

# An Update on Familial Hyperaldosteronism

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## Key words

- GRA
- PASNA
- primary aldosteronism
- *KCNJ5*
- *CACNA1D*
- *CACNA1H*

## Abstract

Familial forms of primary aldosteronism have been suggested to account for up to 6% of cases in referral centers. For many years, the genetics of familial hyperaldosteronism remained unknown, with the notable exception of glucocorticoid-remediable aldosteronism, due to unequal crossing over and formation of a chimeric 11 $\beta$ -hydroxylase/aldosterone synthase gene. Over the past 5 years, mutations in 3 additional genes have been shown to cause familial forms of primary aldosteronism. Gain-of-function heterozygous germline mutations in *KCNJ5*, which encodes an inward rectifier potassium channel, cause autosomal dominant syndromes of PA and hypertension with or without adrenal hyperplasia. Germline mutations in

*CACNA1D*, which codes for an L-type calcium channel, have so far only been found in 2 cases with a syndrome of primary aldosteronism, seizures, and neurologic abnormalities. Both *KCNJ5* and *CACNA1D* mutations in familial hyperaldosteronism were only discovered following identification of similar or identical somatic mutations in aldosterone-producing adenomas. In contrast, a recent exome sequencing study identified germline mutations in *CACNA1H* (a T-type calcium channel), previously undescribed in adenomas, in 5 unrelated families with early-onset primary aldosteronism and hypertension, without any additional shared symptoms. Future exome or genome sequencing studies are expected to shed light on the genetic basis of many cases of familial hyperaldosteronism that remain unexplained.

received 06.08.2015  
accepted 10.09.2015

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DOI <http://dx.doi.org/10.1055/s-0035-1564166>  
Published online:  
October 7, 2015  
Horm Metab Res 2015;  
47: 941–946  
© Georg Thieme Verlag KG  
Stuttgart · New York  
ISSN 0018-5043

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## Abbreviations

ACTH	Adrenocorticotrophic hormone
APA	Aldosterone-producing adenoma
CACNA1D	Calcium channel, voltage-dependent, L type, alpha 1D subunit CACNA1H Calcium channel, voltage-dependent, T type, alpha 1H subunit
CYP11B1	Cytochrome P450, family 11, subfamily B, polypeptide 1
CYP11B2	Cytochrome P450, family 11, subfamily B, polypeptide 2
FH	Familial hyperaldosteronism
GRA	Glucocorticoid-remediable aldosteronism
KCNJ5	Potassium channel, inwardly rectifying subfamily J, member 5
PA	Primary aldosteronism
PASNA	Primary aldosteronism, seizures, and neurologic abnormalities

## Introduction

Primary aldosteronism (PA) is a leading cause of secondary hypertension, with a prevalence of approximately 6–10% in hypertension centers [1–3]. PA involves excessive production of aldosterone despite suppressed renin and normal or low serum potassium levels. The most common causes are aldosterone-producing adenomas (APAs) and bilateral adrenal hyperplasia [2]. Familial aggregation of PA [familial hyperaldosteronism, (FH)] was initially reported in a peculiar subform, glucocorticoid-remediable aldosteronism (GRA) [4], but later also in nonglucocorticoid-suppressible hyperaldosteronism [5]. The first form of primary aldosteronism that was understood on a molecular level was GRA [6], which is due to a fusion of the promoter region of the 11 $\beta$ -hydroxylase gene *CYP11B1* with the coding region of the aldosterone synthase gene *CYP11B2*. Over the past few years, however, exome sequencing studies of APAs have identified several new genetic causes of primary aldo-

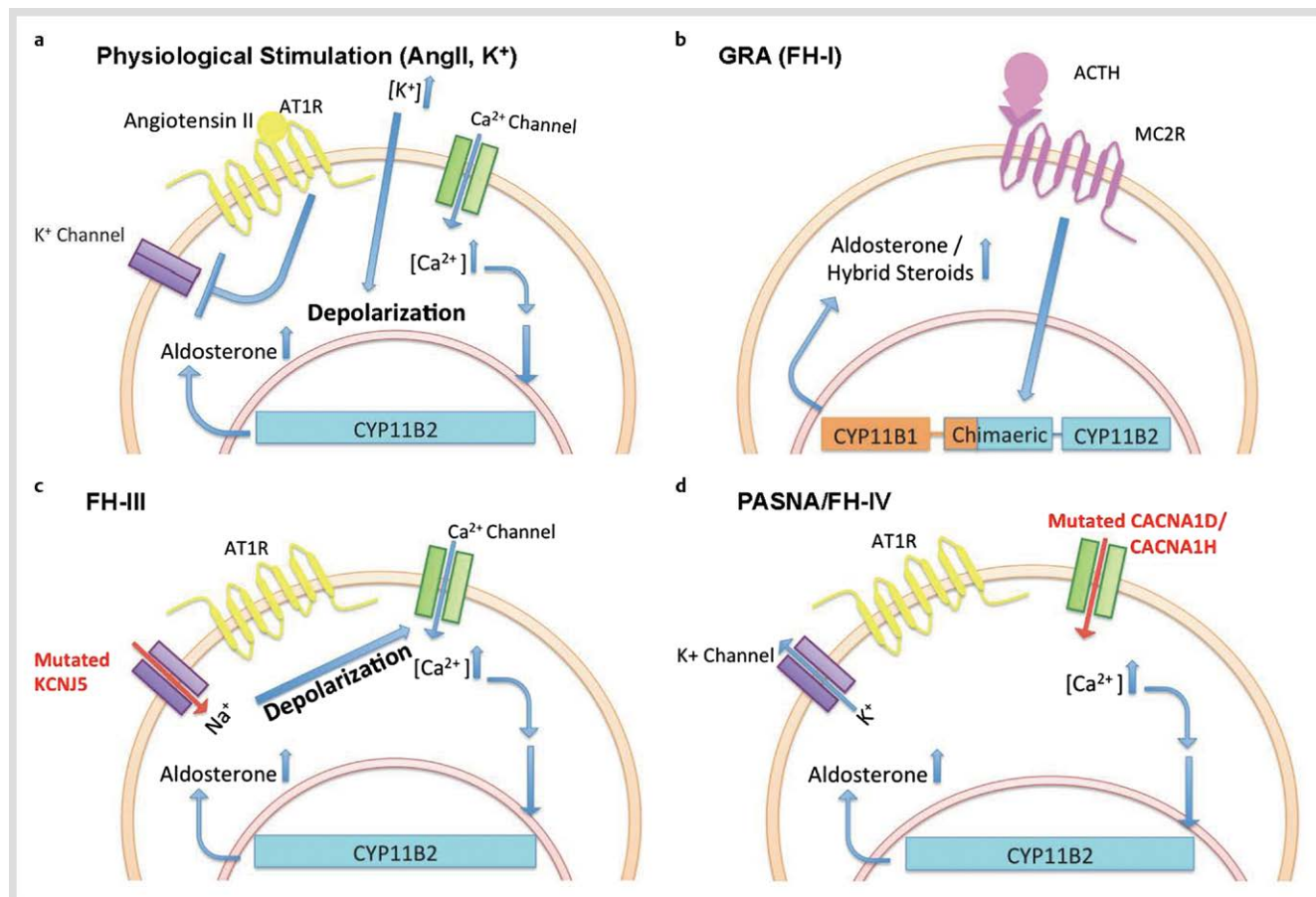
steronism. In the case of 2 genes (*KCNJ5* and *CACNA1D*), the discovery of tumor-specific (somatic) mutations in APAs have led to the identification of the same or related germline mutations in patients with early-onset PA and hypertension [7–10]. Germline mutations in a third gene (*CACNA1H*) were recently discovered through an exome sequencing study of patients with childhood PA [11]. This review will summarize our current knowledge on familial PA, with a focus on the recently described mutations in the calcium channel genes *CACNA1D* and *CACNA1H*.

### Glucocorticoid-Remediable Aldosteronism (GRA, FH-I)

Glucocorticoid-remediable aldosteronism was first described by Sutherland et al. in a family of a father and his son who presented with hypertension, potassium depletion, increased aldosterone secretion, and undetectable plasma renin activity [4]. Daily administration of 2 mg dexamethasone reversibly corrected hypertension and hypokalemia. GRA is inherited as an autosomal dominant trait; patients typically present with hypertension in the first 2 decades of life and carry an increased risk of early cerebral hemorrhage. Linkage of GRA to a chimeric

gene on chromosome 8 was demonstrated in 1992 [6]. The chimeric gene results from a crossing over event between the highly homologous genes *CYP11B1* (11 $\beta$ -hydroxylase) and *CYP11B2* (aldosterone synthase). As a consequence, aldosterone synthase is produced under the control of the 11 $\beta$ -hydroxylase promoter, which is normally involved in cortisol production and is therefore regulated by ACTH (◻ Fig. 1b). This finding explained the clinical features of GRA – aldosterone is produced under the control of ACTH throughout the glucocorticoid-producing zona fasciculata, despite suppressed renin levels. Exogenous administration of dexamethasone suppresses ACTH, and thereby aldosterone production. Hybrid steroids (18-oxocortisol and 18-hydroxycortisol) arise from the joint activities of enzymes involved in cortisol and aldosterone synthesis in the zona fasciculata.

GRA should be suspected in young patients with PA, with or without hypokalemia, especially with a family history of early-onset hypertension and/or cerebral hemorrhage. The diagnosis is based on genetic testing, and screening of first-degree relatives is recommended. Patients are typically treated with low-dose glucocorticoids and/or mineralocorticoid receptor blockers, such as spironolactone or eplerenone.



**Fig. 1** Normal and pathological pathways of aldosterone biosynthesis: **a** Physiological Stimulation. Angiotensin II binds to the Angiotensin II type I receptor (AT1R), inhibiting potassium channels and causing depolarization. Elevated extracellular potassium concentration directly causes depolarization. The resulting activation of voltage-gated calcium channels leads to increased calcium influx, increased transcription of the *CYP11B2* (aldosterone synthase) gene and aldosterone production. **b** FH-I. Adrenocorticotrophic hormone (ACTH) binds to the melanocortin 2 receptor (MC2R) and upregulates transcription of the chimeric gene resulting from the crossover between *CYP11B1*

(11 $\beta$ -hydroxylase) and *CYP11B2* (aldosterone synthase) genes, causing excessive aldosterone production. **c** FH-III. Cell membrane depolarization is caused by mutations of the *KCNJ5* gene that encodes for inward rectifier potassium channels, initiating the activation of voltage-gated calcium channels and calcium influx. This, in turn, triggers increased aldosterone biosynthesis. **d** PASNA/FH-IV. Genetic mutations in the *CACNA1D* or *CACNA1H* genes encoding voltage-dependent calcium channels cause an increase in calcium influx. Increased intracellular calcium concentration leads to increased aldosterone biosynthesis. (Color figure available online only).

### Familial Hyperaldosteronism with *KCNJ5* Mutations (FH-III)

Initially, FH-III referred to patients with massive adrenal hyperplasia refractory to dexamethasone administration [12]. However, the term is now more commonly used to describe all subjects with PA due to germline *KCNJ5* mutations, independent of the phenotype.

Early observations suggested the existence of familial forms of hyperaldosteronism that do not respond to glucocorticoids. These included a family with bilateral excess secretion of aldosterone [5,13]. The index case was reported by Bartter and Biglieri in 1958, before spironolactone was introduced clinically. The male patient was treated by removal of the right adrenal and four-fifth of the left adrenal gland. Both glands were histologically normal [13]. His affected daughter and 2 grandchildren were treated with spironolactone, which normalized blood pressure. Another interesting family of a father and 2 daughters described by Geller et al. developed severe hyperaldosteronism, hypertension and hypokalemia at ages 4–7 years [12]. The second family presented with severe bilateral adrenal hyperplasia and did not respond to medical treatment. All members of this family required bilateral adrenalectomy, with paired adrenal weights up to 82 g (normal: less than 12 g). Since such observations are limited to small nuclear families, the underlying genetic defect remained unknown.

The advent of next-generation sequencing, however, enabled the identification of causal genes in APAs, which proved to be valuable candidate genes in families with nonglucocorticoid-suppressible aldosteronism.

In the initial study, Choi et al. identified recurrent heterozygous somatic gain-of-function mutations of the *KCNJ5* gene as a cause of about 40% of APAs [7]. *KCNJ5* encodes an inward rectifier potassium channel, and the mutations affected amino acids in or close to the channel's selectivity filter. This selectivity filter allows only potassium, and not the smaller sodium ions, to pass through the channel. Two mutations, *KCNJ5*<sup>G151R</sup> and *KCNJ5*<sup>L168R</sup>, account for almost all cases, and additional somatic mutations are rare. By electrophysiology, both mutations were shown to cause abnormal sodium permeability of the channel and subsequent cellular depolarization (◉ Fig. 1c). This is an interesting mechanism because in the zona glomerulosa, binding of angiotensin II to its receptor causes inhibition of potassium channels and cellular depolarization, whereas hyperkalemia directly causes depolarization. The resulting activation of voltage-gated calcium channels leads to calcium influx, which is the signal for aldosterone production and, if present chronically, cellular proliferation [14] (◉ Fig. 1a). Abnormal and constitutive activation of these pathways accounts for the development of aldosterone-producing tumors. The authors reasoned that similar mutations, when present in the germline, might cause hereditary PA with massive adrenal hyperplasia, as present in the family described by Geller et al. [12]. Indeed, primary aldosteronism in this family co-segregated with the presence of a *KCNJ5*<sup>T158A</sup> mutation, which caused sodium influx and depolarization [7]. The identical variant was subsequently also found as a somatic mutation in tumors [8, 15].

Screening of additional families identified germline *KCNJ5*<sup>G151R</sup> mutations, which had previously been described in tumors [10]. None of the 3 affected individuals from the first kindred responded to medical treatment; all required bilateral adrenalectomy, similar to the family with *KCNJ5*<sup>T158A</sup> mutation. Pathol-

ogy demonstrated adrenal hyperplasia, with the exception of the youngest individual, who had adrenalectomy at the age of 18 months, presumably before hyperplasia could develop. A single affected individual with difficult-to-control hypertension and de novo mutation in the second family was lost to follow-up. Similarly, a mother and her daughter, both with *KCNJ5*<sup>I157S</sup> mutations, had massive adrenal hyperplasia and severe hypertension refractory to treatment; both underwent adrenalectomy [16]. An additional patient with de novo *KCNJ5*<sup>E145Q</sup> mutation previously described in an adenoma [17] had a severe phenotype and underwent adrenalectomy [18].

Most interestingly, affected members of the family with primary aldosteronism and normal adrenal histology mentioned above [5] carried a *KCNJ5*<sup>G151E</sup> mutation [10], which has never been found in tumors. The identical mutation was observed in 2 additional families, again with a much milder clinical phenotype. Patients typically responded to medical treatment with mineralocorticoid receptor antagonists and did not require bilateral adrenalectomy [8, 10, 19]. As a result, histology for assessment of potential microscopic hyperplasia is not available for the more recent cases. When heterologously expressed, the *KCNJ5*<sup>G151E</sup> mutation caused severe cell lethality, which could be rescued upon the removal of sodium from the extracellular medium, suggesting that this was a sodium-dependent effect. Indeed, by electrophysiology, it was shown that the mutation caused larger sodium currents than the previously described *KCNJ5*<sup>G151R</sup> mutation at the same residue, suggesting that sodium-dependent lethality prevents the development of macroscopic hyperplasia in these patients in vivo.

Another variant (*KCNJ5*<sup>Y152C</sup>, also not present in tumors) was found in a subject with a milder phenotype [20]. This individual was diagnosed with primary aldosteronism at the age of 48 years (much later than any of the other cases), but already had significant target organ damage, suggesting a longstanding history of hypertension. Unfortunately, despite a significant family history of hypertension, other family members were not available for genetic studies. Functional studies demonstrated a less pronounced effect on Na<sup>+</sup> conductance than that observed with other mutations.

From these studies, it appears that mutations found in tumors typically cause therapy resistant hyperaldosteronism and massive adrenal hyperplasia when present in the germline. The only exception so far is a Japanese patient with *KCNJ5*<sup>G151R</sup> mutation who at the age of 11 years had not developed adrenal hyperplasia and had responded to treatment with spironolactone [21]. It will be interesting to follow this case in the future.

In contrast, specific mutations that have not been found in tumors appear to cause milder forms of hyperaldosteronism, possibly as a result of sodium-dependent lethality or reduced calcium influx (◉ Table 1).

### Primary Aldosteronism with Seizures and Neurologic Abnormalities (PASNA)

The gene with the second highest mutation burden in APAs is *CACNA1D*, which similar to *KCNJ5* was discovered through exome sequencing studies [9, 22]. *CACNA1D* encodes a voltage-gated L-type calcium channel (Ca<sub>v</sub>1.3). *CACNA1D* channels are activated at large depolarizing potentials and are highly expressed in adrenal glomerulosa. Mutations identified in APAs shift the voltage dependence of activation to more hyperpolarized poten-

**Table 1** Phenotypes of families with familial hyperaldosteronism and mutations in *KCNJ5*, *CACNA1D*, or *CACNA1H*.

Kindred	Country of origin	# Affected subjects	Age at diagnosis (years)	Macroscopic adrenal hyperplasia	Response to medical treatment	Adrenalectomy	<i>KCNJ5</i> Mutation	<i>CACNA1D</i> Mutation	<i>CACNA1H</i> Mutation
Geller et al. 2008 [12]	US	3	4,5,7	Y,Y,Y	N,N,N	Y,Y,Y	T158A		
Scholl et al. 2012 [10]	US	3	1,1,1	Y,Y,N <sup>a</sup>	N,N,N	Y,Y,Y	G151R		
Scholl et al. 2012 [10]	UK	1	4	N/A	N/A	N/A	G151R		
Charmandari et al. 2012 [16]	GR	2	2,7	Y,Y	N,N	Y,Y	I157S		
Monticone et al. 2015 [18]	US	1	2	Y	N	Y	E145Q		
Adachi et al. 2014 [21]	J	1	4	N	Y	N (age 11)	G151R		
Mulatero et al. 2012 [8] and Mussa et al. 2012 [19]	I	2	2,18	N,N	Y,Y	N,N	G151E		
Scholl et al. 2012 [10]	US	4	0.2,1,2,11	N,N,N,N	Y,Y,Y,N <sup>b</sup>	N,N,N,Y <sup>b</sup>	G151E		
Scholl et al. 2012 [10]	C	2	4,<6	N,N/A	Y,N/A	N,Y <sup>b</sup>	G151E		
Monticone et al. 2013 [20]	US	1	48	Y	N	Y <sup>c</sup>	Y152C		
Scholl et al. 2013 [9]	US	1	0	N/A	Y	N		G403D	
Scholl et al. 2013 [9]	US	1	5	N	Y	N		I770M	
Scholl et al. 2015 [11]	US	8 (plus 2 carriers without hypertension in adulthood)	3,7,8,9,0.2,5,17,24	N,N,N,N,N/A, A,N, N,N/A	Y,Y,Y,Y,Y,Y,Y	N,N,N,N,N,N,Y <sup>c</sup> ,N			M1549V

C: Canada; GR: Greece; J: Japan; I: Italy; UK: United Kingdom; US: United States; N/A: Not available

<sup>a</sup>At age 18 months; <sup>b</sup>Before aldosterone antagonists became available; <sup>c</sup>Unilateral adrenalectomy without cure

tials; some mutations also affect inactivation. These observations suggest that *CACNA1D* mutations directly cause increased calcium influx, aldosterone production and proliferation. By analogy with *KCNJ5*, the authors of one study reasoned that *CACNA1D* germline mutations might cause a syndrome of primary aldosteronism. They chose gene regions with recurrent mutations in adenomas and sequenced those in 100 cases of early-onset PA. Remarkably, they identified 2 individuals with germline mutations (*CACNA1D*<sup>G403D</sup> and *CACNA1D*<sup>I770M</sup>) [9] (◉ **Table 1**). The mutation I770M had been found as a somatic mutation before, and G403D occurred at the identical position previously found to carry a somatic G403R mutation. Both affected children were born to healthy parents, and both mutations were shown to occur de novo.

The first subject was a 3-year old female who as a newborn had severe hypertension (blood pressure 199/78 mm Hg), biventricular hypertrophy, and a ventricular septum defect. Laboratory evaluation suggested PA, with elevated aldosterone, suppressed renin, and hypokalemia. In addition, however, the patient was diagnosed with seizures, which started at the age of 7 months, cerebral palsy, cortical blindness, and neurologic abnormalities. Interestingly, blood pressure improved upon treatment with amlodipine, and recent follow-up (unpublished) showed cure of hypertension and primary aldosteronism. The second subject was a 10-year old female who at the age of 5 years had severe hypertension (blood pressure 132/90 mm Hg), mild ventricular hypertrophy, and primary aldosteronism with hyperkalemia. There was no evidence of hyperplasia on adrenal CT scan. The subject was also diagnosed with cerebral palsy, spastic quadriplegia, mild athetosis, severe generalized intellectual disability, and complex partial and generalized seizures. Expression of *CACNA1D* in the brain raises the possibility that the neurological phenotype in these patients arises from abnormal neuronal calcium signaling. However, the fact that only 2 subjects have been reported so far and that both also had a complicated perinatal history (sinus bradycardia, intubation with respiratory distress, transient hypoglycemia in one case; resus-

citation after uterine rupture in the second case) complicates any genotype-phenotype correlations. Mouse models may prove instructive for these cases.

Lastly, it should be noted that somatic mutations in members of the P-Type ATPase family (*ATP1A1*, encoding part of the Na<sup>+</sup>-K<sup>+</sup>-ATPase, and *ATP2B3*, encoding the plasma membrane Ca<sup>2+</sup> ATPase) have been reported in APAs [22,23]. No corresponding germline variants have been reported; such variants may not be compatible with survival.

### Primary Aldosteronism due to *CACNA1H* Mutations (FH-IV)

▼ Most recently, a recurrent germline mutation in another voltage-gated calcium channel, Ca<sub>v</sub>3.2, encoded by the *CACNA1H* gene, was reported as a cause of early-onset primary hyperaldosteronism and hypertension [11]. *CACNA1H* is highly expressed in the adrenal glomerulosa and is activated at small depolarizing potentials. It has previously been implicated in glomerulosa membrane potential oscillations and aldosterone production [24].

In the genetic study, the exomes of 40 individuals were sequenced. All had early-onset primary aldosteronism (diagnosed at age 10 years or below), and none had mutations in known genes. Five individuals had an identical, novel, heterozygous *CACNA1H*<sup>M1549V</sup> mutation (◉ **Table 1**). Family analysis showed that 2 mutations occurred de novo (one in the affected subject, another in the affected carrier mother of the index case). In the remaining 3 cases (2 of European, one of Hispanic ancestry), the mutation was inherited from a parent, and no samples were available from grandparents for further analysis of transmission, raising the question whether the variant had been inherited from a common ancestor. Genotyping demonstrated that the carriers were not closely related and further suggested that the variant was either inherited from a very remote common ancestor or arose independently in each case (more likely given its absence from databases).

Finding a recurrent de novo protein-altering mutation and finding the identical, never before seen mutation in 3 independent individuals from a cohort of 40 subjects is highly unlikely to occur by chance, implicating the *CACNA1H* variant in primary aldosteronism.

All index cases had primary aldosteronism and severe hypertension (>99<sup>th</sup> percentile); primary aldosteronism in a large kindred was shown to segregate with the occurrence of the *CACNA1H*<sup>M1549V</sup> mutation.

Interestingly, however, while kindred analysis suggested autosomal dominant inheritance, 2 of the carrier parents did not show hyperaldosteronism or hypertension in adulthood and had not been studied in childhood; one had borderline-low renin levels. Potential explanations for incomplete penetrance of the phenotype include remission with age (as previously observed in one of the *CACNA1D* germline cases), somatic mosaicism and/or effects of additional genetic or environmental variables. Future animal studies may be instrumental in identifying the underlying mechanisms. The *CACNA1H*<sup>M1549V</sup> mutation was also expressed in the adrenal glomerulosa of a subject who had undergone unilateral adrenalectomy in an attempt to treat hypertension. Interestingly, her adrenal gland showed micronodular adrenal hyperplasia with invasion of the capsule, without macroscopic hyperplasia. On electrophysiology, *CACNA1H*<sup>M1549V</sup> caused reduced inactivation of the calcium channel, as well as a slight shift to more hyperpolarized potentials, effects that collectively cause increased calcium influx similar to the mechanism seen in *CACNA1D* mutations (◻ Fig. 1d).

In contrast with patients with the PASNA syndrome, subjects with the *CACNA1H* mutation do not share any extraadrenal symptoms. No *CACNA1H* mutations have been identified in APAs, suggesting that this variant may not be sufficient to cause the proliferation seen in *KCNJ5* mutations.

The incomplete penetrance, in combination with the high frequency of de novo mutations, explains why this gene had not been identified from linkage analysis alone. Solving such cases will likely prove to be a major strength of exome and/or genome sequencing.

### Potential Role of *ARMC5* Mutations in FH

*ARMC5* loss-of-function variants have been implicated in Cushing's syndrome with bilateral macronodular adrenal hyperplasia [25]. In all cases, nodules carried *ARMC5* mutations on both alleles: a germline mutation and a "second hit" specific to the nodule. A recent report similarly implicated *ARMC5* variants in primary aldosteronism. However, the evidence for a causal role is much weaker than in Cushing's syndrome. Of the patients in the cohort, 11% carried variants predicted to be damaging by in silico analysis, but in contrast with Cushing's syndrome no concurrent somatic mutations were observed. Moreover, all variants occurred in African Americans, who carry a high overall burden of rare variants [26]. Further studies will be needed to assess any role of *ARMC5* variants in FH.

### Familial Hyperaldosteronism Without Mutations in Known Genes (FH-II)

Additional families with primary aldosteronism have been described without known mutations; these are now commonly referred to as FH-II and include both cases with adrenocortical

adenomas and bilateral hyperplasia. When relaxed criteria are used (diagnosis of primary aldosteronism in 2 or more members of the same family) [27], up to 6% of cases of primary aldosteronism in referral centers may be classified as familial. However, such numbers should be treated with caution. Considering the high prevalence of hypertension in the general population (about 30%) and using a conservative estimate of about 5% for the prevalence of primary aldosteronism among hypertensive adults, the likelihood for each adult family member tested to be diagnosed with primary aldosteronism by chance alone would be about 1.5%. If, in addition to the index case, more family members are screened, for example, 4 additional individuals within a single family, the likelihood of finding at least one individual with primary aldosteronism by chance alone would be ~5.9%. Unless rare and distinctive traits, such as the presence of hybrid steroids in GRA, early-onset disease or massive hyperplasia are present, small families may not prove to be instructive in identifying additional genes in FH.

Such effects, in combination with incomplete penetrance, may explain why causative mutations remain to be determined in many cases of FH-II. Prior linkage to chromosome 7p22 has so far not led to the identification of causative mutations [28–31]. Nonetheless, studies on some families have been published in whom the presence of a monogenic disorder appears very likely, including a very large kindred first reported by Torpy et al. in 1998 [32]. Next-generation sequencing is expected to be instructive in such cases.

### Approach to Patients with Suspected Familial Forms of Primary Aldosteronism

Given the above considerations, and in line with the recommendations of the Endocrine Society [2], we suggest performing genetic testing in patients who present with primary aldosteronism at less than 20 years of age and in patients with a positive family history of early-onset hypertension, primary aldosteronism, or cerebral hemorrhage. Such testing can be performed in a clinical or a research setting.

### Acknowledgements

U.I.S. was supported by the Ministry of Innovation, Science and Research of the State of North Rhine-Westphalia, Germany.

### Conflict of Interest

The authors declare no conflict of interest.

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