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Monogenic Hypertension Linked to the Renin–Angiotensin–Aldosterone System

ABSTRACT

Mendelian forms of renin–angiotensin–aldosterone system (RAAS)-related hypertension, commonly referred to as monogenic hypertension, represent a rare but significant subset of hypertensive disorders characterized by genetic mutations that disrupt the normal physiological mechanisms of blood pressure regulation. This review focuses on elucidating the germline mutations affecting RAAS pathways that lead to distinct forms of heritable hypertension. By understanding the pathophysiological basis of conditions such as Gordon's syndrome, Liddle syndrome, congenital adrenal hyperplasia, and familial hyperaldosteronism types, this review aims to highlight the unique clinical features, diagnostic challenges, and therapeutic implications associated with these disorders. Recognizing specific clinical presentations and family histories indicative of monogenic hypertension is crucial for diagnosis, particularly as it often manifests as early-onset hypertension, abnormalities in potassium and blood pH, and occasionally, abnormal sexual development or related syndromes. Therefore, employing a targeted diagnostic approach through next-generation sequencing is essential to pinpoint the responsible genetic mutations, enabling accurate and individualized treatment plans. The critical importance of certain readily available specific channel blockers, such as thiazides or low-dose corticosteroids, in managing these disorders must be emphasized, as they play a key role in preventing serious complications, including cerebrovascular events. As advancements in genetic and molecular sciences continue to evolve, a deeper comprehension of the mechanisms underlying RAAS-related monogenic hypertension promises to revolutionize the management of this complex disorder, offering hope for more effective and individualized treatment options.

Keywords: Genetics, hypertension, pathophysiology, prevention, renin–angiotensin–aldosteron system

REVIEW

INTRODUCTION

Hypertension represents a significant public health issue affecting at least 1.278 billion adults aged 30-79 worldwide.[1] Looking from pathophysiological aspect, hypertension is usually classified as primary, often referred as essential hypertension, which is the most prevalent form and secondary hypertension. However, the categorization of hypertension into "primary" and "secondary" forms serves more as a practical framework than as a reflection of a definitive dichotomous division and oversimplifies the underlying complexities. Secondary hypertension is characterized by a specific, treatable cause leading to elevated blood pressure. However, this classification should not imply that primary hypertension lacks a cause. Instead, primary hypertension often signifies a complex interplay of factors, typically involving polygenic predisposition coupled with atherosclerosis and aspects of a Westernized lifestyle. For the purposes of this review, we will adhere to this traditional nosology rather than exploring more critical or innovative paradigms, as such an examination would exceed the intended scope of this paper.

Secondary hypertension accounts for approximately 5%-10% of all cases of systemic arterial hypertension.[2] This indicates that a single identifiable and therefore potentially treatable condition causing hypertension is of significant prevalence, especially considering that systemic hypertension affects nearly 1 in 4 individuals worldwide. Among these cases of secondary hypertension, the identifiable cause sometimes lies in a specific gene, leading to what is known

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as "monogenic hypertension."[3,4] This form of hypertension typically exhibits inheritance patterns that follow Mendelian genetics, and the majority of monogenic hypertension cases are attributed to modifications or activations within the renin–angiotensin–aldosterone system (RAAS) pathways.[4-6]

As this review concentrates on heritable hypertensions due to germline mutations affecting the RAAS system, we will exclude discussion on other genetic conditions such as multiple endocrine neoplasia syndromes, familial pheochromocytoma, neurofibromatosis type 1, von Hippel–Lindau syndrome, chromosomal deletion syndromes, and hypertension and brachydactyly syndrome. These conditions, while hereditary, fall outside the scope of our current exploration.

Germline mutations affecting the RAAS pathways result in increased salt reabsorption, volume expansion, suppressed renin levels, and salt-sensitive hypertension through 3 primary mechanisms: (1) enhanced sodium reabsorption through mutant channels, (2) increased mineralocorticoid receptor activation from alterations in steroid metabolism or changes in receptor affinity, and (3) overproduction of mineralocorticoids accompanied by a breakdown in feedback regulation. Table 1 presents a summary of 3 categories of monogenic hypertension, detailing potassium levels, aldosterone concentrations, and OMIM (Online Mendelian Inheritance in Man) numbers for the implicated genes. But before delving into the disease, it is essential to review the RAAS pathway along with the physiology of the distal and connecting tubules for a comprehensive understanding of these mechanisms.

HIGHLIGHTS

- Monogenic hypertension is a rare but significant type of secondary hypertension caused by genetic mutations that disrupt systems regulating blood pressure. This type of hypertension is characterized by Mendelian inheritance patterns and is usually linked to alterations within the renin–angiotensin–aldosterone system (RAAS).
- Germline mutations in the RAAS pathways lead to increased salt (salt-sensitive) reabsorption, volume expansion, and renin suppression. These effects occur through 3 mechanisms—enhanced sodium reabsorption via mutant channels, increased activation of mineralocorticoid receptors due to steroid metabolism changes, and excessive mineralocorticoid production with disrupted feedback.
- Salt-sensitive (RAAS-related) monogenic hypertension usually presents with early-onset hypertension, often before age 30, and is associated with low renin levels and a family history of similar conditions. It is crucial to diagnose the condition promptly and accurately using targeted genetic testing based on specific phenotypes to manage it effectively and prevent severe complications.
- Broad, non-specific genetic testing is discouraged in favor of phenotype-driven gene analysis. Prompt, precise diagnosis leveraging targeted genetic testing based on specific phenotypes is vital to manage the condition effectively and prevent severe complications.

DISTAL NEPHRON SODIUM HANDLING

Sodium Reabsorption via Distal Nephron Segments

There are 2 main pathways for sodium reabsorption in the distal segment of the nephron (Figure 1): the first, responsible for reclaiming up to 5% of filtered sodium, involves the Na–Cl cotransporter (NCC) in the distal tubules.[7] The second major route occurs where the distal tubules meet the connecting tubules and in the cortical collecting tubules, facilitated by the epithelial sodium channel (ENaC), accounting for approximately 2%-3% of the total sodium reabsorbed. These pathways possess distinct dynamics, functioning in a complementary and competitive manner, and surprisingly activate upon aldosterone stimuli.[8]

Sodium reabsorption via the NCC in the distal tubule is an electroneutral process, meaning its activation does not alter the ion balance or electrical charge within the tubule. The distal tubule lacks water permeability, resembling the continuation of the ascending limb of Henle's loop. Activation of Cl^- and Na–K ATPase occurs basolaterally. This area is also critical for calcium homeostasis, where calcium reabsorption occurs through a selective calcium channel on the apical surface and a Na–Ca exchanger channel basolaterally. This channel mechanism is notably unique, as the reabsorption of sodium on the basolateral side facilitates the extrusion of calcium into the interstitium, a rare occurrence since sodium is not a main intracellular cation and, according to the principles of the Nernst equation, should be pumped out of the cell. The intense activity of the basolateral Na/K ATPase is necessary to compensate for the sodium entering the cell in exchange for calcium extrusion. Considering that the amounts of sodium pumped out by the Na/K ATPase and taken back in by the Na–Ca exchanger are equal, the less sodium absorbed apically, the more balanced and successful the exchange at the basolateral side, resulting in higher calcium absorption. Conversely, increased sodium absorption apically means the Na/K ATPase must pump out more sodium from the tubule, leading to less sodium being exchanged for calcium and thus lower calcium absorption. This also explains why thiazide diuretics, which inhibit the apical NCC, or mutations causing NCC loss-of-function, as seen in Gitelman syndrome, are associated with enhanced calcium absorption and hypocalciuria. The activity and quantity of these channels are modulated by various proteins and transcription factors influenced by luminal sodium and serum potassium concentrations, volume status, and blood aldosterone levels.[9]

As we approach the cortical collecting ducts, principal cells and intercalated cells begin to appear (Figure 1). The ENaC found in principal cells are regulated by aldosterone, leading to the absorption of sodium exclusively. This absorption, unlike the electroneutral process mediated by

Table 1. Clinical Features, Genetic Defects, and Management of Mendelian Forms of Renin–Angiotensin-Aldosterone System-Related Hypertension

	OMIM Genotype	Gene	Protein	Inheritance	K	Aldosterone	Therapy
Augmented Sodium Ion Reabsorption via Overactive Channels							
Liddle syndrome	*60076 *600761,16p12.2 *600228,12p13.31	*SCNN1B* *SCNN1G* *SCNN1A*	ENaC	AD	↓	↓	Amiloride, triamterene
Gordon syndrome	*601844,17q21.2 *605232,12p13.33 *605775,5q31.2 *603136,2q36.2	*WNK4* *WNK1* *KLHL3* *CUL3*	WNK4 WNK 1 Kelch-like 3 Cullin 3	AD	N or ↑	↓, N or ↑	Thiazides
Alterations in Steroid Synthesis or Receptor Affinity							
AME syndrome	*614232,16q22.1	*HSD11B2*	11β-HSD2	AR	N or ↓	↓	MC receptor antagonists, amiloride, triamterene, GC
CAH type IV	*610613,8q24.3	*CYB11B1*	11β-OHase	AR	N or ↓	↓	MC receptor antagonists, GC
CAH type V	*609300,10q24.32	*CYP17A1*	17α-OHase	AR	N or ↓	↓	MC receptor antagonists, GC
Geller syndrome	*600983,4q31.23	*NR3C2*	MC receptor	AD	N or ↓	↓	Amiloride, triamterene, thiazides, Ca antagonists*, spirinolactone contraindicated
Chrousos syndrome	*138040,5q31.3	*NR3C1*	GC receptor	AD, AR	N or ↓	↓	GC, MC receptor antagonists
Excess Mineralocorticoid Synthesis							
GRA (FH type I)	*610613, 8q24.3	*CYP11B1/ CYP11B2*	Aldosterone synthase	AD	N or ↓	↑	GC, MC receptor antagonists, amiloride
FH type II	*600570, 3q27.1	*CLCN2*	Cl channel	AD	N or ↓	↑	MC receptor antagonists
FH type III	*600734, 11q24.3	*KCNJ5*	K channel	AD	N or ↓	↑	MC receptor antagonists (bilateral adrenelectomy)
FH type IV	*607904, 16p13.3	*CACNA1H*	Ca channel	AD	N or ↓	↑	MC receptor antagonists

11β-HSD2, 11β-hydroxysteroid dehydrogenase-2;CAH, congenital adrenal hyperplasia; FH, familial hyperaldosteronism; GC, glucocorticoid; GRA, glucocorticoid-remediable aldosteronism; MC, mineralocorticoid, WNK, with no lysine (K) kinase;11β-OHase, 11β-hydroxylase; 17α-OHase, 17α-hydroxylase; ENaC, epithelial sodium channel.

thiazide-sensitive NCC in the distal tubule, creates electronegativity within the lumen.[7,10] Furthermore, the activity of the basolateral Na/K ATPase, drawing sodium into the interstitium, increases the intracellular potassium concentration. The lumen's electronegativity then drives potassium secretion into the lumen via the renal outer medullary K (ROMK) channels. Thus, NCC and ENaC activations result in different effects and ion absorption patterns. The greater the expression of ENaC in the epithelial channel, the higher the potassium secretion, primarily regulated by aldosterone produced in the zona glomerulosa cells via the CYP11β2 enzyme. Activation of AT1 receptors by angiotensin II (Ag II) is a key regulator of the transcription of the CYP11β2 enzyme complex. This mechanism is distinct from the activation of the CYP11β1 enzyme complex in the zona fasciculata cells by adrenocorticotropic hormone (ACTH). The aldosterone produced binds to mineralocorticoid receptors in principal cells, inducing ENaC production and leading to sodium absorption followed by potassium secretion.

Aldosterone's Bimodal Action

Aldosterone production and its mode of action are 2-fold, meaning it can be stimulated in 2 ways: firstly, in response to hypovolemia through the activation of the RAAS cascade triggered by released renin, and secondly, through the direct stimulation by hyperkalemia.[8] These differing modes of stimulation reflect in their effects because the body is programmed to respond differently to hyperkalemia and hypovolemia. In the case of hyperkalemia, activation of ENaC in the cortical collecting tubules should take precedence, which has a lower potential for sodium retention but facilitates potassium secretion. Conversely, during hypovolemia, activating the distal tubule's NCC channels, which have a higher sodium retention capacity without causing a significant shift in ion balance, would be more rational. Indeed, in the presence of hyperkalemia, NCC channels should be somewhat inhibited to ensure a high luminal sodium concentration is available for ENaC absorption, as potent sodium absorption by NCC would prevent ENaC from effectively absorbing

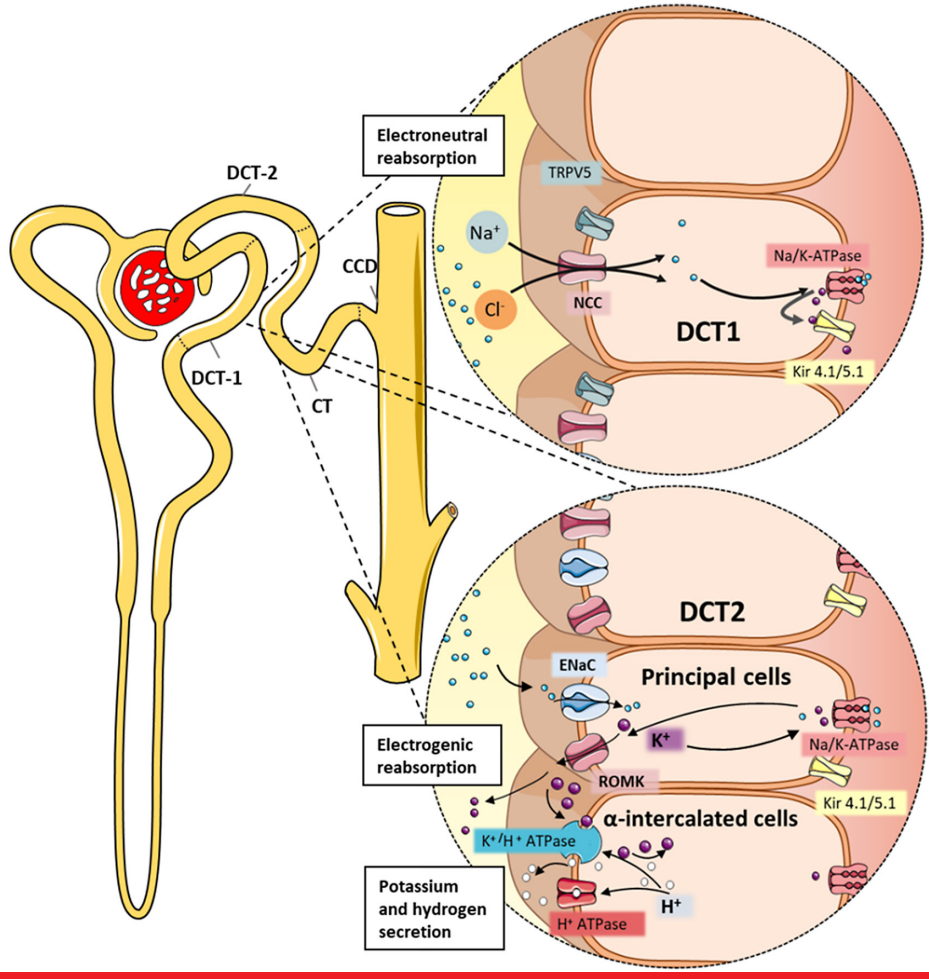

Figure 1. Key Transporters in the aldosterone-sensitive distal nephron by cell type. This figure delineates the primary transporters located in the aldosterone-sensitive distal nephron, organizing them from the proximal to the distal segments. In the early distal convoluted tubule, the Na–Cl cotransporter acts as the principal apical sodium transporter. The basolateral membrane features channels like KCC4 and Kir4.1/5.1 for potassium and others for chloride transport (not shown). The Na–K ATPase facilitates sodium reabsorption by pumping sodium out and importing potassium, creating a conducive gradient. In principal cells within the connecting tubule and cortical collecting duct (CNT/CCD), sodium reabsorption occurs through ENaC on the apical membrane, and potassium is secreted via renal outer medullary K. Kir4.1/5.1 serves as the primary potassium transporter on the basolateral side, with the Na–K ATPase maintaining its critical function. Alpha intercalated cells in the CT/CCD feature an H+ ATPase pump for H^+ secretion and an H^+/K^+ exchanger to balance the secretion of H^+ with the absorption of potassium ions.

sodium and secreting potassium. However, this presents another dilemma, as aldosterone activates both systems.[11] As simplified and illustrated in Figure 2, certain proteins and factors within tubular cells come into play to enable fine-tuning. Notably, the long isoform of WNK1 (L-WNK1), WNK3, WNK4, and the kidney-specific WNK (KS-WNK) of the WNK kinase family, along with the regulatory proteins SPAK, SGK1, and OSR1, orchestrate the activation of NCC and ENaC through phosphorylation processes.[12-15]

Low potassium induces L-WNK1 production and an increase in the L-WNK1/KS-WNK ratio will activate NCC via Ste20 proline-alanine rich kinase (SPAK), leading to electroneutral sodium reabsorption.[16] This reduces sodium delivery to the connecting tubule, providing less substrate for ENaC. Conversely, WNK4 inhibits NCC's movement to the plasma membrane, leading to its degradation.[17] WNK3 and WNK1 act similarly, although WNK3 is more susceptible to inhibition by WNK4. WNK1 suppresses WNK4, presenting 2 patterns: WNK4 dominance versus WNK1-3 dominance.[18] In Xenopus oocytes, the NCC activation by L-WNK1/SPAK was not observed, but the alleviation of WNK4-mediated inhibition was confirmed on both ends.[14] Thus, in environments where L-WNK1 is dominant, NCC activation occurs. When L-WNK1 is inactive due to high potassium levels and cannot inhibit WNK4, WNK4 then inhibits WNK3 and leads to NCC degradation, increasing sodium delivery to the connecting tubules. Under these conditions, ROMK channels, also inhibited by WNK1 in high potassium settings, facilitate potassium secretion as ENaC enhances sodium absorption.

While the predominant outcome of WNK4's activity is the inhibition of NCC, angiotensin II can transform WNK4 into

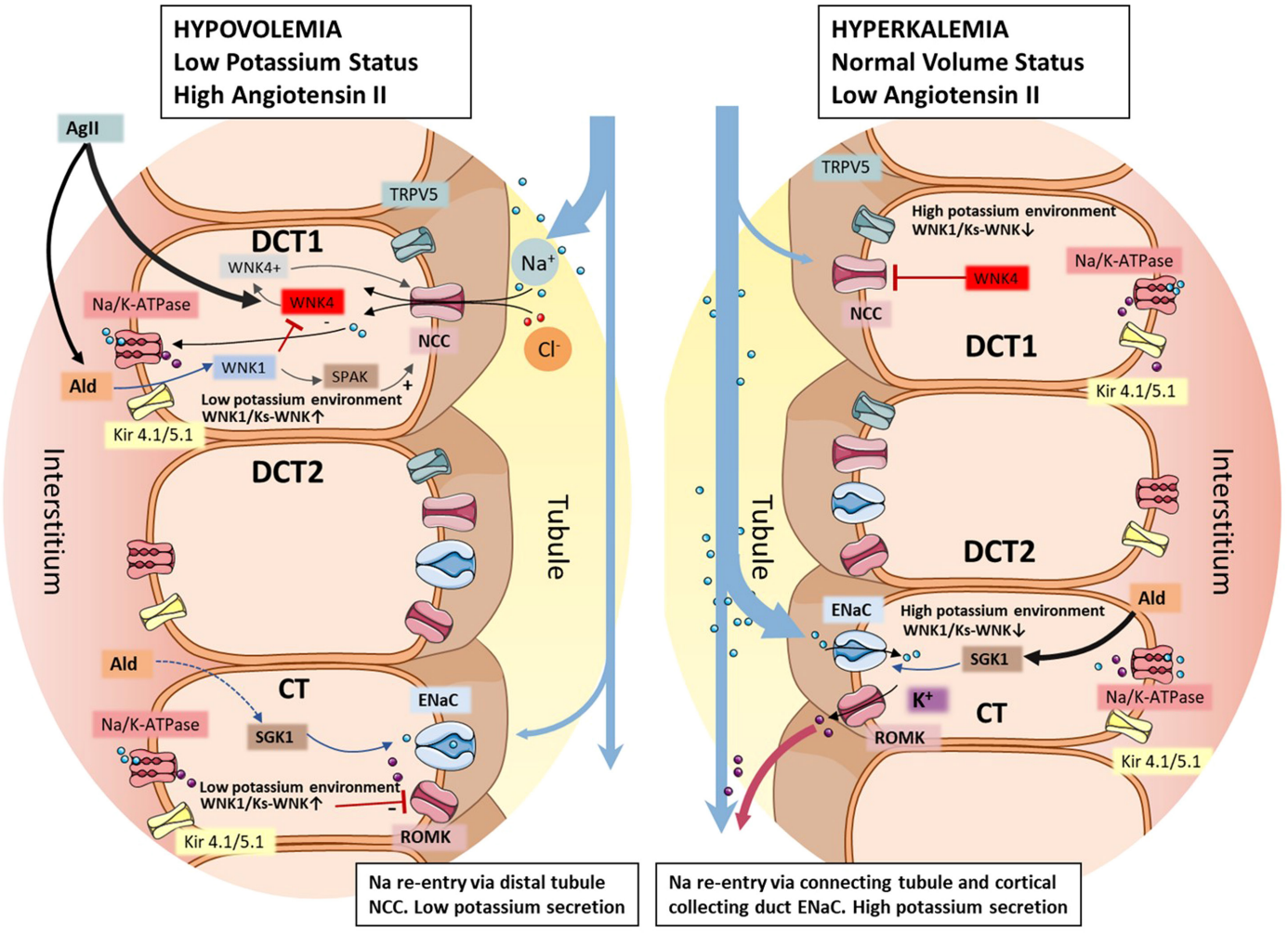

Figure 2. Dynamics of sodium reabsorption in hypervolemia vs. hyperkalemia. This figure outlines the differences in sodium reabsorption mechanisms between conditions of hypervolemia and hyperkalemia. Normally, WNK4 serves as an inhibitor of the Na–Cl cotransporter (NCC) within the distal nephron. In hypovolemia, marked by high angiotensin II and aldosterone levels, WNK4 suppresses the renal outer medullary potassium channel (ROMK) across the distal nephron but acts as a positive regulator of NCC in the distal convoluted tubules 1 and 2 (DCT1 and DCT2). Additionally, the isoform L-WNK1 is elevated in low potassium conditions, mitigating WNK4's inhibitory impact on NCC. L-WNK1 phosphorylates and activates NCC through SPAK, prioritizing sodium reabsorption through NCC and maintaining tubular electroneutrality, which reduces sodium availability for the epithelial sodium channel (ENaC) in principal cells and diminishes electronegativity for potassium secretion by ROMK. Conversely, in hyperkalemia, WNK4 inhibits NCC in DCT1, enhancing distal sodium delivery, while serum- and glucocorticoid-inducible kinase 1 (SGK1) activates ENaC and ROMK in the aldosterone-sensitive distal nephron (ASDN), facilitating sodium and potassium exchange. The inhibition of NCC allows more sodium to reach ENaC, increasing luminal electronegativity and promoting potassium and proton secretion. L-WNK1 is inhibited in high potassium environments. A loss-of-function mutation causing loss of WNK4's ability to inhibit NCC, or gain-of-function mutations in WNK1, leads to persistent activation of NCC, resulting in pseud ohypoaldosteronism type II, also known as Gordon's syndrome. ASDN, aldosterone-sensitive distal nephron; CT, connecting tubule; DCT1/DCT2, distal convoluted tubule segments 1 and 2; ENaC, epithelial sodium channel; L-WNK1, long isoform of WNK1 kinase; NCC, Na–Cl cotransporter; ROMK, renal outer medullary potassium channel; SGK1, serum- and glucocorticoid-inducible kinase 1; SPAK, STE20/SPS1-related proline/alanine-rich kinase; WNK4, with no lysine (K) kinase 4.

an activator of NCC, thereby promoting sodium reabsorption more proximally in the nephron and increasing dependency on NCC.[11,19] This means that angiotensin II can directly stimulate NCC, enhancing sodium reabsorption independently of aldosterone, an effect observed even in organisms without adrenal glands.[20] Na–Cl cotransporter-driven sodium reabsorption is more potent than that mediated by ENaC, especially during hypovolemia. Conversely, under a high potassium load without hypovolemia or angiotensin II, aldosterone stimuli will induce ENaC via SGK1, shifting sodium reabsorption to the less potent distal connecting tubules with potassium secretion.[21] This shift causes relative sodium loss and aids blood pressure control, indicating a potassium-rich diet directs sodium reabsorption from the distal tubules to the connecting tubules.

In familial hyperkalemic hypertension, mutations in the WNK family or its pathways, increased WNK1/KS-WNK ratios, and inhibition of WNK4 leads to NCC activation and electroneutral salt absorption.[22] Potassium cannot be secreted due to the low sodium availability for ENaC, leading to less proton secretion. Conversely, intercalated cells absorb protons in exchange for potassium, causing metabolic acidosis.[7] In this disorder, the body behaves as if it is constantly under a hypovolemia threat. This clinical syndrome, known as Gordon's syndrome, is characterized by hyperkalemia, metabolic alkalosis, and hypertension.[23,24] It is noteworthy that most familial hypertension syndromes are associated with hypokalemia and metabolic alkalosis, highlighting the dramatic difference that a simple shift from ENaC-mediated sodium reabsorption in the connecting tubule to NCC-mediated sodium reabsorption in the distal tubule can cause in sodium reabsorption physiology.

Augmented Sodium Ion Reabsorption via Overactive Channels

Liddle's Syndrome

Liddle's syndrome is marked by the autonomous activation of ENaC-mediated sodium reabsorption in the distal tubule, leading to a presentation of salt-sensitive hypertension, low potassium levels (hypokalemia), and metabolic alkalosis.[8] This condition is inherited in an autosomal dominant manner, often presenting as hypokalemic hypertension at an early age with a family history, characteristic of a low-renin, low-aldosterone disease category. This reflects the autonomous activation of the ENaC despite intact feedback suppression due to low potassium and increased body volume.

The genetic defect in Liddle's syndrome involves either deletions or substitutions in a short proline-rich segment within the intracytoplasmic C-terminus of the ENaC. This segment serves as a recognition site for the intracellular ubiquitin protein ligase (Nedd4), which normally targets ENaC for removal from the cell surface and subsequent degradation. The absence of this removal process leads to ENaC accumulation on the cell surface, resulting in elevated sodium reabsorption and potassium secretion through ROMK channels, which also facilitates proton secretion by hydrogen ATPase in intercalated cells, resulting in hypokalemic metabolic alkalosis.[25]

The differential diagnosis of Liddle's syndrome is based on the combination of clinical features including hypokalemic hypertension in young individuals with suppressed levels of renin and aldosterone. The differential list should begin with conditions such as congenital adrenal hyperplasia, familial cortisol resistance, apparent mineralocorticoid excess syndromes (including excessive licorice ingestion) and deoxy corticosterone-producing adrenal tumors.[26] Nonetheless, a family history of early-onset hypertension with potassium wasting points towards a Mendelian disorder, warranting genetic testing for mutations in SCNN1A, SCNN1B, and SCNN1G genes, which encode the 3 ENaC subunits (α, β, and γ).[27] The absence of a family history does not rule out the diagnosis, as cases without known familial links have been reported. Nearly all pathogenic variants affect the proline-rich PY motif of a subunit.[27]

Treatment for Liddle's syndrome aims to inhibit the overactive channels, typically involving the use of potassium-sparing diuretics such as amiloride and triamterene.[26] These medications block the sodium channels in the collecting tubule directly, effectively correcting both hypertension and hypokalemia. Mineralocorticoid receptor antagonists are not effective in this scenario, as the ENaC accumulation is independent of aldosterone signaling.

Gordon's Syndrome

Gordon's syndrome, also known as pseudohypoaldosteronism type 2 or familial hyperkalemic hypertension, is distinguished by its manifestations of hyperkalemia, metabolic acidosis, and hypertension that appears early in life.[22] This condition arises from mutations affecting the WNK kinase family, which plays a critical role in regulating the thiazide-sensitive NCC.[14,23] Similar to other forms of monogenic hypertension, such as Liddle syndrome, congenital adrenal hyperplasia, glucocorticoid remediable aldosteronism, and apparent mineralocorticoid excess syndromes, Gordon's syndrome may exhibit a hypoaldosteronism phenotype, though aldosterone levels can be normal or elevated, suggesting a renin-independent, potassium-driven mechanism.

Mutations leading to altered degradation of NCC result in enhanced sodium and chloride reabsorption, reducing sodium availability for absorption by ENaC in the connecting tubules and diminishing the drive for potassium secretion via ROMK channels. The regulation and degradation of NCC are controlled by the WNK kinase family.[28] Normally, wild-type WNK4 inhibits the migration of NCC to the plasma membrane, thus favoring sodium reabsorption through the ENaC-ROMK system (Figure 2). However, missense mutations in the WNK4 gene lead to a variant protein with reduced inhibitory capacity, increasing the expression of the NCC and causing hyperplasia in the distal convoluted tubule. A loss-of-function mutation in WNK4 may also result in mild hyperchloremia and calcium leakage, presenting as hypercalciuria, renal stones, and reduced bone mineral density, given WNK4's positive interaction with TRPV5, a calcium channel involved in reabsorption.[23] Similarly, a gain-of-function mutation in WNK1, which typically inhibits WNK4, would enhance NCC expression in the distal tubule, also impairing potassium secretion through ROMK channels. Thus, both gain-of-function mutations in WNK1 and loss-of-function mutations in WNK4 lead to similar effects, including increased chloride permeability via paracellular pathways.[12,29] The most severe and common early-onset forms of Gordon's syndrome are linked to mutations in genes (CUL3 and KLHL3) responsible for the degradation of WNK kinases, with CUL3 mutations leading to the most severe clinical outcomes and WNK1 mutations resulting in the least severe.

Thiazide diuretics can mitigate the effects of excessive NCC activity, effectively reversing the pathological features of Gordon's syndrome through NCC inhibition. This sensitivity to thiazides suggests that Gordon's syndrome is the inverse

of Gitelman syndrome, which involves a loss-of-function mutation in NCC leading to hypokalemia and metabolic alkalosis.[28,30]

Alterations in Steroid Synthesis or Receptor Affinity

Apparent Mineralocorticoid Excess Syndrome

Apparent mineralocorticoid excess (AME) syndrome emerges from a Mendelian loss-of-function mutation in the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which normally transforms cortisol into its inactive counterpart, cortisone.[31-33] Unlike most mutations causing monogenic hypertension, this particular mutation causes loss of function and follows an autosomal recessive inheritance pattern. Under normal circumstances, glucocorticoids like cortisol, which are present in the plasma at significantly higher concentrations compared to mineralocorticoids, have the ability to activate the mineralocorticoid receptor (MR) but become inactivated to prevent overactivation of MR.[34] However, in the absence of the conversion of cortisol to cortisone, glucocorticoids acquire MR-activating properties, leading to the clinical manifestations of hypokalemia and metabolic alkalosis characteristic of AME syndrome. Hypercalciuria and nephrocalcinosis can be seen in AME syndrome and pose extra challenges to manage.[35] Long-term follow-ups of classic AME patients report a persistan nephrocalcinosis can be seen in 89% of patients.[36] This syndrome is categorized as a low-renin, low-aldosterone form of monogenic hypertension.

When diagnosing AME syndrome, it is crucial to consider differential diagnoses such as Cushing's syndrome, where an excess of cortisol could potentially exceed the enzymatic capacity of 11β-HSD2, resulting in a clinical picture similar to AME. Another condition to consider is excessive licorice ingestion, which inhibits the 11β-HSD2 enzyme, leading to cortisol accumulation and a similar set of symptoms.[37] However, AME syndrome has strong genotype–phenotype correlation as the classic form is usually characterized by infantile hypertension with marked hypokalemia, indicating underlying mutations that enhance dimerization or severely impair structural stability.[36] Some variants cause mildly reduced 11β-HSD2 activity, thus milder phenotypes with isolated hypertension at an older age are expected (AME type 2).[36]

The treatment protocol for AME syndrome generally involves the use of mineralocorticoid receptor antagonists alongside dietary sodium restriction.[38] Eplerenone is more specific to MR than spironolactone and can be used with great success in patients with AME, preventing anti-androgenic side effects. A personalized approach for left ventricular hypertrophy and nephrocalcinosis is preferred to prevent complications; however, thiazides, even though theoretically beneficial for nephrocalcinosis, can aggravate potassium loss. Potassium supplementation is needed in most cases, and elevated cortisol levels might be mitigated by administering exogenous corticosteroids that lack mineralocorticoid effects, such as dexamethasone, but should always be used with the lowest as possible doses.[39]

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) encompasses a spectrum of enzyme deficiency syndromes that interrupt the steroidogenesis process, necessitating distinct enzyme catalyzation for the synthesis of 3 different groups of steroid hormones (Figure 3). These deficiencies are typically associated with increased corticotropin (ACTH) stimulation due to the absence of negative feedback inhibition, leading to adrenal gland hyperplasia. Two specific forms of CAH that are linked to hypokalemic hypertension are the deficiencies of the enzymes 11β-hydroxylase (type IV CAH) and 17α-hydroxylase (type V CAH).[40]

In the case of 11β-hydroxylase deficiency, the absence of enzyme activity prevents the production of corticosterone and cortisol, leading to the accumulation of 11-DOC, a precursor with mineralocorticoid activity.[41,42] Accumulated precursors will be directed to adrenal sex steroid production pathway. This results in a clinical profile characterized by hypokalemia and hypertension due to the action of DOC, alongside precocious puberty and virilization caused by the secretion of adrenal androgens.[42] The primary androgens that accumulate are androstenedione and dehydroepiandrosterone (DHEA), which serve as key markers for laboratory confirmation.[43] Given that the predominant trigger is ACTH stimulation resulting from the absence of cortisol's inhibitory feedback, treatment primarily involves administering the minimal yet effective doses of glucocorticoids.

In contrast, 17α-hydroxylase deficiency blocks the production of cortisol and adrenal sex steroids, redirecting steroid synthesis towards aldosterone. This enzyme deficiency similarly leads to increased ACTH, resulting in adrenal hyperplasia and a clinical presentation that includes ambiguous genitalia in males, delayed sexual development in females, and hypokalemic hypertension.[40] Unlike with 11β-hydroxylase deficiency, levels of DHEA will be reduced, and stimulation by ACTH will lead to increased production of pregnenolone and progesterone, without elevating 17α-progesterone or 17α-pregnenolone. The therapeutic approach should encompass glucocorticoids to suppress ACTH and include replacement therapy for sex hormones.[44]

Geller Syndrome

Geller syndrome is characterized by a gain-of-function mutation in the mineralocorticoid receptor that increases its affinity for non-mineralocorticoid steroids, including cortisone and progesterone, particularly notable during pregnancy, which can induce hypokalemia and hypertension.[45,46] Like other gain-of-function mutations, Geller syndrome is inherited in an autosomal dominant manner, making the mutant receptor susceptible to activation by other steroids, especially progesterone. Patients with this syndrome typically present with intractable hypokalemia and hypertension during pregnancy, although the onset of hypertension may precede pregnancy. As a type of low-renin, low-aldosterone monogenic hypertension, management strategies include strict dietary salt restriction for blood pressure control and supplementation of electrolytes in severe cases. However, post pregnancy, the hypertension, metabolic alkalosis, and

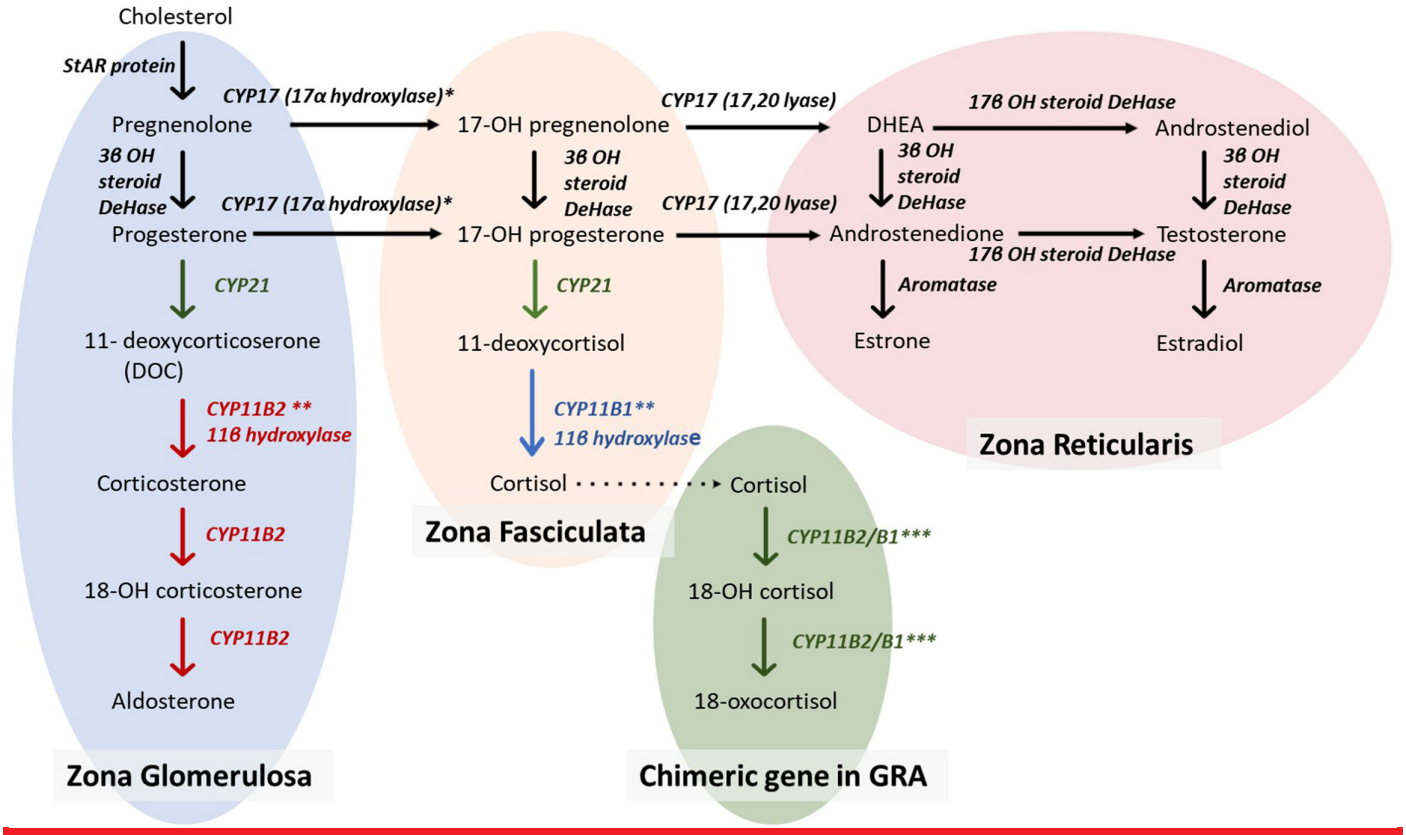

Figure 3. Pathways in steroid synthesis and enzyme disorders. This figure illustrates the steroidogenesis pathways and highlights the enzymes affected in congenital adrenal hyperplasia (CAH) types IV, V, and glucocorticoid remediable aldosteronism (GRA). CYP17 (*) represents the 17α-hydroxylase pathway, deficient in CAH type V and CYP11β1 and 2 (**) represent pathway of 11β-hydroxylase, whose deficiency characterizes CAH type IV. Green arrows and CYP11B2/ CYP11B1(***) indicates ACTH inducible CYB11B2 activity resulting from chimeric gene due to unequal crossover of the genes encoding CYP11B1 and CYP11B2. 18-hydroxy cortisol and 18 oxocortisol are products unique to GRA. Key: 3β OH steroid DeHase (3-β hydroxy steroid dehydrogenase), DHEA (dihydroepiandrosterone).

hypokalemia generally resolve spontaneously.[47] Outside of pregnancy, the optimal management of Geller syndrome has yet to be clearly defined but may involve conventional antihypertensive drugs, with a cautionary note against the use of spironolactone, a steroidal drug, due to its potential to aggravate hypertension.[48]

Chrousos Syndrome

Familial or sporadic glucocorticoid resistance, also known as Chrousos syndrome, arises from mutations in the glucocorticoid receptor gene, leading to reduced effectiveness of cortisol in tissues.[49,50] This resistance in the pituitary gland causes increases in ACTH, cortisol, adrenal androgens, and deoxycorticosterone levels. Symptoms of this glucocorticoid effect deficiency can range from non-existent to chronic fatigue, as elevated cortisol levels might still support somewhat normal glucocorticoid activity in tissues. The severity of resistance often reflects the clinical presentation, including possible hyperandrogenism or mineralocorticoid excess.

Differential diagnosis relies on measuring 24-hour urinary free cortisol over consecutive days, revealing elevated levels without typical hypercortisolism signs.[51] The degree of cortisol and androgen increase, alongside urinary cortisol excretion, indicates the glucocorticoid signal transduction impairment severity. Plasma ACTH levels may vary from normal to high. After initial evaluation, diagnostic procedures should include testing HPA axis responsiveness to dexamethasone.[51] Higher-than-normal dexamethasone doses may be necessary to achieve a 50% reduction in serum cortisol levels compared to healthy individuals.

Treatment for Chrousos syndrome aims to curb excess ACTH and adrenal steroid production. This involves high doses of mineralocorticoid-sparing glucocorticoids, like dexamethasone, taken nightly to reduce ACTH secretion and prevent potential development of pituitary and adrenal adenomas.

Excess Mneralocorticoid Synthesis

This category of monogenic hypertension is marked by excessive aldosterone production resulting from pathogenic gene rearrangements or germline mutations, inherited through Mendelian patterns, commonly known as "familial hyperaldosteronism." The 4 types of familial hyperaldosteronism disorders, inherited in an autosomal dominant manner, fall under the low-renin, high-aldosterone form of monogenic hypertension. Consequently, their laboratory profiles mimic

those of primary hyperaldosteronism, necessitating differentiation from it.

Familial Hyperaldosteronism Type I or Glucocorticoid-Remediable Aldosteronism

To understand the topic comprehensively, the physiology of adrenal cortex ought to be summarized. Three adrenal cortex layers are subspecialized to produce steroid hormones with distinct properties (Figure 3). The outermost layer, the zona glomerulosa, utilizes the enzyme CYP11B2, also known as aldosterone synthase, for aldosterone production. 11β-hydroxylation is required in both layers, zona glomerulosa and zona fasciculata to convert deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol, respectively. In zona glomerulosa, CYP11B2 catalyzes the sequential hydroxylation of the steroid methyl group at C18 (18-hydroxylation) following initial 11β-hydroxylation, triggered by angiotensin II-induced transcription factors or elevated potassium levels. Although CYP11B2 and CYP11B1 share 93% homology and are located on the same chromosome, CYP11B2 does not strongly respond to corticotropin (ACTH). So, ACTH-sensitive steroidogenesis occurs in zona fasciculata, culminating in cortisol production. Unique to individuals with glucocorticoid remediable aldosteronism (GRA) is a mutation where the promoter region of CYP11B1 and the coding sequences of CYP11B2 are fused due to an unequal crossover event.[52,53] This fusion leads to the ACTH-dependent activation of aldosterone synthase, transforming the zona fasciculata into a layer that also produces aldosterone. Moreover, within the zona fasciculata, cortisol can be processed by CYP11B2, resulting in the creation of distinct cortisol derivatives (18-oxocortisol and 18-hydroxycortisol).[54,55] Measuring these specific cortisol products serves as an effective diagnostic tool for identifying GRA. An additional notable aspect of aldosterone production in this context is its insensitivity to potassium, normally a potent stimulant for CYP11B2.[56]

Glucocorticoid-Remediable Aldosteronism is inherited in an autosomal dominant manner and appears to be the most common monogenic form of hypertension in humans.[57] The diagnostic challenge arises because routine lab tests, such as plasma renin activity and aldosterone levels, do not distinguish GRA from primary hyperaldosteronism. Clues that should prompt a clinician's suspicion include the patient's age and family history, as diagnosing GRA relies on a low threshold of suspicion. While hypokalemia might be anticipated, it is not consistently present in all cases, possibly due to the circadian rhythm of ACTH release.[56,58,59] Therefore, hypokalemia should not be considered a strong indicator of GRA, although significant hypokalemia following the administration of a thiazide diuretic is expected. More specific signs include dexamethasone suppressible hyperaldosteronism and increased levels of urinary 18-oxocortisol and 18-hydroxycortisol. Nonetheless, identifying the chimeric gene through genetic testing has emerged as the diagnostic gold standard, largely replacing the need for biochemical testing.[60]

Published data indicate an unusually high rate of early cerebrovascular complications in GRA patients, particularly hemorrhagic strokes resulting from aneurysm rupture, with the mean age at the first event being 32 years.[61] Thus, a family history of early hemorrhagic strokes, occurring before the age of 40, serves as another diagnostic clue, although this is not exclusive to GRA and can also be observed in Liddle's syndrome. Consequently, it has been proposed that GRA patients should be screened using magnetic resonance angiography.[62]

The treatment approach for GRA should be constructed on its underlying pathophysiology. Administering low-dose steroids can efficiently inhibit ACTH release, thereby correcting the excess aldosterone production.[62] Taking the smallest effective amount of prednisone before sleep is aimed at countering the early morning rise in ACTH. Yet, the prolonged administration of even minimal doses of prednisone might not be suitable for children. For these patients, mineralocorticoid receptor antagonists provide a viable alternative. These drugs preserve the pituitary-adrenal axis's function and respect the body's natural ACTH rhythm, effectively controlling both hypertension and hypokalemia, if it exists.[63]

Familial Hyperaldosteronism Type II

Familial hyperaldosteronism type II (FHT-II) shares some similarities with GRA in terms of lacking feedback control and exhibiting low-renin plasma activity. However, FHT-II's mutation is not related to ACTH or any tropic hormones but is identified by a gain-of-function mutation in the CLCN2 gene, which encodes a voltage-gated chloride channel expressed in adrenal glomerulosa.[64] This mutation leads to hyper-depolarization, thereby promoting aldosterone synthase activity in zona glomerulosa cells.

Differing from GRA, FHT-II does not respond to dexamethasone suppression. This condition often correlates with bilateral adrenocortical adenomas due to the continuous activation of adrenocortical cells. Diagnosis relies heavily on clinical suspicion, particularly in individuals with a family history of early-onset hypertension and adrenal disorders (like bilateral adenomas), though biochemical tests may not offer definitive insights as FHT-II presents similarly to primary hyperaldosteronism. Genetic testing for the CLCN2 mutation may aid in diagnosis, with treatment options including mineralocorticoid receptor antagonists or unilateral adrenalectomy.

Familial Hyperaldosteronism Type III

Familial hyperaldosteronism type III (FHT-III), akin to FHT-II, results from gain-of-function mutations in the KCNJ5 gene, which encodes a potassium channel.[65,66] Disease-causing variants lose their ionic selectivity, leading to constant depolarization and subsequent aldosterone synthase activity. Similar to FHT-II, aldosterone levels are not suppressed by dexamethasone, and the treatment approach for FHT-III mirrors that of FHT-II. However, managing the excessive aldosterone production can be particularly challenging in FHT-III, as patients with KCNJ5 germline mutations often experience severe hyperaldosteronism and significant adrenal hyperplasia. In some instances, bilateral adrenalectomy may become necessary to effectively address the condition.[65,67]

Familial Hyperaldosteronism Type IV

Familial hyperaldosteronism type IV (FHT-IV) is attributed to gain-of-function mutations in the CACNA1H gene, responsible for encoding a transiently opening calcium channel located in the zona glomerulosa.[68] These mutations render the channel more likely to open under baseline electrochemical conditions, causing an increased influx of calcium ions and thus stimulating aldosterone synthesis. The treatment strategy for FHT-IV is similar to that applied in FHT-II and FHT-III.

CONCLUSION

Mendelian forms of RAAS-related hypertension are also considered a group of rare diseases, making their diagnosis complex and demanding a blend of expertise, experience, and clinical insight. Despite each condition's unique features, they share commonalities, such as significant hypertension onset before age 30, particularly among individuals with low renin levels, a familial history of monogenic hypertension disorders like multiple endocrine neoplasia or glucocorti coid-remediable aldosteronism, hypertension with accompanying hypokalemia in the patient or family, or a history of early-onset hemorrhagic stroke in a relative. Signs of abnormal sexual development or physical indications of associated syndromes also call for thorough evaluation. Initial diagnosis typically involves confirming low renin activity and assessing serum pH, potassium, and aldosterone levels. Targeted next-generation sequencing for specific gene analysis is recommended for precise genetic diagnosis, whereas broad, nonspecific gene testing is inefficient and impractical. A structured and targeted approach, as illustrated in Figure 4, enables timely and accurate diagnosis. Considering that most monogenic hypertension can be effectively managed with targeted therapies, such as specific channel blockers or low-dose corticosteroids, and the potential for serious complications, including cerebrovascular events and mortality, it is crucial to avoid delays in precise diagnosis.

Research into monogenic forms of hypertension has also revealed new molecular pathways that govern blood pressure and electrolyte balance. This knowledge not only aids in the development of novel hypertension treatments but also facilitates the classification of hypertension subgroups based on genotype–phenotype correlations. Additionally,

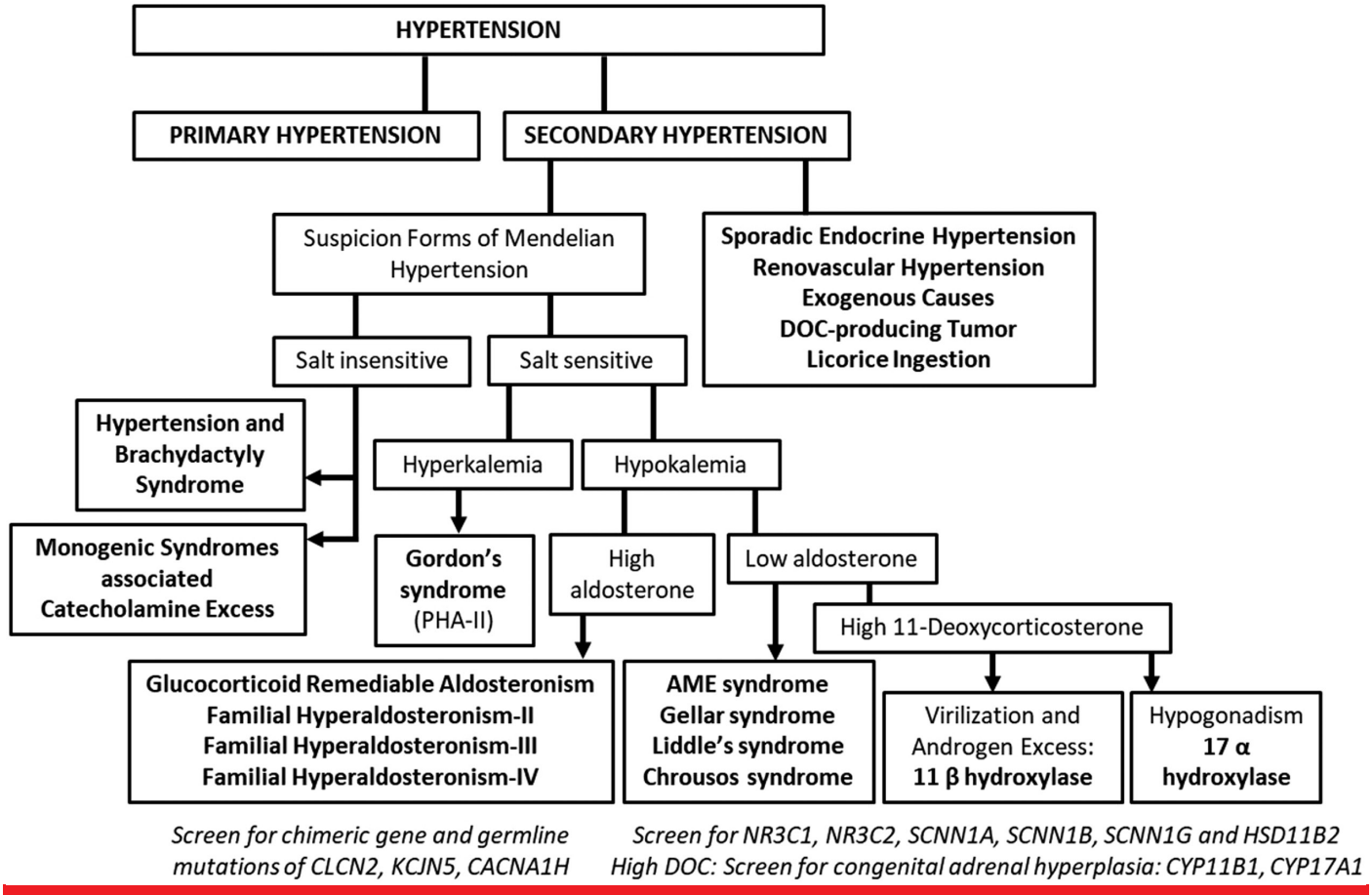

Figure 4. Management of monogenic hypertension patients. This figure outlines the diagnostic approach for patients with monogenic hypertension. Suspicion for Mendelian forms of hypertension arises from clinical observations such as familial history, hypertension presenting at an early age, disturbances in sexual maturity, and imbalances in electrolytes and acid–base levels. Confirmation begins with documenting low renin activity and analyzing serum pH, potassium, and aldosterone levels. Subsequent genetic analysis through targeted next-generation sequencing is advised, focusing on specific genes associated with these conditions. Broad, indiscriminate testing of numerous genes without specific targets is neither practical nor effective.

it has enriched our understanding of tubular physiology and the actions of adrenal cortex hormones. Future advancements in hypertension management are anticipated to be more tailored, thanks to a more profound comprehension of kidney-related blood pressure regulation mechanisms.

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