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Consensus

SFE/SFHTA/AFCE consensus on primary aldosteronism, part 5: Genetic diagnosis of primary aldosteronism

Consensus hyperaldostéronisme primaire SFE/SFHTA, groupe 5: Diagnostic génétique dans l'hyperaldostéronisme primaire

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Abstract

While the majority of cases of primary aldosteronism (PA) are sporadic, four forms of autosomal-dominant inheritance have been described: familial hyperaldosteronism (FH) types I to IV. FH-I, also called glucocorticoid-remediable aldosteronism, is characterized by early and severe hypertension, usually before the age of 20 years. It is due to the formation of a chimeric gene between the adjacent *CYP11B2* and *CYP11B1* genes (coding for aldosterone synthase and 11β-hydroxylase, respectively). FH-I is often associated with family history of stroke before 40 years of age. FH-II is clinically and biochemically indistinguishable from sporadic forms of PA and is only diagnosed on the basis of two or more affected family members. No causal genes have been identified so far and no genetic test is available. FH-III is characterized by severe and early-onset hypertension in children and young adults, resistant to treatment and associated with severe hypokalemia. Mild forms, resembling FH-II, have been described. FH-III is due to gain-of-function mutations in the *KCNJ5* gene. Recently, a new autosomal-dominant form of familial PA, FH-IV, associated with mutations in the *CACNA1H* gene, was described in patients with hypertension and PA before the age of 10 years. In rare cases, PA may be associated with complex neurologic disorder involving epileptic seizures and cerebral palsy (Primary Aldosteronism, Seizures, and Neurologic Abnormalities [PASNA]) due to de novo germline *CACNA1D* mutations.

Keywords: Familial hyperaldosteronism; Glucocorticoid-remediable hyperaldosteronism; Potassium channel; Calcium channel; Phenotypic variability

Résumé

Bien que la majorité des cas d'hyperaldostéronisme primaire (HAP) soit sporadique, il existe à ce jour quatre formes connues d'HAP transmises de façon autosomique dominante, les hyperaldostéronismes familiaux (FH) de type I à IV. Le FH-I, ou hyperaldostéronisme suppressible par les glucocorticoïdes, est caractérisé par une hypertension artérielle (HTA) précoce et sévère, le plus souvent avant l'âge de 20 ans. Il est dû à la formation d'un gène hybride entre les gènes adjacents *CYP11B1* (codant pour la 11β-hydroxylase) et *CYP11B2* (codant pour l'aldostérone synthase). Le FH-I est souvent associé à une histoire familiale d'AVC avant 40 ans. Le FH-II présente les mêmes caractéristiques d'un HAP sporadique et est diagnostiqué seulement sur la base de deux ou plusieurs membres atteints dans une famille. Il n'y a pas de gène causal identifié à ce jour et aucun test génétique ne peut être proposé aux patients. Le FH-III se manifeste avec une HTA sévère, d'apparition précoce chez l'enfant et résistante au traitement, accompagnée d'une hypokaliémie profonde. Des cas modérés, ressemblant à un FH-II, ont été décrits. Il est dû à des mutations gain de fonction du gène *KCNJ5*. Récemment, une quatrième forme d'HAP familial, le FH-IV, a été décrite chez des patients avec une HTA et un HAP avant l'âge de 10 ans. Il est associé à des mutations du gène *CACNA1H*. Très rarement, l'HAP peut s'associer à un syndrome neurologique complexe avec crises épileptiques (*Primary Aldosteronism, Seizures, and Neurologic Abnormalities* [PASNA]) en association avec des mutations de novo du gène *CACNA1D*.

Mots clés : Hyperaldostéronisme familial ; Hyperaldostéronisme suppressible par les glucocorticoïdes ; Canal potassique ; Canal calcique ; Variabilité phénotypique

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1. Introduction

Remarkable discoveries in the genetics of primary aldosteronism (PA) have been made in recent years, notably identifying new familial forms and shedding light on the genetic abnormalities associated with the development of aldosterone-producing adenoma (APA). These abnormalities, transmitted in familial PA and occuring as somatic mutations in APA, implicate genes coding for ion channels and ATPases involved in regulating membrane potential and intracellular ionic homeostasis [1].

The objective of the present working group was to establish recommendations for the exploration of familial forms of PA and the implementation of genetic screening. Sufficient follow-up is presently lacking to assess the contribution of screening for somatic mutations in APA to the management of patients [2]. Genetic abnormalities have been identified for rare familial forms of PA (< 1%), in which screening is important for the management of the patients concerned and their families. There are at present 4 known forms of PA showing autosomal dominant inheritance: these include familial hyperaldosteronism type I (FH-I, also called glucocorticoid-remediable hyperaldosteronism), type II (FH-II) and type III (FH-III) [1]. In FH-I and FH-III, the causal gene is known [3,4]. FH-II is more frequent, but the underlying genetic abnormalities are yet to be identified. Very recently, a new form of familial hyperaldosteronism was reported, referred to as type IV (FH-IV) [5]. Finally, hyperaldosteronism associated with germline mutations was reported in children presenting a complex neurologic disorder [6].

Familial forms of hyperaldosteronism are rare; Table 1 presents reported prevalences [7–9] and Table 2 the clinical and genetic characteristics.

2. Indications for genetic screening of familial hyperaldosteronism type I (FH-I)

FH-I (OMIM #103900) shows autosomal-dominant transmission, with early and severe hypertension, usually before 20 years of age. Patients present with PA of variable severity, due to bilateral adrenal hyperplasia, with associated adenoma in some cases, and elevated production of hybrid steroids, 18-hydroxycortisol and 18-oxocortisol, detectable in urine [7–10]. Prevalence is less than 1%, but may reach 3.1% in pediatric hypertension cohorts [11]. FH-I is caused by a chimeric gene resulting from unequal crossing-over between the adjacent *CYP11B1* and *CYP11B2* genes (coding for 11β-hydroxylase and aldosterone synthase, respectively), whereby aldosterone synthase coding sequences come under the control of *CYP11B1* regulating sequences. Thus, aldosterone biosynthesis is controlled by ACTH instead of AngII, with expression of aldosterone synthase extending throughout the adrenal cortex and following the circadian cycle of cortisol [12,13]. Exogenous glucocorticoids, which diminish the production of ACTH, are effective in reducing hyperaldosteronism and correcting the clinical presentation [14]. Low-dose glucocorticoids (dexamethasone 0.125–0.250 mg/day, or prednisone 2.5 or 5 mg/day) have been shown to be sufficient to normalize blood pressure and plasma potassium levels without affecting hormonal parameters, and may provide prolonged control of hypertension over several years, with normal echocardiographic parameters [15]. In case of failure to control hypertension and/or adverse effects implicating corticosteroids, a mineralocorticoid antagonist (spironolactone or eplerenone) or amiloride may be associated in order to lower doses of dexamethasone or prednisolone [15], or other classes of antihypertensive drugs. In children, eplerenone is preferable, to avoid the side-effects of glucocorticoids (retarded growth) or spironolactone (antiandrogen effects) [14].

Table 1
Prevalence of familial forms of PA in the literature.

	Paris [7] (P, n=300), %	Torino [8] (P, n=300), %	Munich [9] (P, n=166), %
FH-I[a]	NA	0.7	0
FH-II	4.0	4.0	1.2
FH-III	NA	0[b]	0
FH-IV	NA	NA	NA

R: retrospective study; P: prospective study; NA: not analyzed or not available.
[a] Prevalence of glucocorticoid-remediable aldosteronism in pediatric cohorts is 3% [11].
[b] One family with FH-II phenotype was retrospectively identified as carrying a germline mutation of *KCNJ5*; numbers in brackets are numbers of patients per study.

R5.1.1 : FH-I screening criteria
FH-I should be screened for in patients presenting one or more of the following criteria:

- confirmed PA before 20 years of age, with or without hypokalemia;
- confirmed PA in a patient with family history of PA, with or without hypokalemia;
- confirmed PA in a patient with family history of stroke before 40 years of age [6,16].

Strong recommendation level of evidence: ++

Familial screening is indicated in relatives of patients with confirmed FH-I, as adverse cardiac effects, resulting from hyperaldosteronism, may precede onset of hypertension [17].

R5.1.2 : FH-I screening
FH-I screening should be performed by:

- genetic screening for chimeric *CYP11B1/B2* gene.

Strong recommendation level of evidence: ++++

The following tests may also be used, but have limitations (mentioned in brackets):

Table 2
Characteristics of the various forms of familial Primary Aldosteronism.

Form	Age at symptom onset	Hypokalemia	PA in relatives	Particular characteristics	Transmission	Gene	Protein
FH-I	Often < 20 years	+/−	+	Familial history of stroke < 40 years, hybrid steroids in urine	AD	Chimeric *CYP11B1/B2*	Aldosterone synthase
FH-II	Variable, often > 20 years	+/−	+	–	AD	Not known	Not known
FH-III	< 20 years (but variable in moderate forms)	++ in severe forms	< 20 years (variable in moderate forms)	Bilateral adrenal hyperplasia (in severe forms)	AD	*KCNJ5*	GIRK4
FH-IV[a]	< 10 years	+/−	+/−	Not described	AD or de novo	*CACNA1H*	$Ca_v3.2$

AD: autosomal dominant
[a] Only 1 report, of 5 patients, published to date.

- dexamethasone suppression (e.g., 0.5 mg every 6 h for 4 days; no established sensitivity and specificity criteria; limited feasibility);
- urinary hybrid steroid screening: 18oxocortisol, 18OHcortisol (no established sensitivity and specificity criteria; limited feasibility).

R5.1.3 : Genetic screening methods
Genetic screening seeks to detect the chimeric *CYP11B1/B2* gene, and should use one of the following two methods:

- long-range PCR;
- Southern blot.

Strong recommendation level of evidence: ++++

3. Indications for genetic screening of familial hyperaldosteronism type III (FH-III)

Subjects presenting with FH-III (OMIM #613677) show severe hypertension, with onset very early in childhood, resistant to treatment and associated with severe hypokalemia. Hybrid steroid 18-oxocortisol and 18-hydroxycortisol urinary concentrations are elevated; aldosterone production is not suppressed by dexamethasone [18]. FH-III is rare and implicates gain-of-function mutations of the *KCNJ5* gene coding for GIRK4 (G-protein-activated inward rectifier potassium channel 4) [19]. Various germline mutations of *KCNJ5* have been described in families presenting with FH-III. PA severity depends on the type of mutation. Carriers of p.Gly151Arg, p.Thr158Ala, p.Ile157Ser and p.Glu145Gln mutations all show a severe PA phenotype with early resistant hypertension. The hyperaldosteronism is caused by massive bilateral adrenal hyperplasia, requiring bilateral adrenalectomy to control blood pressure [18–22]. Carriers of *KCNJ5* mutations p.Gly151Glu and p.Tyr152Cys show moderate familial hyperaldosteronism, which may be diagnosed later in young adulthood, with or without hypokalemia, similar to FH-II [3,20,23,24]. Hypertension and hypokalemia respond well to spironolactone, and imaging finds no signs of adrenal hyperplasia.

Mutations are all located near to or within the GIRK4 channel selectivity filter and lead to loss of K^+ selectivity with increased Na^+ conductance. Increased cellular influx of Na^+ depolarizes the plasma membrane and activates voltage-dependent Ca^{2+} channels, leading to intracellular accumulation of Ca^{2+} and activation of calcium signaling, which is the main regulator of aldosterone production [25].

R5.2.1 : FH-III screening
FH-III should be screened for in patients presenting one or more of the following criteria

- PA before 20 years of age;
- resistant hypertension with hypokalemia before 20 years of age;
- familial history of PA before 20 years of age;

Strong recommendation level of evidence: ++

R5.2.2 : Clinical exploration
Clinical exploration should include:

- exclusion of chimeric *Cyp11B1/B2* gene.

Strong recommendation level of evidence: ++++

4. Indications for genetic screening of familial hyperaldosteronism type II (FH-II)

Familial hyperaldosteronism type II (FH-II: OMIM #605635) involves autosomal-dominant transmission, but is not associated with formation of a chimeric gene or *KCNJ5* mutations [10]. Patients show varying aldosterone response on postural test and to AngII within a given family, and different PA sub-types (APA or bilateral adrenal hyperplasia) are often found. FH-II patients

R5.2.3 : Genetic screening method
Genetic screening seeks to detect recurrent mutations of *KCNJ5* gene, and should use the following method:

- sequencing of *KCNJ5* gene (exon 2, coding for the region carrying the recurrent mutations found in PA).

Strong recommendation level of evidence: ++++

are indistinguishable from those with sporadic PA, and diagnosis is presently based on finding two or more affected family members. A certain phenotypic variability is also characteristic [7,8]. The underlying genetic defect is as yet unknown, although a locus on chromosome 7p22 has been suggested in certain affected families [26]. Germline *KCNJ5* gene mutations were reported in patients with a moderate FH-III phenotype resembling FH-II [3,20,23,24] (see above). Somatic mutations of *KCNJ5* were also reported recently in APA in patients with non-glucocorticoid-remediable familial hyperaldosteronism initially diagnosed as FH-II [23], suggesting that FH-II may be due to a familial aggregation of sporadic PA in some cases, given its high frequency in patients with hypertension.

R5.3.1 : FH-II screening
FH-II should be screened for in patients presenting the following criterion:

- hypertension with familial history of confirmed PA.

Weak recommendation level of evidence: +

R5.3.2 : Clinical exploration
Clinical exploration should include:

- PA exploration with confirmatory tests and subtype identification;
- exclusion of FH-I and FH-III (on genetic testing).

Weak recommendation level of evidence: ++

NB: as no gene has yet been implicated in FH-II, no genetic tests are available. Also, APA may be found occasionally in MEN1 [27].

5. Hyperaldosteronism associated with complex neurologic disorder in children

A new form of hyperaldosteronism associated with a complex neurologic disorder including seizures (Primary Aldosteronism, Seizures and Neurologic Abnormalities [PASNA]; OMIM #615474) was very recently described in 2 (out of 100) patients with unexplained early PA [6]. Prevalence is not known.

The syndrome is characterized by early onset of PA, with severe hypertension and hypokalemia, without adrenal hyperplasia visible on imaging, in children presenting with a complex neurologic syndrome including cerebral palsy and epileptic seizures.

De-novo mutations of *CACNA1D* gene, coding for Cav1.3, the voltage-dependent L-type calcium channel subunit alpha-1D, were found in these patients [6]. These gain-of-function mutations involve highly conserved amino acids located in the domains responsible for calcium channel opening. They notably affect channel voltage sensitivity, promoting L-type calcium channel opening at lower voltages. This activation in response to less depolarizing potentials is thought to increase intracellular calcium influx and activate calcium signaling, thereby enhancing aldosterone production. Spontaneous oscillations in zona glomerulosa cell membrane potential may contribute to PA pathogenesis.

R5.4.2 : Genetic screening
A genetic disease associating PA, seizures and neurologic abnormalities should be screened for in children with the following criterion:

- early hypertension and PA in the context of complex neurologic syndrome with seizures.

Weak recommendation level of evidence: +

R5.4.2 : Genetic screening method
Genetic screening seeks to detect recurrent mutation of *CACNA1D* gene, and should use the following method:

- sequencing of *CACNA1D* gene.

Strong recommendation level of evidence: ++

6. Familial hyperaldosteronism related to *CACNA1H* gene mutations (FH-IV)

A new form of familial hyperaldosteronism, FH-IV, was recently identified by whole-exome sequencing in 40 patients with hypertension and PA before the age of 10 years [5]. Five patients showed the same heterozygous mutation of *CACNA1H* gene: p.Met1549Val. Genetic screening of relatives revealed autosomal dominant transmission within 4 families and de novo mutation in one case. The phenotype, however, seemed to show incomplete penetrance, with some mutation carriers having no history of PA or hypertension or renin levels at the limit of the normal range. No adrenal abnormalities (mass or hyperplasia)

were found at diagnosis in the index cases carrying the mutation. In one patient who underwent adrenalectomy for resistant hypertension, microscopic adrenal hyperplasia was detected. *CACNA1H* codes for the T-type calcium channel $Ca_v3.2$. The p.Met1549Val mutation changes the functional properties of the channel, facilitating its opening and impairing inactivation. This, like the other genetic abnormalities, leads to increased intracellular calcium concentration and activation of the calcium signaling pathway.

R5.5.1 : FH-IV screening

FH-IV should be screened for in children with the following criterion:

- early hypertension and PA before the age of 10 years.

Weak recommendation level of evidence: +

R5.5.2 : Genetic screening method

Genetic screening seeks to detect recurrent p.Met1549Val mutation of *CACNA1H* gene, and should use the following method:

- sequencing of *CACNA1H* gene.

Strong recommendation level of evidence: ++

Disclosure of interest

The authors declare that they have no competing interest.

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