



# Hereditary causes of primary aldosteronism and other disorders of apparent excess mineralocorticoid activity

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**Abstract:** Secondary hypertension is a common condition with a broad differential diagnosis. Identification of the true cause of hypertension can be critical for guiding appropriate management. Here, we review hereditary conditions underlying the most common cause of secondary hypertension, primary aldosteronism, as well as other disorders impacting various levels of mineralocorticoid action. Recently, several pathogenic variants of ion channels have been described as etiologies of familial aldosteronism. Defects in steroid hormone synthesis cause hypertension in 11 $\beta$ -hydroxylase deficiency and 17 $\alpha$ -hydroxylase deficiency, two types of congenital adrenal hyperplasia. Inappropriate activation of mineralocorticoid receptors underlies the syndrome of apparent mineralocorticoid excess and constitutive activation of the mineralocorticoid receptor. Finally, Liddle syndrome and pseudohypoaldosteronism type 2 are disorders impacting the function of renal sodium channels, the endpoint of mineralocorticoid action. We discuss the pathophysiology, clinical presentation, diagnosis and management of these low renin hypertension states that ultimately result in apparent excess mineralocorticoid activity.

**Keywords:** Familial aldosteronism; 11 $\beta$ -hydroxylase deficiency; 17 $\alpha$ -hydroxylase deficiency; constitutive activation of the mineralocorticoid receptor; syndrome of apparent mineralocorticoid excess; Liddle syndrome; pseudohypoaldosteronism type 2 (PHA2)

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## Introduction

Essential hypertension accounts for the vast majority of cases of hypertension in adults, while secondary causes of hypertension have a prevalence of 10–15% (1,2). Prevalence of secondary hypertension increases with younger age, documented to account for up to 30% in adults under 40 years of age and up to 80% in children under 6 (3-5). While most cases of both essential and secondary hypertension are polygenic, a number of disorders have been found to have monogenic etiology. The diagnosis of these hereditary conditions can be challenging, but can

also be critical for guiding appropriate care for patients and potentially affected family members.

Here we provide an overview of known hereditary disorders that specifically impact mineralocorticoid action and ultimately cause low renin hypertension (*Table 1*). These conditions include familial hyperaldosteronism, defects in steroidogenesis, altered mineralocorticoid receptor activation in the kidney, and changes in the endpoint of mineralocorticoid action, namely the renal epithelial sodium channel (ENaC). These disorders should be considered in the differential diagnosis of young patients presenting with hypertension and hypokalemia, particularly those with a

**Table 1** Hereditary causes of primary aldosteronism and other disorders of apparent excess mineralocorticoid activity

Condition	Mode of inheritance	Gene	Pathophysiology	Electrolyte abnormalities	Aldosterone level	Other clinical features	Management
FH type 1 (glucocorticoid-remediable aldosteronism)	Autosomal dominant	Fusion of <i>CYP11B1</i> and <i>CYP11B2</i> , encoding for 11 $\beta$ -hydroxylase and aldosterone synthase, respectively	Aldosterone production becomes responsive to ACTH stimulation	Low or normal potassium, metabolic alkalosis	Elevated	Early cerebrovascular events	Glucocorticoids, MR antagonists
FH type 2	Autosomal dominant	Gain-of-function variants of <i>CLCN2</i> , encoding ClC-2 chloride channel	Depolarization of adrenal glomerulosa cells through increased chloride conductance, leading to hyperaldosteronism	Low or normal potassium, metabolic alkalosis	Elevated	-	MR antagonists, possible surgery
FH type 3	Autosomal dominant	Gain-of-function or altered ion selectivity variants of <i>KCNJ5</i> , encoding potassium channel	Depolarization of adrenal glomerulosa cells through altered channel selectivity, leading to hyperaldosteronism	Low potassium, metabolic alkalosis	Elevated	Adrenal hyperplasia	MR antagonists, surgery
FH type 4	Autosomal dominant	Gain-of-function variants of <i>CACNA1H</i> , encoding calcium channel	Channel activation at less depolarized potential and impaired channel deactivation, leading to hyperaldosteronism	Low or normal potassium, metabolic alkalosis	Elevated	-	MR antagonists, possible surgery
11 $\beta$ -hydroxylase deficiency	Autosomal recessive	Loss of function variants of <i>CYP11B1</i> , encoding 11 $\beta$ -hydroxylase	Decreased production of cortisol and aldosterone, leading to accumulation of precursors (DOC, 11-deoxycortisol)	Low or normal potassium	Low	Ambiguous genitalia in girls and features of hyperandrogenism in both genders in	Glucocorticoids, MR antagonists
17 $\alpha$ -hydroxylase deficiency	Autosomal recessive	Loss of function variants of <i>CYP17A1</i> , encoding 17 $\alpha$ -hydroxylase	Decreased production of cortisol and sex hormones with shunting to DOC and corticosterone production	Low or normal potassium	Low	Impaired sexual development, absence of secondary sexual characteristics, amenorrhea	MR antagonists, glucocorticoids, sex hormones
Apparent mineralocorticoid excess	Autosomal recessive	Loss of function variants of <i>HSD11B2</i> , encoding 11 $\beta$ -hydroxysteroid dehydrogenase type 2	In the absence of 11 $\beta$ -HSD conversion to cortisone, cortisol binds to MR	Low or normal potassium, metabolic alkalosis	Low	Hypercalciuria, nephrocalcinosis	MR antagonists, thiazides
Constitutive activation of the mineralocorticoid receptor (Geller syndrome)	Autosomal dominant	Gain-of-function variants of <i>NR3C2</i> , encoding mineralocorticoid receptor gene	Mutation causes constitutive activation of the MR, with possible activation by progesterone	Low or normal potassium	Low	Worsening of hypertension in pregnancy	Delivery in pregnancy, non-spirolactone antihypertensives
Liddle syndrome	Autosomal dominant	Gain-of-function variants of <i>SCNN1B</i> or <i>SCNN1G</i> , encoding ENaC subunits $\beta$ and $\gamma$	Constitutive activation of ENaC in distal nephron	Low or normal potassium, metabolic alkalosis	Low	-	Low salt diet, ENaC inhibitors
PHA2 (Gordon syndrome)	Autosomal dominant	Loss of function variants of <i>WNK1</i> and <i>WNK4</i> genes involved in NCC expression	Increased activation of NCC of distal nephron	Elevated potassium, hyperchloremic metabolic acidosis	Normal or elevated	Hypercalciuria	Low salt diet, thiazides

DOC, deoxycorticosterone; ENaC, epithelial sodium channel; FH, familial hyperaldosteronism; MR, mineralocorticoid receptor; NCC, sodium-chloride cotransporter; PHA2, pseudohypoaldosteronism type 2.

family history of hypertension with hypokalemia. The aim of this overview is to be a useful guide in the work-up of patients with low renin hypertension.

### Hereditary causes of primary aldosteronism (PA)

The most common cause of secondary hypertension is PA, which accounts for up to 20% of resistant hypertension and ~8% of all hypertension (6). Although PA is classically characterized by hypokalemia and hypertension, it has become clear that its spectrum extends to normokalemic hypertension as well. The underlying etiology is either a unilateral aldosterone producing adenoma (APA) or bilateral adrenal aldosterone excess, both present in roughly 50% of cases. On diagnostic testing, hypokalemia can be mild or absent, but aldosterone is elevated with suppressed renin. Confirmatory testing includes salt loading, saline infusion, or fludrocortisone application to evaluate for suppression of urinary aldosterone, and, ultimately, adrenal vein sampling for lateralization. In the setting of strong family history of PA and bilateral origin of aldosterone excess, genetic testing for pathogenic variants in genes mentioned below should be considered. Unilateral adrenalectomy is an option in cases of lateralization of aldosterone overproduction; otherwise medical management with mineralocorticoid antagonists is recommended.

Four types of familial hyperaldosteronism have been recognized. Familial hyperaldosteronism type 1, also known as glucocorticoid-remediable aldosteronism (GRA), is an autosomal dominant condition due to the fusion of *CYP11B1* and *CYP11B2* encoding for 11 $\beta$ -hydroxylase and aldosterone synthase, respectively (7). Transcription of *CYP11B1* is usually induced by adrenocorticotrophic hormone (ACTH) leading to cortisol synthesis, and transcription of *CYP11B2* by angiotensin 2 results in aldosterone synthesis. In the setting of GRA-associated gene fusion, *CYP11B2* expression becomes ACTH responsive, resulting in ACTH-induced aldosterone production. Notably, GRA has been associated with increased risk for early hemorrhagic cerebrovascular events (8). In addition to basal plasma aldosterone and renin testing, recommended diagnostic testing includes dexamethasone suppression of aldosterone and genetic testing. The typical protocol for dexamethasone suppression testing is to measure aldosterone before and after administering dexamethasone 0.5 mg every 6 hours for 4 days (9,10), though dexamethasone dosing and duration ranging from 0.75–2.0 mg per day, administered

for 2–15 days, have been reported (11). Unlike other forms of PA, glucocorticoids at physiologic and below physiologic dosing have been shown to be an effective therapeutic option, suppressing ACTH and thereby decreasing aldosterone production (12).

Familial hyperaldosteronism types 2, 3, and 4 are not responsive to glucocorticoids. Familial hyperaldosteronism type 2 is clinically indistinguishable from sporadic PA. No notable differences in age of disease onset, plasma renin, serum aldosterone, or potassium levels are seen. Both APAs and bilateral excess aldosterone production are associated with familial hyperaldosteronism type 2 (13–15). It is likely inherited in an autosomal dominant pattern and has been associated with gain-of-function mutations in the *CLCN2* gene, encoding for chloride channel protein 2 expressed in adrenal glomerulosa cells (16,17). The penetrance of this genetic disorder is currently unknown, but it is suggested to be incomplete.

Familial hyperaldosteronism type 3 is a rare, highly penetrant, autosomal dominant disorder due to mutations in the potassium channel gene *KCNJ5* (18). The initial cases described were in a single family, with multiple members presenting with refractory hypertension and bilateral adrenal gland hyperplasia (19). All family members ultimately required bilateral adrenalectomy to manage their hypertension. Most of the subsequent reported cases of *KCNJ5* pathogenic variants similarly have childhood onset severe hypertension, associated with hypokalemia, aldosterone levels greater than 100 ng/dL and low renin activity less than 1.0 ng/mL/h, ultimately requiring either life-long mineralocorticoid antagonist therapy or bilateral adrenalectomy for management (19–21); adrenal pathology often shows hyperplasia of the zona glomerulosa or fasciculata. However, milder phenotypes and ACTH-dependent aldosterone overproduction have also been reported (22,23).

Familial hyperaldosteronism type 4 is a rare condition due to mutations in *CACNA1H*, encoding for calcium channels expressed in adrenal glomerulosa (24,25). Similar to familial hyperaldosteronism type 2, type 4 is typically indistinguishable from sporadic PA in clinical presentation, and may present with normal appearing adrenal glands, single adenoma, or bilateral hyperplasia.

Another gene with variants associated with PA, which is not classified as a type of familial hyperaldosteronism, is *CACNA1D*. Pathogenic variants in this gene, encoding for calcium channel Cav1.3, can lower depolarization potential and impair channel inactivation; the resulting increase

in calcium influx is thought to stimulate aldosterone production and glomerulosa cell proliferation (26,27). Few individuals with *CACNA1D* mutations have been described, and notably present with a syndrome of PA, seizures and neuromuscular abnormalities (26,28).

### Defects in steroid hormone synthesis

Congenital adrenal hyperplasia (CAH) encompasses a group of inherited disorders resulting in defects in cortisol synthesis. While the most common form of CAH, 21-hydroxylase deficiency, is associated with mineralocorticoid deficiency, 11 $\beta$ -hydroxylase deficiency and 17 $\alpha$ -hydroxylase deficiency are the two types of CAH associated with mineralocorticoid excess, resulting in hypertension.

#### 11 $\beta$ -hydroxylase deficiency

11 $\beta$ -hydroxylase deficiency is the second most common form of CAH, accounting for approximately 5% of CAH cases in some series (29). 11 $\beta$ -hydroxylase deficiency is caused by autosomal recessive mutations in *CYP11B1*, of which more than 20 pathogenic variants have been identified (30-34). *CYP11B1* encodes for the function of 11 $\beta$ -hydroxylase, which converts 11-deoxycortisol to cortisol; the expression of the *CYP11B1* gene in the zona fasciculata is regulated by ACTH. Reduced activity of 11-hydroxylase causes decreased production of cortisol, which results in elevation of ACTH. This elevation then causes accumulation of steroid precursors, deoxycorticosterone (DOC) and 11-deoxycortisol, as well as overproduction of androgens. The mineralocorticoid activity of DOC and related metabolites causes salt retention, hypertension, and hypokalemia. The clinical presentation of 11 $\beta$ -hydroxylase deficiency can be variable (35), depending on degree of enzyme deficiency: classic 11 $\beta$ -hydroxylase deficiency presents with ambiguous genitalia in genetic females and features of hyperandrogenism in both sexes, while these symptoms may be mild in the non-classic form (36). Hypertension is seen in approximately two-thirds of individuals with the classic form of 11 $\beta$ -hydroxylase deficiency (37) and often within the first year of life, but is not seen in those with the non-classic form. In male patients with 11 $\beta$ -hydroxylase deficiency, hypertension and hypokalemia alone can be the clinical presentation. Diagnosis is made by identifying elevated basal 11-deoxycortisol or elevated ACTH-

stimulated 11-deoxycortisol levels, the latter reaching 3-5 times the upper limit of normal in non-classic cases and much higher in classic 11 $\beta$ -hydroxylase deficiency (36). The clinical mineralocorticoid excess is entirely due to DOC, and aldosterone is usually low or absent due to the low renin state. Treatment involves use of glucocorticoids to suppress ACTH-stimulated androgen overproduction and/or mineralocorticoid receptor antagonists. Spironolactone can be used in females for both mineralocorticoid as well as androgen antagonism.

#### 17 $\alpha$ -hydroxylase deficiency

17 $\alpha$ -hydroxylase deficiency is a rare form of CAH caused by mutations in *CYP17A1*, encoding for enzyme activity of both 17 $\alpha$ -hydroxylase and 17,20-lyase (38,39). In most affected individuals, both enzyme activities are impacted, but deficiency of 17,20-lyase with intact 17 $\alpha$ -hydroxylase has also been reported (40,41). More than 100 mutations have been identified in the *CYP17A1* gene in association with 17 $\alpha$ -hydroxylase deficiency (42-44). 17 $\alpha$ -hydroxylase converts progesterone and pregnenolone to 17OH-progesterone and 17OH-pregnenolone, respectively (45). Subsequently, 17,20-lyase converts 21-carbon 17-hydroxysteroids to 19-carbon precursors of sex steroids. 17 $\alpha$ -hydroxylase deficiency therefore decreases production of cortisol and sex hormones, resulting in elevation of ACTH and shunting of precursors to DOC and corticosterone production. Subsequent volume expansion and hypokalemia then suppress renin and aldosterone production. Adrenal crises are rare in the presence of excess DOC and corticosterone. Classic clinical presentation is characterized by hypertension and absence of secondary sexual characteristics in an adolescent; both genetically XX and XY individuals with severe complete deficiency can have female external genitalia and primary amenorrhea (45,46). In partial 17 $\alpha$ -hydroxylase deficiency, hypertension or hypokalemia may not be present, sexual development is impaired to a lesser extent, and XY individuals may be identified to have ambiguous genitalia in infancy (47). Diagnosis is made when basal or ACTH-stimulated DOC and corticosterone are elevated along with low cortisol, androgens, and estrogens (48). Management of 17 $\alpha$ -hydroxylase deficiency includes mineralocorticoid antagonism, physiologic dosing of glucocorticoids and sex hormones to achieve the desired gender and secondary sexual characteristics. In individuals maintaining female phenotype, spironolactone is the drug of choice.

### **Inappropriate activation of the mineralocorticoid receptor**

In addition to overproduction of mineralocorticoids, the overactivation of mineralocorticoid receptors can also result in low renin hypertension. Syndrome of apparent mineralocorticoid excess and constitutive activation of the mineralocorticoid receptor are two such disorders in which mineralocorticoid receptors are inappropriately activated in the absence of mineralocorticoid excess, with associated suppression of aldosterone and renin production.

#### *Apparent mineralocorticoid excess*

Under normal function of the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD), the vast majority of cortisol is converted peripherally to cortisone in tissues where this enzyme is expressed (49). Cortisol binds avidly to mineralocorticoid receptors as aldosterone does, while cortisone does not. In the setting of 11 $\beta$ -HSD deficiency, cortisol, present in the plasma at a concentration approximately 1,000 times higher than aldosterone, binds mineralocorticoid receptors, resulting in the clinical presentation of the aptly named syndrome of apparent mineralocorticoid excess (50,51). A rare disorder with less than 100 cases reported in the literature (52), apparent mineralocorticoid excess is caused by autosomal recessive mutations in *HSD11B2* (53). Patients present in childhood with hypertension, poor growth, and polydipsia. Initial lab findings include hypokalemia with low renin, low aldosterone, and low levels of other mineralocorticoids. Patients may also have metabolic alkalosis. Presentation may be mild in instances of partial residual enzyme function (54). On diagnostic testing, the 24-hour urinary cortisol to urinary free cortisone ratio is high (50). A number of genetic testing options are available. Treatment of apparent mineralocorticoid excess requires use of mineralocorticoid antagonists. Spironolactone may be effective initially, but its effectiveness can wane. Cortisol suppression with small doses of dexamethasone (e.g., 0.75 mg) can be considered in refractory cases. The clinical course can also be complicated by hypercalciuria or nephrocalcinosis, though the etiology of this is not well studied. It is thought to be related to chronic hypokalemia, as seen in Bartter syndrome, and can be treated with thiazide diuretics (55,56). Cure of apparent mineralocorticoid excess after renal transplantation has been reported (57).

#### *Constitutive activation of the mineralocorticoid receptor (Geller syndrome)*

*In vitro* studies have shown that mineralocorticoid receptors are specifically activated by some steroids such as aldosterone, antagonized by other steroids such as progesterone, or have no response to steroids such as estradiol and testosterone (58). Geller *et al.* (58) identified in a 15-year-old boy with severe hypertension, a single missense mutation in the mineralocorticoid receptor gene that resulted in gain-of-function variant and constitutive activation of the mineralocorticoid receptor. The condition was found to have an autosomal dominant inheritance pattern, with 11 of 23 relatives studied also carrying diagnoses of severe hypertension before age 20. The individuals had low serum renin and aldosterone. Two affected female family members had notable hypertension during pregnancy, without edema or proteinuria seen in preeclampsia. Serum aldosterone was undetectably low, while it is typically elevated in pregnancy (59). The cause of worsening hypertension during pregnancy is thought to be due to mutant mineralocorticoid receptor activation by progesterone. Hypertension is expected to improve after delivery. Of note, spironolactone was found to activate the mutant mineralocorticoid receptors *in vitro*, so use of other antihypertensive medications is recommended. The syndrome of constitutive activation of mineralocorticoid receptors is an extremely rare syndrome and no additional cases have been described following the initial publication by Geller *et al.*

#### **Other low renin states**

The final target of mineralocorticoid action is sodium channels of the kidney. Both Liddle syndrome and pseudohypoaldosteronism type 2 (PHA2) are disorders impacting the function of the ENaC of the distal nephron; the resulting increase in renal sodium reabsorption precipitates volume overload, suppressed renin, and electrolyte abnormalities.

#### *Liddle syndrome*

Liddle *et al.* (60) described a family with multiple teenage siblings who presented with hypertension, hypokalemia and metabolic alkalosis. The disorder was also termed pseudoaldosteronism, given its clinical similarity with PA,

but the individuals' renin and aldosterone were both low, even when challenged with low sodium diets. On follow-up, the proband case developed renal disease and underwent kidney transplant, which resolved her disorder—and indicated that her condition was due to a primary renal, rather than mineralocorticoid issue (61). Liddle syndrome was ultimately found to be due to autosomal dominant mutations in *SCNN1B* and *SCNN1G*, encoding for subunits of the ENaC of the distal nephron, which results in constitutive activation of the channel (62). Physiologically, ENaC expression is the endpoint of mineralocorticoid action, leading to increased sodium absorption, as would be appropriate in the setting of volume depletion. Constitutive ENaC activation in Liddle syndrome causes excess sodium resorption in the kidney leading to hypertension with suppressed renin and aldosterone. Typically, patients present in childhood, but sometimes reach early adulthood before diagnosis. More than 20 pathogenic variants in the  $\beta$  and  $\gamma$  subunits of the ENaC have been identified (62–66). The diagnosis is confirmed with genetic testing for variants in *SCNN1B* and *SCNN1G*. The disorder is responsive to low salt diet and medications that block ENaC activity, such as amiloride and triamterene. As ENaC expression is not dependent on mineralocorticoid activation, mineralocorticoid antagonists such as spironolactone are ineffective (67,68).

### **PHA2 (Gordon syndrome)**

Gordon *et al.* (69) first described a case of hypertension and hyperkalemia in a 10-year-old girl without a history of renal impairment. The observation of hyperkalemia led to the classification of this syndrome as PHA2 and differentiates it from PA. PHA2 is a distinct entity from PHA types 1A and 1B, which result in loss of function of the ENaC channel and are accompanied by a clinical constellation resembling mineralocorticoid deficiency, with salt wasting, severe hyperkalemia, and hypotension. PHA2 has been associated with autosomal dominant mutations in the *WNK1* and *WNK4* genes, which are involved in the inhibition of the sodium chloride cotransporter (70–72); the mutations result in increased sodium reabsorption in the distal convoluted tubule, with associated downstream effects on ENaC and renal outer medullary potassium channel that ultimately cause hyperkalemia and hyperchloremic metabolic acidosis. Mutations in the *KLHL3* and *CUL3* genes, encoding proteins that degrade WNK kinases, have also been

associated with PHA2 (73,74). Affected individuals present in adolescence or young adulthood with normal to mildly elevated aldosterone levels; genetic testing confirms the diagnosis. The condition is responsive to low salt diet and thiazide diuretics, which act on the sodium-chloride cotransporter (75).

### **Summary and conclusion**

Advances in genetic studies have allowed progressive elucidation of hereditary causes of hypertension. In particular, genetic testing has helped to characterize a number of low-renin hypertension states that can be challenging to differentiate from PA. While many of these conditions are rare, their management is considerably different from polygenic essential hypertension. Therefore, diagnosis of these disorders is essential for effective treatment of affected patients, as well as guiding testing for family members.

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