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 11β-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.

Abbreviations

- ACTH: Adrenocorticotropic hormone
- APA: Aldosterone-producing adenoma
- CACNA1D: Calcium channel, voltage-dependent, L type, alpha 1D 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 non-glucocorticoid-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 11β-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 (11β-hydroxylase) and CYP11B2 (aldosterone synthase). As a consequence, aldosterone synthase is produced under the control of the 11β-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](image-url) 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. Adrenocorticotropic hormone (ACTH) binds to the melanocortin 2 receptor (MC2R) and upregulates transcription of the chimeric gene resulting from the crossover between CYP11B1 (11β-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, with bilateral adrenal hyperplasia when present in the germline. The only exception so far is a Japanese patient with KCNJ5G151E mutation who at the age of 11 years had not developed adrenal hyperplasia when present in the germline. The only exception so far is a Japanese patient with KCNJ5G151E mutation who at the age of 11 years had not developed adrenal hyperplasia when present in the germline.
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 germline mutations that may not be compatible with survival.

Most recently, a recurrent germline mutation in another voltage-gated calcium channel, CaV3.2, 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 M1549W 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).

### Table 1

<table>
<thead>
<tr>
<th>Kindred</th>
<th>Country of origin</th>
<th># Affected subjects</th>
<th>Age at diagnosis (years)</th>
<th>Macroscopic adrenal hyperplasia</th>
<th>Response to medical treatment</th>
<th>Adrenalectomy</th>
<th>CKN5 Mutation</th>
<th>CACNA1D Mutation</th>
<th>CACNA1H Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celler et al. 2008 [12]</td>
<td>US</td>
<td>3</td>
<td>4,5,7</td>
<td>Y,Y,Y</td>
<td>Y,N,N</td>
<td>Y,Y,Y</td>
<td>T158A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scholl et al. 2012 [10]</td>
<td>UK</td>
<td>1</td>
<td>4</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>G151R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charmando et al. 2012 [16]</td>
<td>GR</td>
<td>2</td>
<td>2,7</td>
<td>Y,Y</td>
<td>N</td>
<td>Y,Y</td>
<td>G151R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monticone et al. 2015 [18]</td>
<td>US</td>
<td>1</td>
<td>2</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>E145Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scholl et al. 2013 [9]</td>
<td>US</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
<td>Y</td>
<td>N</td>
<td>G403D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scholl et al. 2015 [11]</td>
<td>US</td>
<td>8 (plus 2 carriers without hypertension in adulthood)</td>
<td>3,7,8,9,0,2,5,17,24</td>
<td>N,N,N,N,N,A,N, N,N,A</td>
<td>Y,Y,Y,Y,Y,Y,Y,N,N</td>
<td>N,N,N,N,Y,N,Y^c</td>
<td>M1549V</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

^a At age 18 months; ^b Before aldosterone antagonists became available; ^c Unilateral adrenalectomy without cure

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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 (> 99th 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.

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Conflict of Interest

The authors declare no conflict of interest.

References


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Mutation in the KCNJ5 Gene Causing Primary Hyperaldosteronism

1. Introduction

- Familial hyperaldosteronism (FHA) is a condition characterized by aldosterone excess, leading to hypertension. It can be caused by genetic mutations in genes involved in the renin-angiotensin-aldosterone system (RAAS).
- Recent studies have identified mutations in the KCNJ5 gene as a cause of FHA.

2. KCNJ5 and Aldosterone Secretion

- KCNJ5 encodes the inward rectifier potassium channel KIR4.1, which is expressed in the adrenal zona glomerulosa and plays a role in aldosterone secretion.
- Mutations in KCNJ5 lead to altered potassium permeability, affecting the intrinsic electrical activity of the adrenal zona glomerulosa.

3. Clinical Presentation

- FHA patients often present with hypertension, hyperkalemia, and hypokalemia.
- Clinical heterogeneity is common, with some families showing typical FHA symptoms, while others have atypical presentations.

4. Genetic and Molecular Aspects

- KCNJ5 mutations lead to truncation or loss of function of the KIR4.1 channel.
- Phenotype-genotype correlation is observed, with some patients showing severe hypertension and others having milder symptoms.

5. Conclusion

- Identification of KCNJ5 mutations in FHA patients offers a new diagnostic tool and therapeutic target.
- Further research is needed to understand the molecular mechanisms underlying the variation in clinical presentation.

6. References

[Include a comprehensive list of references cited in the text, formatted according to the preferred citation style.]