HHS Public Access

Author manuscript

Curr Hypertens Rep. Author manuscript; available in PMC 2016 May 31.

Published in final edited form as:

Curr Hypertens Rep. 2014 August ; 16(8): 461. doi:10.1007/s11906-014-0461-9.

Genetics, Ancestry, and Hypertension: Implications for Targeted Antihypertensive Therapies

Nora Franceschini,

Department of Epidemiology, University of North Carolina Gillings School of Global Public Health, 137 E. Franklin St., Suite 306, Chapel Hill, NC, USA

Daniel I. Chasman,

Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA, dchasman@research.bwh.harvard.edu

Rhonda M. Cooper-DeHoff, and

Department of Pharmacotherapy and Translational Research and Division of Cardiovascular Medicine, Colleges of Pharmacy and Medicine, University of Florida, Gainesville, FL 32610-0486, USA, dehoff@cop.ufl.edu

Donna K. Arnett

Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA, arnett@uab.edu

Nora Franceschini: noraf@unc.edu

Abstract

Hypertension is the most common chronic condition seen by physicians in ambulatory care and a condition for which life-long medications are commonly prescribed. There is evidence for genetic factors influencing blood pressure variation in populations and response to medications. This review summarizes recent genetic discoveries that surround blood pressure, hypertension, and antihypertensive drug response from genome-wide association studies, while highlighting ancestry-specific findings and any potential implication for drug therapy targets. Genome-wide association studies have identified several novel loci for inter-individual variation of blood pressure and hypertension risk in the general population. Evidence from pharmacogenetic studies suggests that genes influence the blood pressure response to antihypertensive drugs, although results are somewhat inconsistent across studies. There is still much work that remains to be done to identify genes both for efficacy and adverse events of antihypertensive medications.

Correspondence to: Nora Franceschini, noraf@unc.edu.

Compliance with Ethics Guidelines

Conflict of Interest Nora Franceschini and Daniel I. Chasman declare that they have no conflicts of interest.

Rhonda M. Cooper-DeHoff has received research grants from NIH and Abbott Laboratories. She also has received a patent for clinical trial software and royalties from the University of Florida Foundation.

Donna K. Arnett has received a grant from the NIH.

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.

Keywords

Genetics; Hypertension; Genome-wide association studies; Ancestry; Pharmacogenetics

Introduction

Hypertension is the most common chronic condition seen by physicians in ambulatory care [1] and a condition for which life-long medications are commonly prescribed. In the USA, hypertension affects one-third of the adult population, has increased among children and adolescents, affecting disproportionally some ethnic/racial subgroups [2, 3]. From the clinical and public health perspective, the major long-term impact of hypertension is resultant end-organ damage to the kidneys, heart, vessels, and brain, leading to premature mortality, disability, and significantly increased economic and societal cost [4–6]. Evidence from clinical trials has shown that lowering blood pressure reduces the risk of stroke, coronary heart disease, and mortality [7–12], in addition to slowing the progression of chronic kidney disease [13]. African Americans are a subgroup who suffer a greater burden of hypertension and its complications, and are more likely to have uncontrolled hypertension [14] and to require multiple drugs for blood pressure (BP) control compared with other US racial/ethnic subgroups [15]. Genetic factors also contribute to hypertension and may interact with environmental exposures (including pharmacological agents) and social-lifestyle habits in contributing to disparities in hypertension prevalence and severity observed across diverse race/ethnic subgroups.

This review summarizes recent genetic discoveries that surround BP, hypertension, and antihypertensive drug response from studies of the general population and those from pharmacogenomic settings, while highlighting ancestry-specific findings and any potential implication for drug therapy targets. We focused on discovery efforts seeking (1) loci contributing to the inter-individual variation in BP and hypertension risk using large-scale genetic approaches, including genome-wide association studies (GWAS), applied to cohorts of individuals recruited from the general population, and (2) loci identified through GWAS of pharmacologic traits, including those related to clinical response to antihypertensive medications. The first approach is an unbiased scan of the entire genome aiming to provide insights into the genes contributing to the biology of BP regulation, to suggest targets for therapy and for population-level risk reduction. The second approach focuses specifically on identifying genetic variants influencing drug response, including drugs used for the treatment of hypertension, and/or genetic variants associated with side effects of drugs. Pharmacogenetics holds the promise of providing individualized clinical care, by identifying subgroups based on their response to commonly used drugs for hypertension and/or subgroups at higher risk for harmful side-effects of drugs and thus tailoring therapy to an individual’s genetic makeup. Although both approaches have already identified numerous genes related to BP, hypertension, and antihypertensive drug response, the functional variants underlying most associations remain largely unknown and much work is still needed to translate the findings to the clinical care of patients.

Blood Pressure Loci Identified in Studies of the General Population

Common Variants Identified in GWAS and Admixture Models

The heritability of BP is substantial (in the range of 30–55 %), suggesting a large number of contributing genetic variants, the vast majority of which are yet to be discovered [16•, 17]. Genetic analysis of Mendelian, i.e., extreme forms of hypertension and hypotension, has highlighted some pathways of BP regulation in humans and these findings comprise rare genetic variants with large impact in BP [17, 18]. However, identifying genes related to common variation in BP and essential hypertension has proven challenging. Hypertension—and its response to treatment—is a complex trait that is likely influenced by a large number of genetic variants, each with small effects, and possibly modulated by environmental factors including diet, lifestyle, and other exposures. Recent genetic discovery efforts for this class of genetic variation have focused on unbiased scans of the genome for associations with BP traits using data from individuals recruited from the general population, a proportion of them having essential hypertension. This GWAS approach examines the association of hundreds of thousands of genetic markers commonly seen in the population (single-nucleotide polymorphisms, SNPs), and relies on stringent statistical criteria for discovery of loci in order to account for multiple testing (typically $p<5 \times 10^{-8}$). Validation of genomic regions is further provided by replication of the associations in additional samples. Because genetic variants vary in allele frequency across race/ethnicity and the patterns of correlation among genetic markers also vary by ancestry and admixture, studies are performed within each ancestrally homogenous group separately.

The first two BP GWAS [19, 20] discovered 13 BP loci and were followed by a combined effort from the International Consortia of Blood Pressure (ICBP) [16•] reporting additional associations for a total of 28 loci for systolic and diastolic BP and/or hypertension. Subsequent studies reported over 55 loci for BP in GWAS of pulse pressure and mean arterial pressure [21], GWAS using extremes of the BP distribution or hypertension [22, 23], and in studies using gene-centric arrays, which provide a better genomic coverage for some loci [24–26]. The identified genetic variants from GWAS have small effects and explained only a small proportion of the trait variation. For example, 29 SNPs in the 28 loci identified in ICBP explained less than 1 % of the inter-individual variation in BP [16•]. However, findings from GWAS have already uncovered some biology and potential targets for drug therapy (discussed under “Genes, Pathways, and Potential Role for Pharmacogenetics”).

The ICBP and several other recently published studies have studied mostly individuals of European ancestry [16•, 19, 20, 22–25, 27]. Studies of non-European ancestry including East Asians [28•, 29] and African ancestry [30, 31•] have contributed additional information to the genetic architecture of BP, though their sample sizes are limited. For example, a GWAS of BP in East Asians identified four novel BP loci, and evidence for an ethnic-specific variant at *ALDH2* (aldehyde dehydrogenase 2). The *ALDH2* variant was highly correlated with a known functional variant (rs671), which was previously associated with hypertension modulated by alcohol intake in East Asians [28•].

Individuals of African ancestry have more genomic diversity and less linkage disequilibrium (correlations among SNPs) compared with European and Asian populations [32]. These

genomic differences can be helpful in gene discovery and also in narrowing genomic regions within identified loci to identify functional variants for BP. Using admixture mapping approaches followed by association analyses, Zhu et al. [30] Identified the *NPR3* (natriuretic peptide receptor 3) locus for systolic and diastolic BP in African Americans, subsequently shown to be associated with BP traits in individuals of European ancestry [16•] and East Asians [28•]. In a recent meta-analysis of 19 GWAS of African ancestry participants of the Continental Origins and Genetic Epidemiology Network Blood Pressure (COGENT-BP) consortium, three novel loci for BP (*EVX1-HOXA*, *RSPO3*, *PLEKHG1*) [31•] were identified, although the discovery sample (including 29,000 individuals) was half of the ICBP sample, thus highlighting the potential for differences according to ancestry. *RSPO3* (R-spondin 3)-encoded protein activates the Wnt/beta-catenin signaling pathways, and the locus has been previously associated with blood urea nitrogen levels, a measure of kidney function [33]. There was also evidence for an additional novel variant at the previously reported locus *SOX6*. Of interest, genetic loci identified in individuals of African ancestry replicated across European and East Asian individuals in a trans-ethnic meta-analysis. Therefore, studies of non-European ancestry are essential for trans-ethnic gene discovery, as common genetic variants may have broad effects across ancestries in the population.

Rare Variants Influencing BP Traits

In addition to common genetic variants, recent studies have shown that low frequency variants (minor allele frequency between 0.5 and 5 %) [34] can have large effects and may explain some of the missing heritability of complex traits [35]. Importantly, rare variants constitute the vast majority of polymorphic sites in human populations [34]. Low-frequency and population-specific variants are not well captured by current GWAS genotyping platforms, particularly among non-European ancestry populations. Studies of low frequency variants using sequencing data and 1000 Genomes Project imputed data are ongoing, and examples of loci associations with BP traits have not yet been published. However, a candidate gene sequencing study identified rare variants in kidney solute transporters, all of which are targets for diuretics, which were associated with low BP in the Framingham Heart Study [36]. These included variants in the *SLC12A3* (thiazide-sensitive Na-Cl cotransporter, the target of thiazide diuretics), *SLC12A1* (Na-K-Cl cotransporter NKCC2, the target of loop diuretics furosemide and bumetanide) and *KCNJ1* (K+ channel ROMK) genes [36]. Because rare variants tend to be population-specific [37], future studies may provide evidence for ancestry-specific variants at low frequency influencing the genetic architecture of BP traits.

Genes, Pathways, and Potential Role for Pharmacogenetics

Most genomic regions identified in BP GWAS include genes of unknown function, but some loci include genes known or suspected to be involved in BP pathways and/or are targets of antihypertensive drugs (Table 1). The *CYP17A1* (cytochrome P450 enzyme) protein is a key enzyme in the steroidogenic pathway that produces mineralocorticoids and glucocorticoids, and rare Mendelian mutations manifest by congenital adrenal hyperplasia and hypokalemic hypertension [38]. This locus has been identified in GWAS of both European and East Asian individuals [16•, 28•]. The *ADM* (adrenomedullin) protein is a hypotensive peptide found in

human pheochromocytoma [39], a disease manifested by paroxysmal hypertension and a cause of secondary hypertension [40]. *ADRB1* encodes the β-1 adrenergic receptor, a guanine nucleotide-binding regulatory protein-coupled receptor target of β-adrenergic receptor blockers. SNPs nearby or within the gene have been associated with mean arterial pressure in GWAS [21] and a lower risk of essential hypertension [41]. Vasoactive peptides including natriuretic peptides and endothelin have a well-known role in BP control. Several genes in these pathways have been identified in GWAS of BP including *NPPA/NPPB* (precursors of atrial- and B-type natriuretic peptides), *NPR3* (natriuretic peptide clearance receptor), and *EDN3* (endothelin 3). Soluble guanylyl cyclase, the product of the *GUCY1A3-GUCY1B3* genes, generates cyclic guanosine monophosphate (cGMP) under stimulation by nitric oxide, inducing vasodilation. *NOS3* encodes nitric oxide synthase 3, which is responsible for the conversion of l-arginine to the vasodilator nitric oxide. Several calcium and potassium channel genes have been identified in GWAS of BP traits including *ATP2B1, CACNB2* and *KCNJ11*, and their pharmacologic targets are shown in Table 1. Genes related to the rennin-angiotensin-aldosterone system identified in BP GWAS are *ENPEP*, which encodes a glytamyl aminopeptidase involved in the conversion of angiotensin II to angiotensin III, and *AGT*, which encodes angiotensinogen precursor, the target of renin conversion to angiotensin I. *FURIN* encodes a protease involved in the processing of protein precursors including the prorenin receptor. Except for *AGT*, the effect of polymorphisms in these genes in response to therapy has not been studied. *AGT* variants have been also shown to interact with a low-salt diet [42, 43].

Kidney Genes, BP and Hypertension

The role of the kidneys on BP homeostasis is well-defined through mechanisms related to salt reabsorption and volume control. BP GWAS identified two kidney solute transporters, *SLC4A7* (electro-neutral sodium bicarbonate co-transporter) and *SLC39A8* (solute carrier family 39 [zinc transporter], member 8), but their role in BP regulation remains unknown [16•]. *SLC39A8* is the major transporter of cadmium into cells in humans, an environmental metal pollutant that has been associated with endothelial dysfunction, oxidative stress, and hypertension in populations [44–47].

UMOD (uromodulin) is highly expressed in the kidney's thick ascending limb and encodes the Tamm-Horsfall protein, the most abundant protein excreted in normal urine. In GWAS, variants in the promoter of *UMOD* (rs4293393, rs13333226) associated with lower BP and with a better kidney function [23, 48]. Transgenic mice with overexpression of uromodulin manifest salt-sensitive hypertension, aging-related kidney pathology, and activation of the thick ascending limb sodium cotransporter NKCC2, the target of loop diuretics [49]. Hypertensive individuals homozygous for *UMOD* at risk variant rs4293393 demonstrated a lowering of BP salt sensitivity response when treated with furosemide compared to other hypertensive individuals [49]. rs4293393 is common in all ethnic groups represented in HapMap and the 1000 Genomes Project, suggesting a potential role in hypertension across diverse ancestry groups.

Chronic kidney disease is usually accompanied by hypertension. A gene known to cause chronic kidney disease and secondary hypertension is *APOL1* (apolipoprotein L, 1), recently

reviewed in this journal [50]. Two *APOL1* alleles, under positive selection in populations of African ancestry, confer substantial risk of focal segmental glomerulosclerosis, HIV-associated nephropathy and hypertensive-attributed nephropathy [51–53]. This is also an example of ancestry-specific variants common in the population that present risk for hypertension.

GWAS Findings and Drug Repositioning

Sauseau et al. recently examined the utility of GWAS data in identifying drug targets or alternative clinical indications for existing drugs [54]. Using a set of 991 GWAS genes identified from publications listed in the genome catalog up to 2011, they found that 21 % of the genes were amenable to pharmacological modulation using small molecules and 47 % using biopharmaceuticals, which was a significantly higher frequency than those derived from the whole genome. In addition, by combining their gene list with a list obtained from the Pharmaprojects database (www.pharmaprojects.com), 155 genes were identified that were already targets or in development for a clinical disease. By matching drugs and clinical GWAS traits, the authors were able to identify potential novel indications for existing drugs or drugs in development. These data suggest that GWAS findings are enriched for "drug-able" genes in humans, even though the functional variants may not yet have been identified.

GWAS and Hypertension Drug Targets

Johnson et al. studied the association of gene targets of alpha blockers, angiotensin-converting enzyme inhibitors, beta blockers, angiotensin receptor blockers, calcium channel blockers, diuretics, and vasodilators, identified in the DrugBank (www.drugbank.ca), with BP and hypertension using GWAS [27]. Genetic variants within 60 kb of 30 drug target genes were selected and tested for associations with BP and hypertension traits in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (n = 29,136). Replication was performed in over 57,000 European ancestry individuals. The study found associations of a nonsynonymous variant in the *ADRB1* gene with systolic and diastolic BP, and hypertension, and a variant in *AGT* was associated with systolic BP and hypertension [27].

Loci Identified in Pharmacogenetic Studies

Pharmacologic exposures can modify the effects of genes influencing BP and contribute to antihypertensive response and overall cardiovascular risk. Genetic factors can influence the response to pharmacologic agents and/or can guide treatment strategies such as avoiding side-effects and other harmful complications. Despite the promise of pharmacogenomics in the treatment of hypertensive patients, their use is still limited in clinical care. Given the complex regulatory mechanisms for BP, alternative strategies for the investigation of BP genes may prove informative for gene finding, for example, BP responses to pharmacologic interventions [55]. Recent GWAS for antihypertensive pharmacogenetics have identified *NEDD4L* (neural precursor cell expressed, developmentally downregulated 4-like) variants that are associated with antihypertensive response to diuretics [56–58, 66], as well as *PRKCA* variants influencing BP response to thiazide diuretics [59•] (discussed below).

The pharmacogenetics of antihypertensive treatment has been recently summarized [60, 61]. Evidence from studies suggests that genetics influence the BP response to antihypertensive drugs, although results are somewhat inconsistent across studies. Comparison of findings across studies is complicated by differences in study design, methods for assessing BP, pharmacologic exposures (including dose and duration), and small sample size. Pharmacogenetic studies of BP response and antihypertensive drug side effects can be found in the International Consortium for Antihypertensive Pharmacogenetic Studies (ICAPS) at www.pharmgkb.org/page/icaps. These studies include observational studies and clinical trials of antihypertensive drugs, and used candidate gene and GWAS genetic approaches. Below, we focus on findings from GWAS.

GWAS Studies of BP Drug Response

Two GWAS of BP drug response were recently published [59•, 62•]. These studies used data from randomized clinical trials. Gong et al. studied the association of SNPs in 37 BP GWAS loci (Illumina 50 K cardiovascular or Omni 1 M GWAS arrays) with response to atenolol and thiazide diuretics in 461 European and 298 African-ancestry hypertensive participants of the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study, a multicenter, randomized clinical trial of hydrochlorothiazide (HCTZ) versus atenolol [62•]. Although there was no genome-wide significant finding when corrected for multiple testing, a genetic risk score based on nominally significant associations in the array-wide analysis was significantly associated with response to atenolol and thiazides in individuals of European ancestry. Turner et al. studied the association of common variants influencing antihypertensive response to HCTZ in 424 hypertensive European Americans from the PEAR study and the Genetic Epidemiology of Responses to Antihypertensive (GERA) study [59•]. Among ~1.1 million genetic markers tested, an SNP in *PRKCA* (rs16960228) was associated with greater systolic and diastolic BP response among carriers of the allele A, reaching genome-wide significance in a combined metaanalysis of discovery and additional replication samples. An SNP nearby *GNAS-EDN3* (rs2273359), although replicated in independent samples, did not reach the genome-wide threshold for significance for BP response to HCTZ.

He et al. performed a GWAS of BP in response to dietary intervention and cold pressor test in 1,881 Han Chinese participants from the GenSalt study [63]. The GenSalt study included a 7-day low-sodium (51.3 mmol/d), a 7-day high-sodium (307.8 mmol/d), and a 7-day high-sodium plus potassium supplementation (60 mmol/d) diet intervention in addition to BP cold pressor test response. They identified eight novel loci that were associated with one or more traits and replicated in an additional sample of 698 Han Chinese individuals. These included SNPs in or near *PRMT6*, *CDCA7*, and *PIBF1*, which were associated with response to low-salt diet; *IRAK1BP1* associated with high-sodium intervention; *CDCA7*, *ARL4C*, *IRAK1BP1*, and *SALL1*, associated with potassium supplementation; and *TRPM8* and *FBXL13* associated with cold pressor test response. In five of these loci, the SNPs were low-frequency markers (MAF 0.01 to 0.05). The effect sizes were higher than the ones seen in GWAS of BP, suggesting stronger genetic effects to response to interventions. Finally, there was a strong dose–response relationship between the cumulative allele count and the development of hypertension at follow-up.

GWAS Studies of Adverse Response to Antihypertensive Drugs

GWAS studies of adverse response to antihypertensive drugs have also been recently published. Del-Aguilla et al. studied the association of genetic markers with change in fasting plasma glucose and triglycerides in response to HCTZ using data from the PEAR and GERA studies [64]. They identified two genome-wide significant variants (rs12279250 and rs4319515) in the *NELL1* gene associated with increased fasting triglycerides in African Americans. Each at-risk variant allele was associated with a large effect of approximately 28 mg/dl increase in plasma triglyceride levels. Using 33 SNPs previously associated with fasting glucose in white individuals, Gong et al. studied their association with drug-induced glucose changes in the PEAR study [65]. An SNP in the 5' of the *PROX1* gene (rs340874) was significantly associated with atenolol-induced glucose change, with a 2.39 mg/dl increase in serum glucose per each copy of the C-allele. A GWAS of atenolol-induced HDL-C changes in the PEAR study was not significant [66], although 13 regions showed consistent associations among whites and African Americans. These included seven loci previously related to lipid pathways or metabolic traits including *GALNT2*, *FTO*, *ABCB1*, *LRP5*, *STARD3NL*, *ESR1*, and *LIPC*. A study of angiotensin-converting enzyme inhibitor-associated angioedema (175 cases and 489 controls) failed to identify genome-wide significant SNPs associated with this complication [67]. In the INternational VErapamil SR Trandolapril Study (INVEST), a prospective, randomized study comparing two pharmacotherapy strategies to control hypertension in ambulatory patients with coronary artery disease, *TCF7L2* polymorphisms were associated with HCTZ-induced diabetes [68].

Taken together, although GWAS published studies are still limited, their findings suggest genetic effects for common variants in drug-induced side-effects. Nonetheless, GWAS discovery studies of BP drug response are limited by small sample size and are likely too underpowered to identify novel loci.

Ancestry and Choice of Hypertension Medications

A recent report from the authors originally convened as the 8th Joint National Committee [69] recommends different first-line for antihypertensive drugs in African-American compared to non-African-American hypertensive individuals (a calcium channel blocker or thiazide-type diuretics). Based on evidence from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) clinical trials [70], in which black individuals taking a thiazide diuretic showed better stroke, heart failure, and combined cardiovascular outcomes compared to those taking an ACE inhibitor. For the non-African-American population, the new report recommends an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, a calcium channel blocker or thiazide-type diuretic as first-line therapy. African Americans have greater increases in BP in response to sodium intake, i.e., salt sensitivity [71, 72]. A recent study by Tu et al. showed that increases in BP in African-American children and adults were associated with increased plasma aldosterone concentration and reduction in plasma renin activity [73]. This relationship was not seen in white individuals. African-American individuals also had higher BP response to an intervention using the synthetic mineralocorticoid 9-α-fludrocortisone, suggesting aldosterone sensitivity as a mechanism of hypertension [73]. It is likely that there is an

underlying genetic component that explains the racial/ethnic differences in response to therapy seen in clinical trials, although findings are yet to be published.

Future Research and Clinical Perspectives

While some progress has occurred recently in the search for genes contributing to the response to antihypertensive therapy, both in terms of efficacy and adverse events, there is much work that remains to be done. A challenge for researchers in the field is replication of significant findings in a different study population. Not only are trials expensive to conduct, there are few antihypertensive trials that are active and collecting DNA. Another challenge is the need to replicate findings with the same drug or even the same drug class. The recent formation of the ICAPS (International Consortium for Antihypertensive Pharmacogenetic Studies) is a step forward towards replication. A second major challenge is the lack of trans-ethnic GWAS to identify common targets across ancestries. Finally, there is currently an absence of validated genome-based measures with sufficient clinical utility to be implemented in clinical practice.

Conclusions

GWAS have identified over 55 loci associated with blood pressure and hypertension traits. These loci harbor genes that are either established or potential targets for antihypertensive drugs. Studies of non-European ancestry are important to leverage trans-ethnic gene discovery, and to narrow down genomic regions where putative genetic variants (common or rare) are located. Although there is evidence for genes influencing the blood pressure response to antihypertensive drugs, few pharmacogenetic GWAS of antihypertensive drugs have been reported. Challenges for these studies are their small sample sizes, the lack of ancestry diversity, and difficulties in finding replication samples.

Acknowledgments

Funding NIHU01- GM074492 (to RKCD)

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

1. Ashman JJ, Beresovsky V. Multiple chronic conditions among us adults who visited physician offices: data from the national ambulatory medical care survey, 2009. Prev Chronic Dis. 2013; 10:E64. [PubMed: 23618544]
2. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, et al. Prevalence of hypertension in the us adult population. Results from the third national health and nutrition examination survey, 1988–1991. Hypertension. 1995; 25:305–313. [PubMed: 7875754]
3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Executive summary: heart disease and stroke statistics-2014 update: a report from the American Heart Association. Circulation. 2014; 129:399–410. [PubMed: 24446411]
4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360:1903–1913. [PubMed: 12493255]

5. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med. 2005; 165:923–928. [PubMed: 15851645]
6. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet. 2008; 371:1513–1518. [PubMed: 18456100]
7. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the systolic hypertension in the elderly program (SHEP). Shep Cooperative Research group. JAMA. 1991; 265:3255–3264. [PubMed: 2046107]
8. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension detection and follow-up program cooperative group. JAMA. 1979; 242:2562–2571. [PubMed: 490882]
9. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA. 1970; 213:1143–1152. [PubMed: 4914579]
10. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (syst-eur) Trial Investigators. Lancet. 1997; 350:757–764. [PubMed: 9297994]
11. MRC trial of treatment of mild hypertension: principal results. Medical research council working party. Br Med J (Clin Res Ed). 1985; 291:97–104.
12. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). The IPPPSH Collaborative Group. J Hypertens. 1985; 3:379–392. [PubMed: 2864374]
13. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2005; 67:2089–2100. [PubMed: 15882252]
14. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health and Nutrition Examination Survey, 2001 to 2010. Circulation. 2012; 126:2105–2114. [PubMed: 23091084]
15. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. JAMA. 2003; 290:199–206. [PubMed: 12851274]
16. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011; 478:103–109. [PubMed: 21909115] This is the largest GWAS of BP published. It identified 29 SNPs in 28 loci for BP traits and hypertension. The study comprised of 69,395 individuals of European ancestry for discovery and approximately 200,000 individuals were included in the discovery and replication samples
17. Hopkins PN, Hunt SC. Genetics of hypertension. Genet Med. 2003; 5:413–429. [PubMed: 14614392]
18. Wilson FH, Disse-Nicodeme S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, et al. Human hypertension caused by mutations in wnk kinases. Science. 2001; 293:1107–1112. [PubMed: 11498583]
19. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, et al. Genome-wide association study of blood pressure and hypertension. Nat Genet. 2009
20. Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, et al. Genome-wide association study identifies eight loci associated with blood pressure. Nat Genet. 2009
21. Wain LV, Verwoert GC, O'Reilly PF, Shi G, Johnson T, Johnson AD, et al. Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. Nat Genet. 2011; 43:1005–1011. [PubMed: 21909110]
22. Salvi E, Kutalik Z, Glorioso N, Benaglio P, Frau F, Kuznetsova T, et al. Genomewide association study using a high-density single nucleotide polymorphism array and case-control design identifies a novel essential hypertension susceptibility locus in the promoter region of endothelial no synthase. Hypertension. 2012; 59:248–255. [PubMed: 22184326]

23. Padmanabhan S, Melander O, Johnson T, Di Blasio AM, Lee WK, Gentilini D, et al. Genome-wide association study of blood pressure extremes identifies variant near umod associated with hypertension. PLoS Genet. 2010; 6:e1001177. [PubMed: 21082022]
24. Tragante V, Barnes MR, Ganesh SK, Lanktree MB, Guo W, Franceschini N, et al. Gene-centric meta-analysis in 87,736 individuals of European ancestry identifies multiple blood-pressure-related loci. Am J Hum Genet. 2014; 94:349–360. [PubMed: 24560520]
25. Ganesh SK, Tragante V, Guo W, Guo Y, Lanktree MB, Smith EN, et al. Loci influencing blood pressure identified using a cardiovascular gene-centric array. Hum Mol Genet. 2013; 22:1663–1678. [PubMed: 23303523]
26. Johnson T, Gaunt TR, Newhouse SJ, Padmanabhan S, Tomaszewski M, Kumari M, et al. Blood pressure loci identified with a gene-centric array. Am J Hum Genet. 2011; 89:688–700. [PubMed: 22100073]
27. Johnson AD, Newton-Cheh C, Chasman DI, Ehret GB, Johnson T, Rose L, et al. Association of hypertension drug target genes with blood pressure and hypertension in 86,588 individuals. Hypertension. 2011; 57:903–910. [PubMed: 21444836]
28. Kato N, Takeuchi F, Tabara Y, Kelly TN, Go MJ, Sim X, et al. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in East Asians. Nat Genet. 2011; 43:531–538. [PubMed: 21572416] A large GWAS of East Asians. It identified four new loci (ST7L–CAPZA1, FIGN-GRB14, ENPEP and NPR3) and a newly discovered variant near TBX3. The paper compares the effect estimates for the ICBP SNPs between European and East Asian studies
29. Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, et al. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. Nat Genet. 2009; 41:527–534. [PubMed: 19396169]
30. Zhu X, Young JH, Fox E, Keating BJ, Franceschini N, Kang S, et al. Combined admixture mapping and association analysis identifies a novel blood pressure genetic locus on 5p13: contributions from the CARe consortium. Hum Mol Genet. 2011; 20(11):2285–2295. [PubMed: 21422096]
31. Franceschini N, Fox E, Zhang Z, Edwards TL, Nalls MA, Sung YJ, et al. Genome-wide association analysis of blood-pressure traits in African-ancestry individuals reveals common associated genes in African and non-African populations. Am J Hum Genet. 2013; 93:545–554. [PubMed: 23972371] This is the largest GWAS ofBP in African ancestry individuals. The study identified three novel loci for blood pressure traits and allelic heterogeneity in one known locus
32. Parra EJ, Marcini A, Akey J, Martinson J, Batzer MA, Cooper R, et al. Estimating African American admixture proportions by use of population-specific alleles. Am J Hum Genet. 1998; 63:1839–1851. [PubMed: 9837836]
33. Okada Y, Sim X, Go MJ, Wu JY, Gu D, Takeuchi F, et al. Metaanalysis identifies multiple loci associated with kidney function-related traits in East Asian populations. Nat Genet. 2012; 44:904–909. [PubMed: 22797727]
34. Marth GT, Yu F, Indap AR, Garimella K, Gravel S, Leong WF, et al. The functional spectrum of low-frequency coding variation. Genome Biol. 2011; 12:R84. [PubMed: 21917140]
35. Sanna S, Li B, Mulas A, Sidore C, Kang HM, Jackson AU, et al. Fine mapping of five loci associated with low-density lipoprotein cholesterol detects variants that double the explained heritability. PLoS Genet. 2011; 7:e1002198. [PubMed: 21829380]
36. Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet. 2008; 40:592–599. [PubMed: 18391953]
37. Bustamante CD, Burchard EG, De la Vega FM. Genomics for the world. Nature. 2011; 475:163–165. [PubMed: 21753830]
38. Scaroni C, Biason A, Carpene G, Opocher G, Mantero F. 17-alpha-hydroxylase deficiency in three siblings: short- and long-term studies. J Endocrinol Invest. 1991; 14:99–108. [PubMed: 1648117]
39. Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, et al. Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. 1993. Biochem Biophys Res Commun. 2012; 425:548–555. [PubMed: 22925672]

40. Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma A review of the literature and report of one institution's experience. Med (Baltimore). 1991; 70:46–66.
41. Wang H, Liu J, Liu K, Liu Y, Wang Z, Lou Y, et al. Beta1-adrenoceptor gene arg389gly polymorphism and essential hypertension risk in general population: a meta-analysis. Mol Biol Rep. 2013; 40:4055–4063. [PubMed: 23588958]
42. Hunt SC, Geleijnse JM, Wu LL, Witteman JC, Williams RR, Grobbee DE. Enhanced blood pressure response to mild sodium reduction in subjects with the 235t variant of the angiotensinogen gene. Am J Hypertens. 1999; 12:460–466. [PubMed: 10342783]
43. Svetkey LP, Moore TJ, Simons-Morton DG, Appel LJ, Bray GA, Sacks FM, et al. Angiotensinogen genotype and blood pressure response in the Dietary Approaches to Stop Hypertension (DASH) study. J Hypertens. 2001; 19:1949–1956. [PubMed: 11677359]
44. Wolf MB, Baynes JW. Cadmium and mercury cause an oxidative stress-induced endothelial dysfunction. Biometals. 2007; 20:73–81. [PubMed: 16752219]
45. Messner B, Knoflach M, Seubert A, Ritsch A, Pfaller K, Henderson B, et al. Cadmium is a novel and independent risk factor for early atherosclerosis mechanisms and in vivo relevance. Arterioscler Thromb Vasc Biol. 2009; 29:1392–1398. [PubMed: 19556524]
46. Staessen JA, Kuznetsova T, Roels HA, Emelianov D, Fagard R. Exposure to cadmium and conventional and ambulatory blood pressures in a prospective population study. Public Health and Environmental Exposure to Cadmium Study Group. Am J Hypertens. 2000; 13(2):146–156. [PubMed: 10701814]
47. Tellez-Plaza M, Navas-Acien A, Crainiceanu CM, Guallar E. Cadmium exposure and hypertension in the 1999–2004 National Health and Nutrition Examination Survey (NHANES). Environ Health Perspect. 2008; 116(1):51–56. [PubMed: 18197299]
48. Kottgen A, Glazer NL, Dehghan A, Hwang SJ, Katz R, Li M, et al. Multiple loci associated with indices of renal function and chronic kidney disease. Nat Genet. 2009; 41:712–717. [PubMed: 19430482]
49. Trudu M, Janas S, Lanzani C, Debaix H, Schaeffer C, Ikehata M, et al. Common noncoding umod gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. Nat Med. 2013; 19:1655–1660. [PubMed: 24185693]
50. Freedman BI, Murea M. Target organ damage in African American hypertension: role of APOL1. Curr Hypertens Rep. 2012; 14:21–28. [PubMed: 22068337]
51. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic apol1 variants with kidney disease in African Americans. Science. 2010; 329:841–845. [PubMed: 20647424]
52. Kao WH, Klag MJ, Meoni LA, Reich D, Berthier-Schaad Y, Li M, et al. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. Nat Genet. 2008; 40:1185–1192. [PubMed: 18794854]
53. Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nat Genet. 2008; 40:1175–1184. [PubMed: 18794856]
54. Sanseau P, Agarwal P, Barnes MR, Pastinen T, Richards JB, Cardon LR, et al. Use of genome-wide association studies for drug repositioning. Nat Biotechnol. 2012; 30:317–320. [PubMed: 22491277]
55. Lynch AI, Boerwinkle E, Davis BR, Ford CE, Eckfeldt JH, Leiendecker-Foster C, et al. Pharmacogenetic association of the NPPA t2238c genetic variant with cardiovascular disease outcomes in patients with hypertension. JAMA. 2008; 299:296–307. [PubMed: 18212314]
56. Luo F, Wang Y, Wang X, Sun K, Zhou X, Hui R. A functional variant of nedd4l is associated with hypertension, antihypertensive response, and orthostatic hypotension. Hypertension. 2009; 54:796–801. [PubMed: 19635985]
57. Manunta P, Lavery G, Lanzani C, Braund PS, Simonini M, Bodycote C, et al. Physiological interaction between alpha-adducin and wnk1-nedd4l pathways on sodium-related blood pressure regulation. Hypertension. 2008; 52:366–372. [PubMed: 18591455]

58. Svensson-Farbom P, Wahlstrand B, Almgren P, Dahlberg J, Fava C, Kjeldsen S, et al. A functional variant of the NEDD4L gene is associated with beneficial treatment response with beta-blockers and diuretics in hypertensive patients. JHypertens. 2011; 29:388–395. [PubMed: 21052022]
59. Turner ST, Boerwinkle E, O'Connell JR, Bailey KR, Gong Y, Chapman AB, et al. Genomic association analysis of common variants influencing antihypertensive response to hydrochlorothiazide. Hypertension. 2013; 62:391–397. [PubMed: 23753411] Two recent GWAS of blood response to antihypertensive drugs
60. Arnett DK, Claas SA. Pharmacogenetics of antihypertensive treatment: detailing disciplinary dissonance. Pharmacogenomics. 2009; 10:1295–1307. [PubMed: 19663674]
61. Johnson JA. Advancing management of hypertension through pharmacogenomics. Ann Med. 2012; 44(Suppl 1):S17–S22. [PubMed: 22713143]
62. Gong Y, McDonough CW, Wang Z, Hou W, Cooper-DeHoff RM, Langaee TY, et al. Hypertension susceptibility loci and blood pressure response to antihypertensives: results from the pharmacogenomic evaluation of antihypertensive responses study. Circ Cardiovasc Genet. 2012; 5:686–691. [PubMed: 23087401] Two recent GWAS of blood response to antihypertensive drugs
63. He J, Kelly TN, Zhao Q, Li H, Huang J, Wang L, et al. Genome-wide association study identifies 8 novel loci associated with blood pressure responses to interventions in Han Chinese. Circ Cardiovasc Genet. 2013; 6:598–607. [PubMed: 24165912]
64. Del-Aguila JL, Beitelshees AL, Cooper-Dehoff RM, Chapman AB, Gums JG, Bailey K, et al. Genome-wide association analyses suggest nell1 influences adverse metabolic response to hctz in African Americans. Pharmacogenomics J. 2014; 14:35–40. [PubMed: 23400010]
65. Gong Y, McDonough CW, Beitelshees AL, Karnes JH, O'Connell JR, Turner ST, et al. PROX1 gene variant is associated with fasting glucose change after antihypertensive treatment. Pharmacotherapy. 2014; 34:123–130. [PubMed: 24122840]
66. McDonough CW, Gillis NK, Alsultan A, Chang SW, Kawaguchi-Suzuki M, Lang JE, et al. Atenolol induced HDL-C change in the pharmacogenomic evaluation of antihypertensive responses (PEAR) Study. PLoS ONE. 2013; 8(10):e76984. [PubMed: 24116192]
67. Pare G, Kubo M, Byrd JB, McCarty CA, Woodard-Grice A, Teo KK, et al. Genetic variants associated with angiotensin-converting enzyme inhibitor-associated angioedema. Pharmacogenet Genomics. 2013; 23:470–478. [PubMed: 23838604]
68. Karnes JH, Gong Y, Pacanowski MA, McDonough CW, Arwood MJ, Langaee TY, et al. Impact of TCF7L2 single nucleotide polymorphisms on hydrochlorothiazide-induced diabetes. Pharmacogenet Genomics. 2013; 23:697–705. [PubMed: 24128935]
69. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint national committee (jnc 8). JAMA. 2014; 311:507–520. [PubMed: 24352797]
70. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (allhat). JAMA. 2002; 288:2981–2997. [PubMed: 12479763]
71. Luft FC, Miller JZ, Grim CE, Fineberg NS, Christian JC, Daugherty SA, et al. Salt sensitivity resistance of blood pressure. Age and race as factors in physiological responses. Hypertension. 1991; 17:I102–I108. [PubMed: 1846122]
72. Weinberger MH. Salt sensitivity of blood pressure in humans. Hypertension. 1996; 27:481–490. [PubMed: 8613190]
73. Tu W, Eckert GJ, Hannon TS, Liu H, Pratt LM, Wagner MA, et al. Racial differences in sensitivity of blood pressure to aldosterone. Hypertension. 2014

Table 1

Loci with genes in known blood pressure pathways identified in genome-wide association studies in the general population and their pharmacologic targets

Loci with genes related to BP pathways	Pharmacologic targets
Neuroendocrine system	
CYP17A1 (cytochrome P450 enzyme)	
ADM (adrenomedullin)	
ADRB1 (adrenoceptor beta 1) [21]	Primary target for β-adrenergic receptor blockers
Vasoactive peptides	
NPPA/NPPB (precursors of atrial- and B-type natriuretic peptides)	
NPR3 (natriuretic peptide receptor 3)	
EDN3 (endothelin 3)	
Nitric oxide pathways	
GUCY1A3-GUCY1B3 (alpha and beta subunits of soluble guanylate cyclase)	Isosorbide dinitrate is a nitric oxide donor and hydralazine prevents nitric oxide degradation
NOS3 (nitric oxide synthase 3 (endothelial cell))	
Calcium and potassium channels	
ATP2B1 (ATPase, Ca++ transporting, plasma membrane 1)	
CACNB2 (calcium channel, voltage-dependent, beta 2 subunit)	Controls the cell surface expression of the α1c subunit to which calcium channel blockers bind
KCNJ11 (potassium inwardly-rectifying channel, subfamily J, member 11) [24]	Target of verapamil and glyburide
Renin-angiotensin system	
ENPEP (glutamyl aminopeptidase) [28•]	
AGT (angiotensinogen)	
FURIN (furin (paired basic amino acid cleaving enzyme)	
Wnt/beta-catenin signaling pathways	
RSPO3 (R-spondin 3) [31 •]	
Kidney solute transport	
SLC4A7 (electro-neutral sodium bicarbonate co-transporter)	
SLC39A8 (solute carrier family 39 [zinc transporter], member 8)	
Kidney structure or proteins	
UMOD (uromodulin)	Potential target of furosemide (see text)
PLCE1 (phospholipase C, epsilon 1)	
Unknown pathways	
RELA (v-rel avian reticuloendotheliosis viral oncogene homolog A) [24]	Antihypertensive olmesartan and disulfiram