

Blood pressure and human genetic variation in the general population

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Purpose of review

Hypertension is a complex trait with multiple environmental and genetic contributors. Until recently, linkage studies of rare Mendelian disorders of hypertension and hypotension have produced the most notable progress toward understanding the heritable basis of blood pressure (BP). Association studies to identify common variants have been limited in the past by small sample sizes and most findings have lacked replication.

Recent findings

Recently, well powered, targeted candidate gene and genome-wide association studies have reported reproducible associations between rare and common genetic variants and BP and hypertension at the population level.

Summary

Identification of novel genes will lead to an improved understanding of BP regulation and the potential for novel therapies.

Keywords

association, blood pressure, genetics

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Introduction

Elevated blood pressure (BP) or hypertension increases the risk for stroke, congestive heart failure, coronary heart disease and end-stage renal disease [1–3]. Lifestyle changes and antihypertensive therapy are associated with reductions in morbidity and mortality [4–6]. However, current population surveys indicate that control rates are generally poor [7]. An improved understanding of the environmental and genetic determinants of BP variation could point to novel avenues to prevent hypertension and its complications.

The genetic basis of hypertension at the population level has only recently begun to yield to intense investigation. Prior *Current Opinion in Cardiology* reviews from Binder *et al.* in 2007 and Hamet *et al.* in 2007 covered genome-wide linkage approaches in family and population-based studies and early candidate gene studies [8,9]. The current review focuses on genetic discoveries in 2008 and 2009.

Population burden of hypertension

More than a quarter of the world's adult population is hypertensive [10]. In North America, roughly one in three adults have hypertension. Most individuals eventually become hypertensive if they live long enough, with a lifetime risk of approximately 90% in individuals who are normotensive at the age of 55 years [11]. Despite the high prevalence, almost one-third of all hypertensive individ-

uals are unaware, half untreated and three-fourths uncontrolled [3].

Hypertension is a dichotomous trait, but BP shows a continuous relationship to outcomes. A meta-analysis [1] including one million adults found increasing risk of cardiovascular mortality with increasing BP starting as low as 115/75 mmHg. The Framingham Heart Study found high-normal BP [systolic blood pressure (SBP) 130–139 mmHg, diastolic blood pressure (DBP) 85–89 mmHg] to be associated with increased cardiovascular risk [12]. These observations are consistent with a graded and continuous relationship of increasing BP with risk of cardiovascular disease.

Observational studies have reported the association of elevated BP with higher salt intake [13], excessive alcohol consumption [14], higher BMI [15] and reduced physical activity [16]. Interventional trials have established that modification of each of these risk factors lowers BP effectively, in some cases in excess of the BP-lowering effect of single-medication therapy [3–5,17,18].

Genetic factors influence blood pressure and hypertension

Intra-individual BP variation, measurement error, strong environmental contributions and antihypertensive therapy of varying intensity pose challenges to the genetic study of BP. Despite a large number of covarying

factors, family studies [19–22] have shown significant genetic contributions to interindividual differences in BP. Long-term BP estimates have been shown to be highly heritable, with 50–60% of long-term SBP or DBP attributable to additive genetic factors [22].

The genetic architecture – defined by the number of variants, their frequency and strength of effect – that underlies this heritability has been unknown. Genome-wide linkage studies in rare families with Mendelian forms of hypertension and hypotension have successfully identified rare amino acid-altering variants that have relatively strong effects on salt-handling genes (Table 1 [23–50]). These have been well reviewed elsewhere [51]. Although these rare variants clearly play a major role in BP variation within the families that harbor them, what role they play in overall BP variation has been unclear. Studies in the past 2 years have added importantly to our understanding of the genetic architecture of BP variation.

Do rare variants at the population level influence blood pressure?

Richard Lifton's group and others have identified many disease-causing mutations in renal salt-handling genes, placing these genes and pathways centrally in BP regulation (Table 1). Whether genetic variation in these genes at the population level contributes to interindividual differences in BP was an open question. Rare mutations in a gene could lead to a detectable phenotype in a handful of families, but their low prevalence (due to negative selection) could make variation in these genes a negligible contributor to differences in BP in general. A series of reports on a gene responsible for Gitelman's syndrome, an autosomal recessive syndrome characterized by hypochloremic metabolic alkalosis, hypokalemia and hypocalciuria, have expanded our understanding of the genetic architecture of BP.

Homozygous mutations in families

In a linkage study in 12 families, Simon *et al.* [50] mapped Gitelman's syndrome to the *SLC12A3* gene encoding the thiazide-sensitive Na–Cl cotransporter (NCCT). They identified homozygous loss-of-function mutations in *SLC12A3* that result in salt wasting from the distal convoluted tubule. The authors speculated that heterozygous carriers of mutant alleles (one mutated copy and one normal copy of the gene) might be protected against development of hypertension.

Heterozygous mutations in a large family with Gitelman's syndrome

Cruz *et al.* [52] examined an Amish kindred with Gitelman's syndrome, including 60 individuals with zero, 13

with one and 26 with two copies of the mutant allele. BP was significantly lower in heterozygous children but not in adults, perhaps due to limited power, age effects or improved dietary compensation in adults. These observations in a single family raised the intriguing possibility that heterozygous mutations in renal salt-handling genes at the population level might affect BP, not just in families selected for Gitelman's syndrome.

Heterozygous mutations in the general population

In 2008, Ji *et al.* [53**] reported a screen in 3125 individuals (many in families) from the community-based Framingham Heart Study for mutations in three candidate genes in which homozygous mutations cause Gitelman's or Bartter's syndromes: NCCT (*SLC12A3*), NKCC2 (*SLC12A1*) and ROMK (*KCNJ1*) (Table 1). Using criteria of complete conservation across multispecies comparisons with rare allele frequency (<1 per 1000) or known Gitelman's or Bartter's mutations, they identified a final set of 30 putative functional mutations (15 in *SLC12A3*, 10 in *SLC12A1* and five in *KCNJ1*) in 49 individuals. Eighty percent of the carriers of at least one mutation had long-term SBP values below the mean of the entire cohort ($P=0.001$). Carriers had 6.3 mmHg lower SBP ($P=0.0009$) and 3.4 mmHg lower DBP ($P=0.003$) compared with noncarriers. The BP reduction among mutation carriers was observed in all age groups, with an approximately 60% reduction in the risk of developing hypertension by the age of 60 years ($P<0.003$).

Collectively, these studies chart the identification of a gene influencing BP through linkage in rare families with recessive hypotension syndromes, use of large kindreds to examine within-family effects of heterozygosity and ultimately extension to the population level. Along with the finding that rare mutations in *ABCA1* result in marked reduction in high-density lipoprotein levels in the general population [54], these are the first demonstrations that rare mutations of strong effect contribute to variation in common cardiovascular traits. Whether similar unbiased (cf. genome-wide linkage) or targeted (cf. sequencing of candidate genes) approaches could identify common variants that contribute to BP variation at the population level was unclear until recently. The literature is full of reports of small numbers of variants in modest-sized studies that failed to be replicated and led to a general sense that association studies of common variants were hopeless.

Common variants at the population level

Linkage studies are well suited to detect rare variants with strong effects for conditions that are relatively rare but have been an utter failure for common complex diseases [55]. By contrast, association studies are better

Table 1 Mendelian syndromes of hypertension and hypotension

Gene	Gene name (alias)	Disease	Gain(+) or loss(-) of function of the protein product	References
Hypertension				
<i>CYP11B1</i>	Cytochrome P450, family 11, subfamily B, polypeptide 1	11 β hydroxylase deficiency	-	[23]
<i>CYP11B2</i> ^a	Cytochrome P450, family 11, subfamily B, polypeptide 2 (aldosterone synthase)	Glucocorticoid remediable aldosteronism	+	[24]
<i>CYP17A1</i>	Cytochrome P450, family 17, subfamily A, polypeptide 1	Combined 17 α -hydroxylase/17,20-lyase deficiency	-	[25,26]
<i>CYP17A1</i>	Cytochrome P450, family 17, subfamily A, polypeptide 1	Isolated 17,20-lyase deficiency	-	[27]
<i>HSD11B2</i>	Hydroxysteroid (11-beta) dehydrogenase 2	Apparent mineralocorticoid excess	-	[28,29]
<i>NR3C2</i> ^a	Nuclear receptor subfamily 3, group C, member 2	Hypertension, exacerbated in pregnancy	+	[30]
<i>SCNN1B</i> ^a , <i>SCNN1G</i> ^a	Sodium channel, nonvoltage-gated 1, beta and gamma subunits	Liddle's syndrome	+	[31-33]
<i>WNK1</i>	WNK lysine-deficient protein kinase 1	Pseudohypoaldosteronism type II (Gordon Syndrome)	+	[34]
<i>WNK4</i>	WNK lysine-deficient protein kinase 4	Pseudohypoaldosteronism type II (Gordon Syndrome)	-/+	[34-36]
Hypotension				
<i>BSND</i>	Bartter syndrome, infantile, with sensorineural deafness	Bartter's syndrome type 4	-	[37]
<i>CASR</i>	Calcium-sensing receptor	Bartter's syndrome type 5	+	[38,39]
<i>CLCNKB</i>	Chloride channel Kb	Bartter's syndrome type 3	-	[40]
<i>CYP11B2</i> ^a	Cytochrome P450, family 11, subfamily B, polypeptide 2	Corticosterone methyloxidase type I and II deficiency	-	[41,42]
<i>CYP21A2</i>	Cytochrome P450, family 21, subfamily A, polypeptide 2	21-Hydroxylase deficiency	-	[43,44]
<i>HSD3B2</i>	Hydroxy-delta-5-steroid dehydrogenase, 3 beta and steroid delta-isomerase 2	3 β Hydroxysteroid dehydrogenase deficiency type II	-	[45]
<i>KCNJ1</i>	Potassium inwardly-rectifying channel, subfamily J, member 1 (ROMK)	Bartter's syndrome Type 2	-	[46]
<i>NR3C2</i> ^a	Nuclear receptor subfamily 3, group C, member 2	Pseudohypoaldosteronism type I	-	[47]
<i>SCNN1A</i> , <i>SCNN1B</i> ^a , <i>SCNN1G</i> ^a	Sodium channel, nonvoltage-gated 1 alpha, beta and gamma subunits	Pseudohypoaldosteronism type I	-	[48]
<i>SLC12A1</i>	Solute carrier family 12 member 1 (Na-K-2Cl cotransporter, NKCC2, loop diuretic target)	Bartter's syndrome type 1	-	[49]
<i>SLC12A3</i>	Solute carrier family 12 member 3 (Na-Cl cotransporter, NCCT, thiazide diuretic target)	Gitelman's syndrome	-	[50]

Genes that are well described to harbor rare mutations that cause Mendelian forms of hypertension and hypotension are given in Table 1. Different mutations in some of the same genes can lead to both hyper- or hypotension depending on whether they result in gain or loss of protein function.

^aGene associated with both hypertension and hypotension.

suited to detect modest genetic effects of common variants [56]. Association studies were plagued by poor reproducibility, stemming from false-positive reports due to inappropriately permissively significance thresholds and the inability to validate suggestive findings in underpowered replication attempts [57]. The creation of a reference sequence of the human genome, generation of large databases of common genetic variation, growth of high-throughput genotyping platforms and development of rigorous methodological approaches set the stage for the discoveries that followed.

First validated common blood pressure variants identified

Atrial and B-type natriuretic peptides (ANP and BNP) have direct vasodilatory and natriuretic effects and antagonize the renin–angiotensin–aldosterone system [58–60]. In mouse models, knockout of the *NPPA* (encoding ANP) or natriuretic peptide receptor A (*NPR-A*) genes [61,62] results in salt-sensitive hypertension and ANP overexpression [63] lowers BP. The known physiologic effects in humans and animal models make the natriuretic peptide system a compelling candidate to influence interindividual differences in BP, but until recently there was no clear evidence that ANP or BNP influences BP regulation in humans.

In 2009, Newton-Cheh *et al.* [64**] reported a candidate gene association study at the locus on chromosome 1 where *NPPA* and *NPPB* lie in tandem. Thirteen single nucleotide polymorphisms (SNPs) were genotyped in a discovery sample from the Framingham Heart Study ($n = 1705$) and tested for association with plasma ANP and BNP, with subsequent replication in samples from Sweden and Finland (total $n = 14\,743$). Three noncoding SNPs showed consistent association with ANP or BNP at significance

levels that were unambiguous (P value ranging from 10^{-10} to 10^{-70}), presumably through shared regulatory effects given the concordant effects on both peptides.

With the addition of further samples from Sweden (final $n = 29\,717$), we found that two alleles associated with higher ANP and BNP were also associated with lower SBP (0.9–1.5 mmHg) and DBP (0.3–0.8 mmHg) and decreased odds of hypertension (0.85–0.90) (Table 2 [64**–66**,67]). BP associations had much more modest significance than those of natriuretic peptide concentrations (P value ranging from 1×10^{-6} to 6×10^{-5}) [64**]. The identification of *cis*-acting noncoding common genetic variants that influence plasma concentrations of ANP and BNP as well as BP provided the first in-vivo evidence in humans of the relevance of endogenous variation in the natriuretic peptide system in BP regulation in humans.

It is worth pointing out that these weak BP effects could not be detected in such a small discovery sample size ($n = 1705$), were it not for the use of intermediate ANP/BNP traits, which showed much stronger association. Unbiased screens of the genome for BP variants, requiring stringent P value thresholds to distinguish false-from true-positive associations (e.g. $P < 5 \times 10^{-8}$) would require even larger sample sizes to detect such an effect.

Candidate gene studies are like the drunk searching under the lamppost for his keys – focusing only where biologic involvement is already suspected – and thus do not expand our understanding of human biology as much as unbiased surveys that test thousands of genes comprehensively. Genome-wide association studies (GWASs) have only borne fruit for BP when very large sample sizes allowed stringent P value thresholds to be met.

Table 2 Common variants implicated in recent candidate gene and genome-wide association studies with a P value less than 5×10^{-8}

Nearby genes	SNP	Chromosome no.	Allele frequency	Trait	Effect (mmHg)	P	Reference
<i>NPPA/NPPB</i>	rs5068	1	0.94	SBP	1.10	3×10^{-9}	[64**,65**]
<i>MTHFR/CLCN6/NPPA/NPPB</i>	rs17367504	1	0.86	SBP	0.85	2×10^{-13}	[65**]
<i>CYP17A1</i>	rs11191548	10	0.91	SBP	1.16	7×10^{-24}	[65**,66**]
<i>PLCD3</i>	rs12946454	17	0.28	SBP	0.57	1×10^{-8}	[65**]
<i>FGF5</i>	rs16998073	4	0.21	DBP	0.50	1×10^{-21}	[65**]
<i>C10orf107</i>	rs1530440	10	0.81	DBP	0.39	1×10^{-9}	[65**]
<i>SH2B3</i>	rs3184504	12	0.47	DBP	0.46	3×10^{-18}	[65**,66**]
<i>CYP1A2/CSK/LMAN1L</i>	rs1378942	15	0.36	DBP	0.43	1×10^{-23}	[65**,66**]
<i>ZNF652</i>	rs16948048	17	0.39	DBP	0.31	5×10^{-9}	[65**]
<i>PLEKHA7</i>	rs381815	11	0.26	SBP	0.65	2×10^{-9}	[66**]
<i>ATP2B1</i>	rs2681492	12	0.80	SBP	0.85	6×10^{-17}	[66**,67] ^a
<i>ULK4</i>	rs9815354	3	0.17	DBP	0.49	3×10^{-9}	[66**]
<i>CACNB2</i>	rs11014166	10	0.66	DBP	0.37	1×10^{-8}	[66**]
<i>TBX3/TBX5</i>	rs2384550	12	0.65	DBP	0.35	4×10^{-8}	[66**]

Fourteen variants at 13 independent loci are shown; the first two variants are at the same locus but are incompletely correlated and may represent different signals of association. We show allele frequencies for the allele associated with an increase in BP. P values for variants observed in more than one study (or a close proxy) are based on meta-analysis of reported studies. SNP, single nucleotide polymorphism.

^aA correlated SNP was reported in Cho *et al.* [67] and just missed genome-wide significant association with SBP ($P = 1 \times 10^{-7}$).

Genome-wide association studies in small-to-moderately large studies do not reach genome-wide significance

The first few GWASs published by us and others in 2007, including the Wellcome Trust Case Control Consortium [68] (2000 hypertensive cases, 3000 population-based controls), the Diabetics Genetics Initiative [69] (1464 cases with type 2 diabetes and 1467 matched controls) and the Framingham Heart Study 100K project [70] (1327 individuals for SBP and DBP) failed to identify any loci meeting stringent genome-wide significance thresholds. Genome-wide significance has been variably defined but is generally accepted at $P < 5 \times 10^{-8}$, which represents Bonferroni correction for the estimated one million independent common variant tests in the genome for individuals of European ancestry (0.05/1 000 000) [71]. In 2009, further GWASs [67,72–76] of BP traits, hypertension or both in populations of different ancestries and of moderate size have subsequently been reported but none achieved genome-wide significance. A few are highlighted.

In 2009, Wang *et al.* [74] reported a GWAS in 542 Amish individuals and found a SNP at 2q24.3 with modest association with SBP ($P = 8 \times 10^{-5}$). They genotyped an additional 1347 individuals and looked up results from published GWASs for a total sample size of 7125, but did not reach genome-wide significance ($P = 2 \times 10^{-7}$). The SNP lies within an intron of the serine–threonine kinase 39 (*STK39*) gene, which encodes the STE20/SPS1-related proline/alanine-rich kinase protein, known to regulate NCCT and NKCC2 in the kidney [77,78]. No replication of this association has been published.

In 2009, Cho *et al.* [67] reported a GWAS from two population-based cohorts of 8842 individuals with replication in 7861 individuals, all of Korean ancestry. SNP rs17249754 near *ATP2B1* was associated with SBP with borderline significance ($P = 1 \times 10^{-7}$). This SNP is located near the ATPase calcium ion transporting plasma membrane 1 (*ATP2B1*) gene, which encodes a protein involved in calcium movement from cytosol to the extracellular compartment [79]. A correlated SNP at *ATP2B1* was subsequently reported to be associated with SBP and hypertension in a GWAS in European samples (see below).

Adeyemo *et al.* [76] reported the first GWAS for BP and hypertension in an African–American sample ($n = 1017$ individuals, some in families). The authors selected 17 SNPs for follow-up replication in 980 West Africans. Of these, none were genome-wide significant upon joint analysis with the original GWAS result (all $P > 3 \times 10^{-6}$).

Large genome-wide association study meta-analyses and replication identify 13 novel loci

In 2009, two meta-analyses of GWASs of BP, Global BPgen [65**] and CHARGE BP [66**], reported in parallel the first genome-wide significant associations between common genetic variants and BP.

Global BPgen consortium identifies eight blood pressure loci

Newton-Cheh *et al.* [65**] reported findings of the Global BPgen consortium including a stage 1 GWAS meta-analysis in 34 433 individuals from 17 cohorts of European ancestry ascertained through population-based sampling and controls from case–control collections. In total, 2.5 million genotyped and imputed SNPs were tested for association with SBP and DBP under an additive genetic model, adjusting for age, age², sex and BMI, with imputation in individuals treated with antihypertensives. Twelve independent SNPs were selected from the stage 1 GWAS meta-analysis and directly genotyped in up to 71 225 European-derived and 12 889 Asian ancestry individuals (stage 2a). Twenty SNPs associated with SBP or DBP were looked up in the CHARGE BP results (stage 2b).

Eight loci met genome-wide significance for association with BP (three SBP and five DBP) on meta-analysis of stage 1 + 2a + 2b (P range 10^{-23} to 10^{-8} , $n \leq 134\,258$, Table 2) [65**]. Effect sizes were quite modest, generally approximately 1 mmHg or less for SBP and approximately 0.5 mmHg for DBP. All variants were associated with both SBP and DBP, even if ascertained on association with one trait, and all were associated with dichotomous hypertension. Of the eight loci, two harbor genes known to be involved in BP physiology and six do not.

Two loci contain known blood pressure genes

The *MTHFR/CLCN6/NPPA/NPPB* locus included a SNP rs17367504 associated with BP (Table 2). The SNP is partially correlated to the top SNP from our prior candidate gene study and is associated with plasma ANP concentration, making it likely to mediate its effect through regulation of the natriuretic peptide system. However, rs17367504 is also strongly associated with hepatic expression of *CLCN6* [80], which encodes a renally expressed chloride channel, suggesting that a simple SNP → ANP → BP model may not hold. The Global BPgen study did confirm the association of the rs5068 SNP from the candidate gene study with SBP (joint $P = 3 \times 10^{-9}$, Table 2) [64**,65**]. Whether multiple independent variants at the locus exist, potentially acting through different mechanisms, will require much more work to determine.

One locus contains a gene involved in Mendelian hypertension, *CYP17A1* (Tables 1 and 2). *CYP17A1* encodes a protein with both 17 α -hydroxylase activity – mediating a key step in the biosynthesis of glucocorticoids – and 17,20-lyase activity involved in sex steroidogenesis [28,81]. Missense mutations in *CYP17A1* cause adrenal hyperplasia with hypertension and hypokalemia. There are many other genes in the associated interval at this locus, but the well annotated Mendelian hypertension gene certainly stands out as a strong candidate to underlie the common variant association.

Thus, strong candidate genes at these loci appear to be good places to start to explain these common variant associations. But ultimately, it will be necessary to determine the causal variants and to elucidate their relationships to gene expression for regulatory noncoding variants or to gene function via altered proteins for coding or splice variants. Unfortunately, the genetic code for regulatory machinery is only beginning to be understood, and smoking-gun amino acid-altering variants are a minority of common variant associations. Of the remaining six loci identified by Global BPgen, the 12q24 locus includes an amino acid-altering variant.

A missense SNP in SH2B adaptor protein 3 (*SH2B3*) is associated with multiple traits

The missense SNP rs3184504 in the *SH2B* adaptor protein 3 (*SH2B3*) gene codes for an arginine to tryptophan at amino acid 262 (R262W) in the lymphocyte-specific adapter protein (LNK) and is associated with BP. A relationship of this gene to BP physiology has not previously been recognized. In earlier GWASs, the minor T allele (262W) of this SNP was found to be associated in humans with increased odds of autoimmune diseases, including type 1 diabetes [82], celiac disease [83], myocardial infarction (MI) [84,85] as well as higher eosinophil and other blood cell counts [84,85] (Table 3 [65^{••},66^{••},82–86]). The mouse knockout of LNK is associated with higher lymphocyte and platelet counts, suggesting by extension that the 262W allele results in loss of function (Table 3). The increased risk of autoimmune disease seems consistent with a potentially augmented immunologic activity. In fact, strong signatures of positive selection on the 262W allele in European-derived individuals suggest a selective

advantage in human history, perhaps through fighting infection.

The role of *SH2B3* in BP regulation or MI pathogenesis is less clear but could be due to an effect outside the hematopoietic lineage. In an endothelial cell model, exposure to tumor necrosis factor-alpha has been found to upregulate LNK, inhibiting vascular cell adhesion molecule-1 expression and extracellular signal-regulated kinases and increasing endothelial nitric oxide synthase activity via the phosphoinositide 3-kinase/AKT pathway [87]. Given the role of the endothelial cell in atherosclerosis and smooth muscle tone, it seems possible that loss of LNK function from the 262W allele could lead to increased BP and risk of MI through endothelial dysfunction.

CHARGE BP consortium

In a parallel publication, the CHARGE BP consortium [66^{••}] reported results using a sample consisting of 29 136 European-derived individuals with validation of top results in the Global BPgen GWAS. CHARGE BP identified eight genome-wide significant loci, including three in common with Global BPgen and five unique to CHARGE BP (Table 2). The five additional loci have not previously been annotated to harbor genes involved in BP regulation, with the exception of *CACNB2*, which encodes a beta subunit of voltage-gated calcium channels, including the L-type dihydropyridine-sensitive channel.

Next steps

Even larger GWASs are likely to identify additional common genetic variants of even weaker effects. The ongoing International Consortium for BP-GWAS, including the Global BPgen and CHARGE BP consortia as well as others, is one such example, with more than 70 000 individuals with genome-wide genotyping. Sequencing will enable fine mapping of association signals and can potentially identify less common, stronger effect alleles (more ‘Mendelian’) that may be more easily recognized by alteration of amino acids and more tractable for physiologic study because of their greater effect sizes. High-resolution phenotyping of individuals selected on genotype can potentially home in on the mechanisms

Table 3 *SH2B3* 262W allele in human mirrors the mouse knockout

	Eosinophils	Lymphocytes	Platelets	Type 1 diabetes risk	Celiac disease risk	Myocardial infarction	DBP	Selection
Mouse knockout [86]		↑	↑					
<i>SH2B3</i> 262W allele	↑ [84,85]	↑ [84]	↑ [84]	↑ [82]	↑ [83]	↑ [84,85]	↑ [65 ^{••} ,66 ^{••}]	Positive [65 ^{••} ,85]

Shown are the effects in a mouse knockout and in humans for the minor 262W allele.

underlying association of a particular genetic variant, as has recently been applied to the *IL2RA* gene [88].

Conclusion

Until recently, only Mendelian families yielded robust genetic BP findings. Large sample sizes, comprehensive genetic screens and rigorous *P* value thresholds have allowed human genetics to expose additional novel pathways involved in BP regulation through the study of unselected population samples. However, in total, the common and rare variants identified to date that influence BP explain less than a percentage or two of overall population variation in BP [53^{**},65^{**},66^{**}], far less than age or body mass index. It seems unlikely, but requires formal testing, that genetic testing will add clinical utility to predicting future hypertension, beyond that available from a scale, a BP cuff and one's age.

Why are common BP variant effects so weak? BP regulation requires that organ perfusion be achieved through a very dynamic range of daily activities and environments, from sleeping to running through feast or famine. This has likely led to many redundant systems that allow tight regulation of BP and poor tolerance of genetic variants of strong effect that are therefore unable to rise to high frequency due to negative selection.

Why are so few of the antihypertensive targets represented among the common BP variants identified to date? It is possible that evolution has been particularly intolerant of genetic variation in the targets of antihypertensive therapies. However, it is equally possible that hundreds of genes are involved in BP, and that antihypertensive targets represent a small fraction of the total number of BP genes.

What do the weak common variant effects tell us about the potential of novel targets to have large effects on BP control? Not much. The minor allele of the SNP rs3846663 has been associated with a trivial 2.5 mg/dl higher low-density lipoprotein (LDL)-cholesterol in a GWAS [89]. If one did not already know that 3-hydroxy-3-methylglutaryl-coenzyme A reductase is involved in LDL-cholesterol synthesis, then finding this SNP in an intron of the *HMGCR* gene could allow identification of this target for cholesterol-lowering therapy. Identification of novel genetic influences on BP is just a start, as was identification of the first genes underlying familial hypercholesterolemia in the 1970s, with the promise of an improved understanding of BP regulation and identification of novel therapeutic targets.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 287–288).

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