An Update on Familial Hyperaldosteronism

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. 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

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.
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. 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.
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 Barrter 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 G151R and KCNJ5 L168R, 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 typical lethality prevents the development of macroscopic hyperplasia in these patients in vivo.

Another variant (KCNJ5 I157S, 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 a history of hypertension, other family members were not available for genetic studies. Functional studies demonstrated a less pronounced effect on Na+ 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 G151R 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 (CaL.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-
Correlations 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 mutations might cause a syndrome of primary aldosteronism. They chose gene regions with recurrent mutations in adenosomas and sequenced those in 100 cases of early-onset PA. Remarkably, they identified 2 individuals with germline mutations (CACNA1D_{G403D} and CACNA1D_{I770M}) [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.

Most recently, a recurrent germline mutation in another voltage-gated calcium channel, Ca_{v}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_{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 Phenotypes of families with familial hyperaldosteronism and mutations in KCNJ5, CACNA1D, or CACNA1H.

<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>KCNJ5 Mutation</th>
<th>CACNA1D Mutation</th>
<th>CACNA1H Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geller et al. 2008 [12]</td>
<td>US</td>
<td>3</td>
<td>4,5,7</td>
<td>Y,Y,Y</td>
<td>N,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>Charmandari et al. 2012 [16]</td>
<td>GR</td>
<td>2</td>
<td>2,7</td>
<td>Y,Y</td>
<td>N,N</td>
<td>Y,Y</td>
<td>I157S</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,Y</td>
<td>N,Y</td>
<td>E145Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scholl et al. 2012 [10]</td>
<td>C</td>
<td>2</td>
<td>4,6</td>
<td>N/N/A</td>
<td>Y/N/A</td>
<td>N/Y</td>
<td>G151E</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,Y</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,M,N,N,A,A,N,N/A</td>
<td>Y,Y,Y,Y,Y,Y,Y,Y,N,N,N,N,N,Y,Y</td>
<td>N,M1549V</td>
<td></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

*At age 18 months; Before aldosterone antagonists became available; *Unilateral adrenalectomy without cure.

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^{+}-K^{+}-ATPase, and ATP2B3, encoding the plasma membrane Ca^{2+}-ATPase) have been reported in APAs [22,23]. No corresponding germline variants have been reported; such variants may not be compatible with survival.
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 M1549V 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 M1549V 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 M1549V 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 extrarendal 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 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 M1549V 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 M1549V 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).

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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.

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