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Between candidate genes and whole genomes: Time for alternative approaches in blood pressure genetics

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Abstract

Blood pressure has a significant genetic component, but less than 3% of the observed variance has been attributed to genetic variants identified to date. Candidate gene studies of rare, monogenic hypertensive syndromes have conclusively implicated several genes altering renal sodium balance, and studies of essential hypertension have inconsistently implicated over 50 genes in pathways affecting renal sodium balance and other functions. Genome-wide linkage scans have replicated numerous quantitative trait loci throughout the genome, and over 50 single nucleotide polymorphisms (SNPs) have been replicated in multiple genome-wide association studies. These studies provide considerable evidence that epistasis and other interactions play a role in the genetic architecture of blood pressure regulation, but candidate gene studies have limited scope to test for epistasis, and genome-wide studies have low power for both main effects and interactions. This review summarizes the genetic findings to date for blood pressure, and it proposes focused, pathway-based approaches involving epistasis, gene-environment interactions, and next-generation sequencing to further the genetic dissection of blood pressure and hypertension.

Keywords

blood pressure; hypertension; candidate gene; genome-wide association study; GWAS; genome-wide linkage scan; epistasis; pathway; meta-analysis; genetics

Introduction

Nearly one third of US adults over 20 years of age suffer from hypertension [1], a major risk factor for cerebrovascular disease, ischemic heart disease, and cardiac and renal failure [2]. Estimates for the heritability of systolic and diastolic blood pressure (BP) generally range from 31% to 68% [3*], but the genetic nature of hypertension has been debated since the days of Robert Platt and George Pickering in the 1940s. Platt argued that hypertension was caused by a single Mendelian genetic defect that produced a bimodal distribution of BP values [4]. Pickering countered that polygenic inheritance drove a continuous, unimodal BP distribution with values of hypertensives populating the right tail [5]. Platt's theory is

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supported by rare variants with large effects that cause monogenic hypertension syndromes [6], whereas Pickering's theory is substantiated by variants with small effect sizes that collectively contribute to essential hypertension. The completion of the human genome project and the subsequent genome-wide mapping studies have confirmed the polygenic nature of essential hypertension [7].

Researchers have gained insight into the genetic architecture of hypertension, but most of the variance of BP is still unexplained. In this article, we review the BP-influencing variants identified by candidate gene, genome-wide linkage, and genome-wide association studies. We highlight successful strategies used to detect these variants, including meta-analysis of massive sample sizes, pathway-based analysis, inclusion of gene-gene and gene-environment interactions, analysis of population isolates, and analysis of populations of non-European ancestry. Finally, we discuss alternative strategies to leverage pathway analysis, epistasis, gene-environment interactions, and rare variants to deepen our understanding of the pathophysiology of hypertension and BP regulation, as summarized in Figure 1.

Candidate Gene Studies

Candidate gene studies interrogate polymorphisms in a subset of genes selected a priori based on biologic information. The limited number of polymorphisms examined translates into a favorable multiple testing correction that allows detection of small effects using moderate sample sizes. However, use of a moderate sample size precludes the study of rare variants (because very few participants have rare genotypes), and the number of genotyped polymorphisms limits the investigation of possible epistasis. Candidate gene studies ignore causative variants that lack an obvious physiological relationship to the complex disease [8].

Findings from candidate gene studies of Mendelian disorders (Table 1) are more consistent across studies than those of essential hypertension. Associations with essential hypertension are not always well replicated across studies (Table 2). Candidate gene studies often ignore epistasis, gene-environment interactions [9–17], and rare variants [18, 19], which may explain the inconsistent findings. Case-control candidate gene studies of a heterogeneous population may also have inflated type 1 and type 2 errors [20].

Candidate Gene Studies: Pathways

Entire physiological pathways may be more robustly associated with BP than their constituent polymorphisms. Candidate studies of over 15 rare Mendelian hypertensive or hypotensive syndromes have identified genes involved in renal sodium handling, including ion channels and cotransporters, kinase regulators (*WNK1* and *WNK4*), and enzymes and receptors in the aldosterone synthesis or signaling pathways (Table 1). The implicated variants explain less than 1% of the observed population variance in BP. Candidate gene studies of essential hypertension have also implicated many of these renal sodium handling genes (such as *WNK1*, *WNK4*, *SLC12A3*, *SLC12A1*, *KCNJ1*, *SCNN1A*, *SCNN1B*, *SCNN1G*, and *CLCNKB*), as well as other parts of the renin-angiotensin-aldosterone system (RAAS) and dopaminergic signaling pathways involved in sodium homeostasis (Table 2). Renin, angiotensinogen, angiotensin-converting enzyme, and the angiotensin receptor (each playing critical roles in the synthesis and signaling of angiotensin, which stimulates

aldosterone secretion and sodium retention) have yielded inconsistent associations with essential hypertension (Table 2). Three kinases (*WNK1*, *WNK4*, and *SGK1*) regulating the activity of renal ion channels, and subunits of adducin (*ADD1* and *ADD2*) that can activate the Na+/K+ pump (reviewed in references [21] and [22]) have been associated with BP (Table 2).

Both vasoactive and inflammation pathways have been implicated in BP regulation. Vasoactive dopamine (also involved in renal sodium balance) and epinephrine signaling pathways have been studied; polymorphisms in the catecholamine pathway genes *TH*, *COMT*, and *DBH*, dopamine receptor types 1 and 2, a kinase regulating dopamine receptors (*GRK4*), and adrenergic receptors have yielded inconsistent associations (Table 2). The literature as a whole, as well as mechanisms linking these catecholamines to BP, tentatively support the role of genes from these signaling pathways in BP regulation. Several genes involved in vasodilation/vasoconstriction (but not sodium balance), such as nitric oxide synthase (*NOS3*), endothelin-1b (*EDN1*), endothelin-1b receptor (*EDNRA*), and *CYP2C8*, have been associated with BP (Table 2). Similarly, a small number of studies have offered inconclusive results regarding the role of inflammation genes, particularly *IL6* and *TGFβ*. Levels of interleukin-6 were correlated with BP [23], but no genetic associations have been reported. Panoulas et al. [24] demonstrated an association for TGFβ (replicated by He et al. [25]) in 400 patients with rheumatoid arthritis.

Analysis of Interactions in Candidate Gene Studies

Although most studies fail to systematically interrogate epistasis or other interactions, there is considerable evidence that they contribute to BP variability. Pascoe et al. [9] described intragenic interactions in the aldosterone synthase gene, leading to Mendelian hypotension. Participants with two missense variants (R181W and V386A) displayed the elevated serum ratio of 18-hydroxycorticosterone to aldosterone characteristic of the disorder, whereas those with only one missense variant were asymptomatic [9]. This finding exemplifies a strong interaction effect in the absence of the main effects of the individual polymorphisms [9].

Other RAAS components are involved in interactions with BP or essential hypertension. An intragenic interaction between two SNPs in angiotensin-converting enzyme (*ACE* [12]), as well as an intergenic interaction between polymorphisms in the angiotensinogen (*AGT*) and *ACE* genes [11], may influence BP. Epistatic interactions involving adducins, such as those between *ADD1* and *ADD2* [15], *ADD1* and *ACE* [16], and *ADD1* and *CYP11B2* [17], may also influence BP. Numerous dopamine receptor interactions have been described in transgenic mice [26–28].

Gene-environment interactions may also contribute to BP variance. Wang et al. [10] reported an *AGT*-sex-ethnicity between body mass index and *CYP19A1* [29], *CAPN13* [30], *MMP3* [31], *ADRB2* [32], *CYP11B2* [33], and adducin-1 [34]. No association between the adducin G460W variant and BP was found until interactions with body mass index and sex were included [34], emphasizing the need to properly account for interactions to detect BP-influencing variants. Investigators from the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study interrogated interactions between physical activity and 196 SNPs harbored in 24 genes from metabolic and physiological pathways involved in BP

homeostasis [35]. Significant BP-associated interactions were detected between physical activity (dichotomous active vs inactive) and SNPs in *MR*, *SCNN1B*, *APLNR*, *GNB3*, and *BDKRB2* [35]. The effect sizes were substantial: active individuals may have cumulative reductions of up to 8 mm Hg in systolic BP (SBP) and 5 mm Hg in diastolic BP (DBP), compared with inactive individuals who carry the same number of minor alleles of these SNPs.

Genome-Wide Linkage Scans

Candidate gene studies highlighted several major pathways involved in BP homeostasis, but their reliance on prior biological knowledge precluded discovery of unsuspected genes and pathways. Genome-wide linkage scans (GWLS) agnostically query variants distributed throughout the genome. Low-frequency and rare variants with large effects on hypertension can be detected via linkage [36], but GWLS have low power for variants with modest effects [37**], suffer an increased multiple testing burden, and yield broad linkage peaks containing numerous positional candidate genes. Linkage analysis has identified BP quantitative trait loci (QTLs) on every chromosome [8], but these often lack replication.

Early Genome-wide Linkage Scans

Nearly all of the GWLS published between 1999 and 2006 (about two dozen) reported a suggestive association. Only about half of these studies reported a genome-wide significant QTL, and these lacked external replication (reviewed in [38]). One of the largest (N=3,599) early GWLS, the British Genetics of Hypertension Study (BRIGHT), reported just one genome-wide significant QTL at the end of chromosome 6 [39]. Using an expanded sample size (N=3,863) and denser marker set (2 cM spacing instead of 8 cM), the chromosome 6 QTL vanished [40], but a suggestive locus (LOD=2.5) on chromosome 5 appeared. Early results from the Family Blood Pressure Program (FBPP) were also disappointing. One of four FBPP networks, HyperGEN, reported one suggestive locus ($2 < LOD < 3$ [41]), whereas a preliminary meta-analysis of all four FBPP networks (N=6,245) failed to identify any locus with LOD exceeding 2 [42].

Later studies of the FBPP produced more encouraging results. A genome-wide significant QTL on chromosome 1 discovered in GenNet [43] was replicated in two other FBPP cohorts (GENOA and HyperGEN), three previous studies [44–46], and a homologous region of the mouse genome [47]. Based on a combination of known physiology and the human and murine linkage signals, family-based association tests were performed on nine candidate genes on chromosome 1 [43]. Significant associations were detected between BP and *ATB1B*, *RGS5*, and *SELE*. The gene *ATB1B* encodes the β subunit of the Na+/K+ ATPase, which participates in renal sodium absorption, cardiac contraction, and regulation of vascular smooth muscle tone. *RGS5* inactivates the G proteins that mediate vasoconstriction stimulated by angiotensin II and endothelin-1 and is suspected to have a role in angiogenesis and the remodeling of arteries. *SELE* encodes an endothelium-specific adhesion protein that influences vasoactive response. Each SNP has a large effect of 2–5 mm Hg [43].

Genome-wide Linkage Scans of Non-European Populations

A GWLS using 385 microsatellite markers genotyped on 1,089 Mexican Americans from the Veterans Administration Genetic Epidemiology Study (VAGES) revealed significant linkage (LOD = 5.0) between SBP and chromosome 6q14.1 [48]. This broad linkage region in Mexican Americans (1-LOD interval is 23 cM long and contains 180 genes) encompasses loci also linked in European Americans (LOD = 3.3 [45]) and Dutch families (LOD = 2.5 [49]). A SNP in this chromosomal region significantly interacted with a SNP on chromosome 20q12 to influence susceptibility to young-onset hypertension in the Han Chinese of Taiwan [50].

Genome-wide Linkage Scans of Isolated Populations

To reduce genetic heterogeneity and the impact of nonuniform environmental exposures, researchers have performed GWLS using isolated founder populations [51]. Forty-six loci involved in the regulation of arterial pressure were identified by analyzing 120 French-Canadian extended families from an isolated population [52]. Ciullo et al. [53] studied a single extensive (N=2,180), multigenerational family containing 173 individuals with essential hypertension. Linkage analysis after splitting the family into smaller families produced two previously reported QTLs for essential hypertension as well as a novel QTL that has since been replicated [54]. The extended linkage disequilibrium (LD) in a founder population increases power but complicates the identification of the BP-influencing gene [51]. In addition, variants identified in isolated populations may not be relevant to other populations [51].

Follow-up Genome-wide Linkage Scans: Interactions

Bell et al. [55] undertook a systematic two-dimensional scan of the British Genetics of Hypertension (BRIGHT) study (N=4,284) to test for epistasis across all marker pairs. Although several interactions produced a LOD exceeding 4, no pair of markers reached genome-wide significance (defined by LOD ≥ 5.84). Environment can contribute to the heterogeneity of the disease [56]. Linkage analyses can harvest previously undetected QTLs by incorporating gene-environment interactions. A GWLS of 3,289 European and African Americans from HyperGEN yielded 11 novel QTL regions and 15 previously reported QTLs after incorporating gene-age interactions [57]. Numerous loci that lacked any linkage evidence (LOD < 0.5) using the traditional model obtained genome-wide significance (LOD > 3) after including gene-age interactions.

Meta-analysis of Genome-wide Linkage Scans

By harnessing the power of an increased sample size, Simino et al. [54] detected five QTLs (LOD ≥ 3) on chromosomes 6p22.3, 8q23.1, 20q13.12, 21q21.1, and 21q21.3 using overall and ethnicity-specific meta-analyses of 13,044 African American, Asian, European American, and Hispanic American participants from the FBPP. The QTL shoulders (defined by LOD ≥ 2 regions under the linkage peaks) were broad (spanning 11.5 Mbps to 38.4 Mbps) and encompassed a multitude of genes (79 to 541 in each QTL). The potential candidate genes and external corroboration for the association with BP or hypertension included *HLA-A*, *HLA-DRB1*, and *TNFα* for the chromosome 6 QTL region [58–60];

YWHAZ, *ANGPT1*, *ZFPM2*, and *OXR1* for the chromosome 8 QTL region [53, 60–62]; and *KCNB1* and *PTGIS* on chromosome 20 [63–65]. According to the US National Center for Biotechnology Information (NCBI) Gene database (http://www.ncbi.nlm.nih.gov/gene/), the potential candidate genes are diverse, coding for parts of the major histocompatibility complex (*HLA-A* and *HLA-B*); angiopoietin involved in vascular development and angiogenesis (*ANGPT1*); a zinc-finger protein (*ZFPM2*); a cytokine that increases production of both angiotensin II and endothelin-1 (*TNFα*); a voltage-gated potassium channel with a role in insulin secretion, heart regulation, and neurotransmitter release (*KCNB1*); an enzyme producing prostacyclin (a vasodilator and inhibitor of platelet aggregation, *PTGIS*); a signal transduction protein that may play a role in insulin sensitivity (*YWHAZ*); and a protein that may prevent oxidative damage (*OXR1*). The chromosome 21 QTLs had external support [60, 66–69] but lacked strong candidate genes (although this region has been moderately linked to two markers of inflammation, C-reactive protein and fibrinogen [70]).

Genome-wide Association Studies

The lack of compelling linkage evidence shifted attention to association studies. With sufficient sample size and the dense genotyping afforded by new SNP chips (initially 100 k to 500 k SNPs, later 1 M)and through imputations of intervening SNPs based upon HapMap haplotypes, over 80% of common SNPs (minor allele frequency [MAF] ≥ 5%) could be interrogated for association with BP and hypertension [71]. Genome-wide association studies (GWAS) can uncover common variants with small effect sizes that are often missed by candidate gene and linkage analyses [3*]. However, the ability to detect BP-influencing variants may be hindered by a harsh multiple-testing burden (due to 1 million genotyped SNPs), a failure to capture many rare and structural variants, a lack of interaction analysis, and inadequate accounting for shared environment among relatives (in family studies) [37**]. In early GWAS, the few common variants that reached genome-wide significance lacked replication and biological plausibility. (Over 80% of variants identified via GWAS are harbored in noncoding regions [37**].) Later GWAS employing meta-analysis of massive sample sizes and diverse populations have identified over 50 positional candidate genes. These variants generally have small effect sizes (typically less than 1 mm Hg per variant) and collectively explain less than 3% of the BP variability in the population. The functional mechanisms of most implicated variants remain unclear.

Early Genome-wide Association Studies

The Wellcome Trust Case Control Consortium (WTCCC) published the first GWAS of hypertension, analyzing approximately 470,000 genotyped and 2.2 million imputed SNPs [72]. The WTCCC simultaneously investigated 2,000 cases for each of seven complex diseases (including hypertension), using 3,000 shared controls drawn from the Great Britain population regardless of disease status. No hypertension variant reached the genome-wide significance level of $\alpha < 5\times10^{-8}$, possibly due to poor tagging of variants (e.g., *WNK1* promoter) by the Affymetrix chip, the presence of hypertensives in the control sample, and confounding by age (the mean age of the controls was 20 years less than the age of the cases) [72, 73]. A GWAS of quantitative phenotypes (SBP and DBP) measured at two

examinations (1971–1975, N=1,260; and 1998–2001, N=1,233) also failed to produce any genome-wide significant hits in the Framingham Heart Study (FHS) [74]. A SNP intronic to *CDH13* suggestively associated ($P=9.9\times10^{-8}$) with long range SBP in the FHS was supported by the association ($P= 5.30\times10^{-8}$) of a SNP upstream of *CDH13* with hypertension in 1,407 cases and 2,365 controls from Germany and Estonia (the Kooperative Gesundheitsforschung in der Region Augsburg [KORA] S3, KORA S4, and HYPEST cohorts) [75]. Subsequent analysis indicated that even with these relatively large sample sizes, power was extremely limited (< 1%) for several of the replicated variants [76].

Numerous GWAS studies targeting populations of European descent were the subject of two large meta-analyses, CHARGE and GlobalBPgen, discussed in the meta-analysis section below.

Genome-wide Association Studies of Cohorts of Non-European Descent

Although early GWAS were conducted on individuals of European descent, later studies interrogated associations in cohorts of other ancestries to capitalize on differences in allele frequencies and LD patterns [71]. Performing GWAS on participants of African ancestry in particular can provide more genetic variation and shorter BP-associated regions because of less extended LD [37**]. The first GWAS of hypertension and BP in African Americans analyzed 808,465 SNPs in 1,017 participants (509 hypertensives and 508 normotensives) from the Howard University Family Study (HUFS) [60]. SNPs located near or in *PMS1*, *SLC24A4*, *YWHAZ*, *IPO7*, *CACANA1H*, and *MYLIP* were significantly associated with SBP. The meta-analysis of the Korea Association Resource (KARE, N=8,842) and Health2 (N=7,861 Koreans) cohorts yielded a significant association between *ATP2B1* and SBP [77, 78]. The first GWAS of hypertension-related traits in a Japanese population (the Suita Study, N=936) identified a significant association between SBP and a SNP upstream of *CCBE1* [79]. Several issues still haunt GWAS of non-European cohorts, particularly population stratification, imputation difficulties, and less coverage of variants on genotyping platforms [71].

Genome-wide Association Studies of Homogenous Populations

A novel genetic variant associated with essential hypertension was discovered in a population with reduced genetic and lifestyle heterogeneity. Wang et al. [80] interrogated the association of 79,447 SNPs with SBP and DBP using 542 Old Order Amish (from the Amish Family Diabetes Study).

One SNP nearly reaching genome-wide significance ($P=9.1\times10^{-8}$) was harbored in a gene desert (chromosome 9p21.3) 900 kb away from known genes. A cluster of SNPs populating *STK39* was suggestively associated ($9.1\times10^{-5}< P<8.9\times10^{-6}$) with SBP; a meta-analysis of 7,125 participants from six studies (2 Amish and 4 non-Amish Caucasian) revealed an association ($P=1.6\times10^{-7}$) between *STK39* and SBP. The gene *STK39* (serine/threonine kinase) is expressed in the distal nephron and encodes SPAK; the latter kinase interacts with WNK kinases and both Na-Cl and Na-K-2Cl cotransporters and may influence sodium homeostasis [73].

Pathway Analysis of GWAS Results

Differences in LD patterns across populations hinder replication of significant SNPs. Analyzing networks and pathways may be more robust than analyzing individual SNPs. Several pathways including defects in dopamine signaling that were undetected during single-SNP GWAS were identified during a pathway analysis of the genes most strongly associated with hypertension in the WTCCC [81]. Adeyemo et al. [60] followed the discovery GWAS in HUFS with a pathway analysis of the genes represented by the top-scoring SNPs to assess any clustering in networks and pathways of biological relevance to BP regulation (using MetaCore with GO and GeneGo processes). The most strongly associated pathway, the role of HDAC and CaMK in skeletal myogenesis, contained the calcium-gated channels (CACNA1E and CACNA1H), IGF-1, and AKT, known to influence BP regulation, hypertension, and its correlates [60]. Several implicated pathways and processes had straightforward roles in BP, including PIP3 signaling in cardiac myocytes, potassium transport, and blood vessel morphogenesis. Others, such as synaptic vessel exocytosis [60], were less obvious, thereby highlighting the ability of pathway analysis to contribute to physiological understanding of BP regulation. Although specific SNPs lacked replication, several significant pathways were common to the WTCCC and the study by Adeyemo et al. [81].

Pathway analysis may ease replication of findings from an African American sample (such as HUFS), in which the LD pattern depends on admixture proportion, which varies regionally [82].

Epistasis and Gene-Environment Interactions in Genome-wide Association Studies

Incorporating interactions enhanced the capability of linkage and candidate gene analyses to discover BP-influencing variants. The increased degrees of freedom to model epistasis and gene-environment interactions, coupled with a nearly insurmountable multiple testing burden (one million variants are involved in half a trillion variant-variant interactions), prohibit investigators from achieving reasonable statistical power to interrogate them systematically during GWAS [56]. A GWAS of 2,016 Han Chinese with young-onset hypertension yielded no significant single-locus associations but revealed an association with a SNP quartet downstream of LOC344371 and *RASGRP3* on chromosome 2p22.3 [50]. Interactions between every pair of SNPs (>4.2 billion pairs) were examined. Potential epistasis was identified between a SNP intronic to *IMPG1* on chromosome 6q14 (the same locus implicated in the VAGES study [48]) and an intergenic SNP on chromosome 20q12 [50].

Similarly, no significant SNPs were discovered via a GWAS (using 329,091 SNPs) of SBP and DBP using 4,763 individuals born during 1966 in two of the most genetically isolated Finnish provinces [83]. However, several SNP-environment interactions were implicated. Two variants intronic to *PCDH15* and one intergenic on chromosome 4q21.22 appeared to interact with sex ($7.50\times10^{-8}<P<2.43\times10^{-7}$) to influence DBP, while a SNP intronic to *COL25A1* may interact with oral contraceptive use ($P=3.6\times10^{-7}$) to influence DBP [83]. One SNP intronic to *MTHFS* may interact with preterm birth (p-value=3.06×10^{-7}) to influence SBP [83].

Because of the large number of tests performed, the authors treat these results as hypothesis-generating.

In 531 hypertensives and 417 controls from the HyperGEN study, evidence for association between several haplotypes and BP-related traits was stronger when considering interactions. Gu et al. [84] used a clustering technique (self-organizing maps, SOM) on their phenotypic data to identify latent classes interacting with haplotypes. An association in African Americans between a haplotype and DBP response to a grip challenge was stronger (P=0.002 vs 0.014) when considering SOM class membership, and an association between another haplotype and SBP grip response in whites was detected (P=0.03) when considering interaction with SOM class but was otherwise absent (P=0.21) [84].

Meta-analyses of Genome-wide Association Studies

With mounting evidence that common variants have small effects on BP, increased sample sizes have been necessary to achieve sufficient statistical power. Meta-analyses of two massive consortia of European ancestry, Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) [85] and Global Blood Pressure Genetics (Global BPgen) [86], were published in 2009. CHARGE consisted of six population-based cohort studies totaling 29,136 participants, and Global BPgen encompassed 17 cohorts (13 population-based cohorts with 4 case-control studies as controls) with 34,433 participants. Following meta-analysis within each consortium, the SNPs representing the top 10 loci for every BP trait were exchanged for a joint meta-analysis; the joint meta-analysis guided by the top Global BPgen hits was supplemented with up to 71,225 individuals of European ancestry. Significant SNPs were found in or adjacent to *ATP2B1*, *CACNB2*, *CSK-ULK3*, *CYP1A2*, *NT5C2CYP17A1*, c10orf107, *FGF5*, *MTHFR*, *PLCD3*, *PLEKHA7*, *SH2B3-ATXN2*, *TBX3-TBX5*, *ULK4*, and *ZNF652* [85, 86]. As noted by Ehret [3*], these 14 loci are in or near six enzymes, two solute channels, two transcription factors, a cell signaling protein, a growth factor, a structural protein, and a hypothetical gene.

Although the significant SNPs collectively explained less than 2% of BP variation, all loci except *PLCD3* and *ULK4* have been replicated in at least one of the following large samples: the Women's Genome Health Study (WGHS; 23,019 North American women of European descent) [87], the Candidate Gene Association Resource consortium (CARe; 7,473 African Americans) [82], KARE [88], a replication study of three Japanese population-based cohorts (JPN; 23,401 individuals) [89], and a meta-analysis of east Asians (eastA; 50,373 participants) [90]. *FGF5* and *CSK* replicated in the Japanese [89] and Korean [88] cohorts, respectively, in spite of significant interethnic heterogeneity, and differences in effect size and/or allele frequency. Thus some loci may contribute to hypertension in multiple ethnicities [82] but with differential influence. Only two of the loci were near genes previously affiliated with BP (*CYP17A1* and *NPPA/NPPB* near *MTHFR*) [71], so meta-analyses of massive sample sizes may implicate novel BP pathways. To date, GWAS has implicated over 50 genes as influencing hypertension and BP. The International Consortium of Blood Pressure Genome-Wide Association Studies (ICBP-GWAS) has performed a GWAS of SBP, DBP, mean arterial pressure (MAP), and pulse pressure using massive sample sizes (discovery, N≈70,000; replication, N≈200,000 for SBP and DBP; replication,

N≈48,000 for MAP and PP) [91*, 92*]. The novel genes associated with SBP or DBP include *MOV10*, *SLC4A7*, *MECOM*, *SLC39A8*, *GUCY1A3-GUCY1B3*, *NPR3*-C5orf23, *EBF1*, *HFE*, *BAT2-BAT5*, *PLCE1*, *FLJ32810-TMEM133*, *ADM*, *FES*, *GOSR2*, *JAG1*, and *GNAS-EDN3*. The genes significantly associated with PP are *CHIC2/PDGFRA1*, *PIK3CG*, *NOV*, *ADAMTS-8*, and *FIGN*. The genes significantly associated with MAP include *MAP4*, *ADRB1*, and *FIGN*.

A meta-analysis of WGHS and CHARGE produced two novel, genome-wide significant SNPs associated with SBP, near *CASZ1* and *BLK-GATA4* [87]. The association with *CASZ1* was confirmed in both JPN and eastA [89, 90]. A meta-analysis of 21,466 cases and 18,240 controls from 15 different cohorts (including 10 from Global BPgen) identified a significant association between hypertension and a SNP in the promoter region of the uromodulin gene (*UMOD*) [93]. Uromodulin is expressed almost exclusively in the thick ascending limb of the loop of Henle in the kidneys, and clinical functional studies suggest that the variant may influence sodium reabsorption [93]. A meta-analysis of east Asians identified genome-wide significant associations between BP and *ST7L-CAPZA1*, *FIGNGRB14*, *ENPEP*, *NPR3*, and *RPL6-PTPN11-ALDH2* [90]. The SNP associated with *ALDH2* is not polymorphic in Europeans, highlighting the importance of including participants of diverse ancestries. The largest (N=7,473) meta-analysis of GWAS on African Americans (the CARe consortium) identified a significant association between DBP and a SNP in the intergenic region between *GPR98* and *ARRDC3*, as well as a significant association between SBP and a SNP intronic to C21orf91 [82]. Further increases in sample size may uncover new variants [3*], but the small effect sizes may fail to explain much variance [94]. Functional studies will also be required to precisely identify causal variants and their mechanism of action.

Discussion

Decades of research using combinations of candidate gene studies, GWLS, and GWAS have uncovered genetic polymorphisms and environmental factors (such as age, sex, race, and diet) that influence BP. Polymorphisms involved in renal sodium reabsorption contribute to long-term BP regulation, as may variants in inflammation and vasoactive pathways. The identified polymorphisms collectively explain a small fraction of BP variance and often lack replication across studies. Phenotypic heterogeneity [8], genetic heterogeneity, differences in allele frequencies or LD patterns [95**], epistasis [96], and gene-environment interactions may explain the poor replication of implicated genetic variants across studies. Rodent models indicate that some loci are organized in epistatic modules that participate in pathways and cascades [96].

Replication failure can arise when a BP-influencing variant is masked by a polymorphism upstream or downstream in the same pathway or cascade [51, 96]. BP-influencing epistatic interactions in humans are supported by the synergistic interacting physiological pathways of BP regulation [51]. Genetic variants act in parallel on diverse biochemical and functional pathways, so the collective effects should not be expected to be linear [51]. Incorporating gene-environment interactions in the analysis may uncover variants expressed under specific conditions, such as a specific age or gender, thus increasing replicability across studies [57].

Analyzing population isolates and populations of non-European ancestry capitalized on increased risk allele frequencies, more favorable LD patterns, and environments to enhance discovery of BP-associated genes (including population-specific variants).

Selection theory of quantitative genetic variation suggests that causal polymorphisms may be rare [97]. Although low frequency and rare variants outnumber common variants [98], they have not been fully interrogated for association with BP because of cost, as it is necessary to genotype rare alleles in massive sample sizes from the general population to get sufficient power [8]. Sequencing of three salt-handling genes (*SLC12A3*, *SLC12A1*, and *KCNJ1*) in 1,985 unrelated subjects and 1,140 relatives from the Framingham Heart Study (FHS) showed the large influence rare variants might have on BP [19]. Carriers of any of 30 rare variants in the three salt-handling genes (with minor allele frequency less than 0.0005 in FHS) had mean reductions of 6.3 mm Hg in SBP and 3.4 mm Hg in DBP, compared with the entire cohort. Mutation carriers had mean SBP values 6.6 mm Hg less than their noncarrier siblings. These are large effects when compared with those of common variants, for which the effect size is usually 1 mm Hg or less [19]. Compared with noncarriers, mutation carriers had a 59% reduction in risk of developing hypertension by age 60. These three salt-handling genes could explain a nonnegligible proportion of BP variance, as an estimated 100 million people worldwide may harbor a functional mutation in one of these genes [19].

Because of all the barriers to replication, pathways are more robustly associated with BP across populations than individual polymorphisms. For example, Staessen et al. [99] and Yeh et al. [100] were unable to replicate previous associations of a particular polymorphism (−48A- > G) in the dopamine receptor but detected associations in the same gene and elsewhere in the dopamine signaling pathway. Pathway analysis allocates resources towards understanding how existing signals influence BP rather than simply accumulating more independent data [95**], which may yield diminishing returns or may be difficult to analyze. Interactions within the same regulatory network are likely to produce the molecular effects observed on BP, so interrogating the entire systems may elucidate the pathophysiology of hypertension better than single-polymorphism methods [8]. Unraveling the pathophysiology of hypertension should allow more effective treatment and prevention strategies [95**]. Pathway and network analyses may also help prioritize genes and loci for further focused investigations using small studies as opposed to extremely large case/control samples [81]. Nevertheless, although pathway analysis makes a compelling case from a biological perspective, it is no panacea, as it is challenged by several methodologic issues [101].

Future Directions

Candidate gene, GWLS, and GWAS are complementary tools that have significantly enhanced our understanding of the genetic underpinnings of BP regulation, but new approaches are needed to explain the missing variance. We believe that focused studies investigating epistasis, gene-environment interactions, and rare variants in systematic and biologically plausible ways (such as through emphasis on genes in pathways) constitute novel alternative approaches. Although exhaustive epistasis examination in GWLS and GWAS involves an unacceptable multiple testing burden, a focused investigation of gene-environment interactions (e.g., gene-age, gene-sex, and gene-race) seems desirable and

feasible. Existing candidate gene studies can test epistasis and gene-environment interactions using all available genotype and phenotype information. We advocate beginning with examination of epistasis between functionally related genes clustered in pathways, in order to reduce the multiple testing burden, perhaps employing a two-stage method [102]. By focusing on one or more candidate pathways, investigators can test all gene-gene and gene-environment interactions in the spirit of hypothesis generation (i.e., even if there is no a priori belief that such combinations contribute to BP regulation).

Next-generation resequencing approaches will be vital to the discovery of rare variants with potentially larger effects that influence BP. Resequencing in linkage-informative families may help to identify rare and low-frequency variants associated with BP, as shown for the complex phenotype adiponectin [36] (see also [103] and [104]). It is generally expected that such rare variants will account for part of the unexplained variance for BP. (The low-frequency variant for adiponectin explained 17% of the phenotypic variance in the sample.) Another approach to discovering rare variants is to resequence genes harboring common variants associated with BP (as identified in GWAS). Evidence suggests that genes harboring one trait-associated variant (of any allele frequency) are more likely to contain additional variants altering their expression and/or function [105]. A rare missense variant of large effect (odds ratio of 12.5) was discovered through whole genome sequencing followed by imputation of newly discovered variants in GWAS samples [106, 107].

Additional insights into the lack of BP variation may be explained through the study of ambulatory BP or other approaches that provide more frequent measurements [10, 108]. Epigenetic modifications (including DNA methylation, histone modification, and alteration of microRNA expression) are also likely to contribute, as microRNAs have already been implicated in hypertension (e.g., hsa-miR-155 may influence *AGTR1* [109]) and could be key BP regulators by simultaneously influencing multiple genes [56]. Epigenetic modifications constitute one hypothesized mechanism by which environmental factors interact with genes to influence BP. For example, dietary factors cause epigenetic modifications [110, 111]. Therefore, increasing BMI through poor diet may influence BP through epigenetic modifications that alter expression patterns in the cell. Lastly, interrogating noncoding regions (such as regulatory elements) and structural variants by whole genome sequencing [112] may help reveal the “dark matter” of hypertension pathophysiology.

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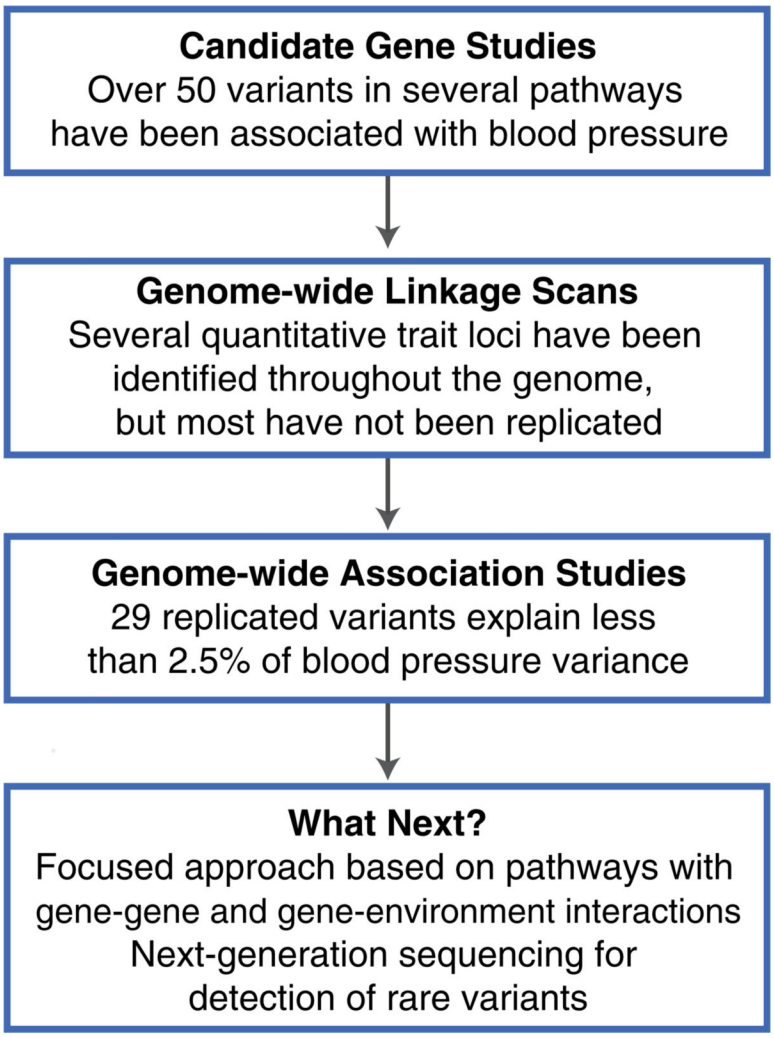

Figure 1.
From candidate genes to linkage to genome-wide association studies: What next for hypertension genetics?

Table 1.

Mendelian hypertension genes

Syndrome	Pathway	Gene(s)	Mechanism	Reference
Glucocorticoid remediable aldosteronism	Steroid/aldosterone synthesis	11β-hydroxylase and aldosterone synthase (*CYP11B1* and *CYP11B2*)	Unequal crossing over results in a chimera with aldosterone synthase activity driven by adrenocorticotropic hormone	[113]
Corticosterone methyloxidase II deficiency	Steroid/aldosterone synthesis	Aldosterone synthase (*CYP11B2*)	Enzyme dysfunction results in reduced aldosterone levels	[9]
Steroid 21-hydroxylase deficiency	Steroid/aldosterone synthesis	Steroid 21-hydroxlase (*CYP21A2*)	Enzyme dysfunction results in reduced aldosterone levels	[114]
Apparent mineralocorticoid excess	Steroid/aldosterone synthesis	11β-hydroxysteroid dehydrogenase (*11B-HSD*)	Impaired conversion of cortisol to cortisone results in cortisol-mediated hyperactivation of MR	[115, 116]
Familial glucocorticoid resistance	Steroid/aldosterone synthesis	Glucocorticoid receptor (*NR3C1*)	Glucocorticoid receptor dysfunction leads to increased cortisol and cortisol-mediated hyperactivation of MR	[117]
Steroid 11β-hydroxylase deficiency	Steroid/aldosterone synthesis	11β-hydroxylase (*CYP11B1*)	Enzyme dysfunction leads to increased levels of MR activating hormones	[118]
17 α-hydroxylase and/or 17,20-lyase deficiency	Steroid/aldosterone synthesis	17-α-hydroxylase (*CYP17A1*)	Enzyme dysfunction leads to increased levels of MR activating hormones	[119]
Hypertension exacerbated by pregnancy	Aldosterone signaling	Mineralocorticoid receptor (*MR*)	Missense mutation makes MR active without ligand, further activated by progesterone in pregnancy	[120]
Pseudohypoaldosteronism type I	Aldosterone signaling/renal ion channel	Mineralocorticoid receptor, or electrogenic sodium channel α, β or γ subunit (*MR*, *SCNN1A*, *SCNN1B*, *SCNN1G*)	Loss-of-function mutation leading to reduced ENaC activity	[121–123]
Pseudohypoaldosteronism type II	Ion channel regulation	With-no-lysine kinase 1 or 4 (*WNK1, WNK4*)	Kinase mutations lead to upregulated *SLC12A3*	[124]
Liddle syndrome	Renal ion channel	Electrogenic sodium channel β or γ subunit (*SCNN1B*, *SCNN1G*)	C terminus deletion leads to reduced ENaC clearance and increased ENaC activity	[125, 126]
Gitelman's syndrome	Renal ion channel	Na-Cl cotransporter (*SLC12A3*)	Loss-of-function mutation leads to lower sodium reabsorption	[127]
Bartter's syndrome type I	Renal ion channel	Na-K-2Cl cotransporter (*SLC12A1*)	Loss-of-function mutations leads to lower sodium reabsorption	[128]
Bartter's syndrome type II	Renal ion channel	Potassium inwardly rectifying channel (*KCNJ1*)	Reduced potassium recycling leads to impaired sodium reabsorption	[129]
Bartter's syndrome type III	Renal ion channel	Chloride channel kb (*CLCNKB*)	Reduced chloride transport leads to impaired sodium reabsorption	[130]
Insulin resistance and hypertension	Transcriptional regulation	Peroxisome proliferator activated receptor gamma (*PPARγ*)	Loss-of-function mutation leads to insulin resistance and hypertension; vascular effects postulated	[131]
Hypertension, hypercholesterolemia, and hypomagnesemia	Protein synthesis	Mitochondrially encoded tRNA isoleucine (*MT-TI*)	Mutation in conserved base near anti-codon impairs ribosome binding	[132]

ENaC epithelial sodium channel; MR mineralocorticoid receptor; tRNA transfer RNA.

Table 2.

Selected essential hypertension candidate genes

Pathway	Gene(s)	References confirming association	References refuting association
Aldosterone signaling	Renin (*REN*)	[133–135]	[136, 137]
Aldosterone signaling	Angiotensinogen (*AGT*)	[10, 11, 138]	[139–141]
Aldosterone signaling	Angiotensin-converting enzyme (*ACE*)	[11, 12, 142]	[143–145]
Aldosterone signaling	Angiotensin II receptor, type 1 (*AGTR1*)	[146–148]	[149–151]
Renal ion channel	Na-Cl cotransporter (*SLC12A3*)	[19, 152]	[153–155]
Renal ion channel	Na-K-2Cl cotransporter (*SLC12A1*)	[19, 156, 157]	[135]
Renal ion channel	Potassium inwardly rectifying channel, subfamily J, member 1 (*KCNJ1*)	[19, 158]	[159]
Ion channel regulation	With-no-lysine kinase 1 (*WNK1*)	[108, 160–162]	[154]
Ion channel regulation	With-no-lysine kinase 4 (*WNK4*)	[154, 160]	[163, 164]
Ion channel regulation	Serum/glucocorticoid regulated kinase 1 (*SGK1*)	[165–167]	[168, 169]
Renal ion channel	Electrogenic sodium channel, α, β, and γ subunits (*SCNN1A*, *SCNN1B*, *SCNN1G*)	[169–171]	[172, 173]
Renal ion channel	Chloride channel kb (*CLCNKB*)	[174, 175]	[155, 159, 176]
Ion channel regulation	Adducin 1 (*ADD1*)	[15–17, 177]	[178–180]
Ion channel regulation	Adducin 2(*ADD2*)	[15, 181]	[177, 182]
Ion channel regulation/ vasoconstriction	Tyrosine hydroxylase (*TH*)	[183]	[184]
Ion channel regulation/ vasoconstriction	Dopamine receptor D1 (*DRD1*)	[99, 185, 186]	[187, 188]
Ion channel regulation/ vasoconstriction	Dopamine receptor D2 (*DRD2*)	[189]	–
Ion channel regulation/ vasoconstriction	Catechol-O-methyltransferase (*COMT*)	[100, 190]	–
Ion channel regulation/ vasoconstriction	Dopamine beta-hydroxylase (*DBH*)	[100, 191]	–
Ion channel regulation	G protein-coupled receptor kinase 4 (*GRK4*)	[192]	[99]
Ion channel regulation/ vasoconstriction	Adrenergic receptor, beta 2 (*ADRB2*)	[135, 193]	[194]
Ion channel regulation/ vasoconstriction	Adrenergic receptor, alpha 1A (*ADRA1A*)	[195, 196]	[135, 197]
Ion channel regulation/ vasoconstriction	Adrenergic receptor, beta 1 (*ADRB1*)	[135, 198]	[199]
Ion channel regulation/ vasoconstriction	Adrenergic receptor, beta 3 (*ADRB3*)	[200, 201]	–
Vasoconstriction	Nitric oxide synthase 3 (*NOS3*)	[201, 202]	[203, 204]
Vasoconstriction	Endothelin 1 (*EDN1*)	[205, 206]	[207]
Vasoconstriction	Endothelin receptor type A (*EDNRA*)	[163, 208]	–
Vasoconstriction	Cytochrome P450, family 2, subfamily C, polypeptide 8 (*CYP2C8*)	[14, 209]	[210]
Inflammation	Interleukin 6 (*IL6*)	–	[24]
Inflammation	Transforming growth factor beta 1(TGFB1)	[24, 25]	–