A genomic deep field view of hypertension

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Blood pressure is regulated by a complex neurohumoral system including the renin-angiotensin-aldosterone system, natriuretic peptides, endothelial pathways, the sympathetic nervous system, and the immune system. This review charts the evolution of our understanding of the genomic basis of hypertension at increasing resolution over the last 5 decades from monogenic causes to polygenic associations, spanning ∼30 monogenic rare variants and >1500 single nucleotide variants. Unexpected early wins from blood pressure genomics include deepening of our understanding of the complex causation of hypertension; refinement of causal estimates bidirectionally between blood pressure, risk factors, and outcomes through Mendelian randomization; risk stratification using polygenic risk scores; and opportunities for precision medicine and drug repurposing.

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Nearly 10 million deaths globally per year are attributable to hypertension, making this the commonest modifiable cardiovascular risk factor in both developed and developing countries.[1,2] The health burden from hypertension arises from strong, continuous, positive relationships between blood pressure (BP) and coronary artery disease (CAD), heart failure, stroke, myocardial infarction, atrial fibrillation, peripheral artery disease, renal failure, and cognitive impairment.[3,4] *Hypertension* is defined by a threshold at the upper end of the BP distribution at which the benefits of action (i.e., therapeutic intervention) exceed those of inaction.[5] This simple yet powerful dichotomization has enabled clinical and public health strategies to reduce the global burden of hypertension[6] but belies the underlying complexity of BP regulation and hypertension causation involving the renin-angiotensin-aldosterone system, natriuretic peptides, endothelial pathways, the sympathetic

Editor's Note

The development of genetics has profoundly affected the field of hypertension, the most important global risk factor for cardiovascular disease. In their illuminating review, Garimella, Padmanabhan, and colleagues provide an overview of the genetic architecture of blood pressure control, ranging from ultrarare high-impact variants to common polymorphisms and their use for pharmacogenomics and risk stratification through polygenic risk scores. They describe how these insights improved our understanding of fundamental processes involved in NaCl handling, its hormonal regulation, and the vascular counterpart of blood pressure control. These advances are balanced by the need to bridge the gap between genome-wide association study variants and actionable practice; to better understand the role of structural variants, epigenetics, and gene-environment interactions; and to address the uneven access to clinical genomic or genetic services.

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nervous system, and the immune system.[7] Perturbations in any component of this system can arise from behavioral, environmental, or genetic factors or a combination of all, leading to increases or decreases in mean BP.

This review charts the evolution of our understanding of the genomic basis of hypertension at increasing resolution over the last 5 decades. The definitions of key terms are presented in Box 1. This has progressed through 2 phases that harken back to the Platt-Pickering debate[8]—an earlier fruitful period of identifying rare variants with large effects through linkage analysis of families with rare hypertension and hypotension syndromes and the more recent (last 15 years) expansion of polygenic discoveries from genome-wide association studies (GWASs) catalyzed by advances in genotyping and sequencing technologies, analytical methods, and large-scale collaborations.[9–14] Currently, the genetic architecture of hypertension encompasses ~30 monogenic rare variants and >1500 single nucleotide variants comprising both low-frequency and common variants reflecting the continuous spectrum of risk alleles influencing BP and consequently hypertension. Although monogenic variants implicate causal genes illuminating underpinning mechanisms, the wealth of common variants contrasts with the paucity of success in connecting to causal pathways. The immediate and direct application of GWAS results in clinical practice or translational studies looks unfeasible, and nascent functional studies to follow up GWAS signals require years to generate actionable results. Notwithstanding these, there have been unexpected early wins including expansion of our understanding of the complex causation of hypertension; confirmation and/or refinement of causal estimates bidirectionally between BP, risk factors, and outcomes through Mendelian randomization; understanding opportunities and requirements for risk prediction using polygenic risk scores; and opportunities for precision medicine and drug repurposing.

Sodium pathways

A direct relationship between excess Na^+ intake and hypertension has been well recognized for a long time and further confirmed by epidemiological studies and clinical trials.[15] This implied that perturbations in physiological pathways that maintain Na^+ homeostasis may be the underlying cause of hypertension. A majority of the early monogenic BP syndromes involved mutations in genes in the kidney tubules and adrenal glands with roles in tubular Na^+ transport mechanisms, suggesting the importance of Na^+ in BP regulation. GWASs have also identified single-nucleotide polymorphisms (SNPs) near genes involved in Na^+ pathways with varying levels of functional validation (Figure 1).

Box 1 | Definition of key terms

Linkage analysis. A powerful tool to detect the chromosomal location of disease genes. It is based on the observation that genes that reside physically close on a chromosome remain linked during meiosis. It attempts to locate a disease-causing gene by identifying genetic markers of known chromosomal location that are co-inherited with the trait of interest. It requires a well-defined trait (phenotype), an extensive pedigree of families usually with multiple generations, and genetic markers and maps.

Genome-wide association studies (GWASs). This involves testing hundreds of thousands of common genetic variations across the DNA of large numbers of individuals to find those statistically associated with a specific trait or disease. GWAS results have a range of applications, such as gaining insight into a phenotype's underlying biology, estimating its heritability, calculating genetic correlations, making clinical risk predictions, informing drug development, and inferring potential causal relationships between risk factors and health outcomes.

Single-nucleotide polymorphisms (SNPs). They are the most common type of naturally occurring genetic variation among people. Each SNP represents a single base substitution in the human genome with a population frequency of >1%. SNPs occur approximately once in every 1000 nucleotides throughout the genome, which means each individual's genome contains ~4 to 5 million SNPs.

Phenome-wide association studies (PheWAS). This is an unbiased approach to test for associations between a specific single-nucleotide polymorphism (SNP) or a combination of genetic variants across a wide range of phenotypes in large populations. The direction of inference in a PheWAS is from a SNP to multiple phenotypes, whereas in genome-wide association studies it is from one phenotype to multiple SNPs. They are well-suited to facilitate the identification of new associations between SNPs and phenotypes as well as between SNPs and pleiotropy. PheWAS have been proposed to enhance drug development through elucidating mechanisms of action, identifying alternative indications, predicting adverse drug events, and opportunities for drug repurposing.

Pleiotropy. A phenomenon whereby a single genetic variant influences ≥2 apparently unrelated phenotypic traits via independent biological pathways, for instance, because of the effects in different tissues or because the effect of the variant on one trait is causally related to variation in another trait.

Polygenic risk score (PRS). A single value estimate of an individual's genetic susceptibility to a phenotype, calculated as a sum of the genome-wide genotypes weighted by corresponding genotype effect size estimates derived from genome-wide association study (GWAS) data. Classic genetic risk scores include only a reduced set of single-nucleotide polymorphisms (SNPs) that fulfill a statistical level of significance. In contrast, PRS include millions of SNPs, explicitly modeling the correlation structure between SNPs without identifying a minimal subset of SNPs for prediction. These risk scores have limited predictive accuracy as they cannot confidently predict the clinical outcome of interest with precision at the individual patient level. PRS-based risk stratification could be of potential utility for diseases that already have population-based screening and prevention programs where additional information from PRS can direct screening toward a more restricted group, which could potentially decrease the risks associated with screening the population overall, and lead to cost savings.

Mendelian randomization (MR). MR uses genetic variation as a natural experiment to investigate the causal relationships between potentially modifiable risk factors and diseases or phenotypes in observational data. Major limitations of evidence from observational studies include unmeasured confounding and reverse causality. The idea behind MR is that as genotype is randomly allocated at conception and is invariant over the lifetime, they can be used as genetic proxies unaffected by confounding or reverse causation to infer causality. A valid MR study depends on the genetic variant (instrument) fulfilling 3 key assumptions: they associate with the risk factor of interest; they share no common cause with the outcome; and they do not affect the outcome except through the risk factor.

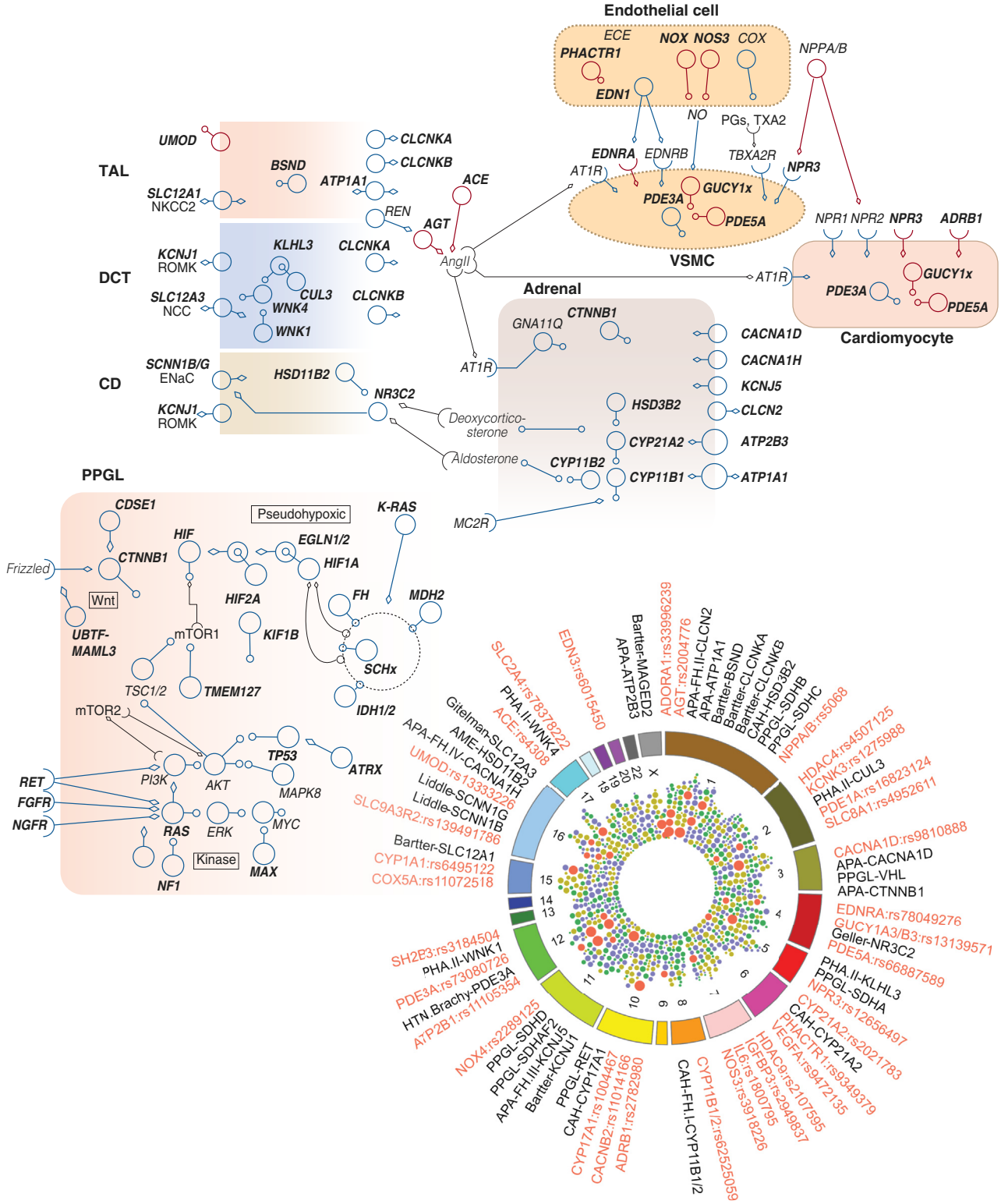

Figure 1 | Genomic landscape of hypertension representing a composite of monogenic and polygenic variants from linkage studies and genome-wide association studies (GWASs) along with the molecular and tissue context of the implicated genes. The genes discovered through linkage analysis or GWASs are depicted in bold within the cells, and the GWAS implicated molecular pathways are in red. The circos plot at the lower right depicts the monogenic (filled red circles) and polygenic (purple, dark green, and light green circles representing, respectively, single-nucleotide polymorphisms [SNPs] associated with systolic blood pressure, diastolic blood pressure, or pulse pressure in GWAS) variants associated with blood pressure. Chromosomes are represented as numbered segments. The monogenic syndromes and causal genes are presented circumferentially along with a selection of GWAS SNPs and their associated genes that have therapeutic potential. CD, collecting duct; DCT, distal convoluted tubule; NCC, Na^+-Cl^- cotransporter; NKCC2, Na^+- (continued)

Monogenic syndromes. Gordon syndrome (pseudohypoaldosteronism type II), which is linked to 4 genetic defects involving the *WNK1*, *WNK4*, *KLHL3*, and *CUL3* genes,[16] is the only form of monogenic hypertension that manifests as low-renin hypoaldosteronism with hyperkalemia and acidosis.[17,18] Mutations in these genes result in the lack of inhibition of WNK4 kinase by the protein products kelch-like 3, cullin 3, and with-no-lysine kinase 1 (WNK1), thereby leading to with-no-lysine kinase 4 (WNK4) accumulation and overactivity of the thiazide-sensitive Na^+-Cl^- cotransporter (NCC), which, in turn, causes hypertension with acidosis and hyperkalemia. Clinically, it is a biochemical and phenotypic "mirror image" of Gitelman syndrome (see below) and treatment is by blocking the Na^+-Cl^- cotransporter with thiazide diuretics.[19]

Liddle syndrome is an autosomal dominant low-renin and low-aldosterone hypertension disorder resulting from frameshift mutations in the genes coding the β and γ subunits of the epithelial Na^+ channel (encoded by *SCNN1B* or *SCNN1G*).[20,21] Consequently, these regions are unable to bind to the ubiquitin ligase neural precursor cell expressed developmentally down-regulated protein 4-2 (Nedd4-2), resulting in disruption of epithelial Na^+ channel internalization and proteasomal degradation with consequent overexpression and increased sodium reabsorption independent of aldosterone.[22] The typical clinical features are suppressed plasma renin and aldosterone levels, hypokalemic metabolic alkalosis, and early-onset hypertension. Blockers of the epithelial Na^+ channel—amiloride and triamterene (not aldosterone antagonists)—ameliorate the condition.

Like Liddle syndrome, the syndrome of apparent mineralocorticoid excess is also characterized by hypertension, hypokalemia, and metabolic alkalosis but caused by a deficiency of 11β-hydroxysteroid dehydrogenase encoded by the *HSD11B2* gene.[23,24] The primary role of this enzyme is the peripheral metabolism of cortisol to cortisone, thus preventing its binding to the mineralocorticoid receptor. Lack of the enzyme results in unopposed mineralocorticoid activation and Na^+ reabsorption.[25] Management is with mineralocorticoid receptor antagonists, K^+ supplements, and dietary Na^+ restriction.

Geller syndrome is caused by heterozygous mutation of the mineralocorticoid receptor gene (nuclear receptor subfamily 3 group C member 2, *NR3C2*),[26] resulting in increased Na^+ reabsorption and hypertension arising from activation of mineralocorticoid receptors by progesterone. This presents as severe hypertension during pregnancy when progesterone levels are increased. Mineralocorticoid receptor antagonists such as spironolactone paradoxically exacerbate hypertension and electrolyte disturbances and are thus contraindicated. This is because the mutation alters the binding parameters of the ligand-binding domain of the mineralocorticoid receptor, increasing its affinity for spironolactone.

The causal role of Na^+ in hypertension is further bolstered by the identification of mutations that result in Na^+ wasting and hypotension. Classic Bartter syndrome types 1 and 2 are disorders of the thick ascending limb of loop of Henle (TAL) resulting from variants in *SLC12A1* and *KCNJ1* genes with the consequent loss of function of Na^+-K^+-Cl^- cotransporter 2 (NKCC2) and K^+ rectifier channel (*KCNJ1*), respectively (Figure 1).[27] Bartter syndrome types 3, 4a, and 4b are specific to the distal convoluted tubule involving the *CLCNKB*, *BSND*, and *CLCNKA* genes, which encode proteins for the Cl^- channels ClC-Kb, barttin, and CLC-Ka, respectively. Type 4 exhibits sensorineural hearing loss in addition to hypotension and hypokalemic metabolic alkalosis seen with all Bartter syndromes.[28–30] Each of these variants is inherited in an autosomal recessive manner, whereas Bartter syndrome type 5 involving the melanoma-associated antigen D2 (*MAGED2*) gene shows X-linked inheritance and exhibits defects in both the TAL and the distal convoluted tubule.[31] Gitelman syndrome (familial hypokalemia hypomagnesemia) is the most common inherited tubulopathy (1 in 40,000), and although similar to Bartter syndrome with respect to hypotension and hypokalemic metabolic alkalosis, it is additionally characterized by hypomagnesemia and hypocalciuria. Gitelman syndrome results from biallelic inactivation of the *SLC12A3* gene[32] encoding the Na^+-Cl^- cotransporter expressed in the apical membrane of cells lining the distal convoluted tubule. To date, >350 mutations have been identified, with most patients being compound heterozygous for the *SLC12A3* gene.[33] The use of next-generation sequencing including genes involved in both Bartter and Gitelman syndromes is recommended to distinguish overlapping clinical phenotypes.[32]

GWAS. The GWAS SNP that has the widest range of evidence supporting a causal role in hypertension through Na^+ pathways is the uromodulin locus.[34] Uromodulin is a protein produced exclusively by the TAL and distal convoluted tubule.[35] Evidence from the last decade indicates its role in a novel hypertension pathway. Carriers of the minor G allele of the *UMOD* promoter SNP rs13333226 have lower levels of urinary uromodulin excretion and a lower risk of hypertension.[34,36] This lower risk of hypertension is the result of resistance to sodium-induced elevations in BP, which has been demonstrated using *UMOD* knockout mice, which show a leftward shift in the pressure-natriuresis curve in response to saline loading.[36] Additionally, *UMOD* overexpression in transgenic mouse models results in a dose-dependent increase in uromodulin excretion and rise in BP, which is mitigated with loop diuretics in both mice and humans homozygous for these alleles.[37] Further support for uromodulin influencing Na^+ homeostasis through tubular mechanisms comes from

Figure 1 | (continued) K^+-Cl^- cotransporter 2; PPGL, pheochromocytoma paraganglioma; *KCNJ1/ROMK*, potassium channel, inwardly rectifying subfamily J member 1/renal outer medullary potassium channel; TAL, thick ascending limb of loop of Henle; VSMC, vascular smooth muscle cell.

general population studies where higher urinary uromodulin concentrations have been shown to associate with higher urinary Na^+, Cl^-, and K^+ excretion and osmolality.[38] Uromodulin has been shown to upregulate Na^+-K^+-Cl^- cotransporter 2 activity by phosphorylation in the TAL.[39] Therefore, in states where the rise in BP is dependent on sodium reabsorption in the TAL, blocking this with loop diuretics may provide an effective means of treating hypertension, as is being investigated in a clinical trial[40] (ClinicalTrials.gov identifier NCT03354897). Although evidence from transplantion studies in humans suggests that the presence of a donor T allele at rs12917707 is associated with lower uromodulin levels and a lower risk of incident kidney failure,[41] the presence of neither donor nor recipient T allele of rs12917707 is associated with the risk of hypertension after kidney transplantation.[42] The definitive evidence that uromodulin is independently associated with BP comes from Mendelian randomization (MR) studies using urinary uromodulin GWAS SNPs as exposures and BP and kidney function GWAS SNPs as outcomes. Ponte *et al.*[43] showed that each 1 mg higher genetically predicted urinary uromodulin/creatinine level was associated with 1 ml/min per 1.73 m^2 lower estimated glomerular filtration rate (eGFR), 6% higher odds of having chronic kidney disease, 0.11 mm Hg higher systolic BP, and 0.09 mm Hg higher diastolic BP (DBP). The independent effect of uromodulin on BP and eGFR was quantified using bidirectional and multivariable MR to show that 28% of uromodulin's total effect on BP was mediated by eGFR with the remainder due to the direct effect.[43]

BP GWAS SNPs located near the natriuretic peptide A and B genes (*NPPA/B*)[44] and natriuretic peptide receptor 3 (*NPR3*)[44] implicate natriuretic peptides, which increase mGFR and inhibit kidney Na^+ reabsorption by decreasing activity of Na^+/K^+ adenosine triphosphatase and Na^+-glucose cotransporter in the proximal convoluted tubule. An association between a low-frequency missense variant rs139491786 in solute carrier family 9, subfamily A, member 3 regulator 2 (*SLC9A3R2*) and BP has now been reinforced by a large exome sequencing study which found that the burden of rare loss-of-function and missense variants in *SLC9A3R2* was strongly associated with a lower risk of hypertension.[11,14] *SLC9A3R2* encodes Na^+/H^+ exchange regulatory cofactor 2, which is a scaffolding protein interacting with Na^+/H^+ exchanger 3 in kidney and intestinal cells modulating Na^+ absorption and thence hypertension.

Adrenal and renin-angiotensin-aldosterone systems

Primary hyperaldosteronism accounts for ~10% of all forms of refractory hypertension and includes sporadic (adrenal adenoma and hyperplasia) and familial forms. There is a surfeit of monogenic mutations in genes of the adrenal steroid and renin-angiotensin-aldosterone pathways. However, only 4 loci have emerged in BP GWASs, namely, cytochrome P450 family 11 subfamily B member 1 (*CYP11B1/2*) (rs62525059 and rs6418), cytochrome P450 family 21 subfamily A member 2 (*CYP21A2*) (rs185819), angiotensinogen (rs699 and rs2493134), angiotensin-converting enzyme (rs4308).[9–14]

Congenital adrenal hyperplasia. Congenital adrenal hyperplasia types IV and V caused by loss-of-function mutations in the genes encoding mutations in 11β-hydroxylase (cytochrome P450 family 11 subfamily B member 1, *CYP11B1*) and 17α-hydroxylase (cytochrome P450 family 17 subfamily A member 1, *CYP17A1*), respectively, are the 2 subtypes of congenital adrenal hyperplasia known to cause monogenic hypertension. The loss of 11β-hydroxylase prevents the conversion of deoxycortisone and deoxycortisol into corticosterone and cortisol, respectively, resulting in high levels of deoxycorticosterone, deoxycortisol, and androgens, mainly androstenedione and dehydroepiandrosterone. Elevated deoxycortisol and deoxycorticosterone levels have mineralocorticoid function leading to hypertension and hypokalemia. Loss of 17α-hydroxylase blocks the production of cortisol and sex hormones and shunts all steroid production in the mineralocorticoid pathway and decreases the production of sex hormones. Antihypertensive therapy for both includes suppression of adrenocorticotropic hormone secretion with glucocorticoids to inhibit excess production of steroids and mineralocorticoids, along with spironolactone, amiloride, and calcium channel blockers.[45]

Familial hyperaldosteronism. Familial hyperaldosteronism type I, also known as glucocorticoid remediable aldosteronism, is an autosomal dominant syndrome due to increased adrenocorticotropic hormone production.[46] A chimeric gene formed by the fusion of the 5' regulatory sequence of 11β-hydroxylase (*CYP11B1*) with the distal coding sequences of aldosterone synthase (*CYP11B2*) leads to the ectopic expression of aldosterone synthase in the zona fasciculata, resulting in continuous aldosterone production under the control of adrenocorticotropic hormone.[47,48] In contrast, familial hyperaldosteronism type II is caused by germline mutations in the chloride voltage-gated channel 2 (*CLCN2*) gene (R172Q), resulting in increased aldosterone production triggered by cellular depolarization from increased Cl^- efflux and Ca^{2+} influx.[48,49] Familial hyperaldosteronism type III is associated with heterozygous germline mutations in the potassium inwardly rectifying channel subfamily J member 5 (*KCNJ5*) gene (T158A, G151R, and G151E) characterized by significant bilateral adrenal hyperplasia with increased aldosterone synthase and enzymes involved in cortisol synthesis.[48] Heterozygous germline mutations in the calcium voltage-gated channel subunit alpha1 H (*CACNA1H*) gene (M1549V and M1549I) causes familial hyperaldosteronism type IV characterized by increased Ca^{2+} influx and aldosterone production.

Somatic mutations causing primary aldosteronism. Somatic mutations in the K^+ channel Kir3.4 (*KCNJ5*), Ca^{2+} channel $Ca_v1.3$ (*CACNA1D*), α_1 subunit of Na^+/K^+ adenosine triphosphatase (ATPase Na^+/K^+ transporting subunit alpha 1, *ATP1A1*), plasma membrane Ca^{2+} transporting adenosine triphosphatase 3 (ATPase plasma membrane Ca^{2+} transporting 3, *ATP2B3*), Ca^{2+} channel $Ca_v3.2$ (calcium voltage-

gated channel subunit alpha1 H, *CACNA1H*), Cl^- channel ClC-2 (*CLCN2*), β-catenin (catenin beta 1, *CTNNB1*), and/or G-protein subunits α q/11 (*GNAQ/11*) are responsible for autonomous aldosterone-producing adenomas and usually present with unilateral adrenal tumors and hypertension. G151R and L168R mutations in *KCNJ5* account for >40% of aldosterone-producing adenomas. The identification of some of these mutations in aldosterone-producing (micro)nodules indicates a pathogenic continuum from a *de novo* mutation in a single cell through nodule to adenoma formation and a clinical continuum from the normal state through subclinical to overt primary aldosteronism.[48]

Adrenergic/noradrenergic pathways

Most genomic signals are monogenic mutations resulting in pheochromocytoma and paraganglioma tumors collectively referred to as pheochromocytoma paraganglioma (PPGL), which represent the second set of tumor syndromes associated with hypertension. Treatment options are summarized in Table 1. The only genetic associations from GWASs are SNPs near the adrenoceptor beta 1 (*ADRB1*) gene (rs740746, rs2782980, rs180912, and rs10787517).[9–14]

Monogenic. PPGLs originate from the chromaffin cells of the embryonic crest. Pheochromocytomas originate from the adrenal medulla, whereas paragangliomas are extra-adrenally located in the abdomen, thorax, pelvis, and neck. They cause hypertension through catecholamine hypersecretion except the head and neck paragangliomas, which arise from the parasympathetic ganglia. PPGLs are due to germline and/or somatic mutations in >20 genes clustered into 3 groups on the basis of the involvement of specific signaling pathways and clinical presentations (Figure 1).[50,51]

Pseudohypoxic signaling cluster. Mutations in genes encoding hypoxia-inducible factor 2α (*HIF2A*), succinate dehydrogenase subunits (*SDHA*, *SDHB*, *SDHC*, and *SDHD*), succinate dehydrogenase complex assembly factor 2 (*SDHAF2*), von Hippel-Lindau tumor suppressor (*VHL*), egl-9 prolyl hydroxylase 1 and 2 (*EGLN1*/2), fumarate hydratase (*FH*), malate dehydrogenase 2 (*MDH2*), and isocitrate dehydrogenase (*IDH*) activate the hypoxia-inducible factor signaling pathway without hypoxic stimulus and cause an increased production of vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor α, leading to cell growth, microvascular proliferation, increased tyrosine hydroxylase, and catecholamine overproduction. PPGLs in this cluster are almost all (except von Hippel-Lindau tumor suppressor) extra-adrenal, present with multiple and recurrent tumors that are aggressive and frequently metastatic, and have poor clinical outcomes.[50,51]

Kinase signaling cluster. Mutations in rearranged during transfection proto-oncogene (*RET*), Harvey rat sarcoma viral proto-oncogene (*H-RAS*), and Kirsten rat sarcoma viral proto-oncogene (*K-RAS*); neurofibromin 1 (*NF1*) tumor suppressor; transmembrane protein 127 (*TMEM127*); Myc-associated factor X (*MAX*); alpha thalassemia/mental retardation syndrome X-linked (*ATRX*); and cold shock domain containing E1 (*CSDE1*) dysregulate phosphatidylinositol-3′-kinase (PI3K)/mechanistic target of rapamycin kinase (mTOR) signaling and present as PPGLs, which are mainly adrenal and generally have good clinical outcomes (an exception is the ATRX mutation–related PPGL).[50,51]

Wnt signaling cluster. These pheochromocytomas are caused by somatic mutations in *CSDE1* and the mastermind like transcriptional coactivator 3 (*MAML3*) fusion genes (upstream binding transcription factor, RNA polymerase I [*UBTF*]-*MAML3*, and transcription factor 4 [*TCF4*]-*MAML3*). Wnt-altered tumors exhibit high expression of *CHGA*, a gene that encodes chromogranin A—a clinical marker of neuroendocrine tumors.[50,51]

Vascular

More recently, a growing list of monogenic disorders leading to hypertension have been associated with sites of action outside the kidney tubules.

Autosomal dominant hypertension with brachydactyly is a sodium-independent autosomal dominant syndrome caused by gain-of-function mutations in the phosphodiesterase 3A gene (*PDE3A*).[52] These mutations increase the protein kinase A–mediated phosphorylation of the phosphodiesterase 3A enzyme, resulting in enhanced cyclic adenosine monophosphate–hydrolytic affinity with decreased cellular cyclic adenosine monophosphate levels in vascular smooth muscle cells, allowing vascular smooth muscle cell proliferation and consequently hypertension. The associated brachydactyly stems from decreased cyclic adenosine monophosphate levels, which lower the levels of parathyroid hormone–related protein, a key moderator of chondrogenesis. Potential treatment options include phosphodiesterase 3A inhibitors that suppress the mutant isoforms or increasing cyclic guanosine monophosphate to indirectly inhibit the enzyme.[53]

Fibromuscular dysplasia is a multibed vascular disorder, predominantly seen in young or middle-aged women characterized by segmental, nonatherosclerotic, and noninflammatory disease of the musculature of arterial walls, leading to stenosis of small and medium-sized arteries. Nonrenal presentations include spontaneous aneurysms and dissections, subarachnoid hemorrhage, stroke, or mesenteric ischemia.[54] Although familial cases are rare, SNPs associated with fibromuscular dysplasia have been identified through GWAS: rs9349379 in the phosphatase and actin regulator 1 gene (*PHACTR1*),[55] rs11172113 in LDL receptor related protein 1 (*LRP1*), rs7301566 in LIM domain and actin binding 1 (*LIMA1*), and rs2681492 in ATPase plasma membrane Ca^{2+} transporting 1 (*ATP2B1*)—all known to be associated with traits related to BP.[56] *PHACTR1* may exert its effect on BP by inhibiting protein phosphatase 1, which subsequently leads[57] to limited endothelial nitric oxide synthase dephosphorylation and impaired endothelial nitric oxide synthesis. The *low-density lipoprotein* receptor protein 1, encoded by *LRP1*, has been shown to play a key role in extracellular and vascular smooth muscle cell remodeling,[58] with its deficiency in mice

Table 1 | BP monogenic genes and their specific treatment along with GWAS loci that are near gene targets for known BP-lowering medications (approved therapies appear in bold, and others with repurposing potential appear in italics)

Monogenic syndromes		
Trait	**Genes**	**Treatment**
Familial hyperaldosteronism I	*CYP11B1/CYP11B2*	**Dexamethasone, MRA**
Familial hyperaldosteronism II	*CLCN2*	**MRA**
Familial hyperaldosteronism III	*KCNJ5*	**MRA, bilateral adrenalectomy**
Familial hyperaldosteronism IV	*CACNA1H*	**MRA**
Primary aldosteronism, seizures, and neurologic abnormalities syndrome	*CACNA1D*	**MRA**, *calcium antagonists*
Autonomous aldosterone-producing adenomas	*KCNJ5*	**Verapamil** (G151R and L168R) **Amiloride** (L168R) *Roxithromycin*, *clarithromycin* (G151R and L168R) *Idremcinal*
Liddle syndrome	*SCNN1B*, *SCNN1G*	**Amiloride**, **triamterene**
Congenital adrenal hyperplasia	*CYP11B1*, *CYP17A1*	**Glucocorticoid supplementation**, **MRA**
Syndrome of apparent mineralocorticoid excess	*HSD11B2*	**MRA, ACTH suppression**
Geller syndrome	*NR3C2*	**Delivery of child in pregnant women.** **Avoid spironolactone**
Gordon syndrome	*WNK4*, *WNK1*, *KLHL3*, *CUL3*	**Thiazide diuretic**
Hypertension and brachydactyly syndrome	*PDE3A*	**Milrinone**, *cilostazol*, *arginine*, *riociguat*
PPGL (TCA)	*SDHA/B/C/D/AF2*, *FH*, *MDH2*, *IDH3B*, *GOT2*, *DLST*, *SLC25A11*, *IDH1/2*	*Ascorbic acid*, *temozolomide*, *olaparib*
PPGL (HIF1/2)	*EGLN1*, *VHL*, *EPAS1*	*Belzutifan*, *ipilimumab*, *nivolumab*, *permbrolizuman*, *sorafenib*, *sunitinib*, *axitinib*, *lenvatinib*, *bevacizumab*
PPGL (PI3K/AKT)	*RET*, *MERTK*, *MET*, *TMEM127*, *FGFR1*	Wortmannin, Torin1, *perifosine*, *everolimus*, *sunitinib*, *crizotinib*, *sorafenib*
PPGL (RAS/MAPK)	*NF1*, *HRAS*, *BRAF* *MAX* *CSDE1*, *UBTF-MAML3*	*Sorafenib*
PPGL	*Other agents*	*Temozolomide*, *histone deacetylase inhibitors*, *^{177}Lu-DOTATE*, *^{123}I-MIBG*
GWASs		
GWAS SNPs	**Nearest genes**	**Gene-drug interactions**
rs62525059, rs6418	*CYP11B1*, *CYP11B2*	**MRA**
rs4308	*ACE*	**ACEI**, omapatrilat
rs699, rs2493134	*AGT*	**ACEI**, omapatrilat
rs33996239	*ADORA1*	Adenosine, pentoxifylline
rs740746, rs2782980, rs180912, rs10787517	*ADRB1*	**β-Blockers**, amiodarone
rs369306257, rs3774442, rs3821843	*CACNA1D*	**Calcium channel blockers**, **MRA**
rs4373814, rs12258967, rs12243859, rs11014166	*CACNB2*	**Calcium channel blockers**, **MRA**
rs13333226	*UMOD*	**Loop diuretics**
rs202102042, rs12744757, rs12406089	*NPPA/B*	**Carvedilol**
rs78049276	*EDNRA*	Ambrisentan
rs9349379	*PHACTR1*	Ambrisentan
rs11608075, rs66682451	*GUCY1A2*	Riociguat
rs12656497,	*NPR3*	Nesiritide
rs73080726, rs141325069	*PDE3A*	Amrinone
rs66887589	*PDE5A*	Pentoxifylline, dipyridamole

ACE, angiotensin I converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ACTH, adrenocorticotropic hormone; *ADORA1*, adenosine A1 receptor; *ADRB1*, adrenoceptor beta 1; *AGT*, angiotensinogen; BP, blood pressure; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *CACNA1D*, calcium voltage-gated channel subunit alpha1 D; *CACNA1H*, calcium voltage-gated channel subunit alpha1 H; *CACNB2*, calcium voltage-gated channel auxiliary subunit beta 2; *CLCN2*, chloride voltage-gated channel 2; *CSDE1*, cold shock domain containing E1; *CUL3*, cullin 3; *CYP11B1*, cytochrome P450 family 11 subfamily B member 1; *CYP11B2*, cytochrome P450 family 11 subfamily B member 2; *CYP17A1*, cytochrome P450 family 17 subfamily A member 1; *DLST*, dihydrolipoamide S-succinyltransferase; *EDRNA*, endothelin receptor type A; *EGLN1*, Egl-9 family hypoxia inducible factor 1; *EPAS1*, endothelial PAS domain protein 1; *FGFR1*, fibroblast growth factor receptor 1; *FH*, fumarate hydratase; *GOT2*, glutamic-oxaloacetic transaminase 2; *GUCY1A2*, guanylate cyclase 1 soluble subunit alpha 2; GWAS, genome-wide association study; HIF1/2, hypoxia-inducible factor 1/2; *IDH1*, isocitrate dehydrogenase (NADP(+)) 1; *IDH2*, isocitrate dehydrogenase (NADP(+)) 2; *IDH3B*, isocitrate dehydrogenase (NAD(+)) 3 non-catalytic subunit beta; *HRAS*, HRas proto-oncogene, GTPase; *HSD11B2*, hydroxysteroid 11-beta dehydrogenase 2; ^{123}I-MIBG, iodine-131 meta-iodo-benzyl-guanidine; *KCNJ5*, potassium inwardly rectifying channel subfamily J member 5; *KLHL3*, kelch like family member 3; ^{177}Lu-DOTATE, lutetium oxodotreotide; *MAML3*, mastermind like transcriptional coactivator 3; *MAX*, MYC associated factor X; *MDH2*, malate dehydrogenase 2; *MERTK*, MER proto-oncogene, tyrosine kinase; *MET*, MET proto-oncogene, receptor tyrosine kinase; MRA, mineralocorticoid antagonist; *NF1*, neurofibromin 1; *NPPA*, natriuretic peptide A; *NPPB*, natriuretic peptide B; *NPR3*, natriuretic peptide receptor 3; *NR3C2*, nuclear receptor subfamily 3 group C member 2; *PDE3A*, phosphodiesterase 3A; *PDE5A*, phosphodiesterase 5A; *PHACTR1*, phosphatase and actin regulator 1; PI3K/AKT, phosphoinositide-3-kinase–protein kinase B/serine/threonine-protein kinase; PPGL, pheochromocytoma paraganglioma; RAS/MAPK, renin-angiotensin system/mitogen-activated protein kinase; SNP, single-nucleotide polymorphism; *RET*, Ret proto-oncogene; *SCNN1B*, sodium channel epithelial 1 subunit beta; *SCNN1G*, sodium channel epithelial 1 subunit gamma; *SDHA*, succinate dehydrogenase complex flavoprotein subunit A; *SDHAF2*, succinate dehydrogenase complex assembly factor 2; *SDHB*, succinate dehydrogenase complex iron sulfur subunit B; *SDHC*, succinate dehydrogenase complex subunit C; *SDHD*, succinate dehydrogenase complex subunit D; *SLC25A11*, solute carrier family 25 member 11; TCA, tricarboxylic acid; *TMEM127*, transmembrane protein 127; *UBTF*, upstream binding transcription factor; *UMOD*, uromodulin; *VHL*, Von Hippel-Lindau tumor suppressor; *WNK1*, WNK lysine deficient protein kinase 1; *WNK4*, WNK lysine deficient protein kinase 4.

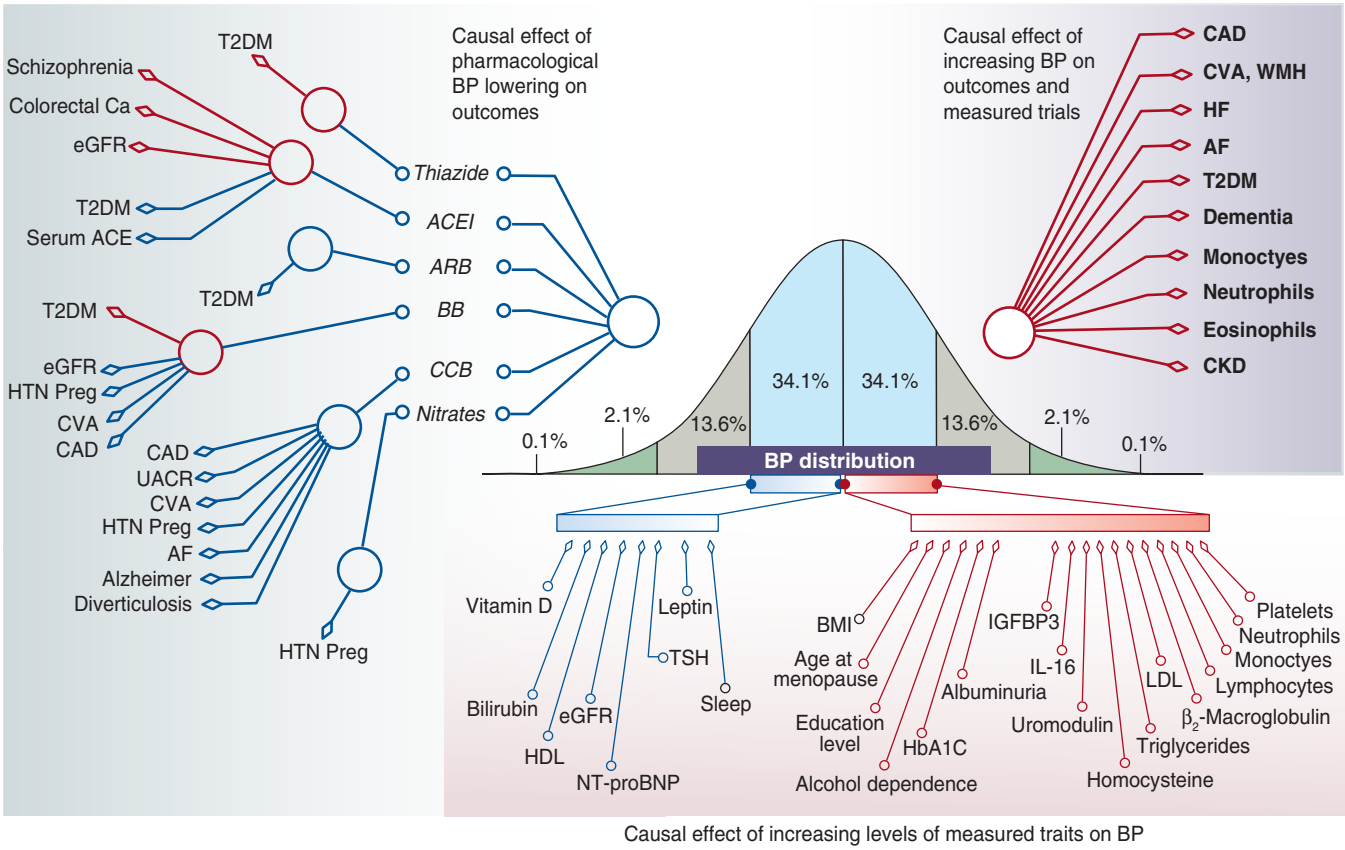

Figure 2 | Causal relationships between genetically determined blood pressure (BP) and a range of traits from Mendelian randomization studies. Increasing BP based on genetic proxies from genome-wide association studies shows a causal effect on the increasing risk of cardiovascular outcomes and phenotypes such as monocytes, neutrophils, and eosinophils (top right). The red arrows denote higher risk of outcomes or increased levels of measured phenotypes in response to BP change. Genetic proxies for the drug effect are used to determine the effect of pharmacological BP lowering on outcomes (left panel). The red arrows denote higher risk of outcomes in response to genetically predicted BP decrease as a marker of drug effect. The panel below the x-axis shows the causal effect of genetically predicted higher levels of a range of measured risk factors on BP (increasing BP: red arrows; decreasing BP: blue arrows). These causal effects represent lifelong influence on the trait, and hence the magnitude of BP effects is small. ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, β-blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HDL, high-density lipoprotein; HF, heart failure; HTN Preg, hypertensive disorders of pregnancy; IGFBP3, insulin-like growth factor binding protein 3; IL-16, interleukin-16; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro–brain natriuretic peptide; T2DM, type 2 diabetes mellitus; TSH, thyroid stimulating hormone; UACR, urine albumin-to-creatinine ratio; WMH, white matter hyperintensity.

leading to vasoconstriction.[59] The *ATP2B1* gene encodes an adenosine triphosphate–dependent Ca^{2+} channel critical for vascular contractility and vasodilatation, and the absence of this gene results in hypertension, increased cellular Ca^{2+}, and a robust BP response to calcium channel blockers.[60,61]

Phenome-wide association studies show that the *PHACTR1* SNP rs9349379 is implicated in 5 diseases with vascular components: CAD, migraine, cervical artery dissection, fibromuscular dysplasia, and hypertension. This SNP has been shown to be a distal regulator of *EDN1*, which encodes endothelin-1 (ET-1),[62] with the G allele associated with higher *EDN1* expression, higher ET-1, and lower risk of all diseases mentioned above except CAD. ET-1 can cause both vasoconstriction and hypertension (paracrine) and vasodilation (autocrine) via its actions on vascular smooth muscle cell ET receptor subtypes A and B, respectively. ET-1 induces angiotensin II, and the effects of ET-1 and angiotensin II on vascular reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, particularly reduced nicotinamide adenine dinucleotide phosphate oxidase 1, reduced nicotinamide adenine dinucleotide phosphate oxidase 2, and reduced nicotinamide adenine dinucleotide phosphate oxidase 5, result in sustained BP elevations.[63] ET-1 results in vasodilatation via its action on ET receptor subtype B by inducing nitric oxide and prostacyclin release.[64] Phenome-wide association studies are likely explained by the potent vasoconstrictive effect of ET-1 on the coronary circulation, which is devoid of ET receptor subtype B. Thus,

unopposed vasoconstrictive ET-1 action on the coronary vasculature is atherogenic and via its action on ET receptor subtype A results in coronary vasospasms.[65]

Outcomes

The causal relationships between high BP and cardiovascular disease (CVD) and non-CVD outcomes have been the subject of MR studies (Figure 2). Genetically predicted systolic BP (SBP) was causally associated with hypertension-related CVD such as CAD, stroke, heart failure, atrial fibrillation, and also a range of additional CVDs including aortic aneurysm, aortic stenosis, dilated cardiomyopathy, endocarditis, peripheral vascular disease, and rheumatic heart disease as well as negatively associated with venous thromboembolism.[66] The authors extrapolated these results from the UK Biobank to estimate an overall 17%, 31%, and 56% decrease in morbidity for a 5, 10, and 23 mm Hg decrease in SBP at a population level.[66] MR studies showed no effect of genetically determined BP and eGFR[44] while affirming a causal role of BP in other cardiovascular outcomes.[66–71] In contrast, MR studies using eGFR as an exposure showed that lower genetically predicted eGFR is associated with higher BP.[72] Although SBP and DBP are correlated traits, SBP alone is included in CVD risk prediction. Epidemiologically, DBP is more closely associated with coronary heart disease development in the young whereas in those older than 60 years SBP is more predictive. BP GWAS SNPs predominantly show association with both SBP and DBP, but a minority of SNPs show exclusive association with just 1 trait. An MR study[73] used 3 sets of BP GWAS SNPs—242 independent SNPs associated with both SBP and DBP, 120 SBP-exclusive SNPs, and 80 DBP-exclusive SNPs—to unravel the distinct effects of SBP and DBP on hypertension outcomes. This study showed that SBP is the causal driver for CAD, stroke, and ischemic stroke while it is DBP for small vessel stroke. Furthermore, SBP is exclusively associated with heart failure, atrial fibrillation, and type 2 diabetes mellitus.[73]

Pharmacogenomics

Genetic variants associated with disease traits have pointed to effective drug targets.[74] Examples include *HMGCR*, which is associated with serum cholesterol levels and is the target for statins[75]; 27 drug target genes of approved rheumatoid arthritis drugs demonstrated a significant overlap with 98 biological rheumatoid arthritis risk genes from GWASs[76]; SNPs in *NR3C2* is associated with moderately increased albuminuria, and an NR3C2 antagonist, finerenone, is now approved for the treatment of chronic kidney disease.[77] Missense variants in the tyrosine kinase 2 gene (*TYK2*) have been associated with systemic lupus erythematosus, and evidence of its interaction with the interferon α/β receptor subunit 1 led to the development of the interferon α/β receptor subunit 1 antagonist anifrolumab for the treatment of systemic lupus erythematosus.[78] This demonstrates the potential of using indirect evidence from genetic association to drive drug discovery. By extension, the growing wealth of GWAS data on BP and hypertension should inform the selection of the best targets with a measurable impact on the successful development of new drugs (Table 1).

Another valuable use of GWAS results is to use gene variants corresponding to the targets of common pharmacological agents for hypertension as a proxy for treatment effects in MR (Figure 2). This allows establishing any relationship with adverse events and offers an insight into drug repurposing.[79] Such studies have shown that calcium channel blockers have a protective effect on stroke, atrial fibrillation, CAD, and diverticulosis[79]; β-blockers and thiazide diuretics increase the risk of T2DM[79]; angiotensin-converting enzyme inhibitors may have an adverse impact on schizophrenia risk[80] and colorectal cancer[81] but reduce the risk of type 2 diabetes mellitus[79]; and the beneficial effect of antihypertensive drugs on Alzheimer disease risk is due to their effect on SBP.[82]

RNA interference is a natural mechanism by which short strands of RNA, such as small, interfering RNA, cause targeted gene suppression.[83] From a hypertension perspective, zilebesiran, an RNA interference therapeutic targeting hepatic angiotensinogen synthesis, is currently in a phase 2 trial (ClinicalTrials.gov identifier NCT05103332) after demonstrating sustained serum angiotensinogen and BP reductions through 6 months in a phase 1 trial.

Polygenic risk scores

GWASs have shown that BP is a polygenic trait influenced by hundreds of DNA variants each of which contributes small-to-moderate effects, and the aggregate effect of these represent the polygenic hypertension risk.[84] A BP genetic risk score accounted for ∼13 mm Hg in variation of BP. However, the BP genetic risk score failed to show a clear predictive link with eGFR,[44] suggesting that BP is not a strong causal risk factor for kidney failure and this is supported by MR studies as noted above. A BP polygenic risk score (PRS) in the top 2.5% conferred a 2.3-fold risk of hypertension and earlier hypertension onset by 10 years and incident CVD.[44,85] PRSs are set at conception and can be used earlier in life than lifestyle, age-related, or other nongenetic risk factors. However, PRSs have limited predictive accuracy, primarily because genetic factors are not the sole risk factors for hypertension and the risk scores contain information only from SNPs that represent a fraction of the genetic contribution to the trait. A number of potential applications are envisaged for PRSs, including cost-effective primary prevention and precision medicine.[84] A possible application of PRSs in hypertension would be in the early stages of the disease to confirm the diagnosis and prioritize patients for more intensive investigation and follow-up or initiation of treatment.

Conclusions

The opportunities for leveraging genomics in hypertension prediction and management have vastly expanded over the last 15 years. Although challenges remain, parallel advances in gene silencing and polygenic risk scores along with growing recognition of genetic inequity indicate areas where the next

wave of application research is expected. Beyond sequence variations, the dark matter of common disease genomics representing structural and epigenetic variations and gene-environmental interactions are now tractable by advances in high-throughput sequencing and omic technologies.

DISCLOSURE

PSG has served as a consultant for Otsuka Inc and Dialysis Clinic Inc. All the other authors declared no competing interests.

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REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet*. 2017;389:37–55.
2. GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1345–1422.
3. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
4. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014;383:1899–1911.
5. Evans JG, Rose G. Hypertension. *Br Med Bull*. 1971;27:37–42.
6. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957–967.
7. Padmanabhan S, Dominiczak AF. Genomics of hypertension: the road to precision medicine. *Nat Rev Cardiol*. 2021;18:235–250.
8. Zanchetti A. Platt versus Pickering: an episode in recent medical history. In: Swales JD, ed. *An essay review*. 30. Med Hist; 1986:94–96.
9. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell*. 2001;104:545–556.
10. Pazoki R, Dehghan A, Evangelou E, et al. Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events. *Circulation*. 2018;137:653–661.
11. Giri A, Hellwege JN, Keaton JM, et al. Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. *Nat Genet*. 2019;51:51–62.
12. Surendran P, Feofanova EV, Lahrouchi N, et al. Discovery of rare variants associated with blood pressure regulation through meta-analysis of 1.3 million individuals. *Nat Genet*. 2020;52:1314–1332.
13. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet*. 2021;53:1415–1424.
14. Backman JD, Li AH, Marcketta A, et al. Exome sequencing and analysis of 454,787 UK Biobank participants. *Nature*. 2021;599:628–634.
15. Adrogue HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med*. 2007;356:1966–1978.
16. Mansfield TA, Simon DB, Farfel Z, et al. Multilocus linkage of familial hyperkalaemia and hypertension, pseudohypoaldosteronism type II, to chromosomes 1q31-42 and 17p11-q21. *Nat Genet*. 1997;16:202–205.
17. Louis-Dit-Picard H, Barc J, Trujillano D, et al. *KLHL3* mutations cause familial hyperkalemic hypertension by impairing ion transport in the distal nephron. *Nat Genet*. 2012;44:456–460. S451–S453.
18. Glover M, Ware JS, Henry A, et al. Detection of mutations in KLHL3 and CUL3 in families with FHHt (familial hyperkalaemic hypertension or Gordon's syndrome). *Clin Sci (Lond)*. 2014;126:721–726.
19. Mabillard H, Sayer JA. The molecular genetics of Gordon syndrome. *Genes (Basel)*. 2019;10:986.
20. Hansson JH, Nelson-Williams C, Suzuki H, et al. Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. *Nat Genet*. 1995;11:76–82.
21. Hiltunen TP, Hannila-Handelberg T, Petajaniemi N, et al. Liddle's syndrome associated with a point mutation in the extracellular domain of the epithelial sodium channel gamma subunit. *J Hypertens*. 2002;20:2383–2390.
22. Abriel H, Loffing J, Rebhun JF, et al. Defective regulation of the epithelial Na^+ channel by Nedd4 in Liddle's syndrome. *J Clin Invest*. 1999;103:667–673.
23. Ulick S, Levine LS, Gunczler P, et al. A syndrome of apparent mineralocorticoid excess associated with defects in the peripheral metabolism of cortisol. *J Clin Endocrinol Metab*. 1979;49:757–764.
24. Morineau G, Sulmont V, Salomon R, et al. Apparent mineralocorticoid excess: report of six new cases and extensive personal experience. *J Am Soc Nephrol*. 2006;17:3176–3184.
25. Ceccato F, Mantero F. Monogenic forms of hypertension. *Endocrinol Metab Clin North Am*. 2019;48:795–810.
26. Geller DS, Farhi A, Pinkerton N, et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science*. 2000;289:119–123.
27. Konrad M, Nijenhuis T, Ariceta G, et al. Diagnosis and management of Bartter syndrome: executive summary of the consensus and recommendations from the European Rare Kidney Disease Reference Network Working Group for Tubular Disorders. *Kidney Int*. 2021;99:324–335.
28. Birkenhager R, Otto E, Schurmann MJ, et al. Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. *Nat Genet*. 2001;29:310–314.
29. Janssen AG, Scholl U, Domeyer C, et al. Disease-causing dysfunctions of barttin in Bartter syndrome type IV. *J Am Soc Nephrol*. 2009;20:145–153.
30. Nozu K, Inagaki T, Fu XJ, et al. Molecular analysis of digenic inheritance in Bartter syndrome with sensorineural deafness. *J Med Genet*. 2008;45:182–186.
31. Laghmani K, Beck BB, Yang SS, et al. Polyhydramnios, transient antenatal Bartter's syndrome, and *MAGED2* mutations. *N Engl J Med*. 2016;374:1853–1863.
32. Blanchard A, Bockenhauer D, Bolignano D, et al. Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2017;91:24–33.
33. Vargas-Poussou R, Dahan K, Kahila D, et al. Spectrum of mutations in Gitelman syndrome. *J Am Soc Nephrol*. 2011;22:693–703.
34. Padmanabhan S, Melander O, Johnson T, et al. Genome-wide association study of blood pressure extremes identifies variant near *UMOD* associated with hypertension. *PLoS Genet*. 2010;6:e1001177.
35. Devuyst O, Dahan K, Pirson Y. Tamm-Horsfall protein or uromodulin: new ideas about an old molecule. *Nephrol Dial Transplant*. 2005;20:1290–1294.
36. Graham LA, Padmanabhan S, Fraser NJ, et al. Validation of uromodulin as a candidate gene for human essential hypertension. *Hypertension*. 2014;63:551–558.
37. Trudu M, Janas S, Lanzani C, et al. Common noncoding *UMOD* gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat Med*. 2013;19:1655–1660.
38. Pruijm M, Ponte B, Ackermann D, et al. Associations of urinary uromodulin with clinical characteristics and markers of tubular function in the general population. *Clin J Am Soc Nephrol*. 2016;11:70–80.
39. Tokonami N, Takata T, Beyeler J, et al. Uromodulin is expressed in the distal convoluted tubule, where it is critical for regulation of the sodium chloride cotransporter NCC. *Kidney Int*. 2018;94:701–715.
40. McCallum L, Brooksbank K, McConnachie A, et al. Rationale and design of the genotype-blinded trial of torasemide for the treatment of hypertension (BHF UMOD). *Am J Hypertens*. 2021;34:92–99.
41. Reznichenko A, Boger CA, Snieder H, et al. *UMOD* as a susceptibility gene for end-stage renal disease. *BMC Med Genet*. 2012;13:78.
42. Abdel-Hady Algharably E, Beige J, Kreutz R, et al. Effect of *UMOD* genotype on long-term graft survival after kidney transplantation in patients treated with cyclosporine-based therapy. *Pharmacogenomics J*. 2018;18:227–231.

43. Ponte B, Sadler MC, Olinger E, et al. Mendelian randomization to assess causality between uromodulin, blood pressure and chronic kidney disease. *Kidney Int*. 2021;100:1282–1291.
44. Evangelou E, Warren HR, Mosen-Ansorena D, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet*. 2018;50:1412–1425.
45. Raina R, Krishnappa V, Das A, et al. Overview of monogenic or Mendelian forms of hypertension. *Front Pediatr*. 2019;7:263.
46. Stowasser M, Bachmann AW, Huggard PR, et al. Treatment of familial hyperaldosteronism type I: only partial suppression of adrenocorticotropin required to correct hypertension. *J Clin Endocrinol Metab*. 2000;85:3313–3318.
47. Pascoe L, Curnow KM, Slutsker L, et al. Glucocorticoid-suppressible hyperaldosteronism results from hybrid genes created by unequal crossovers between *CYP11B1* and *CYP11B2*. *Proc Natl Acad Sci U S A*. 1992;89:8327–8331.
48. Scholl UI. Genetics of primary aldosteronism. *Hypertension*. 2022;79:887–897.
49. Stowasser M, Wolley M, Wu A, et al. Pathogenesis of familial hyperaldosteronism type II: new concepts involving anion channels. *Curr Hypertens Rep*. 2019;21:31.
50. Wachtel H, Fishbein L. Genetics of pheochromocytoma and paraganglioma. *Curr Opin Endocrinol Diabetes Obes*. 2021;28:283–290.
51. Jochmanova I, Pacak K. Genomic landscape of pheochromocytoma and paraganglioma. *Trends Cancer*. 2018;4:6–9.
52. Toka HR, Bahring S, Chitayat D, et al. Families with autosomal dominant brachydactyly type E, short stature, and severe hypertension. *Ann Intern Med*. 1998;129:204–208.
53. Toka O, Tank J, Schachterle C, et al. Clinical effects of phosphodiesterase 3A mutations in inherited hypertension with brachydactyly. *Hypertension*. 2015;66:800–808.
54. Plouin PF, Perdu J, La Batide-Alanore A, et al. Fibromuscular dysplasia. *Orphanet J Rare Dis*. 2007;2:28.
55. Kiando SR, Tucker NR, Castro-Vega LJ, et al. *PHACTR1* is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. *PLoS Genet*. 2016;12:e1006367.
56. Georges A, Yang ML, Berrandou TE, et al. Genetic investigation of fibromuscular dysplasia identifies risk loci and shared genetics with common cardiovascular diseases. *Nat Commun*. 2021;12:6031.
57. Mount PF, Kemp BE, Power DA. Regulation of endothelial and myocardial NO synthesis by multi-site eNOS phosphorylation. *J Mol Cell Cardiol*. 2007;42:271–279.
58. Bres EE, Faissner A. Low density receptor-related protein 1 interactions with the extracellular matrix: more than meets the eye. *Front Cell Dev Biol*. 2019;7:31.
59. Au DT, Ying Z, Hernandez-Ochoa EO, et al. LRP1 (low-density lipoprotein receptor-related protein 1) regulates smooth muscle contractility by modulating Ca^{2+} signaling and expression of cytoskeleton-related proteins. *Arterioscler Thromb Vasc Biol*. 2018;38:2651–2664.
60. Kobayashi Y, Hirawa N, Tabara Y, et al. Mice lacking hypertension candidate gene *ATP2B1* in vascular smooth muscle cells show significant blood pressure elevation. *Hypertension*. 2012;59:854–860.
61. Okuyama Y, Hirawa N, Fujita M, et al. The effects of anti-hypertensive drugs and the mechanism of hypertension in vascular smooth muscle cell-specific ATP2B1 knockout mice. *Hypertens Res*. 2018;41:80–87.
62. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA*. 2017;317:165–182.
63. Dong F, Zhang X, Ren J. Leptin regulates cardiomyocyte contractile function through endothelin-1 receptor-NADPH oxidase pathway. *Hypertension*. 2006;47:222–229.
64. Hirata Y, Emori T, Eguchi S, et al. Endothelin receptor subtype B mediates synthesis of nitric oxide by cultured bovine endothelial cells. *J Clin Invest*. 1993;91:1367–1373.
65. Bohm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet*. 2020;395:1444–1451.
66. Higgins H, Mason AM, Larsson SC, et al. Estimating the population benefits of blood pressure lowering: a wide-angled Mendelian randomization study in UK Biobank. *J Am Heart Assoc*. 2021;10:e021098.
67. Georgakis MK, Gill D, Webb AJS, et al. Genetically determined blood pressure, antihypertensive drug classes, and risk of stroke subtypes. *Neurology*. 2020;95:e353–e361.
68. Malik R, Georgakis MK, Vujkovic M, et al. Relationship between blood pressure and incident cardiovascular disease: linear and nonlinear Mendelian randomization analyses. *Hypertension*. 2021;77:2004–2013.
69. Nazarzadeh M, Pinho-Gomes AC, Bidel Z, et al. Genetic susceptibility, elevated blood pressure, and risk of atrial fibrillation: a Mendelian randomization study. *Genome Med*. 2021;13:38.
70. Sproviero W, Winchester L, Newby D, et al. High blood pressure and risk of dementia: a two-sample Mendelian randomization study in the UK Biobank. *Biol Psychiatry*. 2021;89:817–824.
71. Wan EYF, Fung WT, Schooling CM, et al. Blood pressure and risk of cardiovascular disease in UK Biobank: a Mendelian randomization study. *Hypertension*. 2021;77:367–375.
72. Yu Z, Coresh J, Qi G, et al. A bidirectional Mendelian randomization study supports causal effects of kidney function on blood pressure. *Kidney Int*. 2020;98:708–716.
73. Le NN, Tran TQB, Lip S, et al. Unravelling the distinct effects of systolic and diastolic blood pressure using Mendelian randomisation. *Genes*. 2022;13:1226.
74. Nelson MR, Tipney H, Painter JL, et al. The support of human genetic evidence for approved drug indications. *Nat Genet*. 2015;47:856–860.
75. Kathiresan S, Willer CJ, Peloso GM, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nat Genet*. 2009;41:56–65.
76. Okada Y, Wu D, Trynka G, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*. 2014;506:376–381.
77. Teumer A, Li Y, Ghasemi S, et al. Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria. *Nat Commun*. 2019;10:4130.
78. Diogo D, Bastarache L, Liao KP, et al. *TYK2* protein-coding variants protect against rheumatoid arthritis and autoimmunity, with no evidence of major pleiotropic effects on non-autoimmune complex traits. *PLoS One*. 2015;10:e0122271.
79. Gill D, Georgakis MK, Koskeridis F, et al. Use of genetic variants related to antihypertensive drugs to inform on efficacy and side effects. *Circulation*. 2019;140:270–279.
80. Chauquet S, Zhu Z, O'Donovan MC, et al. Association of antihypertensive drug target genes with psychiatric disorders: a Mendelian randomization study. *JAMA Psychiatry*. 2021;78:623–631.
81. Yarmolinsky J, Diez-Obrero V, Richardson TG, et al. Genetically proxied therapeutic inhibition of antihypertensive drug targets and risk of common cancers: a Mendelian randomization analysis. *PLoS Med*. 2022;19:e1003897.
82. Walker VM, Kehoe PG, Martin RM, et al. Repurposing antihypertensive drugs for the prevention of Alzheimer's disease: a Mendelian randomization study. *Int J Epidemiol*. 2020;49:1132–1140.
83. Wittrup A, Lieberman J. Knocking down disease: a progress report on siRNA therapeutics. *Nat Rev Genet*. 2015;16:543–552.
84. Polygenic Risk Score Task Force of the International Common Disease Alliance. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. *Nat Med*. 2021;27:1876–1884.
85. Vaura F, Kauko A, Suvila K, et al. Polygenic risk scores predict hypertension onset and cardiovascular risk. *Hypertension*. 2021;77:1119–1127.