health Initiative (WHI),[59] Epidemiologic Architecture for Genes Linked to Environment (EAGLE),[60] the Multiethnic Cohort study (MEC),[61] and CALICo (Causal Variants Across the Life Course), which includes five cohort studies: the Atherosclerosis Risk in Communities study (ARIC),[62] the Coronary Artery Risk in Young Adults (CARDIA),[63] the Cardiovascular Health Study (CHS),[64] the Study of Latinos (HCHS/SOL), and the Strong Heart Study.[65,66] These data

from multiple prospective cohort and case–control studies allow analyses of genetic variants within diverse cultural, ancestral, and socioeconomic settings and replication of SNP associations in populations of different ancestry including African Americans, Hispanics, American Indians, and Asians is currently ongoing. Studies such as PAGE may provide insights into genetic susceptibility to BP elevation and HTN across race and ethnic groups and the role of environmental and cultural factors in this regard.

LIMITATIONS AND OPPORTUNITIES

Current genetic discovery efforts have been mostly limited to resting BP measured at a single time point, mostly because large sample sizes with phenotypic measurements are required. The study of BP variability or ambulatory BP monitoring may contribute to deepen current insights into the genetic susceptibility of BP levels, their variability, and temporal changes.[67] Similarly, gene discovery efforts based on BP responses to nonpharmacological (diet and physical activity) and pharmacological interventions may help guide prevention efforts and HTN therapy.

Beyond the challenges outlined for the identification of rare and common SNPs and structural variants, and in addition to studies exploring gene–gene and gene–environment interactions, research on the effect of sex chromosomes and mitochondrial variants on BP are needed. Finally, epigenetic effects on BP phenotypes have been understudied to date, despite experimental models indicating that *HSD11B2* is repressed by DNA methylation, suggesting that epigenetic mechanisms affect interindividual differences in the expression of BP regulation.[68]

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Table 1

Comparison of study design, discovery, and replication samples for blood pressure traits in two published genome-wide association meta-analyses of individuals of European ancestry

Discovery									Strategy for SNP selection for replication	Replication	
Studies[a]	Sample size	Ancestry	Number of studies	Mean age across studies (years)	Mean BMI across studies (kg/m^2)	HTN (%)	Treated HTN	Primary traits[b]		*In silico*	*De novo* genotyping
CHARGE[14]	29,136	European	6 cohort studies (one family design)	38–72	25–27	17–60%	5–35%	SBP, DBP and HTN	$P < 4 \times 10^{-7}$	34,433 from Global Bpgen	N/A
Global BPgen[13]	34,433	European	13 population-based (including isolates) and controls only from 4 case–control studies	31–59[c]	23.5–27.4	15–52%	2–24%	SBP, DBP	$P < 10^{-5}$ (2 SNPs with $P < 5 \times 10^{-8}$)	29,136 from CHARGE	71,225 individuals of European ancestry (13 cohorts), 12,889 Indian Asians

BMI, body mass index; DBP, diastolic blood pressure; HTN, hypertension; N/A, not available; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism.

[a] CHARGE BP discovery studies included: the Age, Gene/Environment Susceptibility Reykjavik Study (AGES), Cardiovascular Heath Study (CHS), Framingham Heart Study (FHS), Rotterdam Study and Rotterdam Extension Study (RES); Global BPgen discovery studies included: the Baltimore Longitudinal Study of Aging, British 1958 Birth Cohort (B58C-T1DGC and B58C-WTCCC), Cohorte Lausannoise (CoLaus), Diabetes Genetic Initiative (DGI), European Prospective Investigation of Cancer-Norfolk-Genome Wide Association Study (EPIC-Norfolk-GWAS), Fenland Study, Finland-United States Investigation of NIDDM Genetics (FUSION) Study, Invecchiarie in Chianti (InCHIANTI), Kooperative Gesundheitsforschung in der Region Augsburg (KORA), the Myocardial Infarction Genetics Consortium (MIGen), Northern Finland Birth Cohort of 1996 (NFBC1966), SardiNIA, Study of Health in Pomerania (SHIP), the Precocius Coronary Artery Disease (PROCARDIS), Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX), and TwinsUK.

[b] Analyses were adjusted for age, age^2, body mass index, study site, and population stratification. Method of adjustment for blood pressure medications in quantitative analyses were: CHARGE, addition of 10 mm Hg to SBP and 5 mm Hg to DBP; Global BPgen, addition of 15 mm Hg to SBP and 10 mm Hg to DBP.

[c] Individuals >70 years were excluded.

Table 2

Loci associated with blood pressure CHARGE and Global BPgen meta-analyses

Loci	Nearby genes	Trait: *P* value[a]	SNP	Coded allele	Coded allele frequency	*β* (s.e.)	Total number with replication	Reference
1p36	*MTHFR*	SBP: 2×10^{-13}	rs17367504	G	0.14	−0.85 (0.11)	82,973	13
	CLCN6							
	NPPA							
	NPPB							
	AGTRAP							
3p22.1	*ULK4*	DBP: 3×10^{-9}	rs9815354	A	0.17	0.49 (0.08)	Up to 63,569	14
4q21	*PRDM8*	DBP: 1×10^{-21}	rs16998073	T	0.21	0.50 (0.05)	101,623	13
	FGF5							
	c4orf22							
10q21	*c10orf107*	DBP: 1×10^{-9}	rs1530440	T	0.19	−0.39 (0.06)	87,273	13
	TMEM26	SBP: 1×10^{-10}	rs1004467	A	0.90	1.05 (0.16)	Up to 63,569	
	RTKN2							
	RHOBTB1							
	ARID5B							
10q24	*CYP17A1*	SBP: 7×10^{-24}	rs11191548	T	0.91	1.16 (0.12)	132,552	14,13
	AS3MT	SBP: 1×10^{-10}	rs1004467	A	0.90	1.05 (0.16)	Up to 63,569	
	CNNM2							
	NT5C2							
10p12	*CACNB2*	DBP: 1×10^{-8}	rs11014166	A	0.66	0.37 (0.06)	Up to 63,569	14
11p15	*PLEKHA7*	SBP: 2×10^{-9}	rs381815	T	0.26	0.65 (0.11)	Up to 63,569	14
12q21	*ATP2B1*	SBP: 4×10^{-11}	rs2681492	T	0.80	0.85 (0.13)	Up to 63,569	14
		DBP:2×10^{-9}	rs2681472	A	0.83	0.50 (0.08)	Up to 63,569	
		HTN: 2×10^{-11}	rs2681472	A	0.83	0.15 (0.02)	Up to 63,569	
12q24	*SHS2B3*	DBP: 3×10^{-18}	rs653178	T	0.53	−0.46 (0.05)	79,661	14,13
	ATXN2	SBP: 5×10^{-9}	rs3184504	T	0.48	0.58 (0.10)	Up to 63,569	
		DBP: 3×10^{-14}			0.49	0.48 (0.06)	Up to 63,569	

Loci	Nearby genes	Trait: *P* value[a]	SNP	Coded allele	Coded allele frequency	*β* (s.e.)	Total number with replication	Reference
12q24.21	*TBX3*	DBP: 4×10^{-8}	rs2384550	A	0.35	−0.35 (0.06)	Up to 63,569	14
	TBX5							
15q24	*CYP1A1*	DBP: 1×10^{-23}	rs1378942	C	0.36	0.43 (0.04)	134,258	14,13
	CYP1A2	DBP: 2×10^{-10}	rs6495122	A	0.42	0.40 (0.06)	Up to 63,569	
	CSK							
	LMAN1L							
	CPLX3							
	ARID3B							
	ULK3							
17q21	*ZNF652*	DBP: 5×10^{-9}	rs16948048	G	0.39	0.31 (0.05)	82,441	13
	PHB							
17q21	*PLCD3*	SBP: 1×10^{-8}	rs12946454	T	0.28	0.57 (0.10)	77,690	13
	ABCD4							
	HEXIM1							
	HEXIM2							

DBP, diastolic blood pressure; HTN, hypertension; SBP, systolic blood pressure; SNP, single-nucleotide polymorphisms.

[a]Only *P* value $<5 \times 10^{-8}$ are reported.

Table 3

Additional published GWAS by race/ethnicities

Study	Race–ethnicity/country	Genotyping platform	Discovery samples	Replication samples	Traits	Findings SNP (*P* value: trait)
WTCCC[18]	Europeans/Europe	Affymetrix GeneChip 500K Mapping Array	2,000 hypertensive cases, 3,000 controls	None	HTN	rs2820037 ($P = 8 \times 10^{-7}$: HTN)
Levy *et al.*[19]	European Americans/United States	Affymetrix Human Mapping 100K	Up to 1,327 individuals	None	SBP, DBP, long-term averaged SBP and DBP	rs10493340 ($P = 2 \times 10^{-7}$: SBP) and rs1963982 ($P = 3 \times 10^{-6}$: DBP)
Adeyemo *et al.*[43]	African Americans/United States and West Africans/Africa	Affymetrix Genome-Wide Human SNP Array 6.0	509 case and 508 control African Americans	980 nondiabetic West African case–controls[a]	HTN, SBP, and DBP (among controls only)	Rs5743185 ($P = 2 \times 10^{-11}$), rs16877320 ($P = 3 \times 10^{-9}$), rs11160059 ($P = 2 \times 10^{-8}$), rs17365948 ($P = 2 \times 10^{-8}$), rs12279202 ($P = 5 \times 10^{-8}$)
Org *et al.*[69]	Europeans/Germany, Estonia, and United Kingdom	Affymetrix GeneChip 500K Mapping Array	Up to 1,017 individuals	~3,766 individuals from three studies	HTN, SBP, and DBP	rs11646213 ($P = 8.3 \times 10^{-6}$)[b]
Yang *et al.*[17]	Han Chinese/China	Affymetrix Human Mapping 100K	175 cases, 175 age- and sex-matched controls	833 cases and 833 normotensive controls	HTN	No significant findings for single locus analyses
Wang *et al.*[70]	Amish and non-Amish European Americans/United States	Affymetrix Human Mapping 100K	542 Amish subjects (119 with type 2 diabetes, 132 with impaired glucose tolerance, and 291 with normal glucose tolerance)	1,347 Amish; ~5,800 individuals from four European-American studies	SBP and DBP	rs4977950 ($P = 9 \times 10^{-8}$: SBP), SNPs in *STK39* ($P < 10^{-7}$)
Cho *et al.*[42]	Korean/Korea	Affymetrix Genome-Wide Human SNP array 5.0	8,842 Korean individuals	7,861 Korean individuals	SBP and DBP	rs17249754[c] ($P = 9 \times 10^{-7}$ for discovery and 1×10^{-7} for combined meta-analysis: SBP)
Takeuchi *et al.*[41]	Japanese/Japan	Infinium HumanHap550 BeadArray (Illumina)	1,526 individuals for GWAS	3,526 individuals from a case–control study and >16,000 individuals from two cohort studies used for replication of published findings	HTN, SBP, and DBP	No significant findings for genome- wide association analysis; replication of seven described loci: *CASZ1*, *MTHFR*, *ITGA9*, *FSF5*, *CYP17A1-CNNM2*, *ATP2B1*, and *CSK-ULK3*

DBP, diastolic blood pressure; GWAS, genome-wide association studies; HTN, hypertension; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism; WTCCC, Wellcome Trust Case Control Consortium.

[a] Replication using $\alpha = 0.05$.

[b] Near the *CDH13* gene.

[c] *ATP2B*.