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REVIEW

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An update on genome-wide association studies of hypertension

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Abstract

Hypertension is a major global health problem associated with cardiovascular and cerebrovascular diseases. It is well established that blood pressure and hypertension are common complex phenotypes affected by multiple genetic and environmental factors. Contemporary genomic tools make it possible to genotype millions of genetic variants across the human genome in an efficient, reliable, and cost-effective manner, which has transformed hypertension genetics research. International collaborations/consortia have enabled the use of unprecedentedly large sample sizes for gene discovery and replication. Genome-wide association studies have reported more than 60 loci associated with blood pressure or hypertension, most of which were not expected to have any association with these phenotypes. In contrast to linkage and candidate gene studies, the reproducibility of genome-wide association studies is much higher and some results have been verified across different ethnicities. These novel findings have provided potential targets for pharmacotherapy and clues for personalized prevention and treatment of hypertension. Although only a small proportion of blood pressure variation is attributed to the genetic variants identified so far, more variants are likely to be discovered by employing larger sample sizes, studying gene–environment interactions, or by exploring low-frequency or rare variants. Advances in epigenetics, which examines trait variation not caused by differences in DNA sequences, will probably reveal a new and important class of genetic components for hypertension.

Keywords: Blood pressure, Hypertension, Genetics, Genome-wide association study, Genes

Background

Hypertension affects approximately 50 million individuals in the United States and approximately 1 billion individuals worldwide (Chobanian et al. 2003), and it is estimated to account for 4.5 % of the global burden of disease (Whitworth and World Health Organization International Society of Hypertension Writing Group 2003). Hypertension plays a major etiologic role in the development of cerebrovascular disease, cardiovascular disease (CVD), and renal failure (Whitworth and World Health Organization International Society of Hypertension Writing Group 2003). CVD alone is responsible for one-third of global deaths and is a leading and increasing contributor to the global burden of disease (World Health Organization 2002). For 40 to 70-year-old individuals, each increment of 20 mmHg in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP) doubles the risk of CVD across the entire blood pressure (BP)

range from 115/75 to 185/115 mmHg (Lewington et al. 2002). The risk of CVD can be lowered by controlling BP. In multiple clinical trials, antihypertensive therapy has been associated with significant reductions in stroke incidence (averaging 35–40 %), myocardial infarction (20–25 %), and heart failure (over 50 %) (Neal et al. 2000). Understanding the genetics of BP can advance our understanding of the physiology of BP regulation and the pathology of hypertension. Finding genes associated with BP could potentially uncover novel targets for pharmacotherapy. Furthermore, the development of precision medicine based on genetic profiles of individuals could increase the efficiency of prevention and treatment of hypertension (Collins and Varmus 2015).

For a long time, BP has been known to be a complex trait influenced by multiple genetic and environmental factors (Lifton 1996; Hamet et al. 1998). Its heritability ranges from 30 to 50 %, estimated in family and twin studies (Miall and Oldham 1963). Early success in dissecting the genetic architecture of hypertension revealed 12 genes that cause a monogenic type of hypertension. These genes are members of two pathways: renal sodium handling and steroid hormone metabolism, the latter of which includes mineralocorticoid receptor activity (Ehret and Caulfield 2013). Inheritance of monogenic hypertension in families follows a clear segregation pattern and casual variants are typically rare and of large effect sizes. However, due to low frequencies of these variants, there is still a lack of clear understanding of essential hypertension (Pickering 1965), which has no evident cause and accounts for 95 % cases of hypertension (Carretero and Oparil 2000).

Genome-wide linkage analysis tests the association between the transmission of genomic regions and phenotypic similarity among family members (Thomas 2004); it was one of the most widely used methods for genetic studies of hypertension. A number of genome-wide linkage scans for BP or hypertension have provided some significant or suggestive linkage signals, whereas external replications have been very difficult (Binder 2007; Simino et al. 2012). Limited statistical power of linkage analysis, small sample sizes, and small effect sizes of underlying variants may be the main reasons. Alternatively, the candidate gene approach focuses on genes in several major pathways that are involved in BP homeostasis. As only a small number of polymorphisms were under investigation, the burden of multiple testing was alleviated, which allowed the identification of variants of small effects in moderate sample sizes. The major limitation is that this method relies on the existing biological knowledge of BP regulation, therefore precludes a large number of genes and chromosomal regions that may harbor novel associated variants lacking immediate physiological relationships with hypertension (Charchar et al. 2008). As in linkage analyses, replication of findings from candidate gene studies were challenging, such as in Basson et al. (2012). With advancements in genotyping technology, hundreds of thousands to millions of single-nucleotide polymorphisms (SNPs) could be measured on a single microarray at a reasonable cost (Fan et al. 2000). The study of hypertension genetics called for a paradigm shift to the genome-wide association studies (GWAS). In this paper, we summarize recent advances in genetic studies of BP/hypertension, focusing on study designs and strategies used therein. We also share our thoughts on some future directions. For a comprehensive review on the genetic and molecular aspects of hypertension, refer to Padmanabhan et al. (2015).

Review

Overview of GWAS methods

GWAS utilize a dense panel of SNPs to investigate associations between genetic markers and complex traits, such as BP. SNPs are distributed across the entire human genome and are measured by high-throughput genotyping platforms, which are commercially available. Many GWAS further impute unmeasured common SNPs based on haplotype data provided by the International HapMap Project (International HapMap Consortium 2005, 2007) and computational approaches implemented in genetic software, such as MACH (Li and Abecasis 2006), IMPUTE (Marchini et al. 2007), and BIMBAM (Servin and Stephens 2007). The number of SNPs in GWAS varies from hundreds of thousands to millions. Association between each SNP and a phenotype of interest is tested typically by a linear or logistic regression for continuous or dichotomous phenotypes, respectively. Additive genetic models are widely assumed in the majority of GWAS. A stringent genome-wide significance threshold of $P < 5 \times 10^{-8}$ is routinely used as a correction for multiple testing, which is based on the estimation of approximately 1 million independent SNPs in a population of European decent (Pe'er et al. 2008). To boost statistical power and find genetic variants with small effects, international collaborations have been established among studies and are organized in consortia. GWAS analyses are first conducted in participating studies; results are then combined using meta-analysis, which helps to achieve an overall sample size much larger than that based on any individual study. This approach has an inherent advantage, in which each study is able to analyze its own data using a standard analysis plan, but otherwise taking study-specific attributes into account, such as adjusting for study-specific covariates that are not common across all participating studies. More recently, GWAS are imputing millions of common and rare variants based on the 1000 Genomes Project (1000 Genomes Project Consortium 2012). Appropriate methods and analysis strategies for effectively harvesting such huge data sets are still evolving.

GWAS of quantitative BP phenotypes in diverse populations

GWAS of quantitative BP phenotypes have been conducted in diverse populations including samples of European ancestry, African ancestry and East Asians. The first GWAS (Wellcome Trust Case Control Consortium 2007) adopted a case–control study design using 3000 shared controls and 14,000 cases (2000 for hypertension) of European ancestry to study seven complex diseases simultaneously. About 500,000 genotyped SNPs were tested yielding 24 association signals at $P < 5 \times 10^{-7}$ significance level for six diseases. Hypertension was the only disease without any significant results and none of the variants previously associated with hypertension showed evidence of association. The first GWAS of quantitative BP phenotypes, SBP and DBP, was conducted by the Framingham Heart Study (Levy et al. 2007). The study analyzed approximately 71,000 genome-wide SNPs, including 1400 family subjects. No significant results were found either. These two studies highlighted the complexity of the genetic mechanisms underlying BP regulation. Research then progressed to population-based cohort studies. Recognizing the need for much larger sample sizes, collaborative consortia were established to look for genes associated with BP/hypertension.

The first two successful GWAS of BP were reported by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (Levy et al. 2009) and the Global Blood Pressure Genetics (Global BPgen) consortium (Newton-Cheh et al. 2009). The CHARGE consortium consisted of six population-based cohort studies with a sample size of 29,000. Global BPgen included 17 cohorts ascertained through population-based sampling or case–control studies with a sample size of 34,000 at the discovery phase. Eight genomic loci were identified to be associated with SBP or DBP by each study; three loci overlapped in both groups. Both consortia analyzed cross-sectional SBP and DBP phenotypes, which are commonly measured in many clinical or epidemiology studies. The additive genetic main effect was tested by both consortia, ignoring possible dominant, recessive, or interaction effects. Approximately 2.5 million SNPs were imputed and tested providing a common ground for the meta-analysis of the results from studies using various platforms for genotyping. Most of the 13 unique loci identified were novel except for *CYP17A1-NT5C2* and *MTHFR-NPPB* that contain BP regulation genes previously known. Results from these two studies and others are listed in Table 1.

A follow-up expanded investigation was conducted by the International Consortium of Blood Pressure (ICBP) (ICBP 2011), consisting of 29 studies of European ancestry, many of which were from CHARGE and Global BPgen consortia. ICBP included GWAS data on 69,000 individuals for gene discovery and 133,000 for replication. The study replicated the previous 13 loci effectively and discovered 16 new loci significant at the genome-wide level. Another study by the ICBP consortium (Wain et al. 2011) analyzed two derived BP phenotypes: mean arterial pressure (MAP) and pulse pressure (PP). MAP, computed as the sum of two-thirds of DBP and one-third of SBP, represents an average BP in a cardiac cycle; PP, a measure of stiffness of main arteries, is the difference between SBP and DBP. This study discovered four novel PP loci and two novel MAP loci. The signals for MAP were strongly associated with both SBP and DBP, reflecting a high correlation between these three BP traits.

BP loci were also discovered in GWAS with much smaller sample size, for example *CDH13* (Org et al. 2009; $N = 1600$) and *STK39* (Wang et al. 2009; $N = 7000$). However, although these studies did not show genome-wide significance during the discovery phase or lacked immediate replication, results were replicated later by other independent studies, suggesting that the so-called "winner's curse" (Yu et al. 2007) for replication could be a "complexity's blessing" at the discovery phase (Shi et al. 2011).

The largest GWAS effort to date involving participants of African origin was done by the Continental Origins and Genetic Epidemiology Network (COGENT) (Franceschini et al. 2013). Discovery samples were obtained from 19 studies with an aggregate sample size of 29,000 individuals. Due to the lack of sufficient samples from similar genetic backgrounds, replication was conducted using a trans-ethnic design with 10,000 samples of African ancestry, 69,000 of European ancestry, and 20,000 of East Asian ancestry. For the top discovery signals ($P < 1 \times 10^{-5}$), meta-analysis was conducted by combining all replication samples from the three ethnicities. Five loci reached genome-wide significance level, three of which were not previously reported to be associated with BP. Other GWAS on samples of African ancestry conducted earlier by Adeyemo et al. (2009) and Fox et al. (2011) also reported genome-wide significant associations. Due to limited

Table 1 Blood pressure/hypertension loci reported by genome-wide association studies and candidate gene studies

Chr	Genes	Lead SNP	Position	Trait	Ethnicity
1p36.22	*CASZ1*	rs880315	10,736,809	SBP	EA(Levy et al. 2009) Asian (Takeuchi et al. 2010) EA (Ho et al. 2011) Asian (Kato et al. 2011) Asian (Lu et al. 2014) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
1p36.22	*MTHFR-NPPB*	rs17367504	11,802,721	SBP	EA (Newton-Cheh et al. 2009) EA (Tomaszewski et al. 2010) Asian (Takeuchi et al. 2010) EA (Johnson et al. 2011b) EA (Ho et al. 2011) Asian (Kato et al. 2011) EA (ICBP 2011) EA (Ganesh et al. 2013) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
1p13.2	*ST7L-MOV10*	rs2932538	112,673,921	SBP DBP	EA (ICBP 2011) Asian (Kato et al. 2011) Asian (Lu et al. 2014) EA (Tragante et al. 2014)
1q32.1	*MDM4*	rs2169137	204,528,785	DBP	EA (Ganesh et al. 2013) EA (Tragante et al. 2014)
1q42.2	*AGT*	rs2004776	230,712,956	HT	EA (Johnson et al. 2011b) EA (Johnson et al. 2011a) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
2p23.2	*KCNK3*	rs1275988	26,691,496	SBP MAP	EA (Ganesh et al. 2014)
2q11.2	*FER1L5*	rs7599598	96,686,103	DBP	EA (Ganesh et al. 2014)
2q24.3	*FIGN*	rs13002573	164,058,698	PP MAP	EA (Wain et al. 2011) Asian (Kato et al. 2011) Asian (Hong et al. 2012) Asian (Lu et al. 2014) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
2q24.3	*STK39*	rs6749447	168,184,876	SBP	EA (Wang et al. 2009) AA (Adeyemo et al. 2009) EA (Tragante et al. 2014)
2q32.1	*PDE1A*	rs16823124	182,359,400	DBP MAP	EA (Tragante et al. 2014)
2q32.2	*PMS1*	rs5743185	189,873,112	SBP	AA (Adeyemo et al. 2009) EA (Levy et al. 2009)
3p25.3	*HRH1*	rs347591	11,248,436	SBP	EA (Ganesh et al. 2013) EA (Tragante et al. 2014)
3p24.1	*SLC4A7*	rs13082711	27,496,418	DBP	EA (ICBP 2011) Asian (Lu et al. 2014) EA (Tragante et al. 2014)
3p22.1	*ULK4*	rs9815354	41,871,159	DBP	EA (Levy et al. 2009) EA (ICBP 2011) EA + AA + Asian (Franceschini et al. 2013) Asian (Lu et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)

Table 1 continued

Chr	Genes	Lead SNP	Position	Trait	Ethnicity
3p21.31	*MAP4*	rs319690	47,885,994	MAP	EA (Wain et al. 2011) Asian (Hong et al. 2012) Asian (Kelly et al. 2013) EA (Simino et al. 2014) EA (Tragante et al. 2014)
3p21.1	*CACNA1D*	rs9810888	53,601,568	DBP	Asian (Lu et al. 2014)
3q26.1	*MIR1263*	rs16833934	164,019,462	DBP	EA (Simino et al. 2014)
3q26.2	*MECOM*	rs419076	169,383,098	SBP DBP	EA (ICBP 2011) EA (Tragante et al. 2014)
4q12	*CHIC2*	rs871606	53,933,078	PP	EA (Wain et al. 2011) Asian (Hong et al. 2012) EA (Tragante et al. 2014)
4q21.21	*FGF5*	rs16998073	80,263,187	DBP	EA (Newton-Cheh et al. 2009) Asian (Takeuchi et al. 2010) Asian (Tabara et al. 2010) Asian (Kato et al. 2011) EA (ICBP 2011) Asian (Kelly et al. 2013) Asian (Lu et al. 2014) EA (Simino et al. 2014) EA (Tragante et al. 2014)
4q24	*SLC39A8*	rs13107325	102,267,552	SBP DBP	EA (ICBP 2011) EA (Tragante et al. 2014)
4q25	*ENPEP*	rs6825911	110,460,482	DBP	Asian (Kato et al. 2011) EA (Tragante et al. 2014)
4q32.1	*GUCY1A3-GUCY1B3*	rs13139571	155,724,361	DBP	EA (ICBP 2011) Asian (Lu et al. 2014) EA (Tragante et al. 2014)
5p13.3	*NPR3-C5orf23*	rs1173771	32,814,922	SBP DBP HT	EA (ICBP 2011) AA (Zhu et al. 2011) EA (Johnson et al. 2011b) Asian (Kato et al. 2011) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
5q33.3	*EBF1*	rs11953630	158,418,394	SBP DBP	EA (ICBP 2011) EA (Simino et al. 2014) EA (Tragante et al. 2014)
6p22.2	*HFE*	rs1799945	26,090,951	SBP DBP HT	EA (ICBP 2011) EA (Johnson et al. 2011b) EA (Ganesh et al. 2013) Asian (Lu et al. 2014) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
6p21.33	*BAT2-CYP21A2*	rs805303	31,648,589	SBP DBP HT	EA (ICBP 2011) Asian (Lu et al. 2014) EA (Tragante et al. 2014)
6p21.32	*HLA-DQB1*	rs2854275	32,660,651	DBP	EA (Tragante et al. 2014)
6p21.1	*CRIP3*	rs10948071	43,312,975	PP	EA (Ganesh et al. 2014)
6q22.33	*RSPO3*	rs13209747	126,794,309	SBP DBP	EA + AA + Asian (Franceschini et al. 2013)
6q25.1	*PLEKHG1*	rs17080102	150,683,634	SBP DBP	EA + AA + Asian (Franceschini et al. 2013)
7p15.2	*EVX1-HOXA*	rs17428471	27,298,248	SBP DBP	EA + AA + Asian (Franceschini et al. 2013)
7p12.3	*IGFBP3*	rs2949837	45,954,779	PP	EA (Ganesh et al. 2014)
7q21.2	*CDK6*	rs2282978	92,635,096	PP	EA (Tragante et al. 2014)

Table 1 continued

Chr	Genes	Lead SNP	Position	Trait	Ethnicity
7q22.3	*PIK3CG*	rs17477177	106,771,412	PP	EA (Wain et al. 2011) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
7q36.1	*NOS3*	rs3918226	150,993,088	DBP	EA (Johnson et al. 2011b) EA (Salvi et al. 2012) EA (Tragante et al. 2014)
8p23.1	*BLK-GATA4*	rs4841569	11,594,668	SBP MAP	EA (Simino et al. 2014) EA (Tragante et al. 2014)
8q24.12	*NOV*	rs2071518	119,423,572	PP	EA (Wain et al. 2011) EA (Tragante et al. 2014)
10p12.31	*CACNB2*	rs11014166	18,419,869	DBP	EA (Levy et al. 2009) EA (Ho et al. 2011) EA (ICBP 2011) Asian (Lin et al. 2011) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
10q21.2	*c10orf107*	rs1530440	61,764,833	DBP	EA (Newton-Cheh et al. 2009) EA (Ho et al. 2011) Asian (Kato et al. 2011) EA (ICBP 2011) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
10q22.2	*VCL*	rs4746172	74,096,084	DBP MAP	EA (Tragante et al. 2014)
10q23.33	*PLCE1*	rs932764	94,136,183	SBP HT	EA (ICBP 2011) EA (Tragante et al. 2014)
10q24.32	*CYP17A1-NT5C2*	rs1004467	102,834,750	SBP	EA (Levy et al. 2009) EA (Newton-Cheh et al. 2009) Asian (Takeuchi et al. 2010) Asian (Hong et al. 2010) Asian (Tabara et al. 2010) EA (Ho et al. 2011) Asian (Kato et al. 2011) EA (ICBP 2011) Asian (Lin et al. 2011) Asian (Kelly et al. 2013) EA (Ganesh et al. 2013) Asian (Lu et al. 2014) Asian (Qi et al. 2014) EA (Simino et al. 2014) EA (Tragante et al. 2014)
10q25.3	*ADRB1*	rs2782980	114,021,768	MAP	EA (Wain et al. 2011) EA (Ganesh et al. 2013) EA (Simino et al. 2014) EA (Tragante et al. 2014)
11p15.5	*LSP1*	rs661348	1,884,062	MAP	EA (Johnson et al. 2011b) EA (Ganesh et al. 2013) EA (Tragante et al. 2014)
11p15.4	*ADM*	rs7129220	10,328,991	SBP	EA (ICBP 2011) EA (Tragante et al. 2014)

Table 1 continued

Chr	Genes	Lead SNP	Position	Trait	Ethnicity
11p15.1	*PLEKHA7*	rs381815	16,880,721	SBP	EA (Levy et al. 2009) Asian (Hong et al. 2010) EA (Ho et al. 2011) EA (ICBP 2011) EA (Johnson et al. 2011b) Asian (Lin et al. 2011) EA + AA + Asian (Franceschini et al. 2013) EA (Ganesh et al. 2013) Asian (Lu et al. 2014) EA (Simino et al. 2014) EA (Tragante et al. 2014)
11q13.1	*EHBP1L1*	rs4601790	65,586,435	MAP DBP	EA (Simino et al. 2014) EA (Tragante et al. 2014)
11q22.1	*FLJ32810-TMEM133*	rs633185	100,722,807	SBP DBP HT	EA (ICBP 2011) EA (Tragante et al. 2014)
11q24.3	*ADAMTS8*	rs11222084	130,403,335	PP	EA (Wain et al. 2011) EA (Tragante et al. 2014)
12q13.13	*HOXC4*	rs7297416	54,049,306	SBP	EA (Tragante et al. 2014)
12q21.33	*ATP2B1*	rs2681492	89,619,312	SBP DBP HT	EA (Levy et al. 2009) Asian (Cho et al. 2009) Asian (Takeuchi et al. 2010) Asian (Hong et al. 2010) Asian (Tabara et al. 2010) EA (Johnson et al. 2011b) EA (Ho et al. 2011) Asian (Kato et al. 2011) EA (ICBP 2011) Asian (Wang et al. 2013b) Asian (Kelly et al. 2013) EA (Ganesh et al. 2013) Asian (Lu et al. 2014) Asian (Qi et al. 2014) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
12q24.12	*SH2B3*	rs3184504	111,446,804	SBP DBP	EA (Levy et al. 2009) EA (Newton-Cheh et al. 2009) EA (Ho et al. 2011) Asian (Kato et al. 2011) EA (ICBP 2011) AA (Fox et al. 2011) EA (Ganesh et al. 2013) Asian (Lu et al. 2014) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
12q24.13	*ALDH2*	rs11066280	112,379,979	SBP DBP	Asian (Kato et al. 2011) Asian (Lu et al. 2014) EA (Tragante et al. 2014)
12q24.21	*TBX3-TBX5*	rs2384550	114,914,926	DBP	EA (Levy et al. 2009) Asian (Kato et al. 2011) EA (ICBP 2011) AA (Fox et al. 2011) Asian (Lu et al. 2014) Asian (Qi et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
12q24.21	*MED13L*	rs11067763	115,760,536	SBP DBP	Asian (Lu et al. 2014)
15q21.1	*FBN1*	rs1036477	48,622,729	PP	EA (Tragante et al. 2014)

Table 1 continued

Chr	Genes	Lead SNP	Position	Trait	Ethnicity
15q24.1	*CYP1A1-ULK3*	rs6495122	74,833,304	DBP	EA (Levy et al. 2009) EA (Newton-Cheh et al. 2009) Asian (Takeuchi et al. 2010) Asian (Hong et al. 2010) Asian (Tabara et al. 2010) EA (Ho et al. 2011) Asian (Kato et al. 2011) EA (ICBP 2011) AA (Fox et al. 2011) EA (Ganesh et al. 2013) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)
15q26.1	*FURIN-FES*	rs2521501	90,894,158	SBP DBP	EA (ICBP 2011) EA (Ganesh et al. 2013) EA (Tragante et al. 2014)
16p12.3	*UMOD*	rs13333226	20,354,332	HT	EA (Padmanabhan et al. 2010) EA (Tragante et al. 2014)
16q22.1	*NFAT5*	rs33063	69,606,314	PP	EA (Tragante et al. 2014)
16q23.3	*CDH13*	rs11646213	82,609,046	HT	EA (Org et al. 2009) AA (Adeyemo et al. 2009) EA (Tragante et al. 2014)
17q21.32	*GOSR2*	rs17608766	46,935,905	SBP	EA (ICBP 2011) EA (Simino et al. 2014) EA (Tragante et al. 2014)
17q21.33	*ZNF652*	rs16948048	49,363,104	DBP	EA (Newton-Cheh et al. 2009) EA (Ho et al. 2011) Asian (Kato et al. 2011) EA (ICBP 2011) EA (Tragante et al. 2014)
20p12.2	*JAG1*	rs1327235	10,988,382	SBP DBP	EA (ICBP 2011) Asian (Lu et al. 2014) EA (Tragante et al. 2014)
20q13.32	*GNAS-EDN3*	rs6015450	59,176,062	SBP DBP HT	EA (ICBP 2011) EA (Simino et al. 2014) EA (Ganesh et al. 2014) EA (Tragante et al. 2014)

Lead SNP and trait are as reported in the first reference for each locus listed in the table. Position is based on dbSNP 142/hg38

Chr Chromosomal region, *AA* African Ancestry, *EA* European Ancestry, *HT* Hypertension

replication resources, neither of these replication efforts were successful except that the *PMS1* gene demonstrated suggestive evidence of association with SBP ($P = 7.2 \times 10^{-7}$) (Adeyemo et al. 2009; Levy et al. 2009).

African American is a recently admixed population, which is estimated to have an 80 % African lineage and a 20 % European lineage on average (Parra et al. 1998). Given significant differences in the prevalence of hypertension in populations of European and African ancestries (Rosamond et al. 2007), admixture mapping (Zhu et al. 2008) was conducted by the Candidate gene Association Resource (CARe) consortium (Zhu et al. 2011). The discovery sample included approximately 6000 unrelated African American subjects from five participating cohorts. Quantitative admixture analyses for SBP and DBP were carried out using 3200 ancestry informative SNPs. After correcting for multiple testing, three loci were significantly associated with SBP and one with DBP. In the meta-analysis of the replication set, which included six independent cohorts with a

sample size of 11,000, a novel variant located between the *SUB1* and *NPR3* genes was identified and shown to be associated with SBP and DBP.

The first large meta-analysis of GWAS of BP traits among East Asians was conducted by the Asian Genetic Epidemiology Network (AGEN) consortium (Kato et al. 2011). AGEN-BP work group included 30,000 individuals from population and family-based studies as part of its two-stage discovery phase and 20,000 at the replication stage. The study identified six novel loci that were genome-wide significantly associated with SBP or DBP, and seven loci previously reported in populations of European decent. In a further study of MAP and PP by AGEN (Kelly et al. 2013), no novel loci were discovered when the five previously identified MAP loci and two PP loci were replicated (Wain et al. 2011). A recent meta-analysis of GWAS in a Chinese population was carried out with approximately 12,000 samples for discovery and 69,000 for replication (Lu et al. 2014). This work lead to the discovery of a total of three novel BP loci and replicated 14 previously reported loci.

GWAS of dichotomous hypertension phenotypes

Most GWAS findings discovered to date were based on quantitative BP traits, for which statistical power is generally larger than for dichotomous outcomes, such as hypertension status. Two studies have reported positive hypertension susceptibility loci. In one GWAS, authors used an extreme case–control design with 1600 hypertensive cases and 1700 controls for discovery, and 20,000 cases and 17,000 controls for replication (Padmanabhan et al. 2010). Compared to the usual case–control studies, cases and controls were drawn from the extremes of the BP distribution, which provided a much sharper contrast between the two groups. The top SNP near gene *UMOD* was reported to be genome-wide significant ($P = 3.6 \times 10^{-11}$). The SNP showed only suggestive association with SBP ($P = 2.6 \times 10^{-5}$) and DBP ($P = 1.5 \times 10^{-5}$) in population-based cohorts ($N = 79{,}000$), therefore would not be discovered by large GWAS of BP phenotypes. In another GWAS of hypertension, a classical two-stage case–control study showed genome-wide significance of an SNP ($P = 2.6 \times 10^{-13}$) in the promoter region of *NOS3* (Salvi et al. 2012).

Candidate gene studies of BP

A number of candidate gene studies have been carried out focusing on genes associated with cardiovascular phenotypes. Methodologies for candidate gene studies have changed significantly in the GWAS era, making it possible to carry out meta-analyses with much larger samples and many more candidate genes in a single investigation using the genotype data from either a subset of GWAS data or measured using high-throughput genotyping microarrays. As a result, reproducibility of candidate gene studies has much improved. Using the Illumina HumanCVD BeadChip array (Keating et al. 2008), 50,000 SNPs capturing variants of approximately 2000 candidate genes for cardiovascular phenotypes in 25,000 individuals were genotyped (Johnson et al. 2011a). The study identified eight significant loci, of which *LSP1* and *NOS3* were novel, concurrently with Salvi et al. (2012). In a different study, 62,000 individuals of European ancestry were genotyped by the same array. This study discovered one novel SNP associated with SBP and one with DBP, and confirmed 10 previously known loci associated with SBP, DBP, MAP or PP. All results were confirmed in an additional 66,000 individuals (Ganesh et al. 2013).

In a study with a larger sample size, 88,000 for discovery and 68,000 for replication, 11 novel BP loci were reported and 27 known associations were replicated (Tragante et al. 2014). As most known hypertension target genes were not significant in GWAS, associations of SBP and DBP with 30 genes known to be antihypertensive drug targets were examined. All GWAS SNPs within 60 kb of each target gene were analyzed. *ADRB1* and *AGT* reached genome-wide significance in this meta-analysis (Johnson et al. 2011b).

GWAS of BP with gene–environment interactions

Essential hypertension is known to be influenced by multiple susceptibility genes, environmental and lifestyle factors, as well as their interactions (Kunes and Zicha 2009). Inspired by the discoveries from analyzing the genetic main effect, researchers started looking for evidence of gene–environment interactions. A large-scale GWAS assessing the pervasiveness of gene–age interactions was recently carried out by CHARGE, Global BPgen, and ICBP consortia (Simino et al. 2014), which included approximately 56,000 individuals for discovery and 43,000 for replication. Samples were stratified by age, and the conventional genetic main effect was examined separately in age bins in each cohort. Meta-regression was then used to test genetic main effects together with interaction effects (Xu et al. 2013), which was more powerful than either of the marginal tests (Kraft et al. 2007). Two out of the 20 genome-wide significant loci were novel. Nine loci demonstrated nominal evidence ($P < 0.05$) of age-dependent effects on BP when testing the interactions alone, and five would have been missed by main-effect-only analysis. Those loci demonstrating age-dependent effects are of particular relevance to essential hypertension, which is marked by a chronically elevated BP.

Gene–alcohol interactions were evaluated in a relatively small sample of 6900 individuals from the Framingham Heart Study (Simino et al. 2013). Using the same test (2 degrees of freedom), a significant locus was discovered. The same group, based on the same sample, identified two significant loci by gene–education interaction analysis (Basson et al. 2014b), and seven loci by gene–smoking interaction analysis (Sung et al. 2014). As these results were not replicated in external samples, they were subject to further validations.

GWAS of other BP phenotypes

Despite the wide availability of cross-sectional BP phenotypes, which allows for the employment of large sample sizes, a single BP measurement is subject to random variations. A number of studies were conducted on other BP-related phenotypes, which are believed to have much larger signal-to-noise ratios. One investigation studied long-term averaging of quantitative BP traits, aimed at reducing the intra-individual variability due to the measurement error (Ganesh et al. 2014). Nineteen significant loci were identified by this study; additionally, four were uniquely identified by the analysis using a discovery sample of 47,000 and replication of 39,000. In contrast to the long-term average, a different study looked into visit-to-visit BP variability in 3800 and 15,000 individuals for discovery and replication, respectively. One locus showed genome-wide significance; however, the result has not been replicated (Yadav et al. 2013). A family study that included 2000 individuals from 500 European nuclear families showed association

between a mean 24-h DBP and an SNP in the promoter regions of *MTHFR* and *CLCN6* genes (Tomaszewski et al. 2010).

GWAS of BP responses to low-sodium, high-sodium, potassium interventions, and cold pressor test were reported (He et al. 2013). This study was based on a relatively small sample of 1900 Han Chinese subjects from approximately 700 families, of which 8 novel loci were discovered. Unlike in GWAS of clinical BP measurements, genetic variants associated with BP responses in such well-controlled experiments demonstrated much greater effect sizes. Estimated effect sizes varied from 0.5 to 6.9 mmHg per coded allele. Due to the shortage of independent samples with the same intervention design, results could not be effectively replicated.

Pharmacogenomic studies of BP

Understanding the genetic basis of how hypertensive patients respond to antihypertensive medicines differently is crucial for the implementation of precision medicine. There are a few GWAS of hypertension using SNP-medication (antihypertensive medications) interactions in a pharmacogenomics setting. A genetic mechanism of BP responses to antihypertensive medicines was investigated by employing an extreme case–control design with approximately 200 individuals of African ancestry and 200 of European ancestry. Approximately 100,000 genome-wide SNPs were genotyped using the Affymetrix Gene Chip Human Mapping 100 K Array. One significant locus was reported to be associated with the DBP response to hydrochlorothiazide (Turner et al. 2008). In a further effort using 1,100,000 SNPs and 650 samples for discovery and 620 for replication (Turner et al. 2013), three loci showed genome-wide significance while not replicated. Combining all samples, one locus became genome-wide significant, which also showed a large effect of 4.2 mmHg per coded allele. In another study, about 300 hypertensive patients were recruited for GWAS of BP responses to three antihypertensive medicines. Associations were tested between quantitative BP responses and approximately 300,000 SNPs, and no significant loci were detected (Kamide et al. 2013). Although SNPs underlying BP responses may have large effects, small sample sizes employed in current pharmacogenomic studies may have limited their discovery.

Future directions

There is no doubt that GWAS achieved considerable success in dissecting the genetic architecture of BP regulation with over 60 novel loci identified. However, a substantial proportion of heritability has not been accounted for. Known loci appear to explain less than 2.5 % of the phenotypic variance for SBP and DBP (ICBP 2011). Rare variants, structural variations, gene–gene, and gene–environment interactions, among many others, have been suggested as potential sources for finding the missing heritability (Manolio et al. 2009).

For height, a classic complex trait with an estimated heritability of 80 %, 697 genome-wide significant variants have been reported that together explain one-fifth of its heritability using samples of 253,000 individuals (Wood et al. 2014). For BP phenotypes, it was estimated that there are 116 (95 % confidence interval 57–174) independent BP variants, with the effect sizes similar to those reported previously (ICBP 2011), which are yet to be

discovered. Meta-analyses based on much larger sample sizes may find more common variants which explain additional BP variation.

With the advent of next-generation sequencing technology (Metzker 2010), it is possible now to detect rare variants via deep sequencing of whole exomes or even the entire genome at a much lower cost. Rare functional mutations were found to have much larger effects on BP than common mutations (Ji et al. 2008), potentially explaining at least a portion of the missing heritability. Sequencing studies of BP/hypertension are still at the initial stages. Early experiments suggest that large sample sizes are necessary (Nguyen et al. 2013; Morrison et al. 2014). While large sample sizes may be able to identify novel rare variants, efficient and cost-effective experimental design can enhance the power of even moderate sample sizes for studying rare variants (Shi and Rao 2011). The recently announced "Initiative on Precision Medicine" by the United States government aims to assemble over time a longitudinal cohort of 1 million or more American subjects (Collins and Varmus 2015), which is likely to be a valuable resource for finding rare variants underlying BP regulation and many other human diseases.

Progress in testing gene–environment interactions has demonstrated great promise for discovering novel BP variants as summarized in this review. Gene–environment interaction studies very much complement current GWAS efforts, which focus solely on testing additive genetic main effect, and will likely help to explain a portion of non-additive heritability. The Gene–Lifestyle Interactions Working Group of CHARGE is leading a large international effort to evaluate gene–lifestyle interactions in large multi-ethnic populations with approximately 300,000 subjects for discovery and replication (Rao and Borecki, Coordinators). This great effort funded by the National Heart, Lung, and Blood Institute of the United States government (Rao and Borecki, Principal Investigators) will likely help decide whether interaction studies can help identify some of the missing heritability.

Genome-wide gene–gene interaction tests are more challenging given the much larger burden of multiple testing. In the first genome-wide SNP–SNP interaction study of high-density lipoprotein cholesterol levels (van Leeuwen et al. 2014), no significant interaction was detected after Bonferroni correction of *P* values. In a focused study of SNP–SNP interaction among a small set of inflammation genes, no interaction was found to be associated with BP at an experiment-wide significance level (Basson et al. 2014a).

Epigenetics investigates trait and gene expression variations that are not caused by changes in the DNA sequence; it includes DNA methylation, histone modification, and alteration of microRNA expression, and more (Cowley et al. 2012). There is evidence indicating that cardiovascular biomarkers are associated with epigenetic modifications (Baccarelli et al. 2010). Introduction of high-throughput technologies now enables epigenetic features to be comprehensively and quantitatively profiled across the genome. As most BP variants detected by GWAS reside in non-coding regions, suggesting regulatory roles, the study of epigenetics could potentially explain some of the BP variance mediated by the changes in gene expressions. Wang et al. (2011) has reviewed the potential of epigenetics in hypertension genetics. The first genome-wide methylation analysis was conducted in young African American males (Wang et al. 2013a). A CpG site in the *SULF1* gene showed higher methylation levels in leukocytes of hypertension case

subjects than in those of healthy controls, confirmed in subjects younger than 30 years. This illustrates the promising future of epigenetic study in essential hypertension.

Conclusions

GWAS of BP allowed the testing of millions of common variants across the human genome for the first time. Tens of BP loci have been identified and reproduced in large cohorts; however, many BP variations are yet to be accounted for. Employing larger sample sizes and studying individuals with diverse genetic backgrounds help to identify more common variants. Next-generation sequencing technology permits the investigation of rare variants, which potentially have much larger effects. Gene–environment interaction analyses may help to identify additional BP variation beyond the additive genetic main effect. With emerging epigenetic approaches, additional BP variance is likely to be explained by epigenetic differences in populations. It is hoped that advances in hypertension genetics will provide insights into the pathogenesis of hypertension, identify novel drug targets, and lead to the development of novel antihypertensive medicines as well as personalized prevention and treatments.

Abbreviations

AGEN: Asian Genetic Epidemiology Network; BP: blood pressure; CARe: Candidate-gene Association Resource; CHARGE: Cohorts for Heart and Aging Research in Genomic Epidemiology; COGENT: Continental Origins and Genetic Epidemiology Network; CVD: cardiovascular disease; DBP: diastolic blood pressure; Global BPgen: global blood pressure genetics; GWAS: genome-wide association studies; ICBP: International Consortium of Blood Pressure; MAP: mean arterial pressure; PP: pulse pressure; SBP: systolic blood pressure; SNP: single-nucleotide polymorphism.

Authors' contributions

JZ conceived of the review and drafted the manuscript. DCR conceived of the review and revised the manuscript. GS conceived of the review, drafted the manuscript, and participated in its design and coordination. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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