Chapter

The Research Progress of Monogenic Inherited Hypertension

Wenxiu Liu and Xinhua Yin

Abstract

Monogenic inherited hypertension, which is caused by a single gene mutation, generally conforms to the Mendel's law, but its phenotype is affected by environmental factors as well. This type of hypertension is characterized by early onset (more common in adolescents), family history, severe hypertension, or refractory hypertension. It is often accompanied by abnormal hormone level and biochemical indicators, including low activity of plasma renin, abnormal potassium, and acid-base metabolization disorder. For adolescents with a family history of moderate to severe hypertension, hormone level (including plasma renin-angiotensin-aldosterone, cortisol, and sex hormone) and blood electrolytes should be measured and the detailed diagnosis should be determined according to medical history, physical signs, and test results. Currently, 17 kinds of monogenic hereditary hypertension have been clearly determined. Thanks to the development of gene detection technology, the diagnostic level of monogenic inherited hypertension has greatly improved and the pathogenesis has been gradually clarified. Our review mainly discussed the research progress in this field.

Keywords: monogenic hereditary disease, hypertension, rennin, potassium, gene detection

1. Introduction

Monogenic inherited hypertension, which was caused by a single gene mutation, generally conforms to the Mendel's law, but the phenotype is also affected by environmental factors. It can be identified in a large and heterogeneous family of hypertensive patients with highly specific etiologies and similar clinical manifestations [1]. It is characterized by early onset (more common in adolescents), familial aggregation, and refractory hypertension and the renin-angiotensin-aldosterone system features typical changes in almost every case. In the following report, we will review some well-characterized disorders.

1.1 Liddle syndrome

Liddle syndrome (LS), known as pseudohypoaldosteronism type I, which was firstly reported by Liddle in 1963 [2], is an autosomal dominant genetic form of low renin arterial hypertension caused by germline mutations in the SCNN1A, SCNN1B, and SCNN1G genes that encode the α, β, and γ subunits of the epithelial

sodium channel (ENaC), respectively. The prevalence of LS across the general hypertensive population still remains unknown. Three small single-center studies have estimated the prevalence to be about 0.91 [3], 1.52 [4], and 6% [5] among hypertensive patients with genetic testing and phenotypical LS, respectively.

The mutation gene was the nonsense p.Agr566* substitution of the β subunit, firstly described in the large kindred by Liddle et al. and subsequently Botero-Velez et al. [6] found that the mutation causes a truncation of the C-terminus of the β subunit with a loss of the PY motif. The first germinal mutation of SCNN1G gene, resulting in the nonsense substitution p.Trp573*, was identified by Hansson et al. in 1995 [7], the mutation erases the γ subunit's C-terminus, causing the loss of the PY motif. Different rare variants of SCNN1A have also been associated with pseudohypoaldosteronism type I, with the possibility of the compound heterozygotes in different ENaC subunits contributing to its phenotype in a digenic manner.

Recently, a germline mutation in the α subunit (p.Cys479Arg) was identified in a Caucasian family suffering from LS [8]. This missense mutation increases the open conformation of the channel, resulting in a two-fold increase in Na^+ current, without affecting channel density at the plasma membrane. It has been reported that there are 31 different mutations responsible for LS in 72 families so far [9].

Most of these mutations are frameshift, missense, or nonsense, impairing the PY motif and increasing ENaC expression at the distal nephron apical membrane, following a subsequent increase in Na^+ reabsorption. LS is characterized by resistant and early onset salt-sensitive arterial hypertension clinically, often associated with a family history of early onset hypertension and sudden death.

On average, hypertension develops around the second decade of life (15.5 ± 3.3 years) [10], with variation in the age of onset and severity of hypertension [6]. Without treatment, subjects will present with complications of severe hypertension during the third or fourth decade of life. Despite the typical phenotype presenting with severe hypertension and hypokalemia, the disease can be clinically heterogeneous, even with mild phenotypes.

Biochemically, the characteristic findings are hypokalemia, metabolic alkalosis, suppressed plasma renin activity (PRA), and low serum aldosterone levels. The diagnosis of LS is based on gene sequencing of SCNN1A, SCNN1B, and SCNN1G. Considering the autosomal dominant inheritance (50% risk of transmission) and the variable phenotype reported in some families, genetic screening also has to be performed in first-degree relatives of a mutation carrier.

As for the treatment of LS, amiloride which is a potassium-sparing diuretics, or triamterene which a direct ENaC inhibitor, combined with a low sodium diet, mitigate sodium-sensitive hypertension by inhibiting sodium transport through ENaC. The drug effect is rapid and exceptionally good. While spironolactone, another potassium-sparing diuretics, has no therapeutic effect on LS.

1.2 Gordon syndrome

Gordon syndrome (GS), also known as pseudohypoaldosteronism type II or familial hyperkalemia hypertension, is a rare form of monogenic hypertension characterized by low renin, hyperkalemia, hyperchloremic metabolic acidosis, and normal glomerular filtration rate [11].

This phenotype was first discovered in 1964 by Paver and Pauline [12], and Gordon [13] identified the phenotype to be an inheritable disorder based on a study of several pedigrees later in the 1980s. The hyperkalemia is a useful discriminator, distinguishing GS from other forms of monogenic hypertension which present with normokalemia or hypokalemia [14].

Although GS is considered to be an autosomal dominant inherited disease, new molecular studies reported some recessive cases [15]. Mutations in four genes such as WNK1 (pseudohypoaldosteronism type IIC), WNK4 (pseudohypoaldosteronism type IIB) [16], CUL3 (pseudohypoaldosteronism type IIE), and KLHL3 (pseudohypoaldosteronism type IID) [17] have been identified to be responsible for GS.

WNKs belong to a large family of serine-threonine protein kinases with pleiotropic effects. The WNK kinases (encoded by the WNK1 and WNK4 genes) regulate the expression of the Na^+/Cl^--cotransporter (NCC) in the distal nephron and the Na^+-K^+-$2Cl^-$-cotransporter (NKCC2) in the thick ascending limb of Henle's loop, which play an important role in the development of hypertension in patients with GS.

However, WNKs phosphorylate these transporters indirectly, and it is controversial how WNKs regulate the transporters and how mutations of WNKs cause activation of the transporters.

Recently, it has been discovered that STE20/SPS1-related proline/alanine-rich kinase and oxidative stress-responsive kinase 1 which are two other serine/threonine kinases downstream of WNKs, phosphorylate and activate NCC and NKCC2 actually [18–20]. While the scaffold protein Cullin3 and the adaptor protein Kelch3 (encoded by the CUL3 and KLHL3 genes, respectively), which accounted for the majority of pathogenic mutations [18], are involved in the ubiquitination and proteasomal degradation of the WNK kinases [21].

Therefore, loss-of-function mutations in these genes result in inhibited degradation of WNKs in the distal nephron and thus upregulation of NCC activity. Different mutant genes are significantly correlated with the clinical manifestations of GS, which can be sorted as CLU3 > KLHL3 > WNK4 > WNK1 according to the age of onset and clinical manifestations.

CLU3 mutants develop early onset, most of them present hypertension when they are minors, and show severe hyperkalemia and metabolic acidosis. Patients with WNK1 may not develop hypertension until late adulthood, and the clinical symptoms are relatively mild, but occasionally they are severe accompanied by periodic paralysis.

Affected subjects have suppressed renin levels consistent with salt-loaded state, while the aldosterone levels are typically low despite their hyperkalemia. Dietary sodium restriction (20 mmol/day) and/or low doses of thiazide diuretics can reverse hypertension and hyperkalemia of patients with GS [13, 22].

1.3 Apparent mineralocorticoid excess syndrome

Apparent mineralocorticoid excess (AME) syndrome is an autosomal recessive disorder due to the loss of functional mutations in HSD11B2 gene on chromosome 16q22, and it is first described in the late 1970s [23].

Approximately 40 causative mutations in HSD11B2 have been identified in 100 AME patients worldwide [24]. In AME syndrome, the function of 11β-HSD2 with a potential age-dependent decline in the activity [25] is impaired, and therefore the MR, which has the same affinity for both aldosterone and cortisol, is protected from cortisol activation by 11β-HSD2 activity under physiological conditions, is occupied and activated by cortisol, resulting in hypertension.

Affected patients display low birth weight, severe hypertension, polyuria and polydipsia, hypokalemia, low PRA, and low aldosterone in the classical AME syndrome which is caused by absolutely or essentially absent of the 11β-HSD2 activity.

While it may be mild when the mutant enzyme retains some activity [26], patients in this type present adult onset, mild-to-moderate hypertension, and normal potassium. The diagnosis of AME is usually suspected in the setting on non-aldosterone dependent low-renin hypertension (LRH) with classic features of MR activation and

confirmed by a high cortisol/cortisone (F/E) ratio in the serum or urine, and/or genetic sequencing of HSD11B2 [27, 28].

It is notable that both glycyrrhizic acid and grapefruit juice are HSD11B2 inhibitors and an excessive intake can induce clinical symptoms and laboratory findings of AME syndrome [29]. Baudrand and Vaidya conceived that lower cortisone levels (in combination with higher F/E ratio) were strongly associated with higher MR activity (lower renin activity and higher urinary potassium excretion) in patients suspected to have mild or non-classical AME [30].

The treatment for classic AME is low-dose dexamethasone in combination with MRAs or renal transplantation in extreme cases.

1.4 Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by defects in different enzymes involved in adrenal steroid production. Among them, the deficiency of 21-hydroxylase caused by CYP21A2 gene mutation is the most frequent cause of CAH (90–95%).

Affected patients present sodium loss but normal blood pressure, followed by 11β-hydroxylase deficiency which is caused by gene mutation of CYP11β1 (5–8%), while the other defects are rare, including CYP17α1 gene mutation caused 17α-hydroxylase (CYP17) deficiency [31].

The 11β-hydroxylase catalyzes the 11-deoxycortisol and 11-deoxycorticosterone (DOC) to cortisol and corticosterone, CYP11B1 deficiency impairs above function and results in low levels of cortisol and high levels of 11-deoxycortisol and 11-DOC and a shunting of metabolites into the androgen synthesis pathway.

Due to the mineralocorticoid function of DOC, two-thirds of the affected subjects display hypertension at diagnosis, together with suppressed renin, low aldosterone levels, and hypokalemia [32]. Due to the excessive androgens, patients present various degrees of virilization of female external genitalia and pseudo-precocious pubertal development in males, together with accelerated somatic growth, but premature closure of growth plates resulting in short stature in adulthood.

The diagnosis can be confirmed via elevated DOC and androgen levels and/or genetic sequencing of 11β-hydroxylase. 17α-hydroxylase deficiency present a clinical phenotype sustained by a reduction in cortisol and adrenal and gonadal sex steroids production associated with an increase in DOC levels, featuring a clinical phenotype of mineralocorticoid excess. The deficiency of sex hormones results in hypogonadism in men and infantilism in women.

High levels of DOC result in MR activation, hypertension, and hypokalemia. Clinical examination of plasma cortisol, sex hormone precursors, and DOC is helpful for diagnosis, and ultrasound examination of genitals is helpful to understand the development of uterus, gonadal, and vagina.

Treatment involves glucocorticoid and MR antagonists to normalize blood pressure and sex hormone replacement therapy [33].

1.5 Mineralocorticoid receptor activating mutations

In 2000, Geller et al. [34] first reported the single-gene genetic hypertension caused by the active mutation of mineralocorticoid receptor (MR), an autosomal dominant genetic disease, also known as the pregnancy aggravated hypertension.

Functional mutation is achieved through a substitution of leucine for serine at codon 810 (abbreviated as S810L) in the MR gene. The worsening in pregnancy is explained by the theory that progesterone activates the mutant S810L MR, where

progesterone typically antagonizes wild-type MR. So termination of pregnancy is a must for pregnant women to lower blood pressure.

While in males and non-pregnant females, cortisone and DOC activate the mutant MR and result in increased sodium reabsorption [35]. Surprisingly, spironolactone is ineffective since its agonist effect on the mutant MR and it can increase MR activation paradoxically.

Treatment with sodium channel blockers such as amiloride to inhibit ENaC may be effective, the novel and potent nonsteroidal selective MR antagonist-finerenone may also be a useful option [36].

1.6 Glucocorticoid resistance syndrome

Glucocorticoid resistance syndrome (GRS) is an autosomal recessive or dominant disease, caused by glucocorticoid receptor gene NR3C1 point mutation or deletion in the chromosome 5q31-q32 [37, 38].

Affected patients are characterized by a various degree of end-organ insensitivity to glucocorticoids, compensatory ACTH hypersecretion, excessive production of cortisol, adrenal androgens, and other adrenal steroids displaying mineralocorticoid activity. The classic phenotype of GRS is chronic fatigue and malaise, low renin hypertension, hypokalemia, and metabolic alkalosis.

Although female fetus virilization is extremely rare, affected children can display precocious puberty and premature adrenarche, and female patients can display acne, hirsutism, male pattern alopecia, and infertility.

The therapy is using overnight low-dose dexamethasone to suppress ACTH secretion, which improves ACTH-induced symptoms, and spironolactone can further help to control hypertension and female hirsutism.

1.6.1 Glucocorticoid remediable aldosteronism

Glucocorticoid remediable aldosteronism (GRA) is an autosomal dominant genetic disease [39], also known as familial hyperaldosteremia type I (FH-I), is the first identified monogenic hypertension.

CYP11B1 and CYP11B2 genes were identified as the culprit of FH-1 [40]. FH-I is a low renin hypertension characterized by severe early onset hypertension which is remediable by glucocorticoid, and is at high risk of experiencing cerebrovascular events at a young age, however milder phenotypes can coexist.

Stowasser et al. described the severity of the hypertension correlates with the sex: female subjects show a less-severe phenotype and a better prognosis [41].

GRA should be suspected when CT and other imaging examinations do not reveal adrenal cortical hyperplasia or tumor. Selective screening of GRA patients combined with typical clinical features can improve diagnostic level.

According to the Endocrine Society guideline, the diagnosis of FH-I should be pursued in patients younger than 20 years old with an onset of confirmed PA and in those who have a family history of primary aldosteronism or stroke at a young age (<40 years).

On the basis of positive dexamethasone suppression test as well as the 18-hydroxycortisol >2 times the normal limit of 24 h urine or > 10 nmol/L, GRA may be considered; and if the chimeric genes of CYP11B2 and CYP11B1 were screened, the definite diagnosis can be made.

The first-line therapy is low doses of glucocorticoid, administered at bedtime to suppress the early morning ACTH. Treatment with mineralocorticoid receptor antagonist is the second line therapy, which may have same effect and avoids side effects of corticoid iatrogenic.

1.6.2 Familial hyperaldosteremia type II

This type may be the most common form of familial hyperaldosteremia, and was first reported in 1991 by Gordon et al. [42].

Familial hyperaldosteremia type II (FH-II) is an autosomal dominant genetic disease with incomplete penetrance in which the pathogenic gene is located on chromosome 7p22, and the genetic basis has been very recently identified in germline mutations in the CLCN2 gene, encoding Cl^- channel ClC-2, which is expressed in adrenal zona glomerulosa [43].

Further studies are needed to establish the impact (in term of prevalence) of CLCN2 mutations on FH-II. Unlike FH-I, FH-II is not a glucocorticoid remediable form of primary aldosteronism, traditionally considered clinically and biochemically indistinguishable in a sporadic form. Some patients with FH-II had unilateral primary aldosteronism caused by aldosterone-producing adenomas and were surgically curable by unilateral adrenalectomy.

1.6.3 Familial hyperaldosteremia type III

Familial hyperaldosteremia type III (FH-III) was reported as a novel form of primary aldosteronism in 2008 [44] and the molecular basis is a germline mutation of the KCNJ5 gene, which is located on chromosome 11q24 and encodes for a K^+ channel, GIRK4, also known as Kir3.4.

The prevalence of this disease is low, it was reported to be about 0.3% of all patients with primary aldosteronism. So far, 12 families and 6 germline mutations have been reported, most affected patients display extremely severe primary aldosteronism (type A) that requires bilateral adrenalectomy to control drug-resistant hypertension.

In 2012, 2 studies independently reported the G151E germline mutation in patients with milder hyperaldosteronism (type B), who had no adrenal hyperplasia and responded well to antihypertensive therapy.

The endocrine society guidelines recommend FH-III genetic testing (KCNJ5 target gene sequencing) for all patients who have early onset of primary aldosteronism.

1.6.4 Familial hyperaldosteremia type IV

Familial hyperaldosteremia type IV (FH-IV) described by Scholl et al. [45] recently, is a rare form of familial primary aldosteronism. It is an autosomal dominant disease and caused by a germline mutation of CACNA1H, which locates on chromosome 16p13 and encodes for a T-type calcium channel, Cav3.2.

Mutations in CACNA1H showed drastically impaired channel inactivation and activation at more hyperpolarized potentials, increased intracellular Ca^{2+}, and aldosterone production. Compared to FH-II patients affected in a sporadic form, this disease displays an incomplete penetrance and the affected patients did not display any peculiar biochemical characteristics.

1.7 Hypertension and brachydactyly syndrome

Hypertension and brachydactyly syndrome (HTNB), also named Bilginturan syndrome, is reported in a Turkish family by Bilginturan et al. [46] in 1973, which is characterized by severe salt-independent hypertension, a short stature, brachydactyly, and death from stroke before the age of 50 years when untreated.

It is autosomal dominant inheritance and full penetrance, and pathogenic genes at 12p12.2-p11.2 [47]. In 2015, Maass et al. [48] identified mutations in the PDE3A gene at 12p12.2 from 6 families with HTNB, which were heterozygous missense mutation.

These mutations were suggested to cause hypertension in the HTNB patients by increasing peripheral vascular resistance. HTNB is less reactive to β blockers, CCB, α blockers, and ACEI, combination therapy maybe more effective.

2. Conclusion

The disorders described above highlight the importance of the identification and diagnosis of monogenic hereditary hypertension. The gold standard for the diagnosis of monogenic forms of hypertension is gene detection. It attaches great significance to carry out gene detection for patients with hypertension who are clinically suspected.

Genetic testing can not only screen pathogenic genes to guide targeted therapy, but also screen the genes of the proband's family to detect all individuals carrying pathogenic genes, which is conducive to early detection, early treatment, and prenatal diagnosis of the disease.

Meanwhile, monogenic hypertension is a hereditary rare disease with relatively definite genes. The study on its genetic mechanism has greatly extended the understanding about the pathologic molecular mechanism of hypertension, which will help us to learn the correlation between hypertension and heredity more deeply.

Acknowledgements

We thank Dr Yue Liu and Dr Wenjia Chen for their efforts on the article topic selecting, and Jiaxing Sun for the modifying English language. This article was supported by the National Natural Science Foundation of China (Grant No. 81700318 and 81570437).

Conflict of interest

The authors declare no conflict of interest.

Author details

Wenxiu Liu and Xinhua Yin*
Department of Cardiology, First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China

*Address all correspondence to: yinxinhua5063@163.com

IntechOpen

References

[1] New MI, Geller DS, Fallo F, et al. Monogenic low renin hypertension. Trends in Endocrinology and Metabolism. 2005;**16**(3):92-97. DOI: 10.1016/j.tem.2005.02.011

[2] Liddle GW, Bledsoe T, Coppage WS. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. Proceedings of the Association of American Physicians. 1963;**76**:199-213

[3] Liu K, Qin F, Sun X, et al. Analysis of the genes involved in Mendelian forms of low-renin hypertension in Chinese early-onset hypertensive patients. Journal of Hypertension. 2018;**36**(3):502-509. DOI: 10.1097/HJH.0000000000001556

[4] Wang LP, Yang KQ, Jiang XJ, et al. Prevalence of Liddle syndrome among young hypertension patients of undetermined cause in a Chinese population. Journal of Clinical Hypertension. 2015;**17**:902-907. DOI: 10.1111/jch.12598

[5] Tapolyai M, Uysal A, Dossabhoy NR, et al. High prevalence of Liddle syndrome phenotype among hypertensive US veterans in Northwest Louisiana. Journal of Clinical Hypertension (Greenwich, Conn.). 2010;**12**:856-860. DOI: 10.1111/j.1751-7176.2010.00359.x

[6] Botero-Velez M, Curtis JJ, Warnock DG. Brief report: Liddle's syndrome revisited-A disorder of sodium reabsorption in the distal tubule. The New England Journal of Medicine. 1994;**330**:178-181. DOI: 10.1056/NEJM199401203300305

[7] Hansson JH, Nelson-Williams C, Suzuki H, et al. Hypertension caused by a truncated epithelial sodium channel γ subunit: Genetic heterogeneity of Liddle syndrome. Nature Genetics. 1995;**11**: 76-82. DOI: 10.1038/ng0995-76

[8] Salih M, Gautschi I, van Bemmelen MX, et al. A missense mutation in the extracellular domain of αENaC causes Liddle syndrome. Journal of the American Society of Nephrology. 2017;**28**:3291-3299. DOI: 10.1681/ASN.2016111163

[9] Tetti M, Monticone S, Burrello J, et al. Liddle syndrome: Review of the literature and description of a new case. International Journal of Molecular Sciences. 2018;**19**(3):812. DOI: 10.3390/ijms19030812

[10] Cui Y, Tong A, Jiang J, et al. Liddle syndrome: Clinical and genetic profiles. Journal of Clinical Hypertension (Greenwich, Conn.). 2017;**19**(5):524-529. DOI: 10.1111/jch.12949

[11] Gordon RD, Geddes RA, Pawsey CG, et al. Hypertension and severe hyperkalaemia associated with suppression of renin and aldosterone and completely reversed by dietary sodium restriction. Australasian Annals of Medicine. 1970;**19**:287-294

[12] Paver WK, Pauline GJ. Hypertension and hyperpotassaemia without renal disease in a young male. The Medical Journal of Australia. 1964;**2**:305-306

[13] Gordon RD. The syndrome of hypertension and hyperkalemia with normal glomerular filtration rate: Gordon's syndrome. Australian and New Zealand Journal of Medicine. 1986;**16**:183-184

[14] Toka HR, Koshy JM, Hariri A. The molecular basis of blood pressure variation. Pediatric Nephrology. 2013;**28**:387-399. DOI: 10.1007/s00467-012-2206-9

[15] Park JS, Park E, Hyun HS, et al. Three cases of Gordon syndrome with dominant KLHL3 mutations. Journal of Pediatric Endocrinology & Metabolism.

2017;**30**:361-364. DOI: 10.1515/jpem-2016-0309

[16] Wilson FH, Disse-Nicodeme S, Choate KA, et al. Human hypertension caused by mutations in WNK kinases. Science. 2001;**293**:1107-1112

[17] Boyden LM, Choi M, Choate KA, et al. Mutations in kelch-like 3 and cullin 3 cause hypertensionnand electrolyte abnormalities. Nature. 2012;**482**:98-102. DOI: 10.1038/nature10814

[18] Vitari AC, Deak M, Morrice NA, et al. The WNK1 and WNK4 protein kinases that are mutated in Gordon's hypertension syndrome phosphorylate and activate SPAK and OSR1 protein kinases. The Biochemical Journal. 2005;**391**(Pt 1):17-24. DOI: 10.1042/BJ20051180

[19] Alessi DR, Zhang J, Khanna A, et al. The WNK-SPAK/OSR1 pathway: Master regulator of cation-chloride cotransporters. Science Signaling. 2014;**7**(334):re3. DOI: 10.1126/scisignal.2005365

[20] Yang SS, Fang YW, Tseng MH, et al. Phosphorylation regulates NCC stability and transporter activity in vivo. Journal of the American Society of Nephrology. 2013;**24**:1587-1597. DOI: 10.1681/ASN.2012070742

[21] O'Shaughnessy KM. Gordon syndrome: A continuing story. Pediatric Nephrology. 2015;**30**:1903-1908. DOI: 10.1007/s00467-014-2956-7

[22] Mayan H, Vered I, Mouallem M, et al. Pseudohypoaldosteronism type II: Marked sensitivity to thiazides, hypercalciuria, normomagnesemia, and low bone mineral density. The Journal of Clinical Endocrinology and Metabolism. 2002;**87**:3248-3254. DOI: 10.1210/jcem.87.7.8449

[23] Ulick S, Levine LS, Gunczler P, et al. A syndrome of apparent mineralocorticoid excess associated with defects in the peripheral metabolism of cortisol. The Journal of Clinical Endocrinology and Metabolism. 1979;**49**:757-764. DOI: 10.1210/jcem-49-5-757

[24] Yau M, Al Azkawi HS, Haider S, et al. A novel mutation in HSD11B2 causes apparent mineralocorticoid excess in an Omani kindred. Annals of the New York Academy of Sciences. 2016;**1376**(1):65-71. DOI: 10.1111/nyas.13162

[25] Campino C, Martinez-Aguayo A, Baudrand R, et al. Age-related changes in 11β-hydroxysteroid dehydrogenase type 2 activity innormotensive subjects. American Journal of Hypertension. 2013;**26**:481-487. DOI: 10.1093/ajh/hps080

[26] Wilson RC, Dave-Sharma S, Wei JQ, et al. A genetic defect resulting in mild low-renin hypertension. Proceedings of the National Academy of Sciences of the United States of America. 1998;**95**:10200-10205. DOI: 10.1073/pnas.95.17.10200

[27] Funder JW. Apparent mineralocorticoid excess. The Journal of Steroid Biochemistry and Molecular Biology. 2017;**165**:151-153. DOI: 10.1016/j.jsbmb.2016.03.010

[28] Carvajal CA, Romero DG, Mosso LM, et al. Biochemical and genetic characterization of 11 β-hydroxysteroid dehydrogenase type 2 in low-renin essential hypertensives. Journal of Hypertension. 2005;**23**:71-77

[29] Karl M, Lamberts SW, Detera-Wadleigh SD, et al. Familial glucocorticoid resistance caused by a splice site deletion in the human glucocorticoid receptor gene. The Journal of Clinical Endocrinology and Metabolism. 1993;**76**:683-689. DOI: 10.1210/jcem.76.3.8445027

[30] Baudrand R, Vaidya A. The low-renin hypertension phenotype: Genetics and the role of the mineralocorticoid receptor. International Journal of Molecular Sciences. 2018;**19**(2):546. DOI: 10.3390/ijms19020546

[31] El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. Lancet. 2017;**390**:2194-2210. DOI: 10.1016/S0140-6736(17)31431-9

[32] Khattab A, Haider S, Kumar A, et al. Clinical, genetic, and structural basis of congenital adrenal hyperplasia due to 11 β-hydroxylase deficiency. Proceedings of the National Academy of Sciences of the United States of America. 2017;**114**:E1933-E1940. DOI: 10.1073/pnas.1621082114

[33] Auchus RJ. Steroid 17-hydroxylase and 17, 20-lyase deficiencies, genetic and pharmacologic. The Journal of Steroid Biochemistry and Molecular Biology. 2017;**165**:71-78. DOI: 10.1016/j.jsbmb.2016.02.002

[34] Geller DS, Farhi A, Pinkerton N, et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. Science. 2000;**289**:119-123

[35] Rafestin-Oblin ME, Souque A, Bocchi B, et al. The severe form of hypertension caused by the activating S810L mutation in the mineralocorticoid receptor is cortisone related. Endocrinology. 2003;**144**:528-533. DOI: 10.1210/en.2002-220708

[36] Amazit L, Le Billan F, Kolkhof P, et al. Finerenone impedes aldosterone-dependent nuclear import of the mineralocorticoid receptor and prevents genomic recruitment of steroid receptor coactivator-1. The Journal of Biological Chemistry. 2015;**290**:21876-21889. DOI: 10.1074/jbc.M115.657957

[37] Chrousos GP, Vingerhoeds A, Brandon D, et al. Primary cortisol resistance in man. A glucocorticoid receptor mediated disease. The Journal of Clinical Investigation. 1982;**69**:1261-1269

[38] Nicolaides NC, Charmandari E. Chrousos syndrome: From molecular pathogenesis to therapeutic management. European Journal of Clinical Investigation. 2015;**45**:504-514. DOI: 10.1111/eci.12426

[39] Sutherland DJ, Ruse JL, Laidlaw JC. Hypertension, increased aldosterone secretion and low plasma renin activity relieved by dexamethasone. Canadian Medical Association Journal. 1966;**95**(22):1109-1119

[40] Lifton RP, Dluhy RG, Powers M, et al. A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature. 1992;**355**:262-265. DOI: 10.1038/355262a0

[41] Stowasser M, Bachmann AW, Huggard PR, et al. Severity of hypertension in familial hyperaldosteronism type I: Relationship to gender and degree of biochemical disturbance. The Journal of Clinical Endocrinology and Metabolism. 2000;**85**:2160-2166. DOI: 10.1210/jcem.85.6.6651

[42] Gordon RD, Stowasser M, Tunny TJ, et al. Clinical and pathological diversity of primary aldosteronism, including a new familial variety. Clinical and Experimental Pharmacology & Physiology. 1991;**18**:283-286

[43] Fernandes-Rosa FL, Daniil G, Orozco IJ, et al. A gain-of-function mutation in the CLCN2 chloride channel gene causes primary aldosteronism. Nature Genetics. 2018;**50**:355-361. DOI: 10.1038/s41588-018-0053-8

[44] Geller DS, Zhang J, Wisgerhof MV, et al. A novel form of human

mendelian hypertension featuring nonglucocorticoid-remediable aldosteronism. The Journal of Clinical Endocrinology and Metabolism. 2008;**93**(8):3117-3123. DOI: 10.1210/jc.2008-0594

[45] Scholl UI, Stölting G, Nelson-Williams C, et al. Recurrent gain of function mutation in calcium channel CACNA1H causes early-onset hypertension with primary aldosteronism. eLife. 2015;**4**:e06315. DOI: 10.7554/eLife.06315

[46] Bilginturan N, Zileli S, Karacadag S, et al. Hereditary brachydactyly associated with hypertension. Journal of Medical Genetics. 1973;**10**:253-259. DOI: 10.1136/jmg.10.3.253

[47] Schuster H, Wienker TE, Bähring S, et al. Severe autosomal dominant hypertension and brachydactyly in a unique Turkish kindred maps to human chromosome 12. Nature Genetics. 1996;**13**:98-100. DOI: 10.1038/ng0596-98

[48] Maass PG, Aydin A, Luft FC, et al. PDE3A mutations cause autosomal dominant hypertension with brachydactyly. Nature Genetics. 2015;**47**:647-653. DOI: 10.1038/ng.3302