Diagnosis and Treatment of Monogenic Hypertension in Children

Se Jin Park[1] and Jae Il Shin[2]

[1]Department of Pediatrics, Daejeon Eulji Medical Center, Eulji University School of Medicine, Daejeon;
[2]Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea.

Although the majority of individuals with hypertension (HTN) have primary and polygenic HTN, monogenic HTN is a secondary type that is widely thought to play a key role in pediatric HTN, which has the characteristics of early onset, refractory HTN with a positive family history, and electrolyte disorders. Monogenic HTN results from single genetic mutations that contribute to the dysregulation of blood pressure (BP) in the kidneys and adrenal glands. It is pathophysiologically associated with increased sodium reabsorption in the distal tubule, intravascular volume expansion, and HTN, as well as low renin and varying aldosterone levels. Simultaneously increased or decreased potassium levels also provide clues for the diagnosis of monogenic HTN. Discovering the genetic factors that cause an increase in BP has been shown to be related to the choice of and responses to antihypertensive medications. Therefore, early and precise diagnosis with genetic sequencing and effective treatment with accurate antihypertensive agents are critical in the management of monogenic HTN. In addition, understanding the genetic architecture of BP, causative molecular pathways perturbing BP regulation, and pharmacogenomics can help with the selection of precision and personalized medicine, as well as improve morbidity and mortality in adulthood.

Key Words: Monogenic hypertension, pediatrics, genetic mutation, antihypertensive agent, genetic sequencing

INTRODUCTION

The prevalence of childhood hypertension (HTN) has increased alongside overweight, obesity, and alterations in dietary habits.[1-3] Between 2009 and 2012, the prevalence of HTN among adults in the United States was reported to be approximately 32.6%, while that among children and adolescents was reported to be 3.6%.[4] This is believed to reflect underdiagnosis given that growing evidence suggests that mild blood pressure (BP) elevation is much more common among children and adolescents than previously thought.[2] This is concerning, as increased

BP in childhood and adolescence is associated with an increased risk of cardiovascular disease in adulthood, also known as the tracking phenomenon.[5]

Historically, childhood HTN has been considered to be polygenic, with genetic, environmental, adaptive, neural, mechanical, and hormonal mechanisms believed to be the basis of HTN.[6] Evidence from family studies has shown that HTN is heritable, with 15%–40% of office systolic BP and 15%–30% of office diastolic BP being attributed to variations in genetic factors.[7] A much smaller component (4%–17%) is attributed to environmental factors.[8] From these findings, it can be understood that BP is a complex and polygenic trait.

However, there are several rare syndromes with monogenic inheritance that present with very high or low BP early in life.[9] The discovery of these monogenic HTN syndromes emphasizes the importance of the genetic and molecular bases of BP and HTN, including more than 25 rare mutations and 53 single nucleotide polymorphisms.[10] Therefore, genetic testing, such as whole genome or exome sequencing, is necessary to diagnose rare monogenic syndromes.

This review highlights recent advances in the monogenic forms of pediatric HTN. We discuss how genetics may assist cli-

nicians in diagnosing and treating patients with monogenic HTN. Genes responsible for hereditary forms of HTN are also mentioned, although syndromes, such as Turner, Williams, and Marfan, are not within the scope of this review.

MONOGENIC HTN SYNDROMES

Monogenic HTN syndromes refer to hypertensive disorders caused by a single gene mutation that follows Mendelian inheritance patterns.[11] According to the 2017 Clinical Practice Guidelines for HTN by the American Academy of Pediatrics, monogenic forms of HTN are uncommon due to the lack of exact incidence data.[1] In the 2016 European Society of Hypertension (ESH) guidelines on HTN in children and adolescents, the Working Group also stated that monogenic causes of HTN are rare, but should be discovered during the pediatric age for successful treatment and avoidance of HTN-related morbidity and mortality in adulthood.[2]

However, some familial disorders are proving common enough to be implicated in the differential diagnosis of any hypertensive child.[12] Genetic testing for familial hyperaldosteronism type I (FH-I) or glucocorticoid-remediable aldosteronism (GRA) has confirmed the presence of genetic mutations in 3% of the population.[13] Other monogenic forms of HTN, including Gordon syndrome (GS), apparent mineralocorticoid excess (AME), familial glucocorticoid resistance, and Liddle syndrome (LS), manifest as HTN with suppressed plasma renin activity (PRA) and increased sodium absorption in distal tubules, causing extracellular volume expansion.[1,12] In primary aldosteronism (PA) such as GRA and FH-II, the most discriminatory test is aldosterone-to-renin ratio (ARR; ng/dL and ng/mL/h, respectively): a value >30 indicates PA,[12] whereas in FH-I, an ARR >10 is an indication to perform genetic testing in a hypertensive child.[13] If a family member has been diagnosed with HTN at an early age or if accompanied by hypokalemia, genetic testing is also recommended.

The test for PRA and aldosterone is usually performed from a vein in the upper arm in the early morning after fasting while lying down on the bed for more than 30 minutes: Renin (reference range, 0.17−5.38 ng/mL/h) and aldosterone (2.5−39.2 ng/dL) levels exhibit diurnal variations and are influenced by position, certain foods, beverages, or medications before the test. When the patients develop symptoms or signs associated with increased aldosterone production, such as elevated BP, muscle weakness, and low potassium, a blood sample is drawn from a vein in the arm or a 24-hour urine sample. At specialized medical centers, blood from the kidneys or adrenal veins is sometimes also collected.

Serum potassium anomalies, metabolic acid-base disorders, and abnormal plasma aldosterone concentrations may be noted. Interestingly, the term "low-renin HTN" (LRH), which describes a phenotype of HTN in which renin activity is low

and hyperaldosteronism is not overt, is also used by the ESH.[2] Hypokalemia is a common feature of most LRH cases, except in GS. Moreover, mild metabolic alkalosis is common in all cases except in GS, which is associated with metabolic acidosis.[12] Notably, urinary electrolytes should not be used to rule out disorders, as all patients progress to a neutral, steady-state electrolyte balance despite extracellular volume expansion. Therefore, monogenic diseases should be suspected in hypertensive children with a family history of early-onset HTN, especially if plasma renin levels are suppressed and distal tubule sodium absorption is increased. Although genetic testing and analysis are warranted to differentiate these disorders, a presumptive diagnosis can be achieved in some patients based on clinical features, laboratory results, and response to specific pharmacological drugs. Therefore, routine use of next-generation sequencing (NGS) is not recommended to discover genetic mutations or variants in asymptomatic children.

The two main organs involved in monogenic HTN are the kidneys and adrenal glands, which regulate Na^+ and volume balance. In this review, monogenic HTN is divided into two categories based on these two organs and is discussed in terms of clinical features, mutations in a single gene, and treatment agents. A summary of the various forms of monogenic HTN is presented in Table 1. Fig. 1 shows a diagnostic and therapeutic approach for patients with LRH.
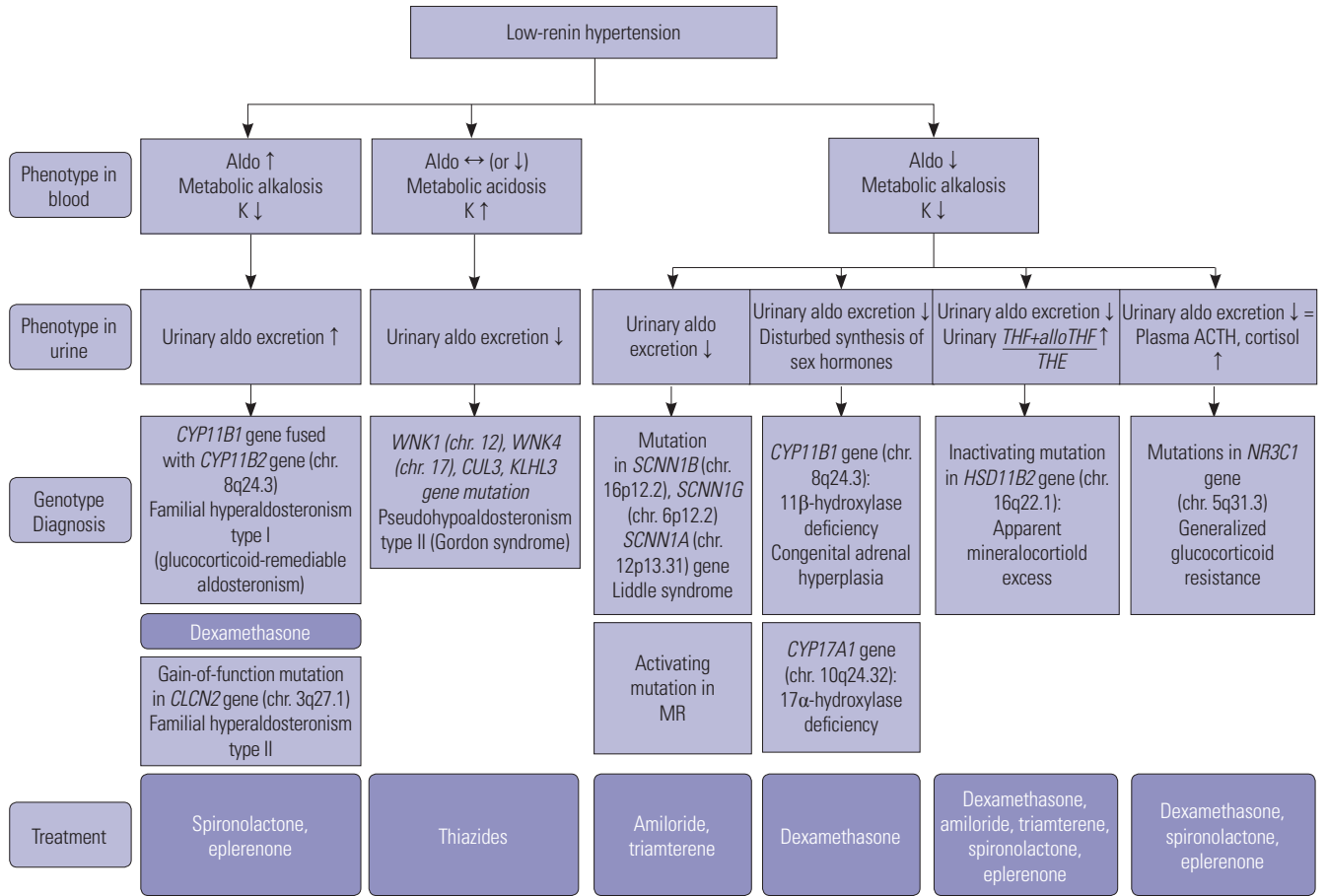
MUTATIONS IN THE ADRENAL GLAND

FH

FH-I/GRA

The first described form of inheritable PA is GRA, also known as FH-I or aldosterone synthase hyperactivity.[13] PA is the most prevalent cause of LRH. GRA is an autosomal dominant disorder that results in high serum aldosterone levels, low renin activity, and HTN. GRA is caused by a chimeric gene, with recombination of the promoter region of the 11β-hydroxylase gene (*CYP11B1*) and aldosterone synthase gene (*CYP11B2*) on chromosome 8q.[14,15] The new chimeric fusion gene encodes for an aldosterone synthase that is activated by not only low blood volume, angiotensinogen II, and high serum K^+ levels, but also adrenocorticotropic hormone (ACTH).[16] Upon ACTH stimulation, aldosterone is expressed in the zona fasciculata and is produced along with cortisol. This causes a significant increase in aldosterone concentration, resulting in increased secretion of K^+ and reabsorption of NaCl and water.[17]

Patients with GRA usually show symptoms of severe HTN, mild hypokalemia, metabolic alkalosis, and low plasma renin levels. Testing for plasma ARR can help in screening to detect high aldosterone levels with suppressed PRA.[18] The gold standard for diagnosis is confirmation of the chimeric *CYP11B1/CYP11B2* gene through genetic sequencing. Some patients with

YMJ

Table 1. Characteristic Features, Genetic Causes, and Treatment of the Various Monogenic Forms of HTN

	Adrenal gland disorders				Distal nephron disorders			
	GRA (FH-I)	FH-II	CAH	FGR	Gordon's	Liddle's	AME	H-P
Mode of inheritance	AD	AD	AR	AR/AD	AD	AD	AR	AD
PRA/Aldosterone level	↓/↑ (N)	↓/↑	↓/↓	↓/↓	↓/N or ↑	↓/↓	↓/↓	↓/↓
Aldo: PRA ratio	↑	↑						
Mechanism for HTN	Excess mineralocorticoid production	Excess mineralocorticoid production	Excess cortisol precursors activate MR	Unresponsive GR to cortisol, consequent overproduction of cortisol and androgens	Increased Na-Cl cotransporter activity in the DCT	Increased renal absorption of salt and water	Stimulation of MR by cortisol	Progesterone binding to MR
Genetic cause	$CYP11B1$ gene fused with $CYP11B2$ gene (chr. 8q24.3)	Gain-of-function mutation in $CLCN2$ gene (chr. 3q27.1)	11β-hydroxylase deficiency: $CYP11B1$ gene (chr. 8q24.3) 17α-hydroxylase deficiency: $CYP17A1$ gene (chr. 10q24.32)	Mutations in $NR3C1$ gene (chr. 5q31.3)	$WNK1$ (chr. 12), $WNK4$ (chr. 17), $CUL3, KLHL3$ gene mutation	Mutations in $SCNN1B$ (chr. 16p12.2), $SCNN1G$ (chr. 16p12.2), $SCNN1A$ (chr. 12p13.31) gene	Inactivating mutation in $HSD11B2$ gene (chr. 16q22.1)	Point mutation: serine → leucine at codon 810 (chr. 4q31)
Treatment	Glucocorticoids, amiloride, triamterene	MR antagonist	Glucocorticoids, MR antagonist	MR antagonist	Low-dose thiazides	Low-salt diet, amiloride, triamterene	MR antagonist (Spironolactone, eplerenone), amiloride	Amiloride, triamterene, thiazides, delivery

AME, apparent mineralocorticoid excess; H-P, hypertension exacerbated by pregnancy; GRA, glucocorticoid-remediable aldosteronism; FH-II, familial hyperaldosteronism type II; CAH, congenital adrenal hyperplasia; FGR, familial glucocorticoid resistance; AD, autosomal dominant; AR, autosomal recessive; MC, mineralocorticoid; HTN, hypertension; PRA, plasma renin activity; Aldo:PRA, ratio of aldosterone to PRA (>30 diagnostic if Aldo in ng/dL, PRA in ng/mL/h); MR, mineralocorticoid receptor; GR, glucocorticoid receptor; DCT, distal convoluted tubule.

Low-renin hypertension

Phenotype in blood	Aldo ↑ Metabolic alkalosis K ↓	Aldo ↔ (or ↓) Metabolic acidosis K ↑	Aldo ↓ Metabolic alkalosis K ↓			
Phenotype in urine	Urinary aldo excretion ↑	Urinary aldo excretion ↓	Urinary aldo excretion ↓	Urinary aldo excretion ↓ Disturbed synthesis of sex hormones	Urinary aldo excretion ↓ Urinary $\frac{THF+alloTHF}{THE}$ ↑	Urinary aldo excretion ↓ = Plasma ACTH, cortisol ↑
Genotype Diagnosis	*CYP11B1* gene fused with *CYP11B2* gene (chr. 8q24.3) Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism) **Dexamethasone** Gain-of-function mutation in *CLCN2* gene (chr. 3q27.1) Familial hyperaldosteronism type II	*WNK1 (chr. 12), WNK4 (chr. 17), CUL3, KLHL3 gene mutation* Pseudohypoaldosteronism type II (Gordon syndrome)	Mutation in *SCNN1B* (chr. 16p12.2), *SCNN1G* (chr. 6p12.2) *SCNN1A* (chr. 12p13.31) gene Liddle syndrome Activating mutation in MR	*CYP11B1* gene (chr. 8q24.3): 11β-hydroxylase deficiency Congenital adrenal hyperplasia *CYP17A1* gene (chr. 10q24.32): 17α-hydroxylase deficiency	Inactivating mutation in *HSD11B2* gene (chr. 16q22.1): Apparent mineralocortiold excess	Mutations in *NR3C1* gene (chr. 5q31.3) Generalized glucocorticoid resistance
Treatment	Spironolactone, eplerenone	Thiazides	Amiloride, triamterene	Dexamethasone	Dexamethasone, amiloride, triamterene, spironolactone, eplerenone	Dexamethasone, spironolactone, eplerenone

Fig. 1. A diagnostic and therapeutic approach to patients with low-renin hypertension. ACTH, adrenocorticotropic hormone; Aldo, aldosterone; (allo)THF, (allo)tetrahydrocortisol; GFR, glomerular filtration rate; PRA, plasma renin activity.

GRA may appear to be particularly at risk for cerebral aneurysms and intracranial bleeding. Therefore, magnetic resonance angiography screening at the onset of puberty is recommended.[19]

As the nomenclature indicates, treatment of GRA includes low-dose glucocorticoids (prednisolone, dose of 2.5–5 mg daily) to suppress ACTH-stimulated aldosterone production, and mineralocorticoid receptor (MR) antagonists, such as spironolactone or eplerenone, to suppress the effects of aldosterone.[20,21] The epithelial sodium channel (ENaC) antagonists amiloride or triamterene can be used as adjunctive therapies. As PRA is already suppressed, antihypertensive agents, such as ACE inhibitors or β-blockers, are ineffective in treating GRA. However, management of PA should be personalized according to patient age, disease severity, anatomic type of disease (unilateral adenoma vs. bilateral hyperplasia), and preference between medicine or surgery.[22] Laparoscopic adrenalectomy is ideal for treating aldosterone excess and improving long-term BP control in unilateral adenoma,[21,23] although medical therapy is assumed to be as effective as surgical therapy if BP is normalized.[22] Presently, further studies are necessary to determine the precise therapeutic criteria for medical and surgical therapies for PA.

FH-II

Recently, the gene responsible for FH-II has been identified in affected subjects as *CLCN2*, which encodes the voltage-gated chloride channel ClC-2 expressed in the adrenal glomerulosa.[24] A gain-of-function mutation causes the depolarization of the glomerular cell membrane and activation of voltage-gated calcium channels, upregulating the expression of *CYP11B2*. This in turn encodes an enzyme for aldosterone biosynthesis.[25] FH-II is characterized by the familial form of PA with aldosterone-producing adenomas or idiopathic bilateral adrenal hyperplasia. It has been reported that HTN due to FH-II usually manifests in adults.[25] The previous diagnostic method to distinguish PA from sporadic PA is the presence of two or more family members affected by PA.[26] Therefore, this condition should be diagnosed when there is a positive family history given the possibility of other familial forms of PA being excluded.[27] However, genetic testing is the standard method for diagnosing FH-II. As FH-II is unresponsive to glucocorticoids, unlike FH-I, using mineralocorticoid antagonists together with unilateral adrenalectomy is advised for the amelioration of symptoms.

FH-III

FH-III is caused by mutations in *KCNJ5*, which encodes an in-

ward rectifying potassium channel, Kir3.4.[28] In FH-III, a gain-of-function germline mutation in the *KCNJ5* gene induces loss of potassium selectivity in the zona glomerulosa potassium channel, resulting in increased Na⁺ influx, a higher cell membrane potential, and lower depolarization threshold; consequently, aldosterone synthesis and secretion increases in the adrenal glomerulosa cells.[29] Patients with FH-III present with severe HTN, hypokalemia, and bilateral hyperplasia. In most cases, bilateral adrenalectomy is required.

FH-IV

Recently, Scholl, et al.[30] described a fourth type of FH, or FH-IV. FH-IV occurs due to a germline gain-of-function mutation in the *CACNA1H* gene, which encodes the T-type voltage-dependent calcium channel Cav3.2.[26] The activation of *CACNA1H* drives excessive calcium to enter adrenal glomerulosa cells and increases hyperaldosteronism.[31] In addition, somatic mutations in *CACNA1H*, including *KCNJ5*, *ATP1A1*, and *ATP2B3*, have been identified in more than 50% of patients with aldosterone-producing adenomas.[32,33] The ongoing discovery of new genetic forms of PA will lead to a reclassification of FH.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by cortisol biosynthesis-related gene mutations. *CYP11B1* and *CYP17A1* each encode 11β-hydroxylase and 17α-hydroxylase, and their mutations are linked to early-onset HTN and hypokalemia.[34] Defects in 11β-hydroxylase and 17α-hydroxylase lead to increased ACTH due to the absence of cortisol's negative feedback and overproduction of 21-hydroxylated steroids, which ultimately activate MR.[35] If MR activation is excessive due to increased 11-deoxycorticosterone (DOC) levels, Na⁺ reabsorption takes place, and intravascular volume expansion increases, ultimately resulting in hypokalemic alkalosis and LRH.[36]

Depending on the severity of the mutations in 11β-hydroxylase deficiency, patients may present with genital ambiguity, hirsutism, premature bone maturation, and precocious puberty. The most common features of 17α-hydroxylase deficiency are the absence of secondary sexual characteristics, amenorrhea, and LRH in affected females.[37] These presentations result from the elevation of DOC levels and resultant MR-mediated LRH and impaired steroidogenesis in both the adrenals and gonads. A hybrid *CYP11B/B1* gene can also be produced from the recombination of *CYP11B2* and *CYP11B1* genes, showing a *CYP11B1* deficiency phenotype (virilization due to excessive androgen synthesis).

Diagnosis is generally based on the presence of clinical features and confirmed by elevated DOC and androgen levels, along with 11β-hydroxylase and 17α-hydroxylase genetic sequencing. In CAH, 21-hydroxylase deficiency is the most common type and is distinguished from 11β-hydroxylase and 17α-hydroxylase in the sense it is a Na⁺-losing condition without

HTN. Treatment involves the use of MR antagonists, such as spironolactone, for HTN.

Familial glucocorticoid resistance

An inherited defect in the glucocorticoid receptor is induced by inactivating mutations in the *NR3C1* gene on chromosome 5q31-q32.[38,39] This is a rare syndrome in families with mutations inherited either by an autosomal recessive or dominant pattern, rendering the glucocorticoid receptor unresponsive to cortisol. Consequently, increased ACTH and cortisol levels cause ACTH-induced overproduction of adrenal mineralocorticoids and androgens and hypercortisolism-mediated MR activation in the kidney tubules. Cortisol has a high affinity for both glucocorticoid receptors and MR. Therefore, the classic clinical features of glucocorticoid resistance are increased plasma ACTH and cortisol, LRH, low aldosterone levels, hypokalemia, hirsutism in females, precocious puberty, chronic fatigue, and malaise.[40] Patients with glucocorticoid resistance do not present with the features of Cushing's syndrome due to glucocorticoid resistance.

This disorder can be diagnosed by markedly elevated cortisol levels and genetic analysis. Treatment with overnight low-dose dexamethasone suppresses ACTH secretion and improves excessive mineralocorticoids, hypercortisolism, and hyperandrogenism. The use of MR antagonists, such as spironolactone and eplerenone, helps to control HTN in familial glucocorticoid resistance.

MUTATIONS IN THE DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT

GS (pseudohypoaldosteronism type II, familial hyperkalemic HTN)

GS (OMINM 145260), also known as type 2 pseudohypoaldosteronism, is an autosomal dominant disorder caused by mutations in the *WNK1*, *WNK4*, *CUL3*, and *KLHL3* genes.[41,42] Mutant *WNK1* genes on chromosome 12 are associated with the overexpression of L-WNK1, leading to the activation of SPS-1-related proline/alanine-rich kinase (SPAK) and enhanced phosphorylation of the NaCl cotransporter (NCC), thereby increasing NaCl reabsorption and HTN. Mutations in *WNK4* genes induce the disruption of *KLHL3* binding, thereby impairing ubiquitination and subsequent proteolysis. This increases *WNK4* levels and phosphorylates NCC via SPAK, together with concomitant inhibition of the renal outer medullary potassium channel (ROMK).[16] The simultaneous suppression of ROMK leads to a decrease in K⁺ secretion and hyperkalemia. Two additional mutations in *CUL3* or *KHLH3* are involved in the pathophysiology of proteasomal degradation of WNK proteins, resulting in the phenotype of GS.

The clinical phenotype of patients with GS is LRH, with vary-

ing but relatively low aldosterone levels, hyperkalemia, metabolic acidosis, hypercalciuria, and low urinary sodium excretion.[43] Interestingly, *CUL3* mutations are related to a more severe presentation with higher BP, more severe hyperkalemia, acidosis, and earlier onset.[42] Dramatic improvement in GS has been observed for treatment with thiazide diuretics that inhibit NCC. Both hyperkalemia and HTN are reversed by low-dose thiazide diuretics and a Na^+- and K^+-restricted diet.[44]

LS

LS, first identified by Liddle, et al.[45] in 1963, is an autosomal dominant genetic disorder caused by gain-of-function mutations in genes encoding the ENaC subunits. Heterozygous mutations in the *SCNN1B* and/or the *SCNN1G* genes located on chromosome 16 lead to a truncated C-terminus on either the β- or γ-subunits of ENaC, resulting in the loss of regulatory binding sites for Nedd4-2 (*NEDD4L*), a ubiquitin ligase required in proteolytic degradation.[46,47] Mutations in *SCNN1B* and *SCNN1G*, encoding β- and γ-subunits, respectively, are the most frequent forms of LS. Additionally, a new heterozygous missense mutation in *SCNN1A* encoding the α-subunit was identified using exome sequencing.[48] Thus, genetic analysis is essential for the definitive diagnosis of LS.

LS-associated Na^+ reabsorption resembles states of mineralocorticoid excess but is independent of aldosterone.[49,50] The inhibited breakdown of ENaC produces an increase in ENaC expression on the apical membrane, which results in increased Na^+ reabsorption, intravascular volume expansion, and severe HTN. Increased Na^+ influx into the principal cell activates Na^+/ K^+ ATPase, causing an increased influx of K^+ into the cell at the basolateral membrane, thereby facilitating the secretion of K^+ into the lumen. Na^+ influx also induces a more negative lumen potential and H^+ secretion in type A intercalated cells. Therefore, hypokalemia and metabolic alkalosis are observed with suppressed PRA and aldosterone.

Patients with LS are recommended a salt-restricted diet and are treated with direct inhibitors of ENaC. Both amiloride and triamterene are highly effective in lowering BP and normalizing potassium levels. A recent trial showed that using ENaC blockers was the most effective treatment for uncontrolled HTN in patients with a low renin and aldosterone phenotype.[51]

AME

The AME syndrome is an autosomal recessive disorder caused by a loss-of-function mutation in the *HSD11B2* gene encoding the 11β-hydroxysteroid dehydrogenase type II enzyme (11β-HSD2), which converts cortisol to cortisone and requires an NAD^+ cofactor.[52] The main effects of cortisol on the kidneys include an increase in glomerular filtration rate, renal plasma flow, Na^+ reabsorption, K^+ secretion, and water diuresis.[16] The inactivating mutation in the *HSD11B2* gene leads to excess cortisol accumulation and activation of MR, resulting in symptoms of mineralocorticoid excess, such as sodium retention,

hypokalemic alkalosis, and LRH. Patients with severe AME may present with hypercalciuria, nephrocalcinosis, and even end-organ damage in the heart, retina, and central nervous system.[53,54]

Mutations in the *HSD11B2* gene result in both mild and severe phenotypes of AME.[22] While 11β-HSD2 expression is almost absent in the severe phenotype of AME early in life, a milder version of AME may appear later in life, possibly due to a decrease in cortisol clearance rate, a potential age-dependent decline in *HSD11B2* activity, less severe mutations or heterozygosity with partial activity of 11β-HSD2, and consumption of exogenous inhibitors of 11β-HSD2, such as licorice or grapefruit.[55-57]

AME should be suspected in children with LRH and low aldosterone with signs of mineralocorticoid excess. Urine steroid profiles have traditionally been used for the diagnosis. Profiling to check for an abnormal ratio of cortisol metabolites, which include tetrahydrocortisol (THF) and allotetrahydrocortisol, to a cortisone metabolite tetrahydrocortisone in a 24-h urine collection is performed. Genetic testing can also be performed to confirm diagnosis. Treatment is composed of MR antagonists, K^+ supplementation, dietary Na^+ restriction, epithelial Na^+ channel blocker (amiloride), and hydrochlorothiazide for hypercalciuria.

Geller syndrome (HTN exacerbated by pregnancy)

Geller syndrome, also referred to as pregnancy-exacerbated HTN, is an autosomal dominant inheritance disorder of HTN resulting from a heterozygous mutation in the MR gene (*NR3C2*).[58,59] This mutation in MR leads to altered nuclear receptor ligand selectivity and activation.[60] Subsequently, steroid hormones, such as progesterone, act as agonists of MR, resulting in increased activation of mineralocorticoid signaling cascades that enhance Na^+ reabsorption and K^+ secretion. As the level of progesterone rises 100-fold during pregnancy, affected women display severe HTN.

The substitution of a leucine for a serine at codon 810 (S810L; MR_{L810}) on chromosome 4q31 alters the conformation of the hormone-binding domain.[61] The MR_{L810} mutation can result in increased expression and activity of ENaC and Na/K ATPase, causing Na^+ reabsorption and inducing gestational HTN. The term is slightly confusing, as the syndrome is not confined to pregnant women. Severe HTN is present in both men and women. This can be explained by the fact that cortisol levels are significantly more abundant than aldosterone in men and bind MR with similar affinity. There is no specific treatment for men and non-pregnant women with Geller syndrome.

Patients with this mutation present with HTN and suppressed PRA and low serum aldosterone levels. Unlike in other types of monogenic HTN, the MR antagonist spironolactone is contraindicated because the mutated MR has increased affinity for spironolactone and paradoxically activates MR, exacerbating HTN.

FUTURE DIRECTION IN RESEARCH

Several areas for future research in the genomics of pediatric HTN were recently highlighted by Padmanabhan and Dominiczak.[62] The key points are summarized in this article. The known genetic architecture of BP encompasses more than 30 genes, with rare variants resulting in monogenic forms of HTN or hypotension, and more than 1477 common single-nucleotide polymorphisms (SNPs) have been shown to be associated with BP. These SNPs identified in genome-wide association studies are pleiotropic and mapped to non-coding regions of the genome, which makes functional mapping challenging.[62] Unraveling these pleiotropic associations can potentially help us understand the causal pathways for HTN and clinical applications for SNPs, including drug repositioning, repurposing, and pharmacogenomics for the treatment of HTN. Drug repurposing is the discovery of new indications for drugs that already exist. To increase the possibility of success in drug development and approval, repurposing drugs is necessary for a target that has a genetic basis. However, drug repurposing should be performed with care to ensure that patients are not exposed to adverse effects from the increased drug target range. Further studies are necessary to clarify which medications are optimal to use by comparing various classes of antihypertensive medications in diverse racial and ethnic populations.

In addition, the clinical phenotypes and genotypes of monogenic HTN vary from milder symptoms, encompassing normotension or normokalemia, to life-threatening conditions.[63-65] Genotype-phenotype interactions and correlations, epigenetic modifications, and non-genetic factors, such as age, nutrition, and environment, are all related to the variable phenotype and penetrance of monogenic HTN. As for testing siblings of patients with monogenic HTN, routine use of NGS is not always recommended in children without HTN, abnormal renin and aldosterone levels, and abnormal serum electrolytes. Even if family screening is available in national reference laboratories in some countries, adverse events of genetic testing should also be considered.

The field of genomics in monogenic HTN has identified numerous genomic signals, but actionable results are lacking. Clinical translation of such genetic data is much needed with the integration of pleiotropic, pharmacogenomics, and functional studies, leading to precision medicine for HTN in the future.

CONCLUSIONS

As the true prevalence of HTN in children is still unknown, monogenic HTN is not a rare condition of secondary HTN, especially for those with a positive familial history, severe early-onset, and refractory HTN that is unresponsive to traditional antihypertensive agents, such as calcium channel blockers and β blockers, together with LRH. Due to specific mutations that contribute to the development of monogenic HTN, genetic testing is beneficial for the early diagnosis and tailored therapy of affected subjects. An increased understanding of the molecular pathways that regulate BP will promote precision medicine. Accordingly, genetic or genomic confirmation is warranted to facilitate new drug development and personalized treatment, which may lead to a new classification of pediatric HTN.

Novel gene mutations causing BP variability will continue to be discovered and increase our knowledge of BP modulation. Further studies are necessary to provide a better understanding of the etiology and therapeutic strategies for monogenic HTN and to improve the prognosis in adulthood.

ORCID iDs

Se Jin Park   https://orcid.org/0000-0002-7650-5393
Jae Il Shin   https://orcid.org/0000-0003-2326-1820

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