

# The genetics of hypertension

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## Abstract

Hypertension, or persistently elevated blood pressure, affects about one third of the adult population worldwide and causes approximately 8.5 million deaths annually. Family studies have demonstrated that blood pressure shows substantial heritability, suggesting that genetic factors contribute to hypertension. Linkage studies and next-generation sequencing efforts have identified several variants with large effect sizes that cause rare monogenic hypertension syndromes. These syndromes often present with early onset and typically affect adrenal and renal regulation of salt reabsorption. In addition, somatic (tumour-specific) mutations have been identified in hormone-producing tumours that cause hypertension (phaeochromocytomas, aldosterone-producing adenomas, cortisol-producing adenomas, pituitary adenomas, reninomas). However, most cases of hypertension are polygenic. Large genome-wide association studies have identified many variants with small effect sizes that add to our understanding of blood pressure as a complex trait. Epigenetic mechanisms also influence gene expression and contribute to blood-pressure alterations. Several proteins that are affected by Mendelian diseases are targets of existing antihypertensive drugs and other such proteins may be good candidates for future drug development.

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## Key points

- Blood pressure is determined by the interplay of genetic factors — including rare variants with large effect sizes that cause monogenic hypertension syndromes and common variants with small effect sizes that contribute to polygenic cases of hypertension — and non-genetic factors such as diet and the microbiome; estimates suggest that the heritability of blood pressure is 30–50%.
- Mendelian diseases are rare causes of hypertension; most monogenic causes of hypertension affect renal salt handling and its regulation, although monogenic forms that affect the vasculature have also been identified.
- Somatic variants that cause hypertension have been identified in hormone-producing tumours of the adrenal gland, pituitary gland, extra-adrenal sympathetic or parasympathetic ganglia and renin-secreting cells of the kidney; some of these variants overlap with Mendelian disease genes.
- Common variants that are associated with blood pressure in genome-wide association studies implicate the kidney, adrenal gland and vasculature in the development of hypertension; progress has been made in identifying the causal roles of these variants.
- Epigenetic mechanisms can also influence gene expression and contribute to the development of hypertension in humans and animal models.
- Monogenic disease genes and hypertension-associated variants identified in GWAS provide important insights into the pathophysiology of hypertension and are potential targets for the development of novel antihypertensive agents.

## Introduction

Hypertension (persistently elevated systemic blood pressure) is typically defined as systolic blood pressure (SBP)  $\geq 140$  mmHg and/or diastolic blood pressure (DBP)  $\geq 90$  mmHg<sup>1,2</sup>. The American Heart Association/American College of Cardiology guidelines use a more stringent threshold of  $\geq 130/80$  mmHg<sup>3</sup>. In 2019, approximately 1.28 billion people aged 30–79 years had hypertension worldwide (around one third of this age group)<sup>4</sup>. Notably, only 47% of women and 38% of men with hypertension were treated; half of whom achieved blood pressure control. High SBP accounted for 10.8 million deaths and was the leading risk factor for premature death in 2019 (ref. 5), primarily owing to ischaemic heart disease, haemorrhagic or ischaemic stroke, other cardiovascular diseases or chronic kidney disease<sup>6</sup>. Generally, blood pressure readings  $>115/75$  mmHg are associated with increasing mortality from cardiovascular disease. People with 2 mmHg lower systolic blood pressure throughout middle age have a 10% lower stroke mortality and 7% lower mortality from ischaemic heart disease or other vascular causes<sup>7</sup>.

The underlying causes of primary hypertension are unknown, whereas secondary forms are due to known disorders, such as excessive hormone production. Factors that contribute to hypertension include a suboptimal diet with excessive sodium intake and/or low potassium intake, low physical activity and alcohol consumption<sup>8,9</sup>;

the microbiome may also affect blood pressure<sup>10</sup>. In addition, genetic factors are involved in the development of hypertension. Twin studies of blood pressure found stronger correlations of blood pressure between monozygotic twins than same-sex dizygotic twins or siblings, suggesting that blood pressure is a heritable trait (reviewed in Luft<sup>11</sup> and Padmanabhan et al.<sup>12</sup>). Based on these studies, the heritability (phenotypic variation that is due to genetic variation) of blood pressure was estimated to be 30–50%<sup>12</sup>.

In most cases, hypertension is a polygenic disorder. Unlike monogenic disorders, polygenic disorders do not follow simple patterns of inheritance (such as autosomal-dominant or -recessive). Instead, each individual variant has a small (either detrimental or protective) effect on the disease, and variants at many loci contribute to the overall disease risk in conjunction with environmental factors, such as lifestyle, geographic location or socio-economic status<sup>8</sup>. The top versus bottom tertile of healthy lifestyle is associated with a 4–5 mmHg lower blood pressure regardless of genetic risks<sup>13</sup>. Rarely, hypertension can be inherited as a monogenic disorder.

Genetic mechanisms in hypertension affect various organs, including the adrenal gland, which produces steroid hormones that regulate renal salt homeostasis and catecholamines that increase blood pressure; the kidney, which reabsorbs salt and thereby governs volume homeostasis and blood pressure; the vasculature, which regulates blood pressure by controlling vascular resistance; and the heart, which generates the force required to pump blood through the circulatory system (Fig. 1).

In this Review, we outline the genetic causes and pathophysiology of monogenic syndromes associated with hypertension, give a brief overview of the monogenic form of hypotension and discuss somatic mutations in tumours that are associated with hypertension. We then discuss how common and rare variants contribute to hypertension at the population level. Given the large number of genetic variants that are associated with blood pressure, we limit our discussion of individual loci to those with very strong signals and known pathophysiology. Many of the identified genes and pathways converge on the adrenal gland and the kidney as regulators of blood pressure. Some of these genes are targeted by antihypertensive drugs and others may be potential drug targets.

## Monogenic forms of hypertension that affect adrenal steroids and their receptors

In response to elevated angiotensin II levels (owing to volume depletion or low blood pressure) and/or hyperkalaemia, the outermost zone of the adrenal cortex, known as the zona glomerulosa, produces the steroid hormone aldosterone, which binds to the mineralocorticoid receptor in target cells. In the kidney, this mechanism leads to increased salt reabsorption, which raises blood pressure, as well as potassium and proton secretion. Several diseases affect the balance of these mechanisms, resulting in hypertension (Fig. 2; Supplementary Table 1). Many of these diseases have been investigated in mouse models (Supplementary Table 2). The common underlying initial mechanism of these forms of hypertension is increased intracellular volume.

### Familial hyperaldosteronism

Primary aldosteronism denotes an excessive aldosterone production from cells of the zona glomerulosa of the adrenal cortex. In familial hyperaldosteronism, it is inherited as an autosomal-dominant disorder or caused by de novo heterozygous variants<sup>14</sup>. Primary aldosteronism results in high blood pressure and is associated with higher cardiovascular risk than primary hypertension<sup>15</sup>. This disorder is diagnosed

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based on an elevated aldosterone to renin ratio and confirmatory testing<sup>14,15</sup> (Box 1).

Familial hyperaldosteronism I (FH-I)<sup>16</sup> is characterized by a decrease in blood pressure and aldosterone levels upon glucocorticoid administration and the presence of the 'hybrid steroids', 18-hydroxy-cortisol and 18-oxocortisol<sup>17</sup>. This disorder results from unequal crossing-over, which fuses the promoter of *CYP11B1*, which encodes 11 $\beta$ -hydroxylase, to the coding sequence of *CYP11B2*, which encodes aldosterone synthase. 11 $\beta$ -hydroxylase is involved in cortisol production under the control of adrenocorticotropic hormone (ACTH), whereas aldosterone synthase controls mineralocorticoid production from the zona glomerulosa. The fusion gene causes ACTH-dependent mineralocorticoid production in the zona fasciculata, where enzymes for glucocorticoid production are present, resulting in the production of hybrid steroids. Glucocorticoids suppress ACTH release from the pituitary gland and thereby reduce mineralocorticoid production and blood pressure. Mineralocorticoid antagonists are also effective antihypertensive therapies<sup>14</sup>.

Familial hyperaldosteronism II (FH-II) is caused by mutations in *CLCN2*, which encodes the voltage-gated chloride channel ClC-2 (refs. 18,19). These mutations increase anion flux, which causes depolarization of glomerulosa cells (owing to their high intracellular chloride concentration), voltage-gated calcium influx and activation of pathways leading to aldosterone production<sup>18,20</sup>. Patients with FH-II have early-onset hyperaldosteronism and sometimes hypokalaemia. They typically respond to mineralocorticoid receptor antagonists (MRAs).

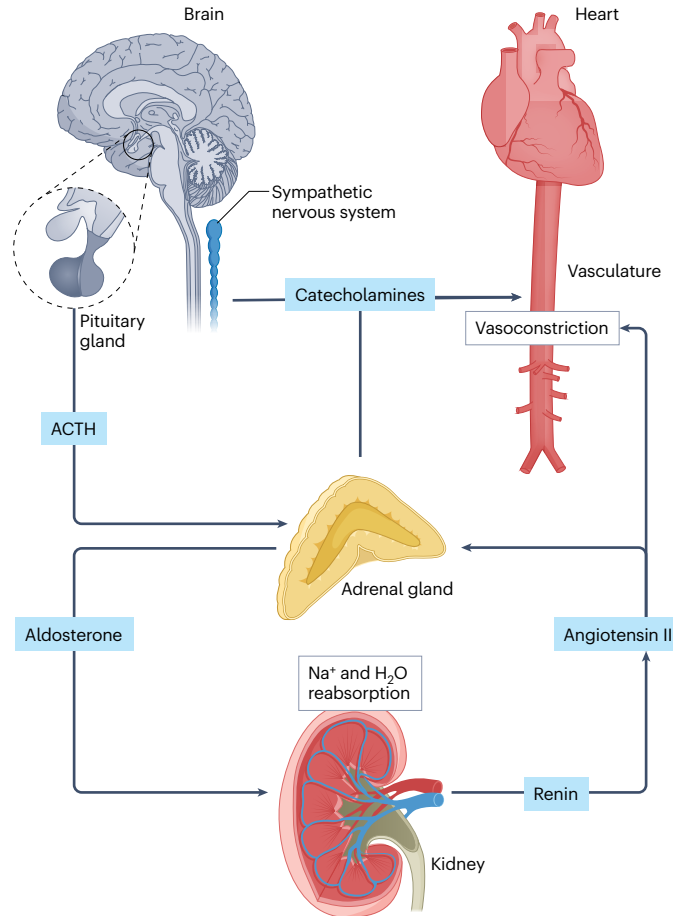
Familial hyperaldosteronism III (FH-III) occurs because of mutations in *KCNJ5*, which encodes the inward rectifier potassium channel Kir3.4. These mutations reduce the selectivity of the channel for potassium ions, enabling passage of sodium, which leads to cellular depolarization and calcium influx similar to that seen in FH-II<sup>21</sup>. Patients with T158A, G151R, I157S and E145Q mutations tend to present early with severe hypertension, often with adrenal hyperplasia<sup>14,21</sup>. If MRAs are not effective, bilateral adrenalectomies are performed. Patients with the G151E and Y152C mutations have milder presentations<sup>14,22</sup> and respond to MRAs.

Familial hyperaldosteronism IV (FH-IV) results from mutations in *CACNA1H*, which encodes the voltage-dependent T-type calcium channel subunit alpha-1H (CACNA1H). These mutations cause activation of the channel at hyperpolarized membrane potentials and impaired channel inactivation, which increases calcium influx, intracellular calcium levels and aldosterone production<sup>23,24</sup>. The only distinguishing feature of this disorder is early-onset primary aldosteronism (typically before the age of 25 years, although incomplete penetrance has been described)<sup>23</sup>.

Primary aldosteronism, seizures and neurological abnormalities (PASNA) syndrome is caused by de novo mutations in *CACNA1D*, which encodes the voltage-dependent L-type calcium channel subunit alpha-1D (CACNA1D), expressed in neuronal, adrenal and heart tissue<sup>25</sup>. These mutations shift channel activation to less depolarized potentials, leading to increased calcium influx<sup>26</sup>. Patients with de novo *CACNA1D* mutations show variable combinations of autism, epilepsy, intellectual disability, a cerebral palsy-like phenotype, heart defects and hyperinsulinaemic hypoglycaemia. Primary aldosteronism is not obligatory, and PASNA syndrome appears to represent a subgroup in a spectrum of such abnormalities<sup>27</sup>.

## Congenital adrenal hyperplasia

Congenital adrenal hyperplasia is an autosomal-recessive disorder characterized by impaired glucocorticoid synthesis and high ACTH



**Fig. 1 | Overview of the organs and pathways that are frequently implicated in genetic causes of hypertension.** Blood pressure is regulated by the interplay of several organs and pathways. The nervous system, particularly the sympathetic system, can control blood pressure via effects on the heart and vascular tone. Catecholamines that are released from the adrenal medulla into the systemic circulation also have a role in regulation of blood pressure. Adrenocorticotropic hormone (ACTH) is released from the anterior pituitary gland and stimulates increased production of cortisol and aldosterone in the adrenal cortex. In the kidney, binding of aldosterone to the mineralocorticoid receptor leads to increased sodium (Na<sup>+</sup>) and water (H<sub>2</sub>O) reabsorption, resulting in an increase in intravascular volume. Activation of the renin–angiotensin–aldosterone system also increases intravascular volume and blood pressure. In response to a reduction in blood pressure, the kidneys release renin into the blood, which leads to the generation of angiotensin II. This peptide hormone increases vascular tone and stimulates the production and release of aldosterone, resulting in an increase in blood pressure.

levels (Fig. 2). Two rare subtypes are associated with hypertension: 11 $\beta$ -hydroxylase deficiency (due to *CYP11B1* mutations and combined 17 $\alpha$ -hydroxylase and 17,20-lyase deficiency (due to *CYP17A1* mutations). 11 $\beta$ -hydroxylase converts 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone. The accumulation of mineralocorticoids and androgens resulting from 11 $\beta$ -hydroxylase deficiency can cause genital ambiguity in females and precocious pseudopuberty, accelerated bone ageing and hypertension in both sexes<sup>28,29</sup>.

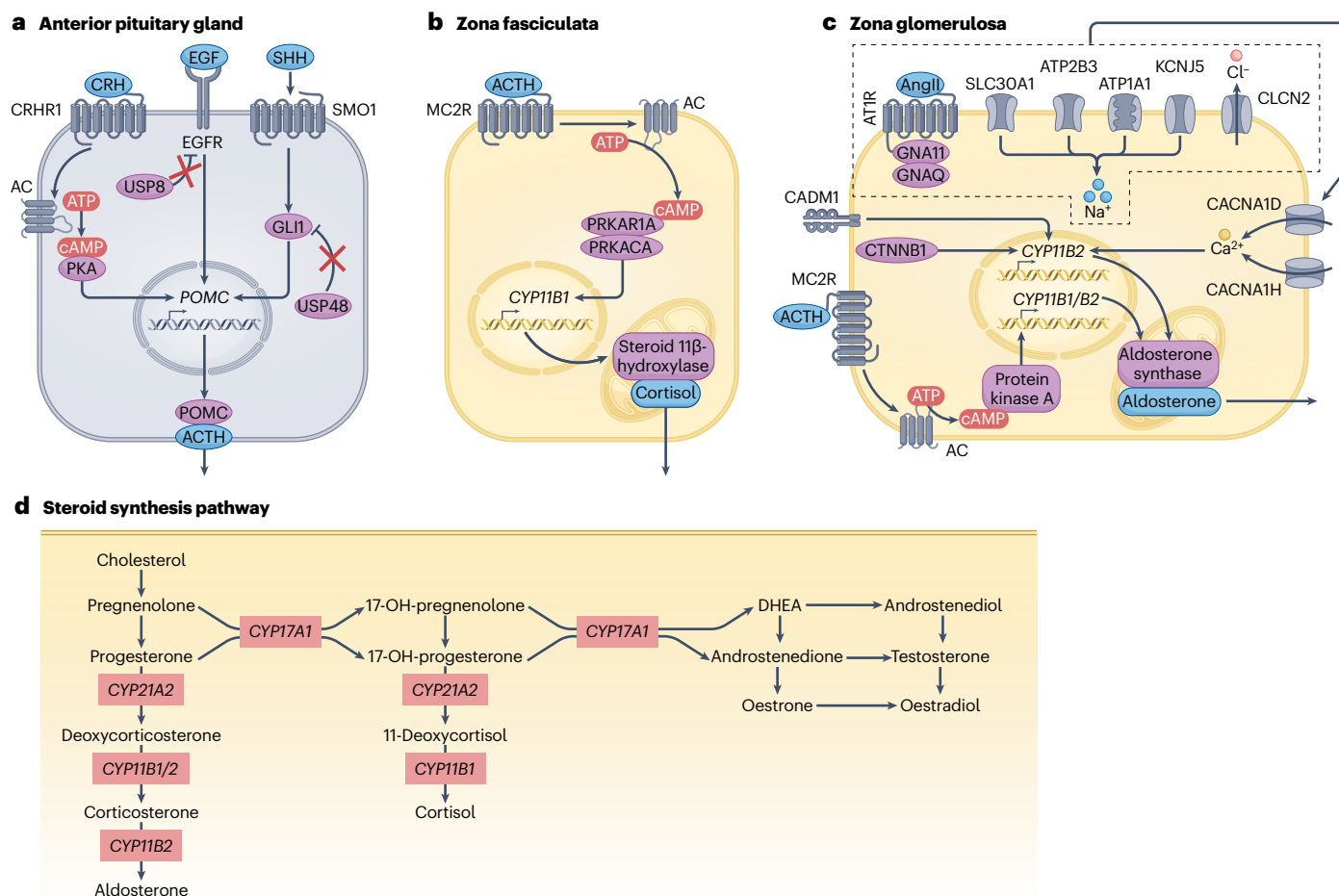
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17 $\alpha$ -hydroxylase catalyses the conversion of pregnenolone into 17-OH pregnenolone and of progesterone into 17-OH progesterone, a precursor of cortisol. 17,20 lyase activity further converts 17-OH pregnenolone into dehydroepiandrosterone and 17-OH progesterone into androstenedione, a precursor of testosterone and oestradiol. Patients with 17 $\alpha$ -hydroxylase and 17,20-lyase deficiency produce high amounts of deoxycorticosterone and corticosterone instead of cortisol. As deoxycorticosterone has mineralocorticoid activity, these patients develop hypertension despite low renin and low aldosterone

levels<sup>30,31</sup>. They also show sexual infantilism and pubertal failure; males have female external genitalia.

## Apparent mineralocorticoid excess

Apparent mineralocorticoid excess is a typically autosomal-recessive disease. Early-onset hypertension is associated with low renin and low aldosterone levels as well as hypokalaemic alkalosis. This disorder is caused by mutations in *HSD11B2*, which encodes 11- $\beta$ -hydroxysteroid dehydrogenase type II<sup>32</sup>. This enzyme converts cortisol into its



**Fig. 2 | Genes involved in adrenal regulation of blood pressure.** **a**, In the anterior pituitary gland, various stimuli, including corticotropin-releasing hormone (CRH), epidermal growth factor (EGF) and sonic hedgehog (SHH), induce increased transcription of the adrenocorticotrophic hormone (ACTH) precursor pro-opiomelanocortin (POMC), resulting in production of ACTH. Mutations in *USP8* or *USP48* disinhibit these pathways, resulting in higher rates of ACTH production relative to the stimulation present. **b**, ACTH activates cells of the zona fasciculata of the adrenal cortex to synthesize cortisol via cAMP–protein kinase A-mediated signalling. Gain-of-function mutations in *PRKACA* and loss-of-function mutations in *PRKARIA* functionally mimic higher ACTH levels. The resulting excess cortisol can act on the mineralocorticoid receptor in the kidney to facilitate volume retention (not shown). **c**, Aldosterone, which is produced in the zona glomerulosa, is a more effective regulator of volume retention than cortisol. Angiotensin II (Ang II) and serum potassium depolarize the cell membrane, resulting in Ca<sup>2+</sup> influx and increased transcription of *CYP11B2*, which encodes aldosterone synthase. The chimeric *CYP11B1/B2* gene can respond to ACTH signalling, resulting in expression

of aldosterone synthase in the zona fasciculata and increased production of aldosterone, facilitating volume retention. The precise roles of *CTNNB1* and *CADMI* variants in the development of hyperaldosteronism are unknown. Mutations in G proteins, several transporters (*SLC30A1*, *ATP2B3*, *ATP1A1*) and ion channels (*KCNJ5*, *CLCN2*) facilitate depolarization of zona glomerulosa cells, prompting calcium influx via voltage-gated calcium channels (*CACNA1D*, *CACNA1H*), which induces increased aldosterone production. Gain-of-function mutations in *CACNA1D* and *CACNA1H* have also been identified. **d**, Enzymes (red boxes) and intermediate products involved in steroid synthesis throughout the adrenal cortex. Cells of the zona glomerulosa express enzymes for synthesis of aldosterone, cells of the zona fasciculata express enzymes for synthesis of cortisol and cells of the innermost zona reticularis express enzymes for the synthesis of sex steroids. Mutations in these enzymes, particularly *CYP17A1*, can lead to the generation of increased levels of steroids that can act on the mineralocorticoid receptor in the kidney, resulting in an increase in systemic intravascular volume via the reabsorption of water and NaCl. AC, adenyl cyclase.

## Box 1 | Screening and diagnosis of monogenic forms of hypertension

A major goal for patients with Mendelian forms of hypertension should be to shorten their path to a correct diagnosis, which can be arduous and long<sup>161</sup>, and receive targeted medical or surgical therapy depending on the specific pathology. Increased awareness of and screening for these disorders are required to achieve this goal.

As most patients with monogenic hypertension have suppressed renin levels, we suggest obtaining renin levels in all patients who present with hypertension in childhood or adolescence, in all patients with severe or resistant hypertension, a positive family history of early-onset hypertension, early stroke or early myocardial infarction, and in all patients with hypokalaemia or unexplained hyperkalaemia. As many commonly prescribed antihypertensive drugs affect renin levels, unmedicated levels are most reliable; beta blockers suppress renin levels, whereas angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics raise renin levels<sup>89</sup>. Normal or elevated renin levels exclude most monogenic forms of hypertension, except for pheochromocytoma or paraganglioma and vascular forms.

Patients with suppressed renin levels should be further investigated by measuring aldosterone and serum potassium. The most common

diagnosis in patients with elevated aldosterone-to-renin ratios is sporadic primary aldosteronism, which requires an extensive work-up<sup>89</sup>. Patients with low renin and low aldosterone levels should be investigated for congenital adrenal hyperplasia, apparent mineralocorticoid excess and Liddle syndrome, whereas patients with low renin levels, hyperkalaemia and hypertension should be tested for PHAI. Given the decreasing cost and increasing availability of panel or exome sequencing, panels containing all or most genes implicated in Mendelian hypertension are good options for patients with otherwise unexplained early-onset hypertension, particularly in the presence of a positive family history.

Somatic mutations that have been implicated in hypertension currently do not guide clinical management, and genetic testing for these mutations is not routinely carried out. In the future, plasma steroidomics could potentially be used to indirectly assess patients with primary aldosteronism for the presence of aldosterone-producing adenomas with *KCNJ5* mutations<sup>162</sup>. This approach has the potential to replace more complicated diagnostic pathways.

inactive metabolite cortisone and thereby prevents cortisol-induced activation of the mineralocorticoid receptor. Loss of function of 11- $\beta$ -hydroxysteroid dehydrogenase leads to mineralocorticoid receptor overstimulation by cortisol and volume retention. Non-classic forms of apparent mineralocorticoid excess with late onset and a milder phenotype have also been described<sup>33</sup>. Patients respond to MRAs, which can be combined with diuretics or glucocorticoids to suppress ACTH and subsequently cortisol<sup>34</sup>.

### Hypertension exacerbated by pregnancy

Hypertension exacerbated by pregnancy was described in a single family with low renin and aldosterone levels and a mutation in *NR3C2*, which encodes the mineralocorticoid receptor<sup>35</sup>. The mutant mineralocorticoid receptor showed constitutive activity, causing increased salt reabsorption and hypertension. Increased activation of this mutant receptor by progesterone explains the exacerbation of hypertension during pregnancy<sup>35</sup>. Cortisone and 11-dehydrocorticosterone are also agonists of the mutant mineralocorticoid receptor<sup>36</sup>.

### Familial glucocorticoid resistance

Heterozygous mutations in *NR3C1*, which encodes the glucocorticoid receptor, result in familial glucocorticoid resistance<sup>37,38</sup>. Patients show high levels of corticotropin-releasing hormone (CRH), ACTH and cortisol as well as bilateral adrenal hyperplasia without Cushing syndrome. The levels of mineralocorticoids (e.g. deoxycorticosterone and corticosterone) and androgens (e.g. androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulfate) are also elevated. The resulting mineralocorticoid excess causes hypertension and/or hypokalaemic alkalosis.

### Hypercortisolism

Hypercortisolism (Cushing syndrome) can be caused by exogenous administration of glucocorticoids or endogenous overproduction of cortisol. The latter can occur autonomously (owing to

cortisol-producing adenoma or adrenal hyperplasia) or because of elevated ACTH levels (owing to Cushing disease (pituitary corticotropinoma) or ectopic ACTH production). In the adrenal cortex, binding of ACTH to a G protein coupled receptor leads to cortisol synthesis, primarily via cAMP signalling involving protein kinase A (PKA) (Fig. 2). Hypertension in the setting of hypercortisolism is primarily due to the mineralocorticoid activity of cortisol.

Several Mendelian syndromes have been implicated in hypercortisolism. Carney complex, an autosomal-dominant multiple neoplasia syndrome, can cause primary pigmented nodular adrenocortical disease or sporadic Cushing syndrome and, less commonly, corticotropinoma. The most common causes are mutations in *PRKARIA*, which encodes cAMP-dependent protein kinase type I-alpha regulatory subunit. Mutations in *AIP*, which encodes aryl hydrocarbon receptor-interacting protein, cause autosomal-dominant familial isolated pituitary adenoma. Similarly, pituitary adenomas can occur as part of autosomal-dominant multiple endocrine neoplasia (MEN) types 1, 2 and 4, which are caused by mutations in *MEN1* (which encodes menin; mutations in *MEN1* are also associated with cortisol-producing adenomas), *RET* (which encodes proto-oncogene tyrosine-protein kinase receptor Ret) and *CDKN1B* (which encodes cyclin-dependent kinase inhibitor 1B), respectively, or as part of tuberous sclerosis complex caused by mutations in *TSC1* or *TSC2*. Cortisol-producing adenomas also occur in patients with familial adenomatous polyposis and *APC* mutations. Primary multinodular adrenal hyperplasia occurs because of germline mutations in *ARMCS* or *PRKACA*. Other germline mutations associated with sporadic Cushing syndrome include mutations in *PDE8B*, *PDE11A* and *PRKACA*, all of which cause overactivation of the cAMP pathway<sup>39</sup>.

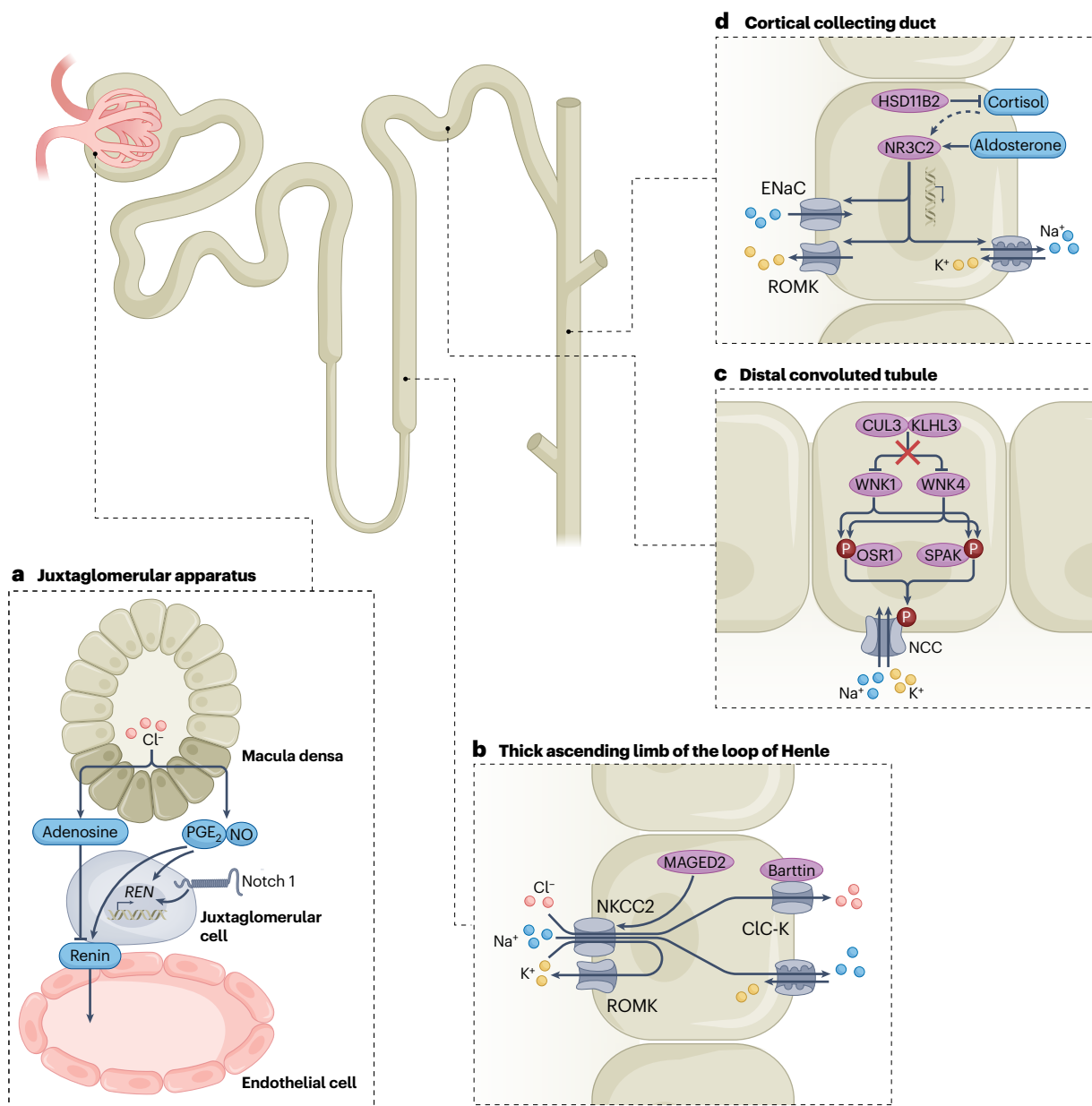
### Monogenic forms of hypertension that affect renal salt reabsorption

Most of the salt reabsorption in the kidney occurs in the proximal tubule. However, fine tuning of salt reabsorption occurs via the thiazide-sensitive sodium chloride cotransporter (NCC, also known

as *SLC12A3*) in the distal convoluted tubule and the epithelial sodium channel (ENaC) in the cortical collecting duct. Increased salt reabsorption in Mendelian syndromes that affect these processes causes hypertension (Fig. 3).

## Pseudohypoaldosteronism type II

Pseudohypoaldosteronism type II (PHAII; also known as familial hyperkalaemic hypertension or Gordon's syndrome), is characterized by hyperkalaemic acidosis and low renin levels<sup>40,41</sup>. Thiazides



**Fig. 3 | Contribution of kidney cells to salt handling and blood-pressure regulation.** **a**, In response to reduced delivery of chloride ( $\text{Cl}^-$ ) to the macula densa, renin is released from juxtaglomerular cells at the distal end of the thick ascending limb of the loop of Henle. Renin production is upregulated by prostaglandin  $\text{E}_2$  ( $\text{PGE}_2$ ) and nitric oxide (NO) signalling and inhibited by adenosine. Activating mutations in the transmembrane receptor gene *NOTCH1* result in a pathological increase in renin release. **b**, In the thick ascending limb of the loop of Henle, salt reabsorption occurs via a set of  $\text{Na}^+$ ,  $\text{Cl}^-$  and  $\text{K}^+$  channels including ROMK, CIC-K, which is regulated by Barttin, and the transporter NKCC2. Mutations in the genes that encode these proteins (*ROMK*, *CLCNKA*,

*CLCNKB*, *BSND* and *SLC12A1*) cause Bartter syndrome (a salt-losing nephropathy associated with hypotension). **c**, In the distal convoluted tubule, salt is reabsorbed via the sodium chloride cotransporter (NCC), which is regulated by the kinases WNK1, WNK4, OSR1 and SPAK. KLHL3 and CUL3 have a role in degradation of WNK1 and WNK4 and loss-of-function mutations in *KLHL3* and *CUL3* lead to increased activation of NCC. **d**, In the cortical collecting duct, salt reabsorption via ENaC and potassium secretion via ROMK are regulated by aldosterone via the mineralocorticoid receptor (NR3C2). Cortisol can also act on this receptor but is physiologically degraded by HSD11B2.

reduce blood pressure and correct hyperkalaemia in patients with this disorder<sup>41</sup>. PHAI is caused by mutations in *WNK1*, *WNK4*, *KLHL3* and *CUL3*, and is autosomal dominant, except for rare recessive cases with *KLHL3* mutations (Fig. 3). *WNK1* and *WNK4* (ref. 42) encode the serine/threonine-protein kinases WNK1 and WNK4. These kinases regulate the activity of NCC, explaining the response to thiazides. *KLHL3* encodes Kelch-like protein 3 (KLHL3) and *CUL3* encodes cullin 3 (CUL3)<sup>43,44</sup>, which are components of an E3 ubiquitin ligase complex that has a role in degrading WNK1 and WNK4. *CUL3* and *KLHL3* mutations prevent WNK1/4 degradation, leading to increased NCC activity. When sodium reabsorption via NCC in the distal convoluted tubule increases (causing hypertension), the amount of sodium that is reabsorbed via ENaC in the cortical collecting duct decreases. As ENaC is electrically coupled with potassium secretion via the ATP-sensitive inward rectifier potassium channel 1 (ROMK), reduced sodium absorption results in reduced potassium secretion, causing hyperkalaemia<sup>45</sup>. The PHAI phenotype is mild in patients with *WNK1* or *WNK4* mutations and particularly severe in those with *CUL3* mutations; patients with homozygous *KLHL3* mutations are more severely affected than those with heterozygous mutations<sup>43</sup>.

## Liddle syndrome

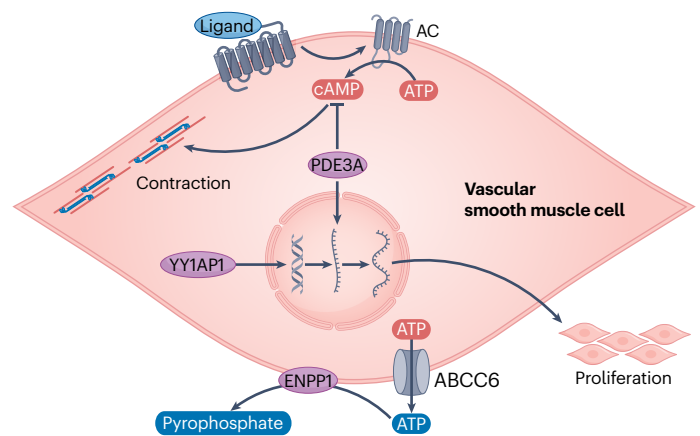
Liddle syndrome is an autosomal-dominant disorder with early-onset hypertension (typical age at diagnosis of 10–30 years<sup>46</sup>), low renin and aldosterone levels and hypokalaemia. Patients respond well to the ENaC blockers amiloride or triamterene<sup>47</sup>. Liddle syndrome can be caused by mutations in the ENaC  $\beta$ -subunit (encoded by *SCNNIB*)<sup>48</sup> or  $\gamma$ -subunit (encoded by *SCNNIG*)<sup>49</sup> that truncate the C-terminus of these proteins, deleting a C-terminal signal sequence (PPXY) that is essential for internalization and proteosomal degradation. The resulting increase in the number of ENaC subunits in the apical membrane of epithelial cells, particularly in the collecting duct, leads to increased sodium reabsorption, an increase in intravascular volume and hypertension. Liddle syndrome can also be caused by rare mutations in the ENaC  $\alpha$ -subunit (encoded by *SCNN1A*) that increase channel activity<sup>50</sup>. Coupling of increased sodium reabsorption via ENaC to increased potassium secretion via ROMK causes hypokalaemia.

## Monogenic forms of hypertension that affect the vasculature

Vascular tone determines peripheral resistance and thereby regulates blood pressure. Of particular relevance for blood-pressure pathophysiology is renal-artery stenosis, which can occur because of either fibromuscular dysplasia (a non-atherosclerotic, non-inflammatory arterial disease) or, more commonly, atherosclerotic lesions (>90% of cases)<sup>51</sup>. The post-stenotic decrease in renal perfusion activates the renin-angiotensin system, causing hypertension.

## Hypertension with brachydactyly

Hypertension with brachydactyly is an autosomal-dominant disorder<sup>52</sup> that results in onset of hypertension at -1–3 years of age<sup>53</sup> and, if untreated, leads to early death from stroke. The distinguishing feature is brachydactyly type E (shortening of the metacarpals). The disorder is caused by mutations in *PDE3A* that cause increased activity of the encoded enzyme, phosphodiesterase 3A<sup>54</sup>. This increased activity leads to increased vascular smooth-muscle-cell proliferation and compromised vascular relaxation, resulting in increased peripheral vascular resistance and hypertension<sup>55</sup> (Fig. 4).



**Fig. 4 | Genes involved in vascular hypertension.** Genes and proteins involved in vascular hypertension include *PDE3A*, *YY1API*, *ENPP1* and *ABCC6*. *PDE3A* encodes a phosphodiesterase that inhibits smooth-muscle contraction via degradation of cAMP. *ABCC6* encodes a transporter that facilitates the release of ATP from the cytosol where it is converted into pyrophosphate by ENPP1; pyrophosphatase prevents crystal formation and mineralization of vessels. YY1API alters cell functions, resulting in reductions in differentiation and proliferation that cause hyperplasia of the tunica media of the arteries. This hyperplasia reduces the structural integrity of the vessels, leading to aneurysms and occlusions of arteries. AC, adenyl cyclase.

## Generalized arterial calcification of infancy

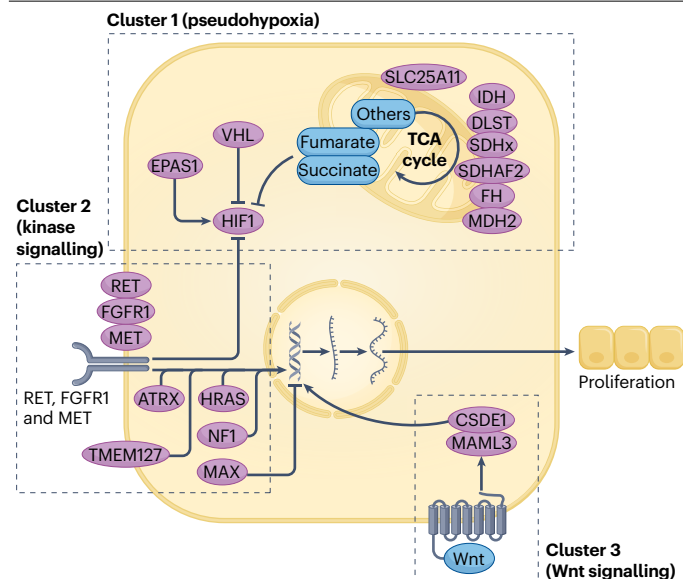
Generalized arterial calcification of infancy is an autosomal-recessive multisystem disorder characterized by vascular calcification and stenosis owing to myo-intimal proliferation, causing hypertension, which is aggravated in patients with renal-artery stenosis. This disorder is caused by mutations in *ENPP1*, which encodes ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)<sup>56</sup> or *ABCC6*, which encodes ATP-binding cassette subfamily C member 6 (ABCC6)<sup>57</sup>. ABCC6 transports ATP into the extracellular space where ENPP1 cleaves ATP into AMP and pyrophosphate. As pyrophosphate prevents hydroxyapatite crystal formation and calcification, mutations in *ENPP1* or *ABCC6* that result in loss of pyrophosphate lead to vascular calcification (Fig. 4).

## Grange syndrome

Grange syndrome is an autosomal-recessive arterial occlusive disease caused by mutations in *YY1API*, which encodes YY1-associated protein 1 (YY1API)<sup>58</sup>. The arterial lesions resemble fibromuscular dysplasia, manifest in childhood or early adulthood<sup>59</sup> and cause hypertension; variably associated features include brachydactyly, syndactyly, bone fragility and learning disabilities. Loss of function of YY1API leads to changes in smooth-muscle-cell function (reduced differentiation and proliferation and cell-cycle arrest) that result in inappropriate hyperplasia after exposure to mitogens, occlusion and aneurysm of arteries<sup>58</sup> (Fig. 4).

## Monogenic forms of hypertension that affect catecholamine production

Catecholamines are stress hormones that are produced by the adrenal medulla (adrenaline and noradrenaline) and sympathetic-nerve terminals (noradrenaline only) and have a role in the 'fight-or-flight' response. Action of catecholamines on alpha adrenergic receptors in vascular



**Fig. 5 | Genes involved in pheochromocytoma and paraganglioma development.** Genes that are mutated in patients with pheochromocytomas and paragangliomas can be functionally clustered. Mutations in cluster 1 genes mimic hypoxic conditions. These variants involve genes with roles in the tricarboxylic acid (TCA) cycle and lead to accumulation of fumarate, succinate and other metabolites that inhibit HIF1, leading to hypoxia signalling, which promotes angiogenesis and cell proliferation. Similarly, mutations in *VHL* and *EPAS1* lead to inhibition of HIF1. Cluster 2 genes have roles in kinase signalling. The precise roles of these genes are complex, but they ultimately act to transduce and regulate the downstream effects of several receptor tyrosine-kinases (*RET*, *FGFR1*, *MET*) and facilitate cell proliferation. As a result, the production of catecholamines increases, leading to the development of hypertension. Mutations in cluster 3 genes increase Wnt signalling. To date, these mutations have only been identified as somatic variants. These mutations affect protein synthesis and cellular proliferation, resulting in an increase in catecholamine-producing cells and the development of hypertension.

smooth-muscle cells leads to vasoconstriction and increased blood pressure. Catecholamine-induced activation of the renin–angiotensin–aldosterone system and increased cardiac output also contribute to a rise in blood pressure<sup>60</sup>.

## Hereditary pheochromocytomas and paragangliomas

Pheochromocytomas and paragangliomas (PPGLs) are neuroendocrine tumours that derive from the adrenal medulla and the extra-adrenal sympathetic or parasympathetic ganglia, respectively. In patients with these tumours, hypertension develops because of catecholamine secretion; additional concerns are mass effects of the tumours and metastatic disease. Around 30–40% of PPGLs are associated with autosomal-dominant germline mutations in susceptibility genes. All patients should be tested for these mutations. When germline mutations are identified, screening for additional tumours and family testing is recommended<sup>61</sup>.

The involved genes have been grouped into two clusters; cluster 1, the pseudohypoxia cluster, comprises genes with roles in metabolic or oxygen-sensing pathways (*SDHx*, *VHL*, *FH*, *EPAS1*, *DLST*), whereas cluster 2 includes genes with roles in kinase signalling (*RET*, *NF1*, *MAX*

and *TMEM127*) (Fig. 5). Somatic mutations have also been identified in genes belonging to these two clusters and to a third cluster (discussed further below)<sup>61</sup>.

Mutations in the succinate dehydrogenase (SDH) subunit genes *SDHA*<sup>62</sup>, *SDHB*<sup>63</sup>, *SDHC*<sup>64</sup> and *SDHD*<sup>65</sup>, as well as in the SDH cofactor gene *SDHAF2* (which encodes succinate dehydrogenase assembly factor 2, mitochondrial<sup>66</sup>), cause hereditary paraganglioma–phaeochromocytoma syndrome. SDH is a mitochondrial enzyme that oxidates succinate to fumarate. Loss of function of SDH causes accumulation of succinate, which activates prolyl hydroxylases and stabilizes hypoxia-inducible factors (HIFs)<sup>61</sup>. Mutations in *FH* (which encodes fumarate hydratase) that result in fumarate accumulation and stabilization of HIFs cause hereditary leiomyomatosis and renal-cell carcinoma syndrome; PPGL rarely develops<sup>61</sup>. Likewise, mutations in *DLST*, which encodes dihydrolipoamide S-succinyltransferase, lead to increased levels of  $\alpha$ -ketoglutarate and 2-hydroxyglutarate and HIF overexpression<sup>67</sup>. Pseudohypoxia also occurs owing to mutations in *SLC25A11*, which encodes mitochondrial 2-oxoglutarate/malate carrier protein<sup>68</sup>. *EPAS1* mutations are rare<sup>69</sup>.

Mutations in *VHL* cause von Hippel–Lindau syndrome, which is an autosomal-dominant cancer syndrome with tumours at multiple sites, including pheochromocytomas<sup>70</sup> and, more rarely, paragangliomas. *VHL* encodes the von Hippel–Lindau disease tumour suppressor (*VHL*), which promotes HIF degradation in normoxia. *VHL* mutations prevent HIF binding, resulting in HIF accumulation and activation of the hypoxia response, which promotes angiogenesis, proliferation and growth. Mutations in *RET*, which encodes proto-oncogene tyrosine-protein kinase receptor Ret, cause MEN type 2 (MEN2), a hereditary tumour syndrome associated with pheochromocytomas<sup>71</sup>.

In rare cases, patients with neurofibromatosis, a disorder with cutaneous abnormalities, characteristic neurofibromas and mutations in *NF1*, can develop hypertension owing to pheochromocytoma<sup>72</sup>. Mutations in *MAX* (which encodes myc-associated factor x) cause susceptibility to pheochromocytoma<sup>73</sup>, as do mutations in *TMEM127* (which encodes transmembrane protein 127, a negative regulator of mTOR)<sup>74</sup>.

## Monogenic forms of hypotension

Loss-of-function variants in the channels, transporters and receptors involved in renal salt reabsorption cause renal salt loss and hypotension. Monogenic forms of hypotension include Bartter syndrome, Gitelman syndrome and pseudohypoaldosteronism type I (PHA1).

### Bartter syndrome

Bartter syndrome is caused by mutations in proteins that have roles in kidney salt reabsorption or its regulation in the thick ascending limb of the loop of Henle (Fig. 3). Autosomal-recessive subtypes include type I with mutations in *SLC12A1*, which encodes Na–K–2Cl cotransporter 2 (NKCC2)<sup>75</sup>, type II with mutations in *KCNJ1*, which encodes ROMK<sup>76</sup>, type III with mutations in *CLCNKB*, which encodes chloride channel protein ClC-Kb<sup>77</sup>, and type IV with mutations in *BSND*, which encodes barttin<sup>78</sup> or mutations in both *CLCNKB* and *CLCNKA*, which encodes chloride channel protein ClC-Ka<sup>79</sup>. X chromosomal recessive type V Bartter syndrome is caused by mutations in *MAGED2*, which encodes MAGE family member D2 (ref. 80). Patients with Bartter syndrome show severe early-onset salt loss (often antenatally with polyhydramnios and prematurity), hypokalaemia, metabolic alkalosis and hyperreninaemic hyperaldosteronism<sup>81</sup>. Those with types I, II, IV and V typically present antenatally or in infancy, whereas type III is typically diagnosed

in childhood. Other distinguishing features are transient hyperkalaemia in type II, hearing loss in type IV and spontaneous resolution of salt loss in surviving children with type V.

## Gitelman syndrome

Gitelman syndrome<sup>82</sup> is an autosomal-recessive disease. Similar to Bartter syndrome, patients show salt loss, hypokalaemic alkalosis and high renin and aldosterone levels; however, they typically present in adolescence or even adulthood and have hypomagnesaemia and very low levels of urinary calcium (which is often elevated in Bartter syndrome). Gitelman syndrome is caused by mutations in *SLC12A3*, which encodes NCC<sup>83</sup>.

## Pseudohypoaldosteronism type I

Patients with PHAI<sup>84</sup> have salt wasting, high levels of renin and aldosterone (similar to Bartter syndrome) and hyperkalaemic acidosis. The autosomal-dominant, milder form of PHAI is caused by loss-of-function mutations in the mineralocorticoid receptor gene (*NR3C2*) and remits with age<sup>85</sup>. The severe autosomal-recessive form is due to loss-of-function mutations in genes that encode ENaC subunits (*SCNN1A*, *SCNN1B*<sup>86</sup>, *SCNN1G*<sup>87</sup>) (Fig. 3). In addition to the kidney, PHAI affects the sweat glands, salivary glands and colon.

## Somatic mutations in hormone-producing tumours that cause hypertension

Unlike germline mutations, which are present in all cells of the body, somatic mutations only affect specific organs or cell types. Somatic variants that cause hypertension have been identified primarily in endocrine disorders due to hormone-producing tumours, including primary aldosteronism, Cushing syndrome, PPGLs and reninomas.

## Aldosterone-producing adenomas

Aldosterone-producing adenomas (APAs) are benign hormone-producing tumours of the adrenal cortex (>10 mm in diameter)<sup>88</sup>. They cause ~30% of cases of primary aldosteronism, are typically unilateral and are usually treated by surgical removal of the affected gland<sup>89</sup>. Somatic mutations in APAs overlap with germline mutations found in familial hyperaldosteronism (Fig. 2). The most frequent are heterozygous gain-of-function *KCNJ5* mutations (almost always G151R or L168R), which are found in ~40% of APAs<sup>21</sup> and are more common in females and young patients. Heterozygous gain-of-function *CACNA1D* mutations<sup>25,90</sup> are found in 14–42% of APAs, with higher prevalence among African Americans<sup>91</sup>, and heterozygous variants in *ATP1A1*, which encodes sodium/potassium-transporting ATPase subunit alpha-1<sup>90,92</sup>, are found in <20% of APAs. *ATP1A1* variants result in aberrant sodium permeability, facilitating depolarization, and intracellular acidification. Unlike *KCNJ5* and *CACNA1D* variants, only somatic *ATP1A1* variants have been identified.

Rare causes of APAs include heterozygous variants in *CLCN2* (ref. 93) and *CACNA1H*<sup>94</sup>. Somatic variants in *ATP2B3*, which encodes plasma membrane calcium-transporting ATPase 3 (ref. 90), and *SLC30A1*, which encodes the proton-coupled zinc antiporter SLC30A1 (ref. 95), have also been identified in APA. These variants result in a persistent sodium conductance, facilitating depolarization and subsequent calcium influx. Somatic mutations in *CADMI*, which encodes cell adhesion molecule 1, have also been identified in APAs<sup>96</sup>. A study that used a human adrenocortical cell line reported that these mutations impair gap junction formation<sup>96</sup>, but their effects have not yet been investigated in vivo.

Somatic mutations in *CTNNB1*, which encodes  $\beta$ -catenin, have also been identified in APAs<sup>97</sup>. These mutations result in augmentation of Wnt signalling<sup>97</sup>. *CTNNB1* mutations can coincide with variants in other genes, such as *GNAI1* and *GNAQ*<sup>98</sup>. These genes encode the G protein subunits  $\alpha 11$  and  $\alpha q$ , respectively, which act downstream of the type-1 angiotensin II receptor to increase aldosterone production. Similar somatic mutations were also found in aldosterone-producing (micro) nodules (<10 mm) that were detected by staining for aldosterone synthase. These nodules may represent APA precursors<sup>88</sup>. The frequency of mutated genes in aldosterone-producing (micro) nodules differs from that of APAs, with *CACNA1D* mutations being the most frequent<sup>99,100</sup>. *KCNJ5* mutations are rare in these nodules, perhaps because their increased proliferation leads to rapid APA formation, whereas other mutations lead to slower growth, resulting in a longer period at the nodule stage<sup>101</sup>.

## Cushing's syndrome

The most common causes of ACTH-dependent Cushing's syndrome are corticotroph adenomas of the anterior pituitary gland that result in Cushing's disease (60–70% of cases)<sup>102</sup>. Less commonly, Cushing's syndrome can occur as a paraneoplastic syndrome secondary to ACTH-producing tumours such as small-cell lung cancer (<20% of all cases).

The most common somatic mutations in corticotroph adenomas (~40% of cases) are mutations in *USP8*, which encodes ubiquitin-specific protease 8 (ref. 103). This protease has a role in ubiquitination-dependent degradation of the epidermal growth factor (EGF) receptor (Fig. 2). *USP8* loss-of-function mutations increase EGF signalling and the synthesis of pro-opiomelanocortin (POMC), which is an ACTH precursor. Mutations in another ubiquitin-specific protease, *USP48* (ref. 104), which encodes ubiquitin-specific protease 48, are less frequent. These mutations increase *POMC* expression. Other mutations in corticotroph adenomas have been identified in *BRAF*<sup>104</sup>, which encodes the serine/threonine-protein kinase B-raf, and *CABLES1* (ref. 105), which encodes CDK5 and ABL1 enzyme substrate 1.

ACTH-independent cases of Cushing's syndrome are most often due to cortisol-producing adenomas<sup>102</sup>. These adenomas most commonly occur because of somatic mutations in *PRKACA*, which encodes cAMP-dependent protein kinase catalytic subunit alpha<sup>106</sup>, and *CTNNB1* (ref. 107) (Fig. 2).

## Sporadic pheochromocytomas and paragangliomas

Around 60% of PPGLs are sporadic<sup>108</sup>. Somatic mutations are found in 30–40% of these tumours, overlapping genes involved in hereditary cases<sup>108</sup> (Fig. 5). Among genes belonging to cluster 1, mutations in *SDHx*<sup>109–111</sup> are rare, whereas mutations in *EPAS1* (ref. 112) (which encodes endothelial PAS domain-containing protein 1) and *VHL*<sup>71</sup> are frequent in sporadic PPGLs. Mutations in *IDH1* (ref. 113) and *IDH2* (ref. 114) (which encode isoforms of isocitrate dehydrogenase) are extremely rare, and only somatic variants have been identified.

The most common somatic variants in PPGLs are in *NFI* (refs. 115,116), which belongs to cluster 2. Variants in *HRAS*<sup>117</sup> (which encodes GTPase HRas), *FGFR1* (ref. 118) (which encodes fibroblast growth factor receptor 1), *RET*<sup>119</sup> (which encodes proto-oncogene tyrosine-protein kinase receptor Ret), *MAX*<sup>120</sup> (which encodes protein max) and *ATRX*<sup>121</sup> (which encodes transcriptional regulator ATRX) are less frequent.

Somatic variants in *CSDE1* (ref. 122) (which encodes cold shock domain-containing protein E1) and a *TCF4-MAML3* fusion gene<sup>122</sup> (which encodes transcription factor 4–mastermind like protein 3)

have also been discovered in sporadic PPGLs. These mutations affect Wnt signalling, comprising a third gene cluster that has not yet been identified in hereditary PPGLs. Furthermore, somatic and rare germline mutations in *KMT2D* (which encodes histone-lysine N-methyltransferase 2D (KMT2D)) have been reported to be implicated in up to 14% of pheochromocytomas<sup>123</sup>, but this result awaits independent confirmation.

## Reninomas

Reninomas are rare (~100 reported cases) tumours of the renin-secreting cells in the juxtaglomerular apparatus of the kidney that cause excessive renin secretion, leading to activation of the renin–angiotensin–aldosterone system and hypertension<sup>124</sup>. Activating rearrangements of *NOTCH1* (which encodes neurogenic locus notch homologue protein 1 (Notch 1)) and partial loss of the *NOTCH1* inhibitor gene *NRARP* (which encodes Notch-regulated ankyrin repeat-containing protein) have been identified in two cases<sup>124</sup>. These aberrations lead to increased Notch signalling, which has an important role in the development of renin-producing cells<sup>125</sup> (Fig. 3).

## Hypertension as a complex trait

Most patients develop hypertension owing to a complex interplay of factors, including variants across many genes. In contrast to monogenic hypertension, in which a single gene variant has a large effect on blood pressure, in polygenic hypertension the effect of each individual variant on blood pressure is very small (typically around  $\pm 0.2$  mmHg<sup>126</sup>, although some variants have been reported to result in increases in SBP of -1 mmHg and in DBP of -0.5 mmHg<sup>127</sup>). The cumulative effects of these alterations on blood pressure result in hypertension<sup>128</sup>.

## Blood-pressure-related variants in genome-wide association studies

Genome-wide association studies (GWAS) analyse genome data for large numbers of individuals to identify associations between genetic variants, most commonly SNPs with an allele frequency >1%, and specific phenotypes or diseases. In hypertension GWAS, the investigated phenotypes are usually SBP, DBP and pulse pressure (PP; defined as SBP minus DBP). As these traits are continuous, estimates of the effect sizes of positive and negative associations of SNPs with blood pressure can be obtained, but large sample sizes are required. Importantly, GWAS can identify associations between genetic variants and traits but cannot establish causality.

The first GWAS of blood-pressure traits were published in 2009 (refs. 127,129). These studies identified plausible associations between blood-pressure traits and SNPs in *CYP17A1*, which is mutated in congenital adrenal hyperplasia; *PLCD3*, which encodes phospholipase C- $\delta 3$ , which has a role in vascular smooth-muscle-cell signalling downstream of angiotensin II and endothelin; *ATP2B1*, which encodes plasma membrane calcium-transporting ATPase 1, which is expressed in the vascular endothelium and pumps calcium out of cells; and *CACNB2*, which encodes voltage-dependent L-type calcium channel subunit  $\beta 2$ .

The emergence of large genotype–phenotype databases such as the UK Biobank (UKBB), the Million Veteran Program (MVP) and the International Consortium for Blood Pressure (ICBP) together with smaller institutional databases enabled analyses of very large cohorts. In 2018 and 2019, two GWAS were published that included ~750,000 individuals from the UKBB and ICBP<sup>130</sup> and ~460,000 individuals from the UKBB and MVP<sup>131</sup>, respectively, in their discovery cohorts. These large datasets enabled the detection of >700 novel genetic loci that

were associated with blood-pressure changes. In 2024, a GWAS of blood pressure that included data for >1 million individuals from the UKBB, ICBP, MVP and the Biorepository of Vanderbilt University study reported 2,103 loci that were significantly associated with changes in one or more of the three blood-pressure traits (SBP, DBP or PP), including 113 novel loci<sup>126</sup>.

Only around 20% of the heritability of blood pressure can be explained by SNPs, and >60% of this SNP-based heritability can be explained by the results of the 2024 GWAS<sup>126</sup>, indicating substantial missing heritability. Potential explanations for missing heritability include rare variants not yet identified by GWAS, an overestimation of heritability in family studies owing to gene–environment interactions (such as the effects of the microbiome), non-additive gene–gene interactions, effects of large duplications or deletions, the existence of common variants with very small effects that do not reach statistical significance in GWAS, or epigenetic effects<sup>132–134</sup>. The latter explanation may be particularly relevant to the missing heritability of blood pressure<sup>128</sup>.

GWAS have also been conducted for preeclampsia, which is a disorder of pregnancy characterized by hypertension, proteinuria and other symptoms. The pathogenesis of pre-eclampsia is incompletely understood but likely involves placental ischaemia owing to incomplete spiral-artery transformation, which leads to the release of angiogenic factors<sup>135</sup>. GWAS have identified associations of pre-eclampsia with several loci related to angiogenesis, endothelial, kidney and immune function, and natriuretic peptide signalling<sup>136</sup>.

## Mapping genome-wide association studies results to specific tissues and genes

As discussed above, many genes and proteins that are involved in monogenic causes of hypertension affect renal salt reabsorption, its regulation or the secretion of catecholamines. Some genes that are mutated in monogenic forms of hypertension have also been identified in hypertension GWAS (e.g. *CYP17A1* and *PDE3A*<sup>128</sup>). However, unlike for many other disorders or traits<sup>137</sup>, the overlap between GWAS risk genes and Mendelian disorder genes is limited in the case of hypertension. This limited overlap might be partially due to pleiotropic associations of many blood-pressure-associated SNPs with other traits, such as adiposity, alcohol intake, birthweight, height, heart rate, haematological traits or education<sup>128</sup>, all of which influence blood pressure.

Several genes that have been identified in hypertension GWAS are enriched in extra-renal or extra-adrenal tissues, such as the heart or vascular tissue (for example, *VEGFA* (which encodes vascular endothelial growth factor A, which stimulates angiogenesis), multiple fibroblast growth factor genes and genes involved in the TGF $\beta$  pathway)<sup>130</sup> or the autonomous nervous system (for example, *ADRA1A*, which encodes  $\alpha$ -1-adrenergic receptor 1A)<sup>126</sup>. Some of the identified genes have roles in pathways that involve more than one organ system; for example, genes with roles in iron overload such as *TMPRSS6* (which encodes transmembrane protease serine 6, which is associated with attenuation of cardiac iron overload), *SMAD7* (which encodes Smad7, a regulator of hepcidin, which regulates iron absorption) and *GSTM1* (which encodes glutathione S-transferase Mu1, which has been implicated in iron-overload-associated cardiomyopathy)<sup>126</sup>. An unbiased, transcriptome-wide association study (TWAS) that utilized the Genotype Tissue Expression database (which links gene expression data to genetic variation) identified the kidney, fibroblasts, adrenal gland, lymphocytes, thyroid, vasculature and central nervous system as tissues and cell types that are highly relevant for genetic regulation of

blood pressure<sup>138</sup>. Compared with GWAS, the TWAS approach is better suited to linking the effects of SNPs in non-coding loci to genes.

## Causality studies of genome-wide association studies results

As GWAS can only establish correlations, other methods must be employed to investigate the causality of the identified variants. The majority of the common variants that have been associated with blood pressure are located outside of coding regions and presumably act via gene regulatory mechanisms<sup>128</sup>, which complicates functional studies of their effects.

GWAS variants can be investigated at low throughput using classical experimental techniques. For example, an SNP in the 5' region of *UMOD*, which encodes uromodulin and is expressed in the thick ascending limb of the loop of Henle, has been associated with reduced uromodulin levels, reduced risk of hypertension and better renal function<sup>139</sup>. In mice, *Umod*-knockout resulted in lower SBP and greater urinary NaCl excretion, and uromodulin was shown to indirectly affect salt reabsorption via the NKCC2 transporter<sup>140</sup>.

CRISPR-Cas9 gene-editing technology was used to introduce a human hypertension-associated coding SNP in *SH2B3* (which encodes SH2B adapter protein 3) into the mouse genome<sup>141</sup>. Mice with this SNP had increased blood pressure, partially due to immune activation. This model demonstrates the potential of genome-editing technologies to enable pathophysiological insight, not only at the gene level but also at the level of single causative SNPs. However, such studies will be limited to variants with comparatively large effect sizes and strong homology in typical animal models.

Massively parallel reporter assays can provide information on the regulatory activity of thousands to millions of sequences and their variants simultaneously. This approach has been used to study GWAS variants in vascular smooth-muscle cells and cardiomyocytes and has led to the identification of putative causal variants<sup>142</sup>. For example, SNPs in *PRDM6*, which encodes putative histone-lysine N-methyltransferase PRDM6, have been associated with blood pressure<sup>143</sup>. A study that used a CRISPR-Cas9-based massively parallel reporter assay identified several causal SNPs within a super-enhancer that attenuated the expression of *PRDM6* (ref. 144). An intronic variant in *PHACTR1* (which encodes phosphatase and actin regulator-1) that is associated with hypertension is also located in an enhancer region. Genome editing of this element in stem cells before their differentiation into endothelial cells resulted in increased endothelial-cell expression of *EDN1*, which encodes the vasoconstrictor endothelin 1. Furthermore, endothelin 1 levels were increased in carriers of the *PHACTR1* variant<sup>145</sup>, demonstrating that SNPs can affect genes that are remote from their location.

High-throughput analyses are required to investigate the vast number of associations identified by GWAS with minimal bias. Fine-mapping and gene-prioritization approaches have been used to identify the causal variants that underlie genome-wide associations<sup>146</sup>. For example, variants can be overlapped with promoter or enhancer regions or transcription-factor binding sites, suggesting regulatory effects. Allele-specific effects of variants on chromatin accessibility can be investigated using ATAC-seq (assay for transposase-accessible chromatin using sequencing). In massively parallel reporter assays, expression levels of DNA fragments containing wild type or variant sequences can be compared. This analysis can uncover effects of variants on transcriptional regulation and identify putatively causal SNPs<sup>147</sup>.

Among the most popular methods of establishing causality from GWAS results are Mendelian randomization analyses, which take advantage of the randomized inheritance of genetic variants and

their association with certain phenotypes, such as blood pressure<sup>128</sup>. A multi-omics study that integrated genotype, gene expression, splicing and DNA methylation data from human kidneys with GWAS data on blood-pressure regulation (including 821 sentinel SNPs) reported that >50% of the GWAS variants that were associated with blood-pressure phenotypes regulated genes that are expressed in the kidney<sup>148</sup>. Around 25% of the SNPs were associated with alternative splicing mechanisms in the kidney, and almost half affected methylation patterns.

Another study from the same group that used TWAS, Mendelian randomization and fine-mapping, reported that 399 kidney genes were potentially causally linked to blood pressure<sup>138</sup>. Some of these genes had roles in pathways for metabolic processing of, for example, amino acids or carbohydrates, enabling correlations with metabolomic parameters. In particular, kidney expression of *SLC5A11*, which encodes sodium/myo-inositol cotransporter 2, was associated with serum myo-inositol levels and PP; variants in *AGMAT*, which encodes agmatinase, were associated with changes in the plasma levels of 4-guanidinobutanoate and SBP; and the association between variants in *AGT*, which encodes angiotensinogen, and blood pressure was largely independent of circulating levels of angiotensinogen, suggesting a role of an intrarenal renin-angiotensin system.

Most of the available causality studies of blood-pressure-related GWAS variants are limited to the kidney, underlining the importance of the kidney in the development of hypertension. However, further investigations are needed into the effects of blood-pressure-associated variants in other tissues such as the vasculature, adrenal glands and regions of the brain.

## Polygenic risk scores

Polygenic risk scores use GWAS data and individual genotypes to estimate disease risk. They sum up risk alleles at known GWAS loci, weighted by their effect sizes. An analysis that used data from the largest GWAS on hypertension conducted to date reported that individuals with polygenic risk scores within the top 10% exhibited, on average, a 16.9-mmHg higher SBP and >7-fold higher odds of hypertension than those with polygenic risk scores within the lowest 10%<sup>126</sup>. Polygenic risk scores are not currently used in clinical settings. Potential future applications could include identification of high-risk individuals for frequent blood-pressure screening or lifestyle interventions. However, a cost-benefit analysis taking into account the potential psychological impact of a high polygenic risk score would be required before implementation of any such strategies in clinical practice.

## Rare variants

GWAS are typically limited to the study of common and low-frequency variants. To assess the contribution of rare variants to blood pressure at the population level, exome-sequencing data have been utilized. An analysis of exome-sequencing data from >269,000 UK Biobank participants identified rare hypertension-associated protein-truncating variants in *FES*, which encodes tyrosine-protein kinase Fes/Fps (a target of naproxen, which increases blood pressure), and *OR4X2*, which encodes olfactory receptor 4X2 (ref. 149). Analysis of >450,000 exomes from UK Biobank participants identified an association between variants in *SLC9A3R2* and a reduced risk of hypertension<sup>150</sup>. The encoded protein, Na<sup>+</sup>/H<sup>+</sup> exchange regulatory cofactor NHE-RF2, may regulate sodium/hydrogen exchanger 3 (NHE3), which is a major determinant of proximal tubular sodium reabsorption in the kidney.

An analysis of the results of a whole-genome sequencing study of blood-pressure phenotypes in >50,000 participants, with follow-up

## Glossary

### Missing heritability

The difference between the heritability of a trait or disease that can be explained by variants identified in genome-wide association studies and heritability estimates from family studies. Such missing heritability has been observed for many traits and diseases.

### Monogenic disorders

Disorders that are caused by a mutation in a single gene. Also known as Mendelian diseases.

### Polygenic disorders

Disorders that are caused by the combined effect of multiple variants in different genes.

### Sentinel SNP

The SNP at a particular locus that has the strongest association with a trait (lowest *P* value) in a genome-wide association study.

### Unequal crossing-over

A homologous recombination event that occurs between different genetic loci with similar sequences during meiosis and can result in gene duplication or deletion.

analysis of genome-wide SNP array data from >700,000 individuals and whole-exome sequencing data from nearly 200,000 individuals, identified two blood-pressure signals with genome-wide significance<sup>151</sup>. These signals were a rare intergenic variant at *LOC100506274* and a novel common variant at the *INSR* (insulin receptor) locus.

A study that analysed exome sequencing data from a cohort of patients with childhood-onset essential hypertension, identified compound heterozygous, rare damaging variants in *SYNE1*, which encodes nesprin 1, in ~20% of patients<sup>152</sup>. The researchers showed that knock-down of *SYNE1* in vascular smooth-muscle cells led to increased cellular stiffness, potentially implicating the vasculature in the pathogenesis of childhood-onset essential hypertension.

## Epigenetics of hypertension

In addition to genetic variants that alter pathways or gene regulation, epigenetic mechanisms can influence gene expression and contribute to blood-pressure alterations. These mechanisms include methylation of the cytosine of CpG sites to 5-methylcytosine (5mC) in promoter, enhancer or coding regions of genes; histone modifications such as methylation and acetylation; and the effects of non-coding RNAs, such as microRNAs (miRNAs). Methylation of several genes involved in blood-pressure regulation has been associated with hypertension in humans and animal models.

In humans, sentinel blood-pressure SNPs identified by GWAS have been associated with local DNA methylation<sup>143</sup>. The genes that are located nearest to the affected CpG sites include *OSR1* (which encodes a protein that activates NCC via phosphorylation), *KCNK3* (which encodes a potassium channel involved in the regulation of vascular tone but also expressed in the zona glomerulosa) and *PRDM6* (ref. 143). Many blood-pressure-associated SNPs that have been identified in the kidney are also associated with changes in the methylation status of DNA<sup>148</sup>. These SNPs include variants that could potentially cause hypertension by altering the methylation status and expression levels of *EDNI* or *FES*. Thus, epigenetic changes may mediate some of the effects of common variants on blood pressure.

Hypomethylation of the promoter of *Agtr1a*, which encodes type-1 angiotensin II receptor A<sup>153</sup>, and of the promoter of *Slc12a2*<sup>154</sup>, which encodes the Na–K–2Cl cotransporter, have been found in spontaneously hypertensive rats. These rats also show histone modifications that result in increased expression of *Ace1*, which encodes angiotensin-converting enzyme 1 (ref. 155). Undermethylation of the promoter of *Agtr1b*, which results in increased expression of the encoded protein type-1 angiotensin II receptor B and increased angiotensin responsiveness, has been demonstrated in the offspring of rats that were fed a low-protein diet during pregnancy<sup>156</sup>. These offspring are a model of fetal programming resulting in reduced birthweight and hypertension.

## Conclusions and future perspectives

Several Mendelian syndromes feature hypertension as a main or an accompanying sign. Most of the mutated genes and proteins in these syndromes are expressed in the kidney or the adrenal gland, suggesting that the resulting changes in renal salt reabsorption or its regulation have sufficiently large effects on blood pressure to cause monogenic diseases. However, monogenic causes of hypertension are rare, and most cases of hypertension are polygenic. Blood-pressure-associated variants identified in GWAS studies have small effect sizes and show little overlap with genes that are involved in monogenic causes of hypertension. However, unbiased studies of organs involved in the pathophysiology of GWAS variants also predominantly implicate the kidney as being a highly relevant organ for the genetic regulation of blood pressure. Emerging data from omics studies have provided insights into the pathophysiology of the many hypertension-associated variants identified in GWAS.

Rare variants with a medium effect size may explain some of the missing heritability of blood pressure. Sequencing individuals with outlier phenotypes such as early-onset, severe hypertension or low blood pressure at advanced age, may be more cost-effective for the identification of these variants than large population-based studies. GWAS of cohorts of patients with the same aetiology of hypertension (for example, low-renin hypertension or obstructive sleep apnoea) may also prove helpful for the identification of novel variants<sup>157</sup>.

Several antihypertensive drugs target proteins that are encoded by Mendelian disease genes. For example, MRAs, which are used for the treatment of resistant hypertension and primary aldosteronism<sup>89,158</sup>, block the mineralocorticoid receptor, which is encoded by *NR3C2*; ENaC blockers, such as amiloride, target ENaC, which is encoded by *SCNNIX*; thiazides inhibit NCC, which is encoded by *SLC12A3*, and loop diuretics inhibit NKCC2, which is encoded by *SLC12A1*. In addition, inhibitors of aldosterone synthase, which is encoded by *CYP11B2*, are currently being investigated in clinical trials; for example, baxdrostat treatment significantly lowers blood pressure in patients with uncontrolled or resistant hypertension<sup>159</sup>. Given the apparently higher success rate of drug development for Mendelian gene targets rather than gene targets identified in GWAS<sup>160</sup>, other monogenic disease genes may also be good candidates for drug development. The increasing use of high-throughput sequencing approaches is likely to lead to the discovery of novel monogenic disease genes and thereby provide new insights into the pathophysiology of hypertension. Similarly, screening of increasingly large cohorts will enable the identification of additional recurrent somatic mutations in hormone-producing tumours. Although the proportion of tumours that can be explained by novel mutations is decreasing, such discoveries can provide insights into disease mechanisms and potential drug targets.

The thousands of hypertension-associated variants identified in GWAS studies also harbour potential as drug targets. However, identifying causal relationships for these SNPs will be crucial to enable pathophysiological understanding of their role in determining blood pressure and translation into clinical application. The example of an intronic variant in *PHACTR1* that increases the expression of *EDNI* (ref. 145) demonstrates the importance of clarifying disease mechanisms before utilizing GWAS findings in drug design. Fine mapping and high-throughput multi-omics studies are promising tools for the identification of disease mechanisms, as the number of associated genes makes individual assessment extremely laborious.

Published online: 11 November 2025

## References

- Kreutz, R. et al. 2024 European Society of Hypertension clinical practice guidelines for the management of arterial hypertension. *Eur. J. Intern. Med.* **126**, 1–15 (2024).
- McEvoy, J. W. et al. 2024 ESC guidelines for the management of elevated blood pressure and hypertension. *Eur. Heart J.* **45**, 3912–4018 (2024).
- Writing Committee, M. et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* **152**, e114–e218 (2025).
- NCD Risk Factor Collaboration Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* **398**, 957–980 (2021).
- GBD 2019 Risk Factors Collaborators Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet* **396**, 1223–1249 (2020).
- Forouzanfar, M. H. et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *JAMA* **317**, 165–182 (2017).
- Lewington, S. 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* **360**, 1903–1913 (2002).
- Rios, F. J., Montezano, A. C., Camargo, L. L. & Touyz, R. M. Impact of environmental factors on hypertension and associated cardiovascular disease. *Can. J. Cardiol.* **39**, 1229–1243 (2023).
- Charchar, F. J. et al. Lifestyle management of hypertension: International Society of Hypertension position paper endorsed by the World Hypertension League and European Society of Hypertension. *J. Hypertens.* **42**, 23–49 (2024).
- O'Donnell, J. A., Zheng, T., Meric, G. & Marques, F. Z. The gut microbiome and hypertension. *Nat. Rev. Nephrol.* **19**, 153–167 (2023).
- Luft, F. C. Twins in cardiovascular genetic research. *Hypertension* **37**, 350–356 (2001).
- Padmanabhan, S., Caulfield, M. & Dominiczak, A. F. Genetic and molecular aspects of hypertension. *Circ. Res.* **116**, 937–959 (2015).
- Pazoki, R. et al. Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events. *Circulation* **137**, 653–661 (2018).
- Mulatero, P. et al. Familial hyperaldosteronism: an European Reference Network on Rare Endocrine Conditions clinical practice guideline. *Eur. J. Endocrinol.* **190**, G1–G14 (2024).
- Adler, G. K. et al. Primary aldosteronism: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **110**, 2453–2495 (2025).
- Sutherland, D. J., Ruse, J. L. & Laidlaw, J. C. Hypertension, increased aldosterone secretion and low plasma renin activity relieved by dexamethasone. *Can. Med. Assoc. J.* **95**, 1109–1119 (1966).
- Lifton, R. P. et al. A chimeric 11 $\beta$ -hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. *Nature* **355**, 262–265 (1992).
- Scholl, U. I. et al. CLCN2 chloride channel mutations in familial hyperaldosteronism type II. *Nat. Genet.* **50**, 349–354 (2018).
- Fernandes-Rosa, F. L. et al. A gain-of-function mutation in the CLCN2 chloride channel gene causes primary aldosteronism. *Nat. Genet.* **50**, 355–361 (2018).
- Schewe, J. et al. Elevated aldosterone and blood pressure in a mouse model of familial hyperaldosteronism with CLC-2 mutation. *Nat. Commun.* **10**, 5155 (2019).
- Choi, M. et al. K<sup>+</sup> channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. *Science* **331**, 768–772 (2011).
- Scholl, U. I. et al. Hypertension with or without adrenal hyperplasia due to different inherited mutations in the potassium channel KCNJ5. *Proc. Natl Acad. Sci. USA* **109**, 2533–2538 (2012).
- Scholl, U. I. et al. Recurrent gain of function mutation in calcium channel CACNA1H causes early-onset hypertension with primary aldosteronism. *eLife* **4**, e06315 (2015).
- Seidel, E. et al. Enhanced Ca<sup>2+</sup> signaling, mild primary aldosteronism, and hypertension in a familial hyperaldosteronism mouse model (*Cacna1h*<sup>M1560V/+</sup>). *Proc. Natl Acad. Sci. USA* **118**, e2014876118 (2021).
- Scholl, U. I. et al. Somatic and germline CACNA1D calcium channel mutations in aldosterone-producing adenomas and primary aldosteronism. *Nat. Genet.* **45**, 1050–1054 (2013).
- Stolting, G. et al. Isradipine therapy in *Cacna1d*<sup>fl<sup>lo</sup>/72<sup>Mei</sup>/+</sup> mice ameliorates primary aldosteronism and neurologic abnormalities. *JCI Insight* **8**, e162468 (2023).
- Ortner, N. J., Kaserer, T., Copeland, J. N. & Striessnig, J. De novo CACNA1D Ca<sup>2+</sup> channelopathies: clinical phenotypes and molecular mechanism. *Pflugers Arch.* **472**, 755–773 (2020).
- Menabo, S. et al. Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency: functional consequences of four CYP11B1 mutations. *Eur. J. Hum. Genet.* **22**, 610–616 (2014).
- White, P. C. et al. A mutation in CYP11B1 (Arg-448-His) associated with steroid 11 beta-hydroxylase deficiency in Jews of Moroccan origin. *J. Clin. Invest.* **87**, 1664–1667 (1991).
- Auchus, R. J. Steroid 17-hydroxylase and 17,20-lyase deficiencies, genetic and pharmacologic. *J. Steroid Biochem. Mol. Biol.* **165**, 71–78 (2017).
- Kagimoto, M., Winter, J. S., Kagimoto, K., Simpson, E. R. & Waterman, M. R. Structural characterization of normal and mutant human steroid 17 $\alpha$ -hydroxylase genes: molecular basis of one example of combined 17 $\alpha$ -hydroxylase/17,20 lyase deficiency. *Mol. Endocrinol.* **2**, 564–570 (1988).
- Mune, T., Rogerson, F. M., Nikkila, H., Agarwal, A. K. & White, P. C. Human hypertension caused by mutations in the kidney isozyme of 11 $\beta$ -hydroxysteroid dehydrogenase. *Nat. Genet.* **10**, 394–399 (1995).
- Carvajal, C. A., Tapia-Castillo, A., Vecchiola, A., Baudrand, R. & Fardella, C. E. Classic and nonclassic apparent mineralocorticoid excess syndrome. *J. Clin. Endocrinol. Metab.* **105**, dgz315 (2020).
- Lu, Y. T. et al. Apparent mineralocorticoid excess: comprehensive overview of molecular genetics. *J. Transl Med.* **20**, 500 (2022).
- Geller, D. S. et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science* **289**, 119–123 (2000).
- Rafestin-Oblin, M. E. et al. The severe form of hypertension caused by the activating S810L mutation in the mineralocorticoid receptor is cortisone related. *Endocrinology* **144**, 528–533 (2003).
- Vingerhoeds, A. C., Thijssen, J. H. & Schwarz, F. Spontaneous hypercortisolism without Cushing's syndrome. *J. Clin. Endocrinol. Metab.* **43**, 1128–1133 (1976).
- Hurley, D. M. et al. Point mutation causing a single amino acid substitution in the hormone binding domain of the glucocorticoid receptor in familial glucocorticoid resistance. *J. Clin. Invest.* **87**, 680–686 (1991).
- Hernandez-Ramirez, L. C. & Stratakis, C. A. Genetics of Cushing's syndrome. *Endocrinol. Metab. Clin. North Am.* **47**, 275–297 (2018).
- Paver, W. K. & Pauline, G. J. Hypertension and hyperpotassaemia without renal disease in a young male. *Med. J. Aust.* **2**, 305–306 (1964).
- Stokes, G. S., Gentle, J. L., Edwards, K. D. & Stewart, J. H. Syndrome of idiopathic hyperkalaemia and hypertension with decreased plasma renin activity: effects on plasma renin and aldosterone of reducing the serum potassium level. *Med. J. Aust.* **2**, 1050–1054 (1968).
- Wilson, F. H. et al. Human hypertension caused by mutations in WNK kinases. *Science* **293**, 1107–1112 (2001).
- Boyd, L. M. et al. Mutations in Kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. *Nature* **482**, 98–102 (2012).
- Louis-Dit-Picard, H. et al. *KLHL3* mutations cause familial hyperkalemic hypertension by impairing ion transport in the distal nephron. *Nat. Genet.* **44**, 456–460 (2012).
- Furusho, T., Uchida, S. & Sohara, E. The WNK signaling pathway and salt-sensitive hypertension. *Hypertens. Res.* **43**, 733–743 (2020).
- Pagani, L. et al. Three reportedly unrelated families with Liddle syndrome inherited from a common ancestor. *Hypertension* **71**, 273–279 (2018).
- Gw, L. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. *Trans. Assoc. Physicians* **76**, 199–213 (1966).
- Shimkets, R. A. et al. Liddle's syndrome: heritable human hypertension caused by mutations in the  $\beta$  subunit of the epithelial sodium channel. *Cell* **79**, 407–414 (1994).
- Hansson, J. H. et al. Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. *Nat. Genet.* **11**, 76–82 (1995).
- Salih, M. et al. A missense mutation in the extracellular domain of  $\alpha$ ENaC causes Liddle syndrome. *J. Am. Soc. Nephrol.* **28**, 3291–3299 (2017).
- Safian, R. D. & Textor, S. C. Renal-artery stenosis. *N. Engl. J. Med.* **344**, 431–442 (2001).
- Bilginturan, N., Zileli, S., Karacadag, S. & Pirnar, T. Hereditary brachydactyly associated with hypertension. *J. Med. Genet.* **10**, 253–259 (1973).
- Toka, O. et al. Childhood hypertension in autosomal-dominant hypertension with brachydactyly. *Hypertension* **56**, 988–994 (2010).
- Maass, P. G. et al. PDE3A mutations cause autosomal dominant hypertension with brachydactyly. *Nat. Genet.* **47**, 647–653 (2015).
- Ercu, M. et al. Phosphodiesterase 3A and arterial hypertension. *Circulation* **142**, 133–149 (2020).
- Rutsch, F. et al. Mutations in ENPP1 are associated with 'idiopathic' infantile arterial calcification. *Nat. Genet.* **34**, 379–381 (2003).

57. Nitschke, Y. et al. Generalized arterial calcification of infancy and pseudoxanthoma elasticum can be caused by mutations in either ENPP1 or ABCC6. *Am. J. Hum. Genet.* **90**, 25–39 (2012).
58. Guo, D. C. et al. Loss-of-function mutations in YY1AP1 lead to grange syndrome and a fibromuscular dysplasia-like vascular disease. *Am. J. Hum. Genet.* **100**, 21–30 (2017).
59. Rath, M. et al. Identification of pathogenic YY1AP1 splice variants in siblings with Grange syndrome by whole exome sequencing. *Am. J. Med. Genet. A* **179**, 295–299 (2019).
60. Tank, A. W. & Lee Wong, D. Peripheral and central effects of circulating catecholamines. *Compr. Physiol.* **5**, 1–15 (2015).
61. Turin, C. G., Crenshaw, M. M. & Fishbein, L. Pheochromocytoma and paraganglioma: germline genetics and hereditary syndromes. *Endocr. Oncol.* **2**, R65–R77 (2022).
62. Burnichon, N. et al. SDHA is a tumor suppressor gene causing paraganglioma. *Hum. Mol. Genet.* **19**, 3011–3020 (2010).
63. Astuti, D. et al. Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. *Am. J. Hum. Genet.* **69**, 49–54 (2001).
64. Niemann, S. & Muller, U. Mutations in SDHC cause autosomal dominant paraganglioma, type 3. *Nat. Genet.* **26**, 268–270 (2000).
65. Baysal, B. E. et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. *Science* **287**, 848–851 (2000).
66. Hao, H. X. et al. SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma. *Science* **325**, 1139–1142 (2009).
67. Remacha, L. et al. Recurrent germline DLST mutations in individuals with multiple pheochromocytomas and paragangliomas. *Am. J. Hum. Genet.* **104**, 651–664 (2019).
68. Buffet, A. et al. Germline mutations in the mitochondrial 2-oxoglutarate/malate carrier SLC25A11 gene confer a predisposition to metastatic paragangliomas. *Cancer Res.* **78**, 1914–1922 (2018).
69. Lorenzo, F. R. et al. A novel EPAS1/HIF2A germline mutation in a congenital polycythemia with paraganglioma. *J. Mol. Med.* **91**, 507–512 (2013).
70. Neumann, H. P. et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N. Engl. J. Med.* **346**, 1459–1466 (2002).
71. Eng, C. et al. Mutations in the RET proto-oncogene and the von Hippel-Lindau disease tumour suppressor gene in sporadic and syndromic pheochromocytomas. *J. Med. Genet.* **32**, 934–937 (1995).
72. Friedman, J. M. et al. Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force. *Genet. Med.* **4**, 105–111 (2002).
73. Comino-Mendez, I. et al. Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. *Nat. Genet.* **43**, 663–667 (2011).
74. Qin, Y. et al. Germline mutations in TMEM127 confer susceptibility to pheochromocytoma. *Nat. Genet.* **42**, 229–233 (2010).
75. Simon, D. B. et al. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nat. Genet.* **13**, 183–188 (1996).
76. Simon, D. B. et al. Genetic heterogeneity of Bartter's syndrome revealed by mutations in the K<sup>+</sup> channel, ROMK. *Nat. Genet.* **14**, 152–156 (1996).
77. Simon, D. B. et al. Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III. *Nat. Genet.* **17**, 171–178 (1997).
78. Birkenhager, R. et al. Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. *Nat. Genet.* **29**, 310–314 (2001).
79. Schlingmann, K. P. et al. Salt wasting and deafness resulting from mutations in two chloride channels. *N. Engl. J. Med.* **350**, 1314–1319 (2004).
80. Laghmani, K. et al. Polyhydramnios, transient neonatal Bartter's syndrome, and MAGED2 mutations. *N. Engl. J. Med.* **374**, 1853–1863 (2016).
81. Bartter, F. C., Pronove, P., Gill, J. R. Jr. & Maccardle, R. C. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalaemic alkalosis. A new syndrome. *Am. J. Med.* **33**, 811–828 (1962).
82. Gitelman, H. J., Graham, J. B. & Welt, L. G. A new familial disorder characterized by hypokalemia and hypomagnesemia. *Trans. Assoc. Am. Physicians* **79**, 221–235 (1966).
83. Simon, D. B. et al. Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. *Nat. Genet.* **12**, 24–30 (1996).
84. Cheek, D. B. & Perry, J. W. A salt wasting syndrome in infancy. *Arch. Dis. Child.* **33**, 252–256 (1958).
85. Geller, D. S. et al. Mutations in the mineralocorticoid receptor gene cause autosomal dominant pseudohypoaldosteronism type I. *Nat. Genet.* **19**, 279–281 (1998).
86. Chang, S. S. et al. Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type I. *Nat. Genet.* **12**, 248–253 (1996).
87. Strautnieks, S. S., Thompson, R. J., Gardiner, R. M. & Chung, E. A novel splice-site mutation in the gamma subunit of the epithelial sodium channel gene in three pseudohypoaldosteronism type I families. *Nat. Genet.* **13**, 248–250 (1996).
88. Williams, T. A. et al. International histopathology consensus for unilateral primary aldosteronism. *J. Clin. Endocrinol. Metab.* **106**, 42–54 (2021).
89. Funder, J. W. et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **101**, 1889–1916 (2016).
90. Beuschlein, F. et al. Somatic mutations in ATP1A1 and ATP2B3 lead to aldosterone-producing adenomas and secondary hypertension. *Nat. Genet.* **45**, 440–444 (2013).
91. Scholl, U. I. Genetics of primary aldosteronism. *Hypertension* **79**, 887–897 (2022).
92. Azizan, E. A. et al. Somatic mutations in ATP1A1 and CACNA1D underlie a common subtype of adrenal hypertension. *Nat. Genet.* **45**, 1055–1060 (2013).
93. Dutta, R. K. et al. A somatic mutation in CLCN2 identified in a sporadic aldosterone-producing adenoma. *Eur. J. Endocrinol.* **181**, K37–K41 (2019).
94. Nanba, K. et al. Somatic CACNA1H mutation as a cause of aldosterone-producing adenoma. *Hypertension* **75**, 645–649 (2020).
95. Rege, J. et al. Somatic SLC30A1 mutations altering zinc transporter ZnT1 cause aldosterone-producing adenomas and primary aldosteronism. *Nat. Genet.* **55**, 1623–1631 (2023).
96. Wu, X. et al. Somatic mutations of CADM1 in aldosterone-producing adenomas and gap junction-dependent regulation of aldosterone production. *Nat. Genet.* **55**, 1009–1021 (2023).
97. Tadjine, M., Lampron, A., Ouadi, L. & Bourdeau, I. Frequent mutations of beta-catenin gene in sporadic secreting adrenocortical adenomas. *Clin. Endocrinol.* **68**, 264–270 (2008).
98. Zhou, J. et al. Somatic mutations of GNA11 and GNAQ in CTNNB1-mutant aldosterone-producing adenomas presenting in puberty, pregnancy or menopause. *Nat. Genet.* **53**, 1360–1372 (2021).
99. Nishimoto, K. et al. Aldosterone-stimulating somatic gene mutations are common in normal adrenal glands. *Proc. Natl Acad. Sci. USA* **112**, E4591–E4599 (2015).
100. Omata, K. et al. Cellular and genetic causes of idiopathic hyperaldosteronism. *Hypertension* **72**, 874–880 (2018).
101. Nishimoto, K. et al. Case report: nodule development from subcapsular aldosterone-producing cell clusters causes hyperaldosteronism. *J. Clin. Endocrinol. Metab.* **101**, 6–9 (2016).
102. Reincke, M. & Fleseriu, M. Cushing syndrome: a review. *JAMA* **330**, 170–181 (2023).
103. Reincke, M. et al. Mutations in the deubiquitinase gene USP8 cause Cushing's disease. *Nat. Genet.* **47**, 31–38 (2015).
104. Chen, J. et al. Identification of recurrent USP48 and BRAF mutations in Cushing's disease. *Nat. Commun.* **9**, 3171 (2018).
105. Hernandez-Ramirez, L. C. et al. Loss-of-function mutations in the CABLES1 gene are a novel cause of Cushing's disease. *Endocr. Relat. Cancer* **24**, 379–392 (2017).
106. Beuschlein, F. et al. Constitutive activation of PKA catalytic subunit in adrenal Cushing's syndrome. *N. Engl. J. Med.* **370**, 1019–1028 (2014).
107. Tissier, F. et al. Mutations of  $\beta$ -catenin in adrenocortical tumors: activation of the Wnt signaling pathway is a frequent event in both benign and malignant adrenocortical tumors. *Cancer Res.* **65**, 7622–7627 (2005).
108. Lenders, J. W. M. et al. Genetics, diagnosis, management and future directions of research of pheochromocytoma and paraganglioma: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. *J. Hypertens.* **38**, 1443–1456 (2020).
109. Huang, Y. C. et al. Somatic SDHA mutations in paragangliomas in siblings: case report of 2 cases. *Medicine* **99**, e22497 (2020).
110. van Nederveen, F. H., Korpershoek, E., Lenders, J. W., de Krijger, R. R. & Dinjens, W. N. Somatic SDHB mutation in an extraadrenal pheochromocytoma. *N. Engl. J. Med.* **357**, 306–308 (2007).
111. Weber, A., Hoffmann, M. M., Neumann, H. P. & Erlic, Z. Somatic mutation analysis of the SDHB, SDHC, SDHD, and RET genes in the clinical assessment of sporadic and hereditary pheochromocytoma. *Horm. Cancer* **3**, 187–192 (2012).
112. Comino-Mendez, I. et al. Tumoral EPAS1 (HIF2A) mutations explain sporadic pheochromocytoma and paraganglioma in the absence of erythrocytosis. *Hum. Mol. Genet.* **22**, 2169–2176 (2013).
113. Gaal, J. et al. Isocitrate dehydrogenase mutations are rare in pheochromocytomas and paragangliomas. *J. Clin. Endocrinol. Metab.* **95**, 1274–1278 (2010).
114. Richter, S. et al. Metabolome-guided genomics to identify pathogenic variants in isocitrate dehydrogenase, fumarate hydratase, and succinate dehydrogenase genes in pheochromocytoma and paraganglioma. *Genet. Med.* **21**, 705–717 (2019).
115. Burnichon, N. et al. Somatic NF1 inactivation is a frequent event in sporadic pheochromocytoma. *Hum. Mol. Genet.* **21**, 5397–5405 (2012).
116. Welander, J. et al. Integrative genomics reveals frequent somatic NF1 mutations in sporadic pheochromocytomas. *Hum. Mol. Genet.* **21**, 5406–5416 (2012).
117. Crona, J. et al. Somatic mutations in H-RAS in sporadic pheochromocytoma and paraganglioma identified by exome sequencing. *J. Clin. Endocrinol. Metab.* **98**, E1266–E1271 (2013).
118. Welander, J. et al. Activating FGFR1 mutations in sporadic pheochromocytomas. *World J. Surg.* **42**, 482–489 (2018).
119. Burnichon, N. et al. Integrative genomic analysis reveals somatic mutations in pheochromocytoma and paraganglioma. *Hum. Mol. Genet.* **20**, 3974–3985 (2011).
120. Burnichon, N. et al. MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. *Clin. Cancer Res.* **18**, 2828–2837 (2012).
121. Fishbein, L. et al. Whole-exome sequencing identifies somatic ATRX mutations in pheochromocytomas and paragangliomas. *Nat. Commun.* **6**, 6140 (2015).
122. Fishbein, L. et al. Comprehensive molecular characterization of pheochromocytoma and paraganglioma. *Cancer Cell* **31**, 181–193 (2017).
123. Juhlin, C. C. et al. Whole-exome sequencing defines the mutational landscape of pheochromocytoma and identifies KMT2D as a recurrently mutated gene. *Genes. Chromosomes Cancer* **54**, 542–554 (2015).

124. Treger, T. D. et al. Targetable NOTCH1 rearrangements in reninoma. *Nat. Commun.* **14**, 5826 (2023).
125. Belyea, B. C. et al. Overexpression of notch signaling in renin cells leads to a polycystic kidney phenotype. *Clin. Sci.* **137**, 35–45 (2023).
126. Keaton, J. M. et al. Genome-wide analysis in over 1 million individuals of European ancestry yields improved polygenic risk scores for blood pressure traits. *Nat. Genet.* **56**, 778–791 (2024).
127. Levy, D. et al. Genome-wide association study of blood pressure and hypertension. *Nat. Genet.* **41**, 677–687 (2009).
128. Padmanabhan, S. & Dominiczak, A. F. Genomics of hypertension: the road to precision medicine. *Nat. Rev. Cardiol.* **18**, 235–250 (2021).
129. Newton-Cheh, C. et al. Genome-wide association study identifies eight loci associated with blood pressure. *Nat. Genet.* **41**, 666–676 (2009).
130. Evangelou, E. et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat. Genet.* **50**, 1412–1425 (2018).
131. Giri, A. et al. Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. *Nat. Genet.* **51**, 51–62 (2019).
132. Yang, J., Zeng, J., Goddard, M. E., Wray, N. R. & Visscher, P. M. Concepts, estimation and interpretation of SNP-based heritability. *Nat. Genet.* **49**, 1304–1310 (2017).
133. Genin, E. Missing heritability of complex diseases: case solved? *Hum. Genet.* **139**, 103–113 (2020).
134. Manolio, T. A. et al. Finding the missing heritability of complex diseases. *Nature* **461**, 747–753 (2009).
135. Ives, C. W., Sinkey, R., Rajapreyar, I., Tita, A. T. N. & Oparil, S. Preeclampsia-pathophysiology and clinical presentations: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **76**, 1690–1702 (2020).
136. Honigberg, M. C. et al. Polygenic prediction of preeclampsia and gestational hypertension. *Nat. Med.* **29**, 1540–1549 (2023).
137. Freund, M. K. et al. Phenotype-specific enrichment of mendelian disorder genes near GWAS regions across 62 complex traits. *Am. J. Hum. Genet.* **103**, 535–552 (2018).
138. Xu, X. et al. Genetic imputation of kidney transcriptome, proteome and multi-omics illuminates new blood pressure and hypertension targets. *Nat. Commun.* **15**, 2359 (2024).
139. Padmanabhan, S. et al. Genome-wide association study of blood pressure extremes identifies variant near UMOD associated with hypertension. *PLoS Genet.* **6**, e1001177 (2010).
140. Graham, L. A. et al. Validation of uromodulin as a candidate gene for human essential hypertension. *Hypertension* **63**, 551–558 (2014).
141. Alexander, M. R. et al. A single nucleotide polymorphism in sh2b3/lnk promotes hypertension development and renal damage. *Circ. Res.* **131**, 731–747 (2022).
142. Oliveros, W. et al. Systematic characterization of regulatory variants of blood pressure genes. *Cell Genom.* **3**, 100330 (2023).
143. Kato, N. et al. Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. *Nat. Genet.* **47**, 1282–1293 (2015).
144. Gunawardhana, K. L. et al. A systems biology approach identifies the role of dysregulated PRDM6 in the development of hypertension. *J. Clin. Investig.* **133**, e160036 (2023).
145. Gupta, R. M. et al. A genetic variant associated with five vascular diseases is a distal regulator of endothelin-1 gene expression. *Cell* **170**, 522–533 (2017).
146. Broekema, R. V., Bakker, O. B. & Jonkers, I. H. A practical view of fine-mapping and gene prioritization in the post-genome-wide association era. *Open Biol.* **10**, 190221 (2020).
147. Degner, K. N., Bell, J. L., Jones, S. D. & Won, H. Just a SNP away: The future of in vivo massively parallel reporter assay. *Cell Insight* **4**, 100214 (2025).
148. Eales, J. M. et al. Uncovering genetic mechanisms of hypertension through multi-omic analysis of the kidney. *Nat. Genet.* **53**, 630–637 (2021).
149. Wang, Q. et al. Rare variant contribution to human disease in 281,104 UK Biobank exomes. *Nature* **597**, 527–532 (2021).
150. Backman, J. D. et al. Exome sequencing and analysis of 454,787 UK Biobank participants. *Nature* **599**, 628–634 (2021).
151. Kelly, T. N. et al. Insights from a large-scale whole-genome sequencing study of systolic blood pressure, diastolic blood pressure, and hypertension. *Hypertension* **79**, 1656–1667 (2022).
152. Copeland, I. et al. Exome sequencing implicates ancestry-related Mendelian variation at SYNE1 in childhood-onset essential hypertension. *JCI Insight* **9**, e172152 (2024).
153. Pei, F. et al. Differential expression and DNA methylation of angiotensin type 1A receptors in vascular tissues during genetic hypertension development. *Mol. Cell Biochem.* **402**, 1–8 (2015).
154. Lee, H. A. et al. Promoter hypomethylation upregulates Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter 1 in spontaneously hypertensive rats. *Biochem. Biophys. Res. Commun.* **396**, 252–257 (2010).
155. Lee, H. A. et al. Tissue-specific upregulation of angiotensin-converting enzyme 1 in spontaneously hypertensive rats through histone code modifications. *Hypertension* **59**, 621–626 (2012).
156. Bogdarina, I., Welham, S., King, P. J., Burns, S. P. & Clark, A. J. Epigenetic modification of the renin-angiotensin system in the fetal programming of hypertension. *Circ. Res.* **100**, 520–526 (2007).
157. Alexander, M. R., Edwards, T. L. & Harrison, D. G. GWAS for defining the pathogenesis of hypertension: have they delivered? *Hypertension* **82**, 573–582 (2025).
158. Williams, B. et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* **386**, 2059–2068 (2015).
159. Flack, J. M. et al. Efficacy and safety of baxdrostat in uncontrolled and resistant hypertension. *N. Engl. J. Med.* **393**, 1363–1374 (2025).
160. Nelson, M. R. et al. The support of human genetic evidence for approved drug indications. *Nat. Genet.* **47**, 856–860 (2015).
161. Etges, A. et al. A novel homozygous KLHL3 mutation as a cause of autosomal recessive pseudohypaldosteronism type II diagnosed late in life. *Nephron* **146**, 418–428 (2022).
162. Constantinescu, G. et al. Integration of artificial intelligence and plasma steroidomics with laboratory information management systems: application to primary aldosteronism. *Clin. Chem. Lab. Med.* **60**, 1929–1937 (2022).

## Author contributions

All authors researched data for the article, contributed substantially to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

## Competing interests

Rockefeller University has filed a patent application (PCT/US2018/033362, Compositions and methods for diagnosing and treating diseases and disorders associated with mutant KCNJ5), listing U.I.S. as an inventor. The other authors declare no competing interests.

## Additional information

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41581-025-01020-6>.

**Peer review information** *Nature Reviews Nephrology* thanks the anonymous reviewers for their contribution to the peer review of this work.

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