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Pathogenesis and treatment of primary aldosteronism

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Abstract

Early diagnosis and appropriate treatment of primary aldosteronism, the most frequent cause of secondary hypertension, are crucial to prevent deleterious cardiovascular outcomes. In the last decade, the discovery of genetic abnormalities responsible for sporadic and familial forms of primary aldosteronism has improved the knowledge of the pathogenesis of this disorder. Mutations in genes encoding ion channels and pumps lead to increased cytosolic concentrations of calcium in zona glomerulosa cells, which triggers *CYP11B2* expression and autonomous aldosterone production. Improved understanding of the mechanisms underlying the disease is key to improving diagnostics and to developing and implementing targeted treatments. This Review provides an update on the genetic abnormalities associated with sporadic and familiar forms of primary aldosteronism, their frequency among different populations and the mechanisms explaining excessive aldosterone production and adrenal nodule development. The possible effects and uses of these findings for improving the diagnostics for primary aldosteronism are discussed. Furthermore, current treatment options of primary aldosteronism are reviewed, with particular attention to the latest studies on blood pressure and cardiovascular outcomes following medical or surgical treatment. The new perspectives regarding the use of targeted drug therapy for aldosterone-producing adenomas with specific somatic mutations are also addressed.

Introduction

Arterial hypertension is a major cardiovascular risk factor. Among the secondary forms of hypertension, primary aldosteronism is the most frequent form, accounting for approximately 5% of patients with hypertension in primary care and 10% to 20% of patients with hypertension referred to specialist care¹⁻³. Primary aldosteronism is caused by autonomous aldosterone production from the adrenal gland, which in the majority of cases is attributable to a unilateral aldosterone producing adenoma (APA) or to bilateral adrenal hyperplasia⁴. The majority of cases of primary aldosteronism are sporadic, while approximately 6% of patients carry a familial form of the disease⁵. So far, four different Mendelian forms of the disease, transmitted as autosomal dominant traits, have been associated with different genetic defects⁶⁻¹⁰.

Aldosterone production in primary aldosteronism is autonomous from its physiological regulators and inappropriate to the salt and blood volume status of the individual. In these conditions, high aldosterone production leads to blood volume expansion, sodium retention and increased urinary excretion of potassium and hydrogen, which lead to hypertension, hypokalaemia and metabolic alkalosis¹¹. Patients with primary aldosteronism are at increased risk of cardiovascular disease compared with patients with essential hypertension matched for age and blood pressure^{12,13}. Indeed, increased risk of stroke, myocardial infarction, atrial fibrillation and renal damage has been consistently reported among different studies of patients with primary aldosteronism^{12,14-17}. A meta-analysis published in 2018 that compared 3,838 patients with primary aldosteronism and 9,284 patients with essential hypertension reported a statistically significant increased risk of stroke, coronary artery disease, atrial fibrillation, heart failure and left ventricular hypertrophy in the patients with primary aldosteronism¹³. This finding is attributable to the deleterious effects of aldosterone itself, which promotes cardiac and vascular fibrosis and tissue damage independently of blood pressure levels¹⁸⁻²¹.

Underdiagnosed and hard to diagnose

The diagnosis of primary aldosteronism is based on an increased aldosterone to renin ratio, calculated from the plasma aldosterone and plasma renin activity or direct plasma renin concentration, at normal dietary salt intake and serum potassium levels and without antihypertensive drugs affecting the renin-angiotensin-aldosterone system. Primary aldosteronism is confirmed with a commonly used confirmatory test (oral sodium loading, saline infusion, fludrocortisone suppression, captopril challenge test, furosemide upright test) followed by subtyping of unilateral versus bilateral forms by adrenal imaging and adrenal vein sampling (AVS)⁴. Primary aldosteronism is found in up to 5% of patients with hypertension in primary care^{1,2}, but its prevalence increases with severity of hypertension and reaches more than 20% in patients with severe or treatment-resistant hypertension (use of three or more conventional antihypertensive drugs, including a diuretic)³

²². However, only a minority of patients with primary aldosteronism are offered appropriate management and therapeutic options²³. Simplifying the screening procedures and extending them to all patients with hypertension instead of restricting these procedures to defined categories of patients with severe or resistant hypertension, hypokalaemia or familial hypertension has been suggested and is indeed recommended in certain countries^{23,24}. Confirmation of primary aldosteronism requires one or more different confirmatory tests, including oral salt loading or captopril challenge tests⁴. Subtyping unilateral forms of primary aldosteronism (which can be cured with unilateral adrenalectomy), is an extremely important, though difficult, step. AVS is technically challenging and is therefore performed in reference centres only; when performed, protocols and criteria for lateralization differ between centres⁴. Comprehensive profiling of multiple steroids might enable some of these issues to be overcome, in particular enabling the achievement of increased aldosterone lateralization indices in patients with APA and the stratification of APA versus bilateral adrenal hyperplasia on the basis of

peripheral steroid profiles^{25,26}. Published in 2016, an outcome-based randomised diagnostic trial compared CT-based management with AVS-based management to determine the presence of APA (with subsequent treatment consisting of adrenalectomy) or bilateral adrenal hyperplasia (subsequent treatment with mineralocorticoid receptor antagonists (MRAs))²⁷. No differences in the daily defined doses of antihypertensive medication required to control blood pressure or in health-related quality of life were found between patients in the CT-based group vs the AVS-based group. Furthermore, biochemical cure was achieved at similar proportion between the two groups. However, results from this study have been widely debated and are still a matter of controversy, particularly considering its limitations with regard to the selection of patients, chosen endpoints and the AVS procedures used²⁸. Indeed, a study published in 2018 showed lower complete biochemical success in patients with APA diagnosed only by CT than in those diagnosed using AVS²⁹. In addition, AVS-guided surgery provided a higher rate of cure of hypertension in a large multicentre study that compared the two diagnostic approaches³⁰. Further studies are certainly required to minimize the use of AVS given its cost and complexity and more broadly to identify biomarkers that can be used to simplify the diagnostic procedures of primary aldosteronism.

Pathogenesis of primary aldosteronism

Germline mutations in inherited forms of primary aldosteronism. Two forms of familial hyperaldosteronism (FH) were described several decades ago; FH-I was the first form of FH to be associated with a specific genetic defect and FH-II included all other cases^{6,31}. A third form, FH-III, associated with severe hypertension and profound hypokalemia and not attributable to FH-I, was reported in 2008³². In 2018, whole-exome sequencing studies^{9,10} have identified germline mutations in genes encoding ion channels in a number of patients diagnosed with FH-II, which has enabled the reclassification of familial forms of primary aldosteronism according to the underlying genetic defect.

FH-I (also known as glucocorticoid-remediable aldosteronism) is characterized by severe hypertension in childhood or young adults with autosomal dominant inheritance^{33,34}. FH-I is due to a chimeric gene, resulting from an unequal crossing over event that fuses the regulatory regions of *CYP11B1*, encoding 11 β -hydroxylase, to the coding sequence of *CYP11B2*, encoding aldosterone synthase^{6,35}. These enzymes are responsible for the last steps of cortisol and aldosterone biosynthesis, respectively. Formation of the chimeric gene leads to ectopic expression of *CYP11B2* throughout the adrenal cortex, with inappropriate regulation of aldosterone biosynthesis by adrenocorticotrophic hormone (ACTH) and aldosterone being also produced in the zona fasciculata^{36,37}. In addition, high levels of the hybrid steroids 18-oxocortisol and 18-hydroxycortisol are excreted in the urine, due to the expression of aldosterone synthase in the adrenal zona fasciculata and/or zona reticularis^{38,39} (Figure 1).

FH-II is the most common form of familial hyperaldosteronism, with a prevalence of 1.2–6% in adults with primary aldosteronism^{5,40-42}. The phenotypic presentation is variable and indistinguishable from that of primary aldosteronism without familial inheritance. Diagnosis used to be based on the presence of two or more affected family members, after FH-I had been excluded^{31,40}. In the past 9 years, the identification of germline mutations in genes encoding ion channels in patients diagnosed with FH-II allowed the reclassification of some patients as having FH-III and FH-IV^{8,43,44} (see later section). In a study published in 2018, a germline mutation in *CLCN2*, encoding the chloride channel ClC-2, was identified in the first reported FH-II family⁹. The same mutation was found in four other unrelated patients and four additional *CLCN2* mutations were identified in unrelated patients with early onset primary aldosteronism⁹. Concomitantly, a *de novo* germline *CLCN2* mutation was identified in a 9-year-old girl with hypertension due to primary aldosteronism¹⁰. *CLCN2* mutations induce a gain of function of

ClC-2 channels. They induce major changes in channel properties, leading to sustained chloride efflux from the cell. This efflux leads to plasma membrane depolarization, activation of calcium signalling and increased *CYP11B2* expression, which increases aldosterone production¹⁰ (Figure 1). Currently, the term FH-II is used for familial forms of primary aldosteronism that are associated with germline *CLCN2* mutations⁴⁵.

FH-III was described as severe early-onset hypertension refractory to medical treatment associated with profound hypokalaemia, high concentrations of the hybrid steroids 18-oxocortisol and 18-hydroxycortisol in urine and massive bilateral adrenal hyperplasia³². Germline mutations in *KCNJ5*, which encodes the G protein-activated inward rectifier potassium channel GIRK4, were identified in affected patients⁷ (Figure 1). Variable severity of hyperaldosteronism was observed among FH-III kindreds, which was associated with the type of *KCNJ5* mutation in some patients^{43,46-48} but not in others⁴⁹. Investigation of the adrenal glands of two patients with FH-III showed adrenal enlargement, with loss of zonation and expression of aldosterone synthase throughout the adrenal cortex. Remarkably, aldosterone synthase was often co-expressed with 11 β -hydroxylase or 17 α -hydroxylase, or with both, which explains the increased levels of the hybrid steroids 18-hydroxycortisol and 18-oxocortisol in these patients⁵⁰. In addition, aldosterone and cortisol co-secretion has been observed in one patient carrying a germline *KCNJ5* mutation⁵¹.

Germline mutations in *CACNA1H*, which encodes the pore-forming $\alpha 1$ subunit of the T-type voltage-dependent calcium channel Cav3.2, are responsible for FH-IV. A recurrent germline *CACNA1H* mutation (p.Met1549Val) was identified in five children with primary aldosteronism diagnosed before they were 10 years old, which in two patients was associated with developmental delay or attention deficit disorder⁸. No adrenal abnormality was observed

on adrenal imaging, but histological examination in one patient showed micronodular adrenal hyperplasia⁸. Additionally, a *de novo* germline *CACNAIH* mutation affecting the same codon (p.Met1549Ile) was identified in a patient with early onset primary aldosteronism associated with multiplex development disorder⁴⁴. Germline *CACNAIH* mutations were also identified in patients with mild primary aldosteronism, previously diagnosed as FH-II, which suggests that *CACNAIH* might be a susceptibility gene for different forms of the disease⁴⁴ (Figure 1).

Finally, *de novo* germline mutations in *CACNAID*, which encodes Cav1.3 (the voltage-dependent L-type calcium channel subunit alpha-1D), were described in two children with a severe early-onset form of hyperaldosteronism that was associated with a complex neurologic disorder (Primary Aldosteronism, Seizures and Neurologic Abnormalities (PASNA))⁵². Following the first description, two other cases of PASNA associated with *de novo* germline *CACNAID* mutations were described, one of the patients also presenting congenital hyperinsulinism.^{53,54} In addition, a germline *CACNAID* mutation (G403D) previously identified in one patient with PASNA, was identified in a patient with congenital hyperinsulinism, seizures, but without signs of hyperaldosteronism⁵⁵, suggesting that PASNA is a complex disease with different clinical manifestations.

Somatic mutations in aldosterone producing adenomas. In most cases, lateralized aldosterone production is attributable to an APA, which can be a unique nodule or found within a multinodular adrenal gland⁵⁶⁻⁵⁹. In some cases, AVS identifies lateralized aldosterone production in adrenal glands without nodules observed at imaging, which is associated with the presence of micronodules or unilateral adrenal hyperplasia⁶⁰. In APA, somatic mutations are found in genes associated with familial forms of primary aldosteronism, *KCNJ5*⁷ and *CACNAID*^{52,61}, as well as in genes encoding ATPases, *ATP1A1* and *ATP2B3*^{61,62}. The most

frequent genetic abnormalities are recurrent mutations in *KCNJ5*, which are found in more than 40% of APA⁶³, ranging between 12% and 80% across different studies, with higher frequencies in patients from Asia⁶⁴. *CACNA1D* mutations are found in up to 10% of patients with APA, while *ATP1A1* and *ATP2B3* are less frequent⁶⁵.

In addition to these genes, somatic mutations in *CTNNB1* have been described in 2–5% of patients with APA^{52,66,67}, and an association with pregnancy or menopause was suggested⁶⁸. Somatic mutations in *PRKACA* have been described in rare cases⁶⁹. As these mutations are similar to those found in cortisol producing adenoma and adrenocortical cancer⁷⁰⁻⁷⁵, their specific role in APA development remains an open question.

Studies published in the past 3 years that performed genetic testing on adrenal nodules expressing aldosterone synthase using immunohistochemistry-guided next-generation sequencing (NGS) show that somatic mutations in APA driver genes are found in 88–90% of patients⁷⁶⁻⁷⁸. The increased detection of mutations when compared with studies performing Sanger sequencing in DNA extracted from frozen APA is attributable to improved identification of aldosterone producing structures in multinodular adrenals with APA, as well as improved sensitivity and coverage of candidate genes with NGS. Aldosterone synthase immunohistochemistry-guided NGS also showed that somatic *CACNA1D* mutations are the most frequent genetic event found in APA from African American patients⁷⁷.

Somatic mutations were also identified in micronodules in adrenal glands from patients with lateralized primary aldosteronism without APA⁶⁰ and in different secondary nodules from patients with multinodular adrenal glands^{56,59,78}. In these cases, different micronodules of the same adrenal might have different mutations. Other adrenal structures with somatic mutations are the aldosterone producing cell clusters (APCC, discussed later), which are groups of

aldosterone synthase expressing cells found in normal adrenals that are supposed to autonomously produce aldosterone⁷⁹. Somatic mutations are found in *CACNA1D* and *ATP1A1* in APCC from normal adrenals⁷⁹. In a study published in 2020, *KCNJ5* mutations were also observed in APCC from different adrenals with an APA⁷⁸, which suggests that *KCNJ5* mutations in APCC could be more prevalent than previously observed. In addition, an increase in the number or enlargement of APCC with somatic mutations in *CACNA1D* and a *KCNJ5* mutation in a micro-APA has been reported in patients with bilateral adrenal hyperplasia⁸⁰.

Mechanisms leading to autonomous aldosterone production. Aldosterone is synthesized from cholesterol in the zona glomerulosa of the adrenal cortex through different enzymatic reactions that are catalyzed by cytochrome P450 enzymes and hydroxysteroid dehydrogenases. The last steps in aldosterone biosynthesis are catalyzed by aldosterone synthase, encoded by *CYP11B2*, which is an enzyme specifically expressed in the zona glomerulosa. In zona glomerulosa cells, activation of Ca^{2+} signalling, following stimulation by angiotensin II or an increase in extracellular concentrations of potassium, is the major trigger for aldosterone biosynthesis⁸¹.

All mutations affecting ion channels and pumps identified in primary aldosteronism lead to increased intracellular concentrations of Ca^{2+} and autonomous aldosterone production, but the underlying mechanisms leading to activation of Ca^{2+} signalling are different for each type of channel and pump. Schematically, mutations affecting GIRK4, the $\alpha 1$ subunit of the Na^+, K^+ -ATPase or CLC-2, all induce cell membrane depolarization, followed by opening of voltage-gated Ca^{2+} channels and increased intracellular concentrations of Ca^{2+} . By contrast, mutations in PMCA3, Cav1.3 and Cav3.2 directly increase intracellular levels of Ca^{2+} .

GIRK4 is a G protein-activated inward rectifier potassium channel composed of two transmembrane domains (M1 and M2), a pore region (H5) and an intracellular N-terminus and

C-terminus (Figure 1). Mutations in GIRK4 localize near or within the selectivity filter (p.Gly151Arg, p.Thr158Ala and p.Leu168Arg) and induce a change in the ion selectivity of the channel⁷. In addition to the loss of K⁺ selectivity, the mutated channels gain permeability to sodium, inducing cell membrane depolarization, opening of voltage-gated Ca²⁺ channels, stimulation of Ca²⁺ signalling and ultimately increased *CYP11B2* expression and aldosterone biosynthesis^{7,82,83}. Some mutations localized far away from the selectivity filter (p.Arg115Trp and p.Glu246Gly) do not change the channel selectivity but rather decrease the abundance of the mutated channels at the membrane⁸⁴. An increased degradation of mutant channels in the cytoplasm causing a decrease in GIRK4 expression has been suggested to be the mechanism responsible for aldosterone overproduction and adenoma development⁸⁴. Although *in vitro* studies have shown no changes in aldosterone production when GIRK4 expression is downregulated by short hairpin RNA in HAC15 cells (a human adrenocortical carcinoma cell line)⁸², it has been suggested that effects of *KCNJ5* mutations on cell growth may be determined by the expression level of the mutated GIRK4 channel⁸⁵.

CLCN2 encodes CIC-2, a voltage-gated chloride channel composed of 18 transmembrane helices and an intracellular N-terminus and C-terminus⁸⁶ that forms dimers (Figure 1). CIC-2 mutations are localized in different regions of the protein, in so-called ‘inactivation domains’ (p.Tyr26Asn, p.Gly24Asp, p.Met22Lys and p.Lys362del), or in regions of unknown function (p.Arg172Gly and p.Ser865Arg)^{9,10,87}. CIC-2 mutations induce a loss of the voltage-gating of the channel, leading to increased chloride currents at resting potential. This change results in cell membrane depolarization, followed by opening of voltage-gated calcium channels, and to increased aldosterone biosynthesis through activation of Ca²⁺ signalling¹⁰. In addition to germline mutations in FH-II, a somatic *CLCN2* mutation was described in one case of APA⁸⁸. In the last year, two mouse models have been described, which recapitulate the human disease

induced by *CLCN2* mutations. Deletion of eight amino acids in the N-terminal region of mouse ClC-2 leads to increased chloride conductance in zona glomerulosa cells, cell membrane depolarization and increased intracellular concentrations of Ca^{2+} . Homozygous mice have high serum levels of aldosterone in the presence of low renin activity, marked hypertension and hypokalaemia⁸⁹. Similarly, heterozygous mice carrying a missense mutation homologous to the most common *CLCN2* mutation associated with FH-II exhibited a mild form of primary aldosteronism associated with increased chloride efflux and zona glomerulosa cell membrane depolarization⁹⁰. These two animal models support the role of ClC-2 in zona glomerulosa pathophysiology and represent new valuable tools for the study of primary aldosteronism.

Mutations in the $\alpha 1$ subunit of the Na^+, K^+ -ATPase also lead to cell membrane depolarization due to loss of pump activity and reduced affinity for potassium^{61,62}. Moreover, disturbed pH homeostasis has been reported for some mutations (p.Leu104Arg, p.Val332Gly)⁹¹. The Na^+, K^+ -ATPase is a member of the P-type ATPase family and is composed of two subunits (α and β). Four isoforms of the α subunit have been described, and they are composed of 10 transmembrane domains (M1 to M10) and an intracellular N-terminus and C-terminus. The Na^+, K^+ -ATPase allows exchange of three cytoplasmic sodium ions for two extracellular potassium ions⁹². The mutations identified in the $\alpha 1$ subunit are localized in the M1^{62,93-95} and M4 domains^{61,62}; interestingly, these two domains have a crucial role in K^+ binding and gating⁹⁶. Mutations of the Na^+, K^+ -ATPase depolarize adrenocortical cells, disturb the K^+ sensitivity and reduce the intracellular pH level; however, in the human adrenocortical cell line H295R they do not induce an overt increase of intracellular levels of Ca^{2+} , suggesting that increased aldosterone production might result from a combination of different signalling abnormalities⁹¹.

Mutations affecting calcium channels (Cav1.3 and Cav3.2) and the plasma membrane calcium ATPase 3 (PMCA3) directly increase the intracellular concentration of Ca^{2+} . Similarly to Na^+, K^+ -ATPase, PMCA3 belongs to the P-type ATPase family. It is composed of 10 transmembrane domains (M1 to M10) and an intracellular N-terminus and C-terminus. All the mutations in PMCA3 that have been identified in APA are in frame deletions of amino acids localized in the M4 domain between amino acids 422 and 433^{8,62,63,94,95,97}. Comparison of PMCA3 with the structure of the sarcoplasmic reticulum type Ca^{2+} -ATPase (SERCA) suggested that mutated amino acids could influence the ATP-driven conformational transition of the pump, modulating Ca^{2+} occlusion and transport⁹⁸, leading to a reduced capacity of the cells to extrude Ca^{2+} , thus increasing the intracellular concentration of Ca^{2+} . It has also been suggested that, in addition to the loss of the physiological pump function, *ATP2B3* mutations could be responsible for Na^+ and possibly Ca^{2+} leak into the cell, inducing cell depolarization and thus contributing, via this additional mechanism, to increased intracellular Ca^{2+} concentrations⁹⁸.

CACNA1D encodes the $\alpha 1$ subunit of the L-type Ca^{2+} channel Cav1.3 and *CACNA1H* encodes the $\alpha 1$ subunit of the T-type Ca^{2+} channel Cav3.2. They are both composed of four repeat domains (I to IV), each consisting of six transmembrane segments (S1 to S6), and mediate Ca^{2+} influx into the cell upon membrane depolarization. Mutations in the Cav1.3 channel affect highly conserved amino acids in different regions of the protein, which have been associated with different channel functions^{52,61}. In particular, mutations shift the voltage-dependence of the channels towards more negative potentials or are responsible for delayed voltage-dependent inactivation of the channel, resulting in increased Ca^{2+} entry into the cells, followed by activation of Ca^{2+} signalling and increased aldosterone production. Similarly, mutations in Cav3.2 affect different domains and are responsible for alterations of different channel

properties, including activation, deactivation and inactivation, leading again to increased Ca^{2+} entry into the cells^{8,44} (Figure 1).

Development of APA and APCC

Although the mechanisms responsible for autonomous aldosterone production have been clearly established during the past decade, those responsible for APA development are less well characterized. Two hypotheses for APA development have emerged in the past few years, the APCC model and the two-hit model.

The APCC model is based on the idea that mutations in one of the APA driver genes could occur in some zona glomerulosa cells, leading to the formation of APCC that might then develop into possible APCC-to-APA translational lesions (pAATL, discussed later), which could ultimately lead to APA development⁹⁹. APCC are aldosterone producing structures present in normal adrenals as well as in adrenal tissue adjacent to APA or in adrenals from patients with idiopathic hyperaldosteronism^{80,100,101}. Next-generation sequencing of DNA isolated from 23 APCC from 11 healthy adrenal glands identified *CACNAID* mutations in eight APCC and *ATPIA1* mutations in two⁷⁹. No mutations in *KCNJ5*, the most frequent alteration observed in APA, were identified in normal adrenals⁷⁹; however, these mutations can be found in APCC from adrenals with APA⁷⁸. Analysis of adrenal glands from 15 patients with idiopathic hyperaldosteronism discovered an accumulation of APCC in comparison with healthy adrenals. *CACNAID* mutations were found in 59% of APCC from adrenals of patients with idiopathic hyperaldosteronism; 33% of micro-APA also carried a somatic mutation, including one *KCNJ5* mutation⁸⁰. In addition to APCC, a study published in 2017 described intermediate structures between APCC and APA called pAATL¹⁰². These structures, consisting of a subcapsular APCC-like part and an inner micro-APA-like part, carry different types of somatic mutations

in the different parts of the structure, including *KCNJ5* mutations⁹⁹. These results suggest that APA could derive from APCC, although the sequence of events leading to the transition of zona glomerulosa cells to APA through APCC and pAATL remains to be established. This hypothesis is also supported by evidence showing that a subgroup of APCC has a metabolic profile similar to that of APA¹⁰³.

The two-hit model is based on the concept of two consecutive events leading to APA development, with the first event leading to abnormal cell proliferation that creates a propitious environment for the occurrence of somatic mutations in APA driver genes. Adrenals with APA are characterized by adrenal cortex remodelling, reduced vascularization and zona glomerulosa hyperplasia¹⁰¹. At the molecular level, these changes are associated with activation of WNT- β -catenin signalling in the entire adrenal cortex and in two-thirds of APA^{104,105}. Resected adrenals often show multiple micronodules in addition to APA, with some of these micronodules expressing aldosterone synthase^{56,101,106}. Remarkably, different mutations in APA driver genes were identified in different micronodules from the same adrenal gland^{56,59}, which suggests that these mutations occur in a previously remodelled adrenal gland. Reported in 2016, the case of a young patient with lateralized primary aldosteronism and macronodular adrenal hyperplasia further supported a two hit model¹⁰⁷. The patient carried a germline heterozygous *APC* mutation that was associated with *APC* inactivation in all nodules of the resected adrenal, whereas a *KCNJ5* mutation was identified exclusively in the aldosterone synthase positive nodule¹⁰⁷. These data suggest that the *APC* mutation had induced adrenal cortex remodelling and nodule formation, while the *KCNJ5* mutation was driving the hormonal secretory pattern.

New diagnostic opportunities

Genetic diagnosis in familial forms of primary aldosteronism might enable targeted treatment in mutation carriers and improved management of affected family members. In particular, FH-I can lead to left ventricular abnormalities well before the onset of hypertension¹⁰⁸. In patients with APA, the identification of any surrogate biomarker of somatic mutations would enable the identification of patients who are suitable candidates for AVS, which would simplify the current diagnostic procedures for a large proportion of patients with low probability of having an APA^{109,110}.

The correlation between the mutation status and particular clinical, biochemical or histological features has been investigated in many different studies. It is generally accepted that *KCNJ5* mutations are more prevalent in women^{64,65}, and patients with younger age, higher aldosterone levels and larger tumours than in patients without these mutations⁶⁴. Other associations, including with the lateralization index at AVS, have been reported^{94,111}, but are not replicated across studies¹¹². Mutations in *CACNA1D*, *ATP1A1* and *ATP2B3* are mainly associated with male sex and smaller tumours^{52,61-63,66,95,113}, while *CTNNB1* mutations seem to be more prevalent in female patients^{52,66-68}.

In the past few years, steroid profiling has enabled the identification of a 7-steroid fingerprint that can be used to correctly classify 92% of APA according to genotype in peripheral venous plasma¹¹¹. In particular, levels of the hybrid steroid 18-oxocortisol were considerably higher in adrenal and peripheral venous samples from patients with *KCNJ5* mutations than in samples from other groups¹¹¹, an association that was confirmed by other studies^{78,114-116}. These steroid biomarkers, together with peculiar computed tomography imaging characteristics of APA carrying *KCNJ5* mutations (larger tumour size and lower pre-contrast Hounsfield units) compared with tumours carrying mutations in other genes⁶⁶, could guide clinical assessment

towards subtype diagnosis for surgery or targeted medical treatment. Another approach is to use the peculiar pharmacological characteristics of mutated proteins to identify APA carrying somatic mutations to select patients for AVS. In this context, an ongoing study is evaluating the acute changes of plasma concentrations of aldosterone and renin in peripheral venous blood of patients with primary aldosteronism after roxithromycin administration, which specifically blocks mutated GIRK4 channels¹¹⁷. It is hypothesized that aldosterone levels will fall after macrolide treatment in patients with APA carrying *KCNJ5* mutations, allowing simplified diagnosis and treatment of those patients.

Treatment of primary aldosteronism

Current treatments and outcomes for primary aldosteronism. Surgical adrenalectomy in lateralized primary aldosteronism or therapy with MRA in bilateral forms are the recommended treatments for primary aldosteronism⁴. The goal of primary aldosteronism treatment is the normalization (or improvement) of blood pressure and correction of hypokalaemia. However, different studies have shown that patients with primary aldosteronism are at increased risk of cardiovascular complications independently of blood pressure levels^{12,14,118-120}. A meta-analysis of studies comparing cardiovascular events and target organ damage in patients with primary aldosteronism and essential hypertension confirmed an increased risk of stroke, coronary artery disease, atrial fibrillation, heart failure, type 2 diabetes mellitus and left ventricular hypertrophy¹³. Thus, treatment of primary aldosteronism should not just be targeted at blood pressure control but also at decreasing aldosterone production or efficiently blocking the mineralocorticoid receptor (MR). The Endocrine Society Guidelines for primary aldosteronism management recommend unilateral laparoscopic adrenalectomy for patients with unilateral primary aldosteronism or treatment with an MRA for patients unable or unwilling to undergo surgery. For patients with bilateral disease, MRA is recommended⁴.

Different studies have described an improvement in hypertension after adrenalectomy¹²¹⁻¹²⁴, and a large longitudinal study has shown that adrenalectomy for unilateral primary aldosteronism reduces all-cause mortality compared with MRA treatment alone¹²⁰. After adrenalectomy, patients with APA exhibit a reduced risk of incident stroke after surgery¹²⁵, a regression of left ventricular hypertrophy¹²³ and decreased risk of atrial fibrillation after a median follow-up of 11.8 years¹²⁶. In addition, a prospective study performed in 20 patients with APA by the TAIPAI study group highlighted an improvement in myocardial fibrosis, intima-media thickness and arterial stiffness after surgery^{127,128}. Surgical treatment for APA was also associated with improved metabolic outcomes and increased insulin sensitivity¹²⁹.

Primary aldosteronism is associated with reduced quality of life and psychological symptoms, with women being more affected than men^{121,130,131}. An improvement in quality of life was observed in different studies following treatment, more so after adrenalectomy than in patients receiving MRA^{30,121,132-134}. In 2019, a disease-specific quality of life questionnaire for primary aldosteronism was developed and validated for use in clinical practice¹³⁵. This questionnaire may allow a better diagnosis and care of psychological issues related to primary aldosteronism, helping physicians to inform and identify potential cases of depressive disorders associated with the disease.

An international panel of 31 experts from 28 centres were involved in the Primary Aldosteronism Surgical Outcome (PASO) study, which has achieved consensus in developing criteria for classifying surgical outcome and follow-up of patients with unilateral primary aldosteronism¹²⁴. They proposed clinical (blood pressure and use of anti-hypertensive drugs) and biochemical (plasma levels of potassium, aldosterone concentration and concentration or activity of renin in plasma) parameters for classifying complete, partial or absent surgical

success. The analysis of clinical and biochemical data from ~700 patients with primary aldosteronism who had undergone adrenalectomy showed that 94% achieved biochemical cure (normalization of potassium levels and the aldosterone-to-renin ratio), while normalization of blood pressure without the use of anti-hypertensive drugs was achieved in only 37% of patients¹²⁴.

The use of standardized definitions and nomenclature for APA outcomes is of great importance for the comparison of different cohorts of patients and to identify factors that influence the success of adrenalectomy. Using the PASO criteria, findings from previous studies showing that younger patients and women are more likely to have a favourable surgical outcome¹²² have been clearly confirmed in the PASO multicentre study¹²⁴. Similar results were obtained in a large multicentre study evaluating the outcomes of 1,625 patients undergoing AVS for primary aldosteronism subtyping. Hypertension was cured after adrenalectomy in 19.6% of the patients, with women showing a more favourable outcome than men³⁰. Finally, the evaluation of 574 patients with primary aldosteronism undergoing surgery within the Japanese Nationwide Cohort highlighted five variables as independent predictors for blood pressure normalization: ≤ 7 years of hypertension, BMI ≤ 25 kg/m², no more than one antihypertensive medication, absence of medical history of type 2 diabetes mellitus and female sex¹³⁶. Female sex, duration of hypertension and lower number of antihypertensive agents were also predictors of hypertension improvement after adrenalectomy in Brazilian patients with primary aldosteronism¹³⁷. Interestingly, in a multivariate analysis, only the presence of a somatic *KCNJ5* mutation was an independent predictor of blood pressure normalization¹³⁷.

Lifelong MRA therapy, the recommended medical option for patients with bilateral primary aldosteronism and patients with unilateral primary aldosteronism unable or unwilling to

undergo surgery, improves hypertension in patients with primary aldosteronism^{138,139}. Spironolactone is the MRA of choice at the highest tolerable dose that enables control of blood pressure and hypokalaemia^{23,140}. The adverse effects of spironolactone include gynecomastia, decreased libido and erectile dysfunction in men, and menstrual irregularity in women¹⁴¹. The MRA eplerenone has higher MR selectivity than spironolactone and is therefore associated with fewer adverse effects^{142,143}. However, it is less potent than spironolactone and is not approved for treatment of primary aldosteronism in the USA and Europe. Third-generation, non-steroidal MRAs, which are more specific than spironolactone and more potent than eplerenone, are currently under development for the treatment of heart failure and chronic kidney disease¹⁴⁴ and might provide new therapeutic options in primary aldosteronism.

Different studies have tested the efficacy of MRAs for reducing cardiometabolic risks, with some of them suggesting that MRAs might not be effective^{14,118,119,123,145}. A large cohort study of 602 patients with primary aldosteronism receiving MRA therapy compared with 41,853 patients with essential hypertension has shown an increase in cardiovascular events, type 2 diabetes mellitus risk and mortality in medically treated patients with primary aldosteronism¹⁴⁶. Interestingly, the excess risk of cardiovascular events and mortality was observed in patients with primary aldosteronism whose renin activity remained suppressed, but not in those who normalized their renin levels¹⁴⁶. Accordingly, an increase in atrial fibrillation events was also observed in patients with primary aldosteronism treated with MRA who had suppressed renin activity, in comparison with medically treated patients with unsuppressed renin and patients treated by adrenalectomy¹⁴⁷. In addition, patients with primary aldosteronism receiving MRA had a higher risk of developing chronic kidney disease than patients undergoing adrenalectomy or patients with essential hypertension¹⁴⁸. Based on these findings, it was suggested that suppressed renin activity, which is associated with an increase in cardiovascular risk, might be

a biomarker of incomplete MR blockade. In addition, a medical-surgical approach has been proposed that combines unilateral adrenalectomy to attenuate the severity of primary aldosteronism followed by lifelong MRA therapy in patients with bilateral but asymmetric aldosterone production. This combined approach could be particularly useful in young patients, patients with cardiovascular comorbidities, chronic kidney disease or with persistently elevated blood pressure despite high doses of MRA¹⁴⁹.

Targeted treatment for primary aldosteronism.

In patients with FH-I, aldosterone production can be suppressed by treatment with exogenous glucocorticoids, which suppress ACTH production diminishing the stimulatory drive on the adrenal cortex. Hypertension can be efficiently controlled by the use of low doses of glucocorticoids, without requirement for complete suppression of ACTH and of hybrid gene expression^{4,37}. Mineralocorticoid receptor antagonist may be added in the absence of complete normalization of blood pressure with glucocorticoid treatment^{4 37}. To date, no targeted treatment is available for patients with FH-II, FH-III and FH-IV; however, some evidence of therapeutic possibilities has come from mechanistic studies on cell systems. For instance, the discovery of recurrent mutations in genes encoding ion channels and ATPases in primary aldosteronism has opened new perspectives for targeted therapy for carriers of specific mutations^{109,110,117}. *In vitro* studies showed that the pharmacology of mutant GIRK4 channels is distinct from wild-type channels and that they were blocked by calcium and sodium channel blockers, such as verapamil and amiloride¹⁰⁹. In particular, high therapeutic doses of verapamil were able to specifically block GIRK4 channels carrying the recurrent p.Leu168Arg mutation¹⁰⁹.

Macrolide antibiotics, in particular roxithromycin, are also able to selectively inhibit GIRK4 channels carrying the two most frequent mutations (p.Gly151Arg and p.Leu168Arg), with a decrease in *CYP11B2* expression and aldosterone production in adrenocortical HAC15 cells¹¹⁰. These results were confirmed in a study testing the effects of the macrolide clarithromycin on aldosterone synthesis and secretion in cells obtained from APA tissues with and without *KCNJ5* mutations¹⁵⁰. In a dose-dependent manner, clarithromycin reduced *CYP11B2* expression and aldosterone secretion specifically in cells isolated *ex vivo* from *KCNJ5* mutated APA¹⁵⁰. These results suggest that the use of macrolides could be useful for noninvasive diagnosis and targeted treatment of APA with *KCNJ5* mutations and for the treatment of patients with FH-III¹¹⁷. In addition to the inhibition of mutant GIRK4 with macrolides, calcium channel blockers might be used for patients with *CACNA1H* mutations in FH-IV or for patients with somatic *CACNA1D* mutations in APA, targeting the mutated calcium channels. In the same context, patients with PASNA seemed to well respond to the use of nifedipine for the treatment of hypertension and hypokalemia^{52,54}.

Data on specific treatments for APA with somatic mutations, together with clinical studies evaluating the possibility of translating these findings to patient care, represent a great opportunity for the development of personalized treatments for a common endocrine form of arterial hypertension.

Conclusions

A large number of genetic and clinical studies have improved our knowledge of the pathogenesis and management of primary aldosteronism over the past few years (Figure 2). Genetic studies have been driven by the availability of high throughput genetic technologies. These technologies have enabled the discovery of genetic abnormalities in a large number of APA, and have also opened an entirely new field of research on the somatic genetics of aldosterone producing cellular structures of the normal adrenal cortex and in different types of

primary aldosteronism. It seems that immunohistochemistry-guided NGS enables the identification of somatic mutations in the majority of patients with APA, which suggests that no further genes are involved in the disease, or if they were, they would account for a limited number of cases. Accumulation of APCC with somatic mutations has been reported in bilateral forms of primary aldosteronism; those results require replication to confirm that APCC are the sole cause of bilateral adrenal hyperplasia. The two pathogenic models of APA development, the APCC model and the two-hit model, are not mutually exclusive. Both mechanisms could be responsible for APA development depending on specific conditions, such as the adrenal microenvironment or genetic susceptibility. Most importantly, genetic studies have opened extremely interesting diagnostic and treatment opportunities. Surrogate biomarkers of the mutation status might enable simplification of the procedure for diagnosis and subtype identification of primary aldosteronism. Innovative therapies might be used to specifically target mutation carriers in cases in which surgery is not possible or in bilateral forms, using specific channel inhibitors.

In summary, primary aldosteronism is the most frequent form of secondary arterial hypertension. Appropriate treatment may cure patients and decrease cardiovascular risk. However, the diagnosis of primary aldosteronism is complex and the disease is largely underdiagnosed. New knowledge on the genetic basis of primary aldosteronism may unveil the pathophysiology of bilateral and familial forms and the mechanisms of APA development, allowing the development of new pharmacological approaches specifically targeting mutated proteins.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

Figure 1 | Genetic and pathogenic mechanisms of familial hyperaldosteronism and targeted treatment. Familial hyperaldosteronism type I (FH-I) is due to unequal crossing-over between the *CYP11B1* and *CYP11B2* genes, resulting in the fusion of the regulatory sequences of *CYP11B1* to the coding sequence of *CYP11B2*. This unequal crossing-over leads to ectopic aldosterone synthase expression in the zona fasciculata and stimulation of aldosterone production by ACTH. Targeted treatment is based on the use of glucocorticoids. FH-II is due to mutations in the *CLCN2* gene, which encodes the chloride channel ClC-2, resulting in an increased efflux of Cl⁻ ions, leading to cell membrane depolarization, opening of voltage-gated-Ca²⁺ channels and increased aldosterone production. No targeted treatments for FH-II are currently available. FH-III is due to mutations in the potassium channel GIRK4, encoded by *KCNJ5*. These mutations are responsible for a change in the channel selectivity, with a loss of K⁺ selectivity and an increased Na⁺ influx, leading to cell membrane depolarization, opening of voltage-gated-Ca²⁺ channels and increased aldosterone production. No targeted treatments for FH-III are available so far, but macrolides specifically block the mutated channels and might represent potential pharmacological options. Mutations in *CACNA1H*, encoding the Ca²⁺ channel Cav3.2, are responsible for FH-IV. These mutations result in changes in calcium current properties, leading to an increased intracellular concentration of Ca²⁺ and aldosterone production. Specific calcium channel blockers acting on mutated Cav3.2 channels could be a useful development for patients with FH-IV.

Figure 2 | Timeline of the major discoveries in the understanding of the genetic basis of primary aldosteronism. Clinical advances^{8,10,32,33,52,151-153} are shown in purple boxes, with key genetic discoveries^{6,7,52,61,62,70} highlighted in green boxes. The publication of guidelines^{4,154} is indicated in pink boxes. APA, aldosterone producing adenoma; FH, familial hyperaldosteronism.

Key points

- Primary aldosteronism is the most frequent form of secondary and curable hypertension
- The condition is largely underdiagnosed, preventing patients from targeted treatment and prevention of cardiovascular complications
- Different genetic abnormalities have been identified in aldosterone producing adenoma and familial forms of the disease
- Most genetic abnormalities increase intracellular calcium signalling in the adrenal zona glomerulosa, increasing aldosterone production
- New approaches are currently developed to achieve more rapid and precise diagnosis of the condition and for more efficient targeted treatment

Table of contents text:

This Review outlines the latest understanding of the pathogenesis of primary aldosteronism. Current treatment options are also discussed, including the potential for targeted therapies.

Glossary

Autonomous aldosterone production: Aldosterone production which is is autonomous from its physiological regulators and inappropriate to the salt and volume status of the individual

Bilateral adrenal hyperplasia: One of the two major causes of primary aldosteronism, also called idiopathic hyperaldosteronism, in which aldosterone is produced autonomously from both adrenal glands.

Essential hypertension: Arterial hypertension without known identifiable cause, defined after having excluded all forms secondary to a defined disease. It represents 85-95% of cases.

Aldosterone lateralization index: Value reflecting the production of aldosterone from one adrenal compared to the other, calculated by dividing the aldosterone to cortisol ratio in the dominant adrenal vein by the ratio in the non-dominant adrenal vein, measured by adrenal vein sampling.

Lateralized aldosterone production: Autonomous aldosterone production from one adrenal gland

Lateralized primary aldosteronism: Primary aldosteronism due to autonomous aldosterone production from one adrenal gland.

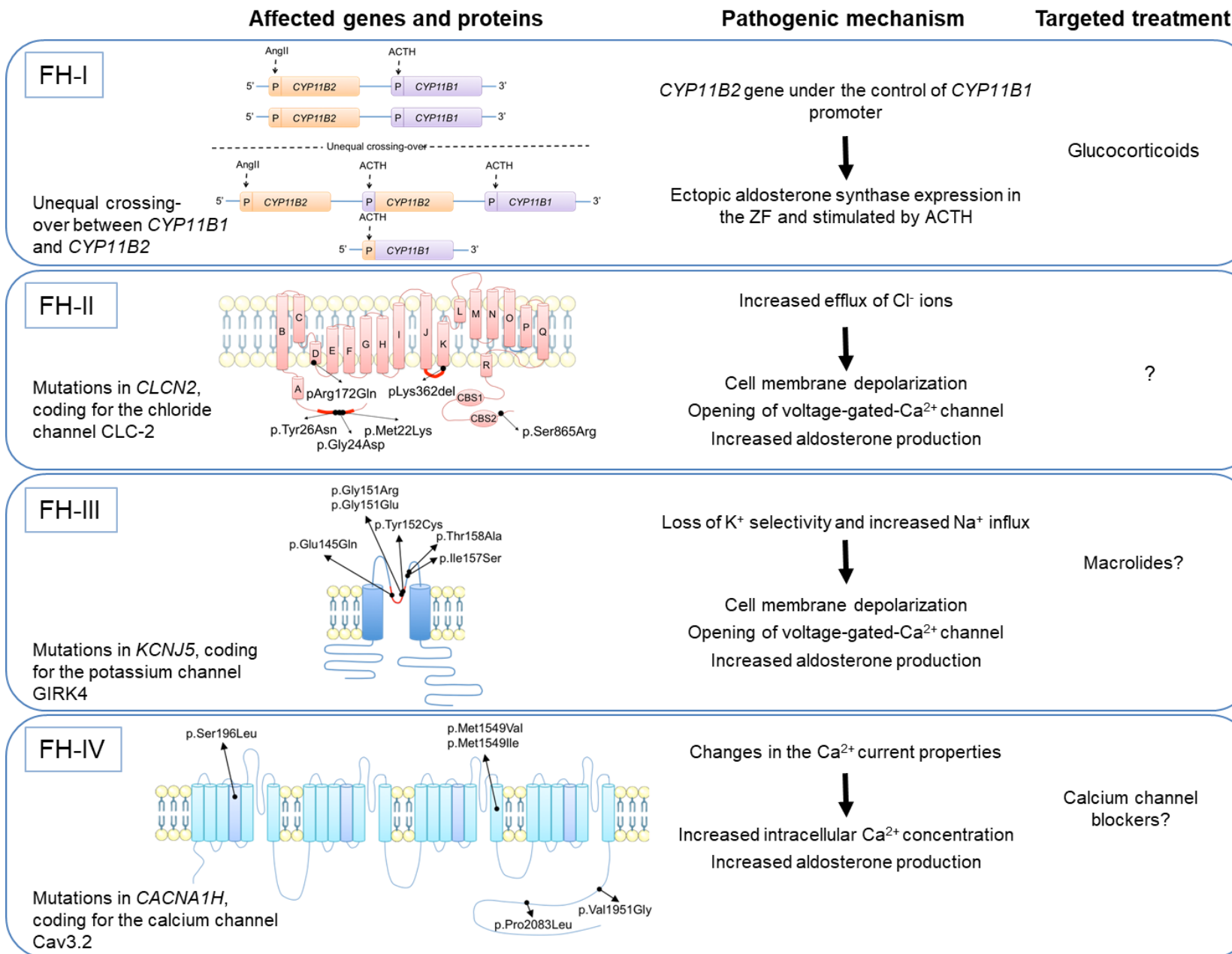


Figure 1

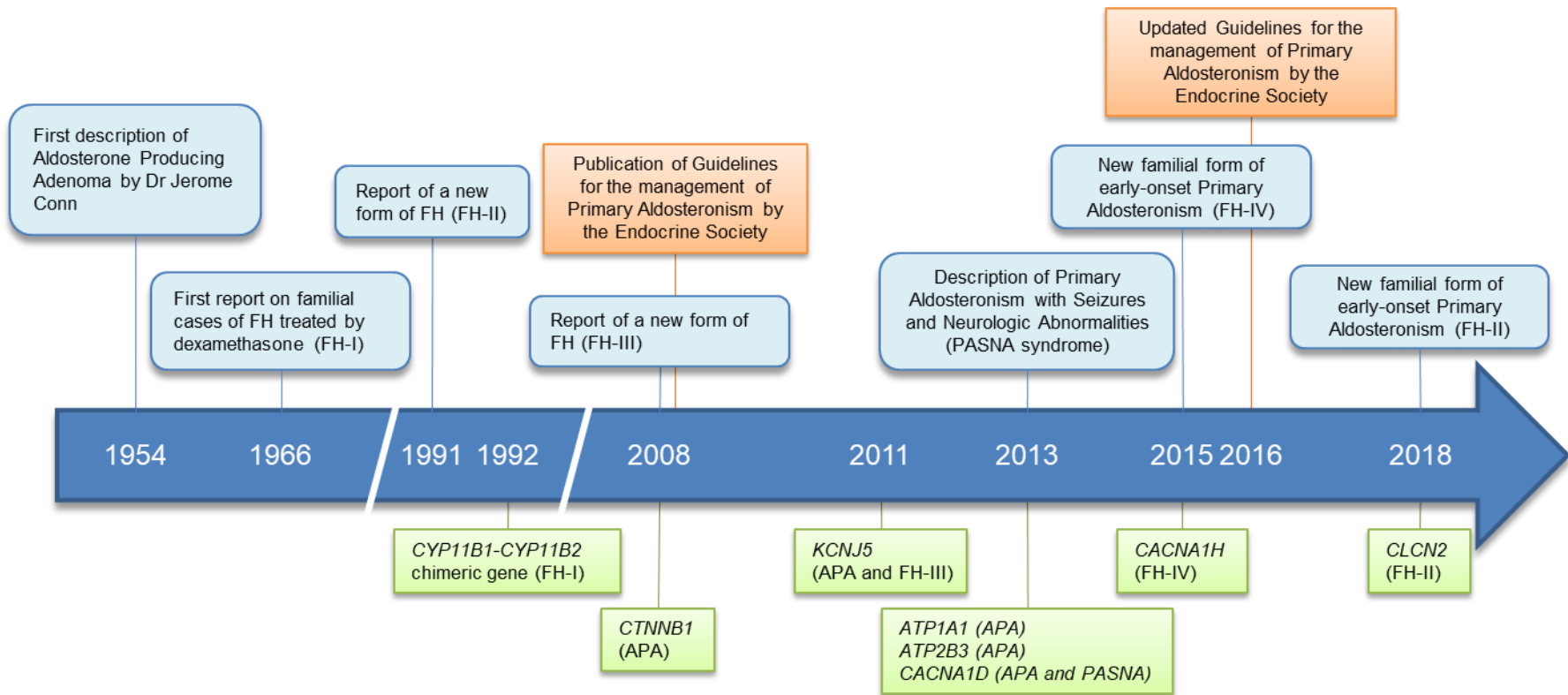


Figure 2

