World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Endocrine hypertension: When and how to screen for a genetic cause

Zineb Serhane [1,*], Sara Hassane [1], Zineb El Azime [1,2], Mohammed-Amine Essafi [1,2], Hayat Aynaou [1,2] and Houda Salhi [1,2]

[1] *Endocrinology, Diabetology, Metabolic Diseases and Nutrition Department, Hassan II University Hospital, Fez.*
[2] *Faculty of Medicine, Pharmacy and Dental Medicine of Fez.*

World Journal of Advanced Research and Reviews, 2026, 31(01), 479–500

Publication history: Received on 23 May 2026; revised on 07 July 2026; accepted on 09 July 2026

Article DOI: https://doi.org/10.30574/wjarr.2026.31.1.1870

Abstract

Aims: Hypertension affects more than one billion adults worldwide, and secondary causes account for approximately 10–15% of cases. Endocrine hypertension is particularly relevant because it is a potentially curable form of secondary hypertension, however, its hereditary and monogenic causes remain under-recognized. This review aims to provide a practical, phenotype-first approach to genetic screening in endocrine hypertension, focusing on situations in which molecular diagnosis can change treatment, surveillance and family counselling.

Methods: A structured narrative review was conducted using PubMed/MEDLINE, Google Scholar, Semantic Scholar, ScienceDirect and the Cochrane Library, covering peer-reviewed English and French publications from January 1992 to June 2026, with emphasis on 2016–2026. MeSH terms and free-text keywords combined endocrine hypertension phenotypes with genetic descriptors. Guidelines, consensus statements, original studies, reviews, case series and selected informative case reports were included, while non-genetic, duplicate, non-peer-reviewed, animal or in vitro-only studies were excluded. Evidence was synthesized using a phenotype-first clinical approach.

Results: Genetic screening should be guided by age at onset, family history, biochemical profile, tumor multiplicity or bilaterality, recurrence, and syndromic features. Multi-gene next-generation sequencing panels are now central to diagnosis but should be selected according to the endocrine phenotype and complemented, when needed, by copy-number analysis, MLPA, long-range PCR, array-CGH or tumor sequencing. Interpretation requires caution because variants of uncertain significance, incomplete penetrance, parent-of-origin effects and mosaicism may complicate clinical decision-making.

Conclusion: Indiscriminate genetic testing is not recommended in endocrine hypertension, but timely identification of patients in whom a molecular diagnosis can guide precision treatment, long-term surveillance and rational cascade screening of relatives.

Keywords: Monogenic Hypertension; Endocrine Hypertension; Genetic Testing; Pheochromocytoma; Paraganglioma; Familial Hyperaldosteronism; Cushing Syndrome; Acromegaly; Primary Hyperparathyroidism; Next-Generation Sequencing.

1. Introduction

Hypertension is a leading contributor to cardiovascular and renal morbidity worldwide, with 1.28 billion adults worldwide suffering from hypertension according to the latest WHO estimates (**1**). Although most cases are essential and polygenic, secondary hypertension is sufficiently frequent (10 to 15% of hypertension cases (**2**) to justify systematic consideration, particularly in early onset, resistant hypertension, hypokalemia, adrenal incidentaloma or suggestive

* Corresponding author: Z. Serhane

clinical features (**3-5**). Endocrine hypertension warrants specific attention, as many of its causes are curable and some of its phenotypes suggest inherited predisposition syndromes (**3-5**).

The term monogenic hypertension classically refers to Mendelian disorders in which a single pathogenic variant produces a recognizable hypertensive phenotype (**6**). In endocrine practice, the concept is broader and includes two overlapping groups: first, true monogenic disorders of sodium handling or steroidogenesis, and second, hereditary endocrine tumor syndromes in which hypertension is a consequence of hormone excess (**7**). This distinction is clinically useful. In Liddle syndrome or apparent mineralocorticoid excess, the genotype directly determines renal sodium retention. In hereditary PPGL, MEN1-related pituitary or parathyroid disease, or Carney complex, the genotype confers tumor susceptibility, and hypertension appears only when the relevant tumor becomes functional (**7**).

Although its phenotypic expression may be heterogeneous depending on the degree of penetrance, monogenic hypertension generally displays distinctive clinical and pathophysiological features. Thus, a phenotype-first strategy remains essential. The approach to human genetics has evolved considerably over the past 15 years. The introduction of next-generation sequencing (NGS) technologies has led to major advances in the genetics of monogenic hypertension, improving our understanding of the pathophysiology of these disorders and facilitating screening, diagnostic evaluation, and therapeutic decision-making (**6,8**).

Although numerous reviews describe individual hereditary endocrine disorders, few provide an integrated phenotype-based approach to genetic testing across the entire spectrum of endocrine hypertension. The aim of this review is to provide clinicians with a practical phenotype-driven algorithm of when to suspect a genetic cause of endocrine hypertension, which genes should be prioritized, and which testing modalities should be used. It is intended as a concise but detailed review for endocrinology practice, based on the literature synthesis and selected recent guidelines and consensus statements.

2. Literature review

2.1. Methods

This narrative review was based on a comprehensive literature search conducted across PubMed/MEDLINE, Google Scholar, Semantic Scholar, ScienceDirect, and Cochrane library. The search covered publications from January 1992 through June 2026, with particular emphasis on literature published between 2016 and 2026 to capture recent advances in genetics of endocrine hypertension.

Search strategies employed Medical Subject Headings (MeSH) terms and free-text keywords related to endocrine hypertension and genetic screening. The main terms included: “Endocrine Hypertension”, “Monogenic Hypertension”, “pheochromocytoma and paraganglioma”, “primary aldosteronism”, “familial hyperaldosteronism”, “congenital adrenal hyperplasia”, “Liddle syndrome”, “Gordon syndrome”, “Pseudohypoaldosteronism Type II”, “Geller syndrome”, “Glucocorticoid Resistance”, “Chrousos syndrome”, “apparent mineralocorticoid excess”, “Cushing syndrome”, “Adrenocortical Hyperplasia”, “Cushing disease”, “acromegaly”, “Pituitary Gigantism”, “Carney Complex”, “McCune–Albright Syndrome”, “Familial Isolated Pituitary Adenoma”, “Multiple Endocrine Neoplasia”, “primary hyperparathyroidism”. Boolean operators were used to combine disease-specific terms with genetic descriptors such as “mutation”, “germline”, “genomic”, “genetic testing”, ”gene panel”, “next-generation sequencing”, “copy-number variation”, “MLPA”, “whole-exome sequencing”, and “whole-genome sequencing”, alongside specific gene names relevant to each condition.

Inclusion criteria encompassed clinical practice guidelines, expert consensus statements, original research articles, narrative or systematic reviews, case series and selected case reports, focusing on genetic, or molecular mechanisms, genotype-phenotype correlations, or genetic testing strategies in endocrine hypertension. Publications were required to be peer-reviewed, in English or French.

Exclusion criteria eliminated article abstracts without full text, non-peer-reviewed or duplicate publications, letters to the editor without original data, editorials, commentaries, animal studies, in vitro studies without clinical correlation, and studies without genetic focus or addressing only pharmacological or surgical management without genetic context. For rare disorders, isolated case reports were considered only when they contributed relevant mechanistic, diagnostic, or therapeutic information.

The final synthesis was organized according to a phenotype-first clinical approach, rather than by gene alone. Data were extracted on clinical indications for genetic testing, biochemical clues, age at presentation, familial and syndromic

features, relevant genes, preferred molecular techniques, limitations of testing, and implications for surveillance, and cascade screening of relatives.

2.2. Classification and general pathophysiology of monogenic hypertension:

Monogenic hypertension refers to a group of rare hypertensive disorders caused by a single pathogenic genetic alteration following a Mendelian pattern of inheritance (**6**). Unlike essential hypertension, it is usually characterized by early-onset, severe or resistant hypertension, often associated with familial clustering, although incomplete penetrance may explain milder phenotypes, normotension in some carriers, or absence of typical electrolyte abnormalities (**9,10**).

Most monogenic hypertension syndromes result from gain- or loss-of-function mutations that disrupt mineralocorticoid, glucocorticoid or sympathetic signaling pathways, or directly alter renal sodium reabsorption and its regulation (**6-8**). Accordingly, most forms share a common mechanism: increased renal sodium reabsorption, extracellular volume expansion and suppressed renin secretion. Therefore, plasma renin, interpreted together with aldosterone, potassium level and acid–base status, is a useful first-line tool when a genetic form is suspected. However, renin interpretation may be influenced by sodium intake, posture and antihypertensive treatment (**4,6**).

A practical classification distinguishes salt-insensitive and salt-sensitive forms (*Figure 1*)(**4**). Salt-insensitive monogenic hypertension includes familial pheochromocytoma–paraganglioma, related to genes such as *SDHA, SDHB, SDHC, SDHD, SDHAF2, RET, VHL, NF1, MAX* and *TMEM127*, and hypertension with brachydactyly caused by *PDE3A* variants (**11**). These disorders usually have normal renin and aldosterone levels and are driven by catecholamine excess or increased vascular resistance rather than primary renal sodium retention (**11**).

Salt-sensitive low-renin forms are classified according to potassium and aldosterone levels. Low renin with hypokalemic metabolic alkalosis and raised aldosterone suggests familial hyperaldosteronism, including *CYP11B1/CYP11B2, CLCN2, KCNJ5, CACNA1H* and *CACNA1D*-related forms (**4**). Low renin with hypokalemic alkalosis but reduced aldosterone suggests aldosterone-independent **mineralocorticoid excess**, including Liddle syndrome, apparent mineralocorticoid excess, 11β- or 17α-hydroxylase deficiency, Geller syndrome and glucocorticoid resistance (**4**). By contrast, low-renin hypertension associated with hyperkalemia and metabolic acidosis is typical of Gordon syndrome, caused by variants in *WNK1, WNK4, KLHL3* or *CUL3* (**4-8**).

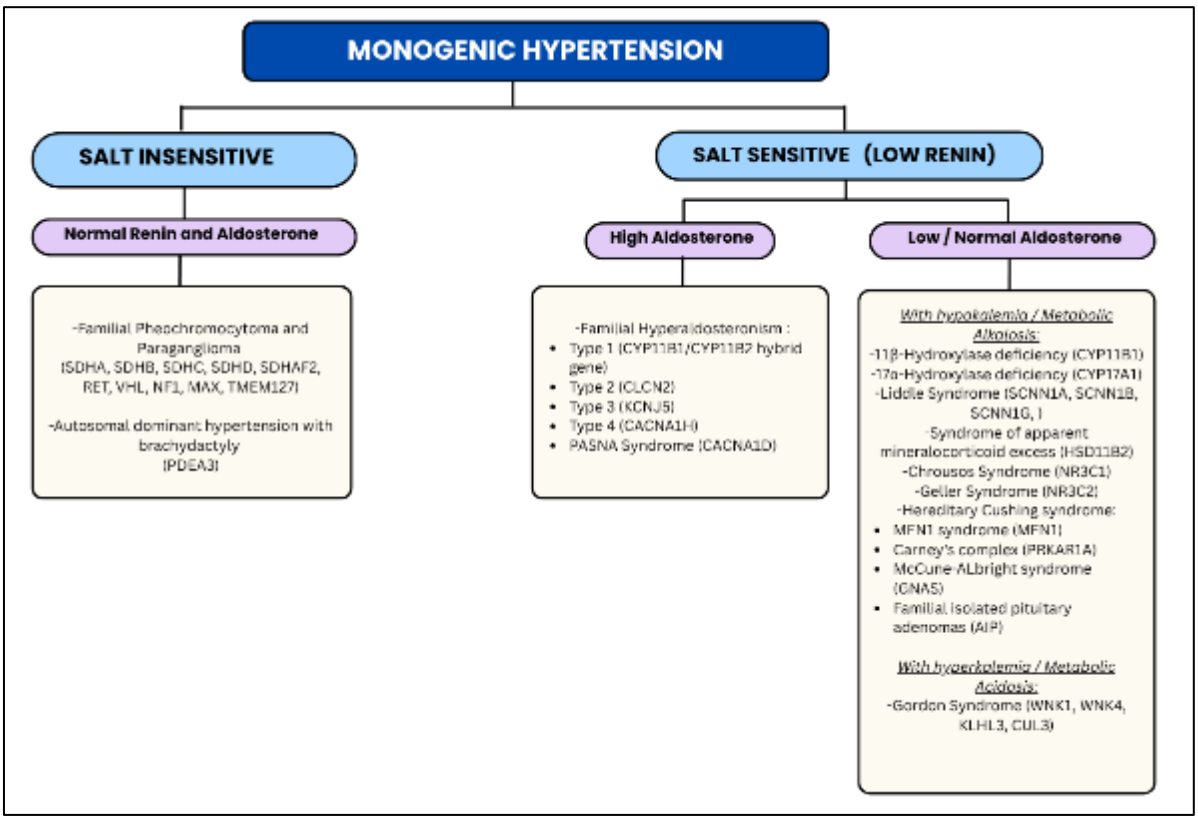


Figure 1 Practical classification of monogenic hypertension (adapted from (4))

3. General principles of genetic screening in endocrine hypertension:

Genetic testing in endocrine hypertension should be considered when it may change management, including tumor surveillance, surgical strategy, metastatic or recurrence risk assessment, cascade screening of relatives, or selection of targeted therapy (**4,6,8**). It is particularly relevant in early-onset, familial clustering, bilateral, multifocal, recurrent or malignant tumors, unusual tumor location, or syndromic phenotypes combining hypertension with renal, neurocutaneous, parathyroid, pituitary, gastrointestinal or other endocrine manifestations (**4-9**).

A key step is to determine whether germline testing, tumor sequencing, or both are required. Germline testing must be performed on non-tumor DNA, usually blood or saliva, and remains essential for familial counselling (**11**). Tumor sequencing may be useful when germline testing is negative, particularly in PPGL, adrenal or pituitary tumors, because it can identify somatic drivers, mosaicism, or a tumor variant that should then be specifically investigated in germline DNA (**4,7,11**). However, tumor-only results should not be used for cascade family screening without germline confirmation (**4,7**).

Because many endocrine hypertension syndromes are genetically heterogeneous and clinically overlapping, phenotype-oriented NGS panels are generally preferred over sequential single-gene testing because they focus on clinically actionable genes, provide better sequencing depth and coverage, simplify interpretation, reduce incidental findings and are usually faster and more cost-effective. (**4,6,8**). Nevertheless, NGS has important limitations: it may detect variants of uncertain significance, miss large deletions, duplications, structural rearrangements, chimeric events, repeat expansions or low-level mosaicism (**12,13**), and may require more complex and expensive complementary techniques such as MLPA, copy-number analysis, long-range PCR, chromosomal microarray, or whole-exome/whole-genome sequencing according to the suspected disorder (**6,12**).

Pre-test counselling should explain the possible outcomes of testing: identification of a pathogenic or likely pathogenic variant, absence of an informative variant, or detection of a variant of uncertain significance (VUS) (**12,13**). A VUS should not be used as a stand-alone basis for prophylactic surgery, predictive testing of relatives, or major changes in surveillance (**12,13**). Post-test counselling should translate the result into a gene-specific follow-up plan, clarify penetrance and inheritance patterns, and organize cascade testing when appropriate (**4,6,13**). In children, testing is justified when it modifies surveillance or treatment during childhood, such as in *VHL*, *SDHB*-related PPGL, MEN syndromes, selected familial hyperaldosteronism or severe low-renin monogenic hypertension (**4,6,8**).

Age thresholds should be used pragmatically. Young onset strongly supports testing, but older patients may also warrant genetic evaluation when there is multiglandular disease, recurrence, bilaterality or syndromic features (**4**); conversely, isolated typical adenomas in older patients have a lower pre-test probability, except for PPGL, where germline testing remains recommended because hereditary disease is frequent even in apparently sporadic cases (**14**).

Despite major advances, numerous challenges remain, including incomplete genotype–phenotype correlations, variable penetrance, VUS interpretation, psychological impact, cost-effectiveness, access to NGS and the need for periodic reanalysis as new genes are discovered (**4-6**). Therefore, genetic testing in endocrine hypertension should remain clinically driven, multidisciplinary and accompanied by expert genetic counselling.

4. Genetics of monogenic hypertension with normo-kalemia, normal renin and aldosterone levels:

4.1. Familial pheochromocytoma and paraganglioma:

Pheochromocytomas and paragangliomas are rare catecholamine-secreting neuroendocrine tumors arising from chromaffin cells of the adrenal medulla and extra-adrenal sympathetic or parasympathetic paraganglia respectively (**14**). PPGL represent the endocrine tumor group with one of the strongest indications for genetic testing, since more than 25 susceptibility genes have been identified, associated with at least 12 distinct genetic syndromes (**15**). Approximately 30–40% of unselected patients carry a germline pathogenic variant, and somatic or fusion driver alterations are also frequent, explaining the high molecular heterogeneity of these tumors (**14,16**). Therefore, in routine practice, all patients with PPGL should be offered germline genetic testing after appropriate counselling, regardless of age, family history or syndromic presentation, because an apparently sporadic presentation does not reliably exclude hereditary disease (**14,15**).

PPGL susceptibility genes are commonly classified into a three-cluster classification system with important clinical implications (**17**). Cluster I (pseudohypoxic) includes mutations in genes involved in hypoxia sensing and the

tricarboxylic acid cycle: *SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL, FH, EPAS1/HIF2A, EGLN1/PHD2, MDH2, DLST, GOT2* and *SLC25A11*; they are often noradrenergic, extra-adrenal, and particularly in *SDHB***-** or *FH***-**related disease, associated with a higher metastatic risk (**16-18**). SDHx-related disease may also predispose to renal cell carcinoma and SDH-deficient gastrointestinal stromal tumors, supporting the need for surveillance beyond PPGL alone (**15,17**). Cluster II (kinase signaling) encompasses mutations affecting RAS/RAF/MAPK and PI3K/AKT pathways: *RET, NF1, TMEM127, MAX, HRAS, MET* and related pathway genes, more often present as adrenal pheochromocytomas with adrenergic or mixed catecholamine secretion, whereas Cluster III (Wnt signaling) involves alterations in *CSDE1* and *MAML3* fusion genes (**15**,**17**).

A practical approach begins with careful phenotyping before the genetic result is available. Tumor location, multiplicity, metastatic behavior and biochemical profile can help prioritize interpretation. Head-and-neck paragangliomas, extra-adrenal sympathetic tumors, multifocal disease, dopamine secretion or elevated 3-methoxytyramine should raise suspicion for SDHx-related disease, particularly *SDHB* when metastatic risk is high (**15,17,18**). Bilateral adrenal pheochromocytomas suggest *RET, VHL, MAX* or *TMEM127*, while an adrenergic biochemical profile with elevated metanephrine is more typical of *RET* or *NF1*-related disease (**16–18**). A noradrenergic phenotype with elevated normetanephrine is more suggestive of *VHL* or SDHx-related tumors, whereas dopamine-secreting or clinically silent paragangliomas may occur in SDHx disease and should not delay genetic testing (**16–18**).

The majority of experts recommend that for first-line testing, a phenotype-oriented germline NGS panel over sequential single-gene testing. The minimum panel should include *SDHA, SDHB, SDHC, SDHD, VHL, RET, NF1, TMEM127, MAX* and *FH*; expanded panels may include *SDHAF2, EPAS1, EGLN1, MDH2, DLST, SLC25A11, KIF1B, MEN1, MET* and other emerging genes according to the clinical context and local availability (**19–21**). When sequencing is negative but clinical suspicion remains high, copy-number analysis or MLPA should be added, particularly for *SDHx, VHL* and *MEN1* deletions; tumor sequencing may further help identify somatic drivers or guide targeted germline confirmation in young-onset, metastatic, multiple or phenotypically suggestive PPGL (**15,19,20**).

The clinical value of genetic testing lies in the fact that the result changes management. *SDHB* carriers require prolonged whole-body surveillance because of higher metastatic risk; *SDHD* and *SDHAF2* show a parent-of-origin effect, with disease usually expressed after paternal transmission; *RET* variants require MEN2-oriented assessment, including medullary thyroid carcinoma screening; *VHL* variants require renal, retinal, pancreatic and central nervous system surveillance; and *FH* variants should prompt renal cancer surveillance and assessment for cutaneous or uterine leiomyomas (**15–17**). Thus, the genetic diagnosis determines not only the follow-up of PPGL, but also which parts of the body need to be monitored and for how long.

Family screening should be targeted and genotype directed. Once a pathogenic or likely pathogenic germline variant is identified, cascade testing is recommended for first-degree relatives and may be extended to selected second-degree relatives, particularly in *SDHD*/*SDHAF2* families (**15**). In addition, carrier testing allowing a one-time evaluation may be offered to second-degree relatives of an individual carrying an *SDHB, SDHA, SDHC, TMEM127* or *MAX* mutation, particularly in cases of metastatic disease (**15,19**). Relatives should not undergo broad imaging or non-targeted genetic panels in the absence of a confirmed pathogenic familial variant. In children, presymptomatic testing is justified when the result changes surveillance during childhood; early testing is generally appropriate for *VHL* and *SDHB*, whereas later testing may be considered for lower-penetrance genes according to expert counselling and family context (*Table 1*) (**15,17**).

Table 1 Minimum recommended age for presymptomatic genetic testing according to the predisposing syndrome (19)

Predisposition syndrome / disease	**Gene**	**Minimum age for presymptomatic genetic testing**
Multiple endocrine neoplasia type 2	RET	MEN2B: from birth; MEN2A: from 3 years of age
von Hippel–Lindau disease	VHL	From 5 years of age
Hereditary SDHB-related paraganglioma	SDHB	From 6 years of age
Hereditary leiomyomatosis and renal cell carcinoma syndrome	FH	From 8 years of age
Hereditary SDHD-related paraganglioma	SDHD	From 10 years of age if the mutation is inherited from the paternal lineage
Hereditary SDHC-related paraganglioma	SDHC	From 10 years of age

Hereditary SDHA-related paraganglioma	SDHA	From 10 years of age
Hereditary TMEM127-related pheochromocytoma	TMEM127	From 10 years of age
Hereditary MAX-related pheochromocytoma	MAX	From 10 years of age

4.2. Hypertension with brachydactyly syndrome:

Hypertension with brachydactyly syndrome, formerly referred to as autosomal dominant hypertension with brachydactyly, is a very rare Mendelian form of salt-independent hypertension caused by activating missense mutations in *PDE3A*, the gene encoding phosphodiesterase 3A, an enzyme involved in cyclic adenosine monophosphate degradation (**22**). Clinically, it is characterized by severe hypertension, often beginning in childhood or adolescence, associated with short stature and brachydactyly type E, while renin and aldosterone levels are usually not consistent with a classical low-renin mineralocorticoid phenotype (**23**). The underlying mechanism involves mutant PDE3A overactivity and altered phosphorylation, leading to reduced cAMP signalling in vascular smooth muscle cells, increased vascular smooth muscle proliferation and contraction, and consequently increased peripheral vascular resistance (**23**). In parallel, impaired cAMP-dependent regulation of parathyroid hormone-related peptide may contribute to abnormal chondrogenesis and the brachydactyly phenotype (**23**). Although only a limited number of families have been reported, this syndrome should be considered in patients with early-onset severe familial hypertension associated with brachydactyly or short stature, because molecular confirmation allows appropriate family screening and may prevent delayed diagnosis (**22**,**23**).

5. Genetics of and primary aldosteronism

Primary aldosteronism (PA) is the most common endocrine cause of hypertension, affecting 5-10% of all hypertensive patients and up to 20% of those with resistant hypertension (24-26). Most PA cases are sporadic, mainly due to aldosterone-producing adenomas or bilateral adrenal hyperplasia, but familial hyperaldosteronism (FH) should be considered in patients with early-onset PA, severe or resistant hypertension, hypokalemia, bilateral adrenal disease, or a family history of PA or early hemorrhagic stroke (**25**). Although familial forms are rare, their diagnosis is clinically important because they may require specific treatment, influence surgical decisions and allow targeted screening of relatives (**24-27**). Four distinct familial hyperaldosteronism subtypes (FH-I through FH-IV) have been described, each with unique genetic mechanisms and clinical features (**28,29**):

FH type I, or glucocorticoid-remediable aldosteronism (GRA), is the most frequent form of monogenic hypertension (**30),** resulting from an unequal crossover between the *CYP11B1* (11β-hydroxylase) and *CYP11B2* (aldosterone synthase) genes, creating a chimeric gene in which aldosterone synthase activity is placed under ACTH regulation rather than angiotensin II control (**31**). It may present with variable severity, from mild PA to severe childhood hypertension with complicated by early cerebrovascular events; suggestive features include suppressed plasma renin activity, elevated aldosterone, high hybrid steroids such as 18-hydroxycortisol and 18-oxocortisol (**25,29,31**), and familial clustering. A pathognomonic feature is the suppression of aldosterone secretion by dexamethasone administration, reflecting the ACTH-dependent regulation of the chimeric enzyme, but it has limited feasibility and no established sensitivity nor specificity criteria (**32**). Routine NGS is not sufficient to detect this chimeric gene; long-range PCR or Southern blot-based methods are required to detect the chimeric CYP11B1/CYP11B2 gene (**25,28**). Genetic testing for FH-I is recommended in patients with PA diagnosed before age 20 years or those with a family history of PA or hemorrhagic stroke before age 40 years (**26-28**).

FH type II is mainly associated with germline gain-of-function mutations in the *CLCN2* gene, which encodes a voltage-gated chloride channel in zona glomerulosa cells (**33**). Unlike FH-I, FH-II does not respond to glucocorticoid suppression and typically presents with unilateral or bilateral adrenal hyperplasia or adenomas (**33**). The clinical phenotype is heterogeneous, with variable age of onset and severity, more often before the age of 20 (**33**). Genetic testing involves targeted CLCN2 sequencing and should be considered in patients with early-onset PA and a positive family history of PA (**26-28**).

FH type III is caused by germline activating mutations in the *KCNJ5* gene, which encodes the G protein-activated inward rectifier potassium channel Kir3.4 (**34**). These mutations, more commonly found as somatic alterations in sporadic aldosterone-producing adenomas, have variable phenotypes depending on the type of mutation: allele *T158A* or *G151R* are associated with a more severe phenotype, while *G151E* is associated with milder symptoms (**34**). Affected individuals often require bilateral adrenalectomy due to massive bilateral adrenal hyperplasia, refractory hypertension

and severe hypokalemia (**34**). Hybrid steroid levels are elevated, and a paradoxical increase in blood pressure and mineralocorticoid concentrations may occur during the dexamethasone suppression test (**35**). *KCNJ5* exon 2 sequencing is recommended for patients with very early onset PA and a family history of the condition (<20 years old) and PA associated with bilateral adrenal hyperplasia (**26-28**).

FH type IV results from germline mutations in *CACNA1H*, which encodes the α1H subunit of the T-type calcium channel Cav3.2 (**36**). This rare form presents with very early onset PA, typically at or before 10 years of age (**36**). *CACNA1D* gain-of-function variants cause **PASNA syndrome**, in which PA may occur with seizures, neurological impairment, autism-spectrum features, congenital heart disease or hyperinsulinemic hypoglycemia (**37**). *CACNA1D* is therefore not a classic FH gene but should be considered when PA appears in a complex neurodevelopmental syndrome (**37**). Genetic sequencing of CACNA1H and CACNA1D gene should be considered in children with PA (<10 years old), particularly when accompanied by neurological manifestations for CACNA1D (**26-28**).

A practical genetic approach should remain phenotype driven. Initial endocrine evaluation is still based on the aldosterone–renin ratio, followed when appropriate by confirmatory testing and subtype assessment with adrenal imaging and adrenal venous sampling if surgery is considered (**24-28**). However, when a familial form is likely, genetic testing can avoid unnecessary confirmatory procedures (aldosterone suppression test) in relatives and can identify patients who require lifelong family-based surveillance (**26**). Current guidance supports genetic screening in patients with young-onset PA, particularly before 20 years of age, and in all first-degree relatives of patients with genetically proven FH (**24**). The main clinical, genetic and therapeutic characteristics of familial hyperaldosteronism subtypes and PASNA syndrome are summarized in Table 2.

A practical PA genetic panel should include CYP11B1/CYP11B2 chimerism testing when FH-I is suspected, and sequencing of CLCN2, KCNJ5, CACNA1H and CACNA1D according to phenotype (**26-28**). Emerging genes such as ARMC5, PDE2A and PDE3B have been reported in selected patients with PA or bilateral adrenal hyperplasia, but their role in familial PA remains incompletely established and should be interpreted cautiously (**38,39**). Somatic variants in KCNJ5, CACNA1D, ATP1A1, ATP2B3, CTNNB1, CLCN2 and related genes are frequent drivers of sporadic aldosterone-producing adenomas, but they do not by themselves establish hereditary risk; therefore, tumor sequencing can be useful for research and may increasingly inform precision management, but germline testing remains the basis of family counselling (**24**, **40**52).

Table 2 Clinical, genetic and therapeutic overview of familial hyperaldosteronism subtypes and related PASNA syndrome (4,28)

Subtype	molecular defect	Inheritance type	Typical age at onset	Hypokalemia	Familial occurrence	Key clinical features	Main treatment
FH-I	*CYP11B1/CYP11B2* chimeric gene	AD	Often < 20 years	+/−	Frequent	Glucocorticoid-remediable aldosteronism; family history of early stroke (<40 years); increased hybrid steroids in urine	Dexamethasone or prednisone; MRA
FH-II	*CLCN2*	AD	Variable, often > 20 years	+/−	Frequent	Non-glucocorticoid-remediable; phenotype may resemble sporadic PA	MRA
FH-III	*KCNJ5*	AD	Usually < 20 years (but variable in moderate forms)	++ in severe forms	Often present, usually early onset	Severe PA; possible bilateral adrenal hyperplasia; more severe phenotypes in some variants	MRA; bilateral adrenalectomy in severe cases
FH-IV	*CACNA1H*	AD or *de novo*	Usually, < 10 years	+/−	Variable	Very early-onset PA; rare form	MRA
PASNA syndrome	*CACNA1D*	Usually, *de novo*	Childhood	Variable	Usually, absent	Primary aldosteronism with seizures, neurological abnormalities, developmental impairment, and heart defects	MRA

Abbreviations: AD: autosomal dominant**;** AR**:** autosomal recessive; PA: primary aldosteronism; FH: familial hyperaldosteronism; GRA: glucocorticoid-remediable aldosteronism; MRA: mineralocorticoid receptor antagonist

6. Genetics of Congenital adrenal hyperplasia and other low-renin monogenic syndromes:

Early-onset hypertension with suppressed renin should trigger a structured biochemical classification before gene testing. When aldosterone is high, PA and FH dominate the differential diagnosis. When both renin and aldosterone are low, the clinician should consider congenital adrenal hyperplasia with deoxycorticosterone excess, Liddle syndrome, apparent mineralocorticoid excess, activating mineralocorticoid receptor mutations, glucocorticoid resistance and exogenous mineralocorticoid-like exposure (**4**). Hyperkalemic acidosis suggests Gordon syndrome rather than mineralocorticoid excess (**4**).

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders caused by pathogenic variants in genes encoding enzymes of adrenal steroidogenesis (**41,42**). Although most CAH forms are not primarily hypertensive, 11β-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency and, more rarely, cytochrome P450 oxidoreductase deficiency may present with low-renin hypertension due to excess mineralocorticoid precursors (**42-44**).

11β-hydroxylase deficiency, is the second most common form of CAH (**7,42**), caused by loss-of-function mutations in *CYP11B1*, which encodes steroid 11β-hydroxylase, and results in accumulation of 11-deoxycortisol and deoxycorticosterone (a potent mineralocorticoid), leading to hypertension, hypokalemic alkalosis, suppressed renin and low or low-normal aldosterone (**42-44**). The associated deviation toward adrenal androgen synthesis explains virilisation in affected girls, precocious puberty in boys, accelerated growth and compromised final height when diagnosis is delayed (**42,44**). Genotype–phenotype correlation remains imperfect, and patients carrying the same variant may show variable degrees of hypertension, virilisation and biochemical severity (**44**).

17α-hydroxylase/17,20-lyase deficiency, caused by mutations *in the CYP17A1* gene, which encodes 17α-hydroxylase impairing cortisol and sex-steroid synthesis while increasing deoxycorticosterone and corticosterone production, resulting in hypokalemic hypertension with sexual infantilism, primary amenorrhea, undervirilisation in 46,XY individuals and absent or delayed puberty in both sexes (**45,46**). Diagnosis is supported by steroid profiling, ACTH-stimulated precursor patterns and targeted genetic testing of *CYP17A1* (**45,46**).

P450 oxidoreductase deficiency due to *POR* variants may also cause variable impairment of steroidogenic enzymes, including 17α-hydroxylase activity, and can rarely lead to mineralocorticoid precursor excess and hypertension, often with complex reproductive or skeletal features (**42,44**).

Hypertensive CAH should be suspected in children, adolescents or young adults with early-onset hypertension associated with hypokalemia, suppressed renin and low aldosterone, particularly when accompanied by hyperandrogenism, virilisation, ambiguous genitalia, precocious or delayed puberty, growth acceleration, primary amenorrhoea, sexual infantilism or unexplained adrenal steroid abnormalities (**42-45**). Genetic testing is indicated after biochemical confirmation, especially in patients with suggestive clinical features, atypical steroid profiles or familial disease, as molecular diagnosis guides treatment, enables genetic counselling and allows prenatal or familial testing when an index case has been identified and the familial pathogenic variant is known (**42-45**). Treatment is based mainly on glucocorticoid replacement to suppress ACTH-driven overproduction of mineralocorticoid and androgen precursors, often improving blood pressure, potassium levels and androgen excess; additional antihypertensive or mineralocorticoid receptor blockade may be required in selected cases (**41,42**).

Liddle syndrome is an autosomal dominant disorder caused by gain-of-function variants in *SCNN1B, SCNN1G* and, more rarely, *SCNN1A*, encoding epithelial sodium channel (ENaC) subunits (**47**). Constitutive ENaC activation increases distal sodium reabsorption and potassium secretion, resulting in early-onset, often resistant hypertension with hypokalemic alkalosis (**47,48**). Treatment relies on ENaC blockers such as amiloride or triamterene, whereas mineralocorticoid receptor antagonists are usually ineffective (**48**).

Apparent mineralocorticoid excess is an autosomal recessive disorder caused by loss-of-function mutations in *HSD11B2*, which encodes 11β-hydroxysteroid dehydrogenase type 2, the enzyme that converts cortisol into cortisone in aldosterone-sensitive tissues (**49**). Impaired cortisol inactivation allows cortisol to activate mineralocorticoid receptors, producing low-renin, low-aldosterone hypertension with hypokalemia, and sometimes hypercalciuria or nephrocalcinosis (**50**). Diagnosis is supported by an increased urinary cortisol-to-cortisone ratio and confirmed by genetic testing (**50**). Unlike Liddle syndrome, apparent mineralocorticoid excess may respond to mineralocorticoid receptor antagonists, although ENaC blockade can also be useful (**49**).

Primary generalized glucocorticoid resistance, or Chrousos syndrome, is caused by inactivating mutations in *NR3C1*, leading to impaired glucocorticoid receptor signalling and loss of negative feedback on the hypothalamic–pituitary–adrenal axis (**51**). The resulting ACTH excess increases cortisol, deoxycorticosterone, corticosterone and adrenal androgen production without typical Cushingoid features, and may cause hypertension, hypokalemic alkalosis, hyperandrogenism, menstrual disorders or infertility (**51**). Treatment is based on high-dose mineralocorticoid-sparing glucocorticoids, particularly dexamethasone, to suppress ACTH-driven steroid excess (**52**).

Geller syndrome is an extremely rare autosomal dominant disorder caused by gain-of-function variants in *NR3C2*, encoding the mineralocorticoid receptor (**53**). The mutant receptor can be abnormally activated by progesterone and cortisol, explaining severe or pregnancy-exacerbated hypertension with hypokalemia and suppressed renin–aldosterone activity (**53**). Spironolactone should be avoided because it may paradoxically activate the mutant receptor, whereas salt restriction and amiloride may help control blood pressure and potassium loss (**53**).

Gordon syndrome, also known as pseudohypoaldosteronism type II or familial hyperkalemic hypertension, is an dominant autosomal disease caused by activating mutation in genes regulating the thiazide-sensitive sodium–chloride cotransporter (NCC), mainly *WNK1, WNK4, KLHL3* and *CUL3* (**54**). These variants increase NCC activity in the distal convoluted tubule, leading to sodium retention, volume expansion, hypertension, hyperkalemia and metabolic acidosis (**54**). Its characteristic therapeutic response to low-dose thiazide diuretics is an important diagnostic clue (**54**).

Overall, there is no clear consensus because of the rarity of these disorders. They should be suspected in children, adolescents or young adults with severe, resistant or familial hypertension associated with suppressed renin, unexplained dyskalemia, and metabolic alkalosis or acidosis. A phenotype-oriented NGS panel is useful for simultaneous screening of the main genes, but negative sequencing does not exclude the diagnosis because large deletions, duplications or structural variants may be missed; MLPA, copy-number analysis, whole-exome sequencing or Sanger confirmation may therefore be required according to the clinical context (**4,44**).

7. Genetics of Cushing syndrome:

Cushing syndrome results from chronic glucocorticoid excess and is often associated with hypertension (70–80%) (**55**). This is due to increased vascular sensitivity to catecholamines and angiotensin II, higher angiotensinogen production, reduced vasodilation, sodium retention and mineralocorticoid receptor activation when cortisol exceeds 11β-HSD2 capacity (**55**). Most cases are sporadic; therefore, genetic testing should be guided by clinical features such as age at onset, adrenal bilaterality, family history and associated syndromic features (**56–58**). In practice, hereditary Cushing syndrome is mainly considered in ACTH-independent disease due to primary adrenal lesions and, less often, in ACTH-dependent forms from pituitary or ectopic ACTH secretion. Genetic yield is higher in bilateral adrenal disease than in isolated pituitary cases, as bilateral hyperplasia often reflects germline, mosaic or tumor-suppressor predisposition (**56, 58-60**).

7.1. ACTH-independent Cushing syndrome

ACTH-independent Cushing syndrome accounts for a minority of endogenous cases and results from autonomous cortisol secretion by unilateral adrenal tumors, bilateral adrenal hyperplasia or, more rarely, adrenocortical carcinoma (**55,57**). Distinguishing **macronodular from micronodular hyperplasia** is clinically useful as it guides genetic evaluation (**58,60**). A genetic cause is found in about 25% of primary bilateral macronodular adrenal hyperplasia (PBMAH) and over 70% of primary pigmented nodular adrenocortical disease (PPNAD), supporting genetic testing in bilateral adrenal hyperplasia (**56**).

Unilateral cortisol-producing adrenal adenomas are usually sporadic, often driven by somatic activating *PRKACA* mutations (**58**). Although these mutations are associated with smaller, more cortisol-secreting tumors and younger age at diagnosis, tumor testing rarely changes management because adrenalectomy is usually curative (**56**). In children, however, even apparently unilateral adrenal Cushing syndrome should prompt genetic evaluation since inherited or mosaic disease is more likely (**56–58**).

Primary bilateral macronodular adrenal hyperplasia (PBMAH) is the main inherited cause of macronodular ACTH-independent Cushing syndrome. Germline inactivating *ARMC5* variants are found in about 25% of sporadic cases and up to 80% of familial forms (**61**). *ARMC5*-related PBMAH is often associated with more severe hypercortisolism, higher prevalence of hypertension, larger bilateral adrenal hyperplasia and multiple nodules (**62**); meningiomas may also occur, supporting surveillance beyond the adrenal glands (**56**). **Food-dependent Cushing syndrome** is a specific PBMAH subtype in which cortisol secretion is stimulated by aberrant adrenal receptors, classically the gastric inhibitory

polypeptide receptor (**63**). Germline *KDM1A* variants should be considered when cortisol rises after meals, when dynamic testing suggests GIP-dependent PBMAH, or in the presence of low fasting morning cortisol with elevated midnight cortisol and/or 24-hour urinary free cortisol (**56,60,63**). A personal or familial history of monoclonal gammopathy or multiple myeloma also supports *KDM1A* testing (**56**).

McCune–Albright syndrome is a major cause of neonatal or pediatric ACTH-independent Cushing syndrome, combining **bimorphic adrenal hyperplasia** with café-au-lait macules, polyostotic fibrous dysplasia, precocious puberty, hyperthyroidism or growth hormone excess (**58,64**). It results from post-zygotic mosaic activating *GNAS* variants, therefore blood testing may be negative and molecular analysis of affected tissue can be more informative when the phenotype is suggestive (**56,58,59**). **Rare macronodular forms** may also occur in MEN1, APC-related familial adenomatous polyposis, FH-related hereditary leiomyomatosis and renal cell carcinoma, Beckwith–Wiedemann syndrome related to CDKN1C mutation, or with susceptibility variants in *MC2R, PDE11A* or *PDE8B* (**56–60**).

Micronodular adrenal hyperplasia (MAD), especially **primary pigmented nodular adrenocortical disease** (PPNAD), is strongly associated with Carney complex (26-60% of cases (**65**)), usually due to inactivating *PRKAR1A* variants and cAMP–PKA pathway dysregulation (**58,65**). It typically occurs in children or young adults and may associate paradoxical cortisol responses to dexamethasone with lentigines, blue naevi, cardiac or cutaneous myxomas, Sertoli cell tumors, thyroid lesions and pituitary involvement (**58–60**). Identifying a *PRKAR1A* variant is clinically important because it requires lifelong screening for cardiac myxomas and other Carney complex manifestations (**58**). Rare *PDE11A* and *PDE8B* variants may also predispose to micronodular adrenal hyperplasia through impaired cAMP degradation (**56**).

In practice, genetic screening for adrenal Cushing syndrome is recommended in all children with adrenal Cushing syndrome, in adults with bilateral micro- or macronodular adrenal hyperplasia, and in patients with a family history or syndromic features (**56**). A phenotype-guided panel should include *ARMC5* for PBMAH, *PRKAR1A* for MAD, PPNAD or Carney complex, *GNAS* for neonatal or mosaic McCune–Albright-like disease, and *KDM1A* for suspected GIP-dependent PBMAH; broader panels may include *MEN1, APC, FH, PDE11A, PDE8B, PRKACA* and *TP53* when clinically justified (**56,59,60**). NGS is preferred as first-line testing, with MLPA or copy-number analysis if negative; exome or genome-wide sequencing may be discussed when suspicion remains high (**56**). Family screening should be gene-specific and adapted to the age-related risk of each syndrome, starting around 3 years for *PRKAR1A*, potentially from 18 years for *ARMC5*, *KDM1A* or *PRKACA* duplication (**56**).

7.2. ACTH-dependent Cushing syndrome

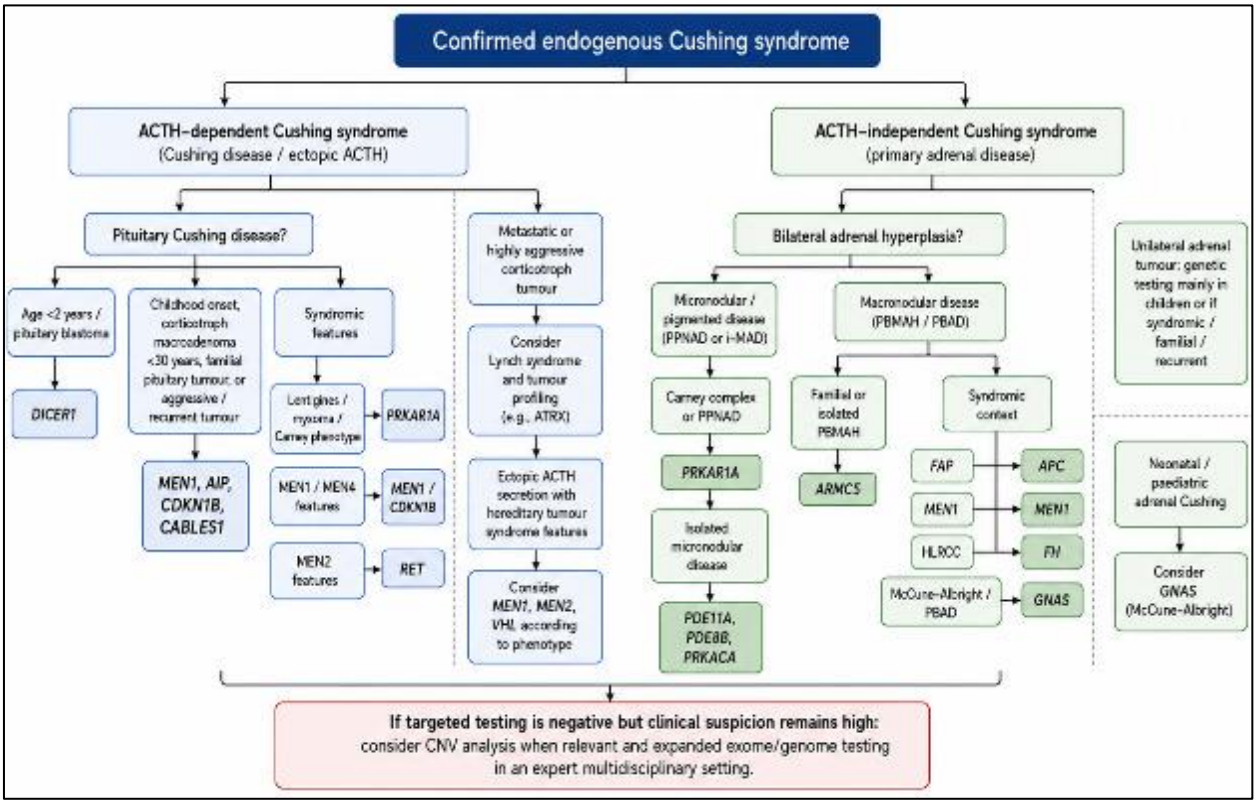
ACTH-dependent Cushing syndrome is usually caused by a sporadic corticotroph pituitary neuroendocrine tumor, while ectopic ACTH secretion is less frequent and typically arises from bronchial, thymic, pancreatic or other neuroendocrine tumors (**56,59**). In pituitary Cushing disease, somatic alterations such as *USP8, USP48* and *BRAF* act as tumor drivers; *USP8* mutations are the most frequent and may be associated with smaller tumors and better response to somatostatin analogues (**66-68**). These somatic findings help characterize tumor biology but do not indicate inherited predisposition or justify cascade testing unless a germline alteration is identified (**58**).

Rare germline forms of Cushing disease may occur within hereditary endocrine tumor syndromes or, less commonly, as isolated familial or apparently sporadic disease (**56**). In multiple endocrine neoplasia type 1, corticotroph adenomas are uncommon, accounting for only a small proportion of MEN1-associated pituitary tumors, but Cushing disease may be the presenting manifestation in children and young adults (**69**); in MEN4, caused by *CDKN1B* mutations, isolated pediatric Cushing disease or MEN1-like presentations have also been reported (**70**). Carney complex predominantly affects the somatotroph axis, although corticotroph adenomas are rare possible manifestations (**71**), while *DICER1* syndrome should be suspected in children younger than 2 years with pituitary blastoma and Cushing disease (**72**). Exceptional associations have also been described with tuberous sclerosis, MEN2/*RET* mutations and germline *USP8* variants, although causal links remain limited or based on isolated cases (**56**). In isolated Cushing disease, germline *CABLES1* variants have been reported in rare corticotroph macroadenomas, but their prevalence and clinical significance remain uncertain (**73**). *AIP* mutations may also occur in pediatric or young-adult corticotroph adenomas, although much less frequently than in somatotroph or lactotroph tumors, and often in sporadic cases with incomplete penetrance or variable expressivity (**563**).

Germline testing in Cushing disease should remain selective and is recommended in the presence of syndromic features, family history of pituitary adenoma, corticotroph macroadenoma before 30 years old, or any childhood corticotroph microadenoma in childhood (**56**). A phenotype-guided NGS panel should include at least *MEN1* and *AIP*, with extension to *CDKN1B, PRKAR1A, DICER1, CABLES1, USP8, RET* or other genes according to the clinical context; broader exome or

genome-wide analysis may be discussed if suspicion remains high (**56**). Family screening should follow syndrome-specific guidelines only when a pathogenic variant is identified in a recognized hereditary tumor syndrome (**56**).

Ectopic ACTH secretion is usually sporadic, but MEN1, MEN2, VHL or other predisposition syndromes should be considered when ACTH-secreting neuroendocrine tumors occur in a suggestive context; in MEN1, Cushing syndrome may result from pituitary, thymic, pancreatic or adrenal involvement, justifying systemic surveillance (**56**).



(Abbreviations : CNV : copy number variation ; FAP : familial adenomatous polyposis ; HLRCC : hereditary leiomyomatosis and renal cell carcinoma ; i-MAD : isolated micronodular adrenal disease ; MEN : multiple endocrine neoplasia ; PBMAH : primary bilateral macronodular adrenal hyperplasia ; PBAD : primary bimorphic adrenal disease ; PPNAD : primary pigmented nodular adrenocortical disease ;)

Figure 2 Practical algorithm for genetic screening in Cushing syndrome (adapted from 56,58,62)

8. Genetics of acromegaly and pituitary gigantism:

Acromegaly results from chronic growth hormone (GH) excess, usually due to a somatotroph pituitary neuroendocrine tumor, whereas pituitary gigantism reflects GH excess occurring before epiphyseal closure (**74**). Hypertension is reported in approximately 30–40% of patients and is mediated by several mechanisms: GH and IGF-1 promote renal sodium retention through increased epithelial sodium channel and Na^+/K^+-ATPase activity, expand extracellular volume, increase cardiac output and left ventricular hypertrophy, and contribute to vascular remodelling and endothelial dysfunction (**4**). The hypertensive phenotype therefore reflects combined renal, cardiac and vascular effects rather than a single mineralocorticoid-like mechanism.

Most somatotroph tumors are sporadic, and somatic *GNAS* mutations are found in approximately 40% of sporadic GH-secreting adenomas (**75**). However, hereditary acromegaly should be suspected in patients with onset at a young age, familial pituitary tumors, pituitary hyperplasia, multifocal pituitary tumors (≥2), or associated syndromic manifestations (**74-76**).

Familial isolated pituitary adenoma (FIPA) is the most common familial presentation of acromegaly/gigantism and is defined by at least two pituitary tumors of any type in the same family without any other syndromic features (**77**). According to the underlying genetic background, FIPA can be divided into three main subgroups: *AIP* mutation-positive families; families with *GPR101* duplication, corresponding to X-linked acrogigantism (X-LAG); and genetically unexplained FIPA, which remains the most frequent subgroup (**74**).

Germline *AIP* mutations is thought to reduce Gαi-2 and Gαi-3 expression and to impair the tumor-suppressor regulator ZAC1, leading to increased cAMP signalling and promoting pituitary tumorigenesis (**74**). They account for approximately 10–20% of FIPA families and are associated with young-onset, predominantly GH- or prolactin-secreting macroadenomas, often sparsely granulated, large, invasive and relatively resistant to first-generation somatostatin receptor ligands, partly related to reduced somatostatin receptor subtype 2 expression (**74,77**). Because penetrance is incomplete, around half of *AIP*-positive acromegaly may appear sporadic (**77**); nevertheless, prospective screening of relatives improves outcomes by allowing earlier diagnosis of smaller and less invasive tumors (**77**).

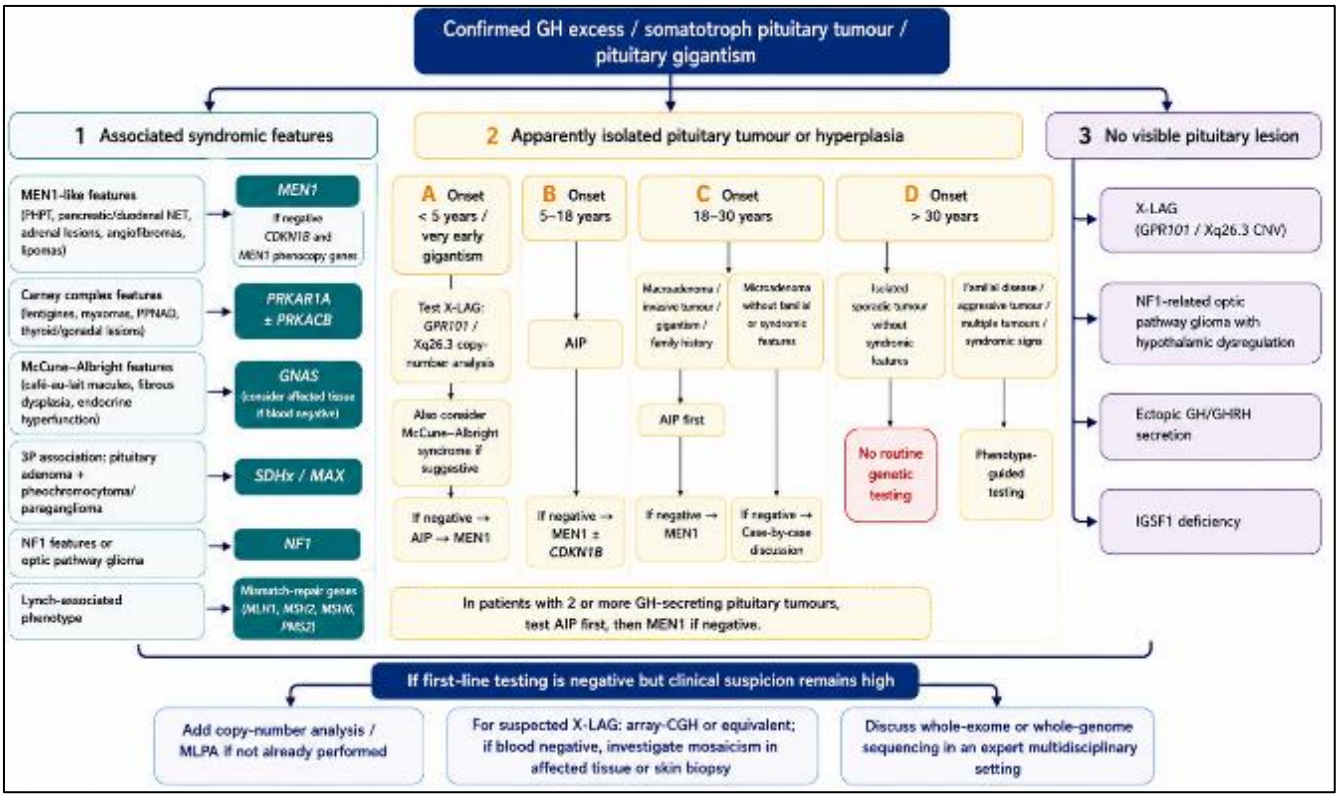
X-linked acrogigantism (X-LAG) is caused by microduplication of the Xq26.3 region involving GPR101, leading to overexpression of an orphan G-protein-coupled receptor, with increased cAMP signaling, a key pathway involved in GH secretion and pituitary cell proliferation in response to GHRH. X-LAG is a major genetic cause of very early-onset pituitary gigantism, typically beginning before 5 years of age (**78,79**). It presents with rapid linear growth acceleration, markedly high GH and IGF-1, pituitary hyperplasia or mixed somatotroph–lactotroph tumors and often requires multimodal treatment because disease control may be difficult (**79**). It is often associated with increased appetite, fasting hyperinsulinemia and acanthosis nigricans (**79**). For genetic diagnosis, array-CGH or equivalent copy-number analysis should be performed to detect *GPR101*-containing Xq26.3 microduplications, and if blood testing is negative despite strong clinical suspicion, mosaicism should be investigated using DNA from affected tissue or a skin biopsy (**78**). Preimplantation genetic diagnosis or prenatal testing should be considered in affected mothers, since complete penetrance has been reported in familial X-LAG cases.

Syndromic forms of acromegaly should be actively searched for since they change both patient management and family surveillance (**75**). MEN1, caused by germline *MEN1* mutations, is associated with primary hyperparathyroidism (90% of cases of MEN1), duodenopancreatic neuroendocrine tumors (60%) and pituitary tumors (30-40%), among which somatotroph tumors account for a minority but may occasionally be the presenting manifestation (≤15%) (**80-82**). MEN4, caused by *CDKN1B* variants, is rarer and may mimic MEN1 with pituitary, parathyroid or neuroendocrine involvement ; although GH secreting pituitary adenoma are more frequent than in MEN1 (**75**). McCune–Albright syndrome results from post-zygotic mosaic *GNAS* activation and should be suspected in patients with GH excess associated with café-au-lait macules, fibrous dysplasia, precocious puberty or other endocrine hyperfunction; because of skull-base fibrous dysplasia and the predominance of pituitary hyperplasia, medical therapy is often preferred over surgery (**75**). Carney complex, usually related to *PRKAR1A* mutations, may present with somatotroph hyperplasia or GH-secreting tumors associated with lentigines, cardiac myxomas, thyroid or gonadal tumors and primary pigmented nodular adrenocortical disease (**76**). The "3P association" combines pituitary adenomas with pheochromocytoma or paraganglioma and may involve SDHx, MAX, VHL, MEN1 or RET, supporting targeted testing when GH excess coexists with PPGL features (**76**). Children with neurofibromatosis type 1 (NF1) rarely develop pituitary tumors, but about 10% of those with optic pathway gliomas may show GH/IGF-1 excess and acromegalic features, likely due to hypothalamic dysregulation rather than a primary pituitary adenoma (**83).**

Overall, Genetic testing in acromegaly should be phenotype-driven rather than universal. Current consensus recommends sequential testing for *AIP* and *MEN1* in this order, unless syndromic MEN1 features are present in the patient or any family member, in patients with a family history of any type of pituitary tumors, GH-secreting tumors with onset at ≤18 years including all cases of pituitary gigantism, and GH-secreting macroadenomas diagnosed at ≤30 years (**75,76**). In patients with two or more GH-secreting pituitary tumors, genetic testing may be considered; in the absence of syndromic features, *AIP* should be tested first, followed by *MEN1* if negative (**75**). Testing *AIP* before *MEN1* in isolated young-onset somatotroph tumors is pragmatic, as *AIP* is linked to early, often aggressive macroadenomas ; *MEN1* should be tested first or in parallel if a syndromic context is suspected (**77**,**80**). In gigantism beginning at ≤5 years, GPR101 microduplication should be assessed first, followed by sequential genetic testing for AIP and MEN1 after X-LAG is ruled out (**75**). When clinical features suggest a syndrome, testing should be expanded to CDKN1B for MEN4, PRKAR1A/PRKACB for Carney complex, GNAS for McCune–Albright syndrome, SDHx or MAX for the 3P association, NF1 for neurofibromatosis type 1 and mismatch-repair genes (MSH2, MSH6, MLH1, and PMS2) when Lynch syndrome is suspected (**75**).

There is no universally accepted genetic panel for all patients with acromegaly, but reference laboratories increasingly use NGS panels including *AIP, MEN1, CDKN1B, PRKAR1A,* SDHx and other phenotype-guided genes (**74-76**). Copy-number analysis or MLPA should be added when NGS is negative but suspicion remains, particularly for large deletions or duplications, and array-CGH is required for suspected X-LAG (**76**). In highly suggestive cases with negative targeted testing, a whole-genome study may be proposed after multidisciplinary discussion (**76**). Presymptomatic testing of relatives may be proposed according to the causal gene: from birth for Xq26.3 microduplication, from around 5 years

for MEN1 and Carney complex, and from around 10 years for *AIP* mutation carriers, although the timing should be individualized according to family history and expert counselling (**76**).



(Abbreviations: CNV: copy-number variant; MLPA: multiplex ligation-dependent probe amplification; MEN: multiple endocrine neoplasia; NET: neuroendocrine tumor; NF1: neurofibromatosis type 1; PHPT: primary hyperparathyroidism; PPNAD: primary pigmented nodular adrenocortical disease; X-LAG: X-linked acrogigantism ;)

Figure 3 Practical algorithm for genetic screening in GH excess (adapted from 74-76)

9. Genetics of Primary hyperparathyroidism and familial calcium disorders:

Primary hyperparathyroidism (PHPT) is defined by excessive parathyroid hormone secretion leading to hypercalcemia, and genetic forms account for up to 10% of cases in clinical practice (**84**). Although hypertension is not a direct diagnostic feature of PHPT, it is frequently observed and may result from combined effects of PTH and hypercalcemia, including renin–angiotensin–aldosterone system activation, increased catecholamine sensitivity, vascular smooth muscle calcium influx, endothelial dysfunction, vascular remodeling, arterial stiffness, myocardial hypertrophy and insulin resistance (**4**).

Hereditary PHPT may occur as part of syndromic endocrine tumor disorders or as isolated familial disease (*Table 3*) (**84**). MEN1 is the most common syndromic cause and is caused by germline inactivating variants in *MEN1*; PHPT is present in approximately 90% of affected patients, usually occurs at a younger age than sporadic disease, is frequently multiglandular, and may coexist with pancreatic neuroendocrine tumors and pituitary adenomas (**81**). MEN2A, caused by activating *RET* variants, may include PHPT in about 20% of patients, usually in association with medullary thyroid carcinoma and/or pheochromocytoma, whereas MEN4, caused by *CDKN1B* variants, is a rarer MEN1-like syndrome in which PHPT and pituitary tumors are the most frequent manifestations (**85**).

Hyperparathyroidism-jaw tumor syndrome is caused by germline pathogenic variants in *CDC73*, encoding the tumor suppressor parafibromin, and should be suspected in PHPT associated with parathyroid carcinoma, atypical or cystic parathyroid tumors, loss of parafibromin expression, ossifying jaw fibromas, renal lesions or uterine tumors (**86**). This diagnosis is particularly important because *CDC73*-related disease carries a substantially increased risk of parathyroid carcinoma and therefore influences both surgical strategy and long-term surveillance (**84,86**).

Familial hypocalciuric hypercalcemia (FHH) is an essential differential diagnosis of PHPT, caused by inactivating variants in *CASR* in type 1, *GNA11* in type 2 and *AP2S1* in type 3, and is typically suggested by lifelong mild hypercalcemia

with inappropriately normal or mildly elevated PTH and low urinary calcium excretion (**86**). Activating *GCM2* variants are associated with familial isolated PHPT, often with incomplete penetrance and a tendency toward recurrent disease (**84**). In clinical practice, particularly in adolescents and adults, distinguishing primary hyperparathyroidism (PHPT) from FHH is essential, because parathyroidectomy may be appropriate in PHPT and in neonates with neonatal severe hyperparathyroidism (resulting from biallelic or severe CASR defects), but is usually not indicated in older patients with FHH (**87**).

Genetic testing should not be systematic in all patients with PHPT (**84**), unlike PPGL, where germline testing is recommended more broadly (**16,19**). This difference is explained by the higher hereditary yield in PPGL, its gene-specific metastatic and syndromic risks, and the impact on surveillance and family screening (**16,19**). In contrast, most PHPT cases are sporadic single-gland disease, making indiscriminate testing less informative and more likely to generate variants of uncertain significance (**84**). Therefore, genetic testing in PHPT should be proposed in familial PHPT, defined by at least two affected first- or second-degree relatives, in syndromic presentations, and in apparently sporadic isolated PHPT when diagnosis occurs before 50 years of age (**84**). In patients older than 50 years, testing remains indicated when PHPT is recurrent, multiglandular (metachronous or synchronous), associated with parathyroid carcinoma, atypical parathyroid tumor or loss of parafibromin expression (**84**). Additional red flags include pediatric onset, severe hypercalcemia with very high PTH levels (>500pg/ml) suggesting parathyroid carcinoma, low urinary calcium (FeCa <1%) suggesting FHH, or associated endocrine/neoplastic features such as medullary thyroid carcinoma, pheochromocytoma, pancreatic neuroendocrine tumors, pituitary adenoma, jaw tumor, uterine or renal tumors (**84**).

A practical first-line approach is phenotype-guided genetic testing, using targeted analysis when the syndrome is clinically evident and an NGS panel when the presentation is isolated or overlapping. The currently recommended first-line panel includes MEN1, CDKN1B, CDC73, CASR, GNA11, AP2S1 and GCM2 (**84)**; RET should be added when MEN2A is suspected, particularly in the presence of medullary thyroid carcinoma or pheochromocytoma (**84,86**). Recently described genes, such as *CDKN1A, CDKN2B, CDKN2C* and *PRUNE2*, may be considered as second-line investigations when first-line genetic testing is negative despite persistent clinical suspicion (**84**). If panel testing is negative despite familial disease or pediatric onset, broader genomic analysis, including whole-genome sequencing, may be discussed in an expert multidisciplinary setting (**84**). Variant interpretation should follow standard pathogenicity classification (**12),** and variants of uncertain significance should not be used alone for predictive testing, prenatal diagnosis or major management decisions (**84**).

Identifying a germline pathogenic variant has direct clinical consequences. It guides the extent of parathyroid surgery, particularly in multiglandular MEN1-related disease, alerts clinicians to carcinoma risk in *CDC73*-related disease, prevents unnecessary surgery in FHH, and enables structured surveillance for associated endocrine and non-endocrine tumors (**84**). It also allows genetic counselling and cascade testing of relatives, with the age of presymptomatic screening adapted to the causal gene and the expected age at which surveillance becomes clinically useful (*Table 3*) (**84**).

Table 3 Main genetic causes of familial or syndromic primary hyperparathyroidism (84)

Category	Disorder	Gene	Gene location	Genetic mechanism	Main PHPT-related features	Associated manifestations	Suggested age for familial screening
Syndromic PHPT	Multiple endocrine neoplasia type 1 (MEN1)	*MEN1*	11q13	Tumor suppressor; loss of function; AD	PHPT in ~90% of MEN1 patients; usually multiglandular hyperplasia and/or multiple adenomas; often early onset and recurrent	Pancreatic/duodenal NETs, pituitary adenomas, adrenal lesions, thymic/bronchial NETs, cutaneous lipomas, collagenomas, facial angiofibromas	From 5 years
	Multiple endocrine neoplasia type 2A (MEN2A)	*RET*	10q11.21	Proto-oncogene; gain of function; AD	PHPT in ~20% of MEN2A patients; usually mild, due to adenoma or hyperplasia	Medullary thyroid carcinoma, pheochromocytoma	Between birth and 5 years, according to the *RET* variant
	Multiple endocrine neoplasia type 4 (MEN4)	*CDKN1B*	12p13.1	Tumor suppressor; loss of function; AD	MEN1-like phenotype; often multiglandular PHPT with adenoma and/or hyperplasia	Pituitary adenomas, other NETs, adrenal, renal or reproductive organ tumors	may be considered from adolescence
	Hyperparathyroidism-jaw tumor syndrome (HPT-JT)	*CDC73* / *HRPT2*	1q31.2	Tumor suppressor; loss of function; AD	PHPT in 80–90% of HPT-JT patients; single- or multiglandular disease; increased risk of atypical parathyroid tumor and carcinoma	Ossifying fibromas of the jaw, Wilms tumor or renal mixed epithelial and stromal tumor, uterine lesions including adenomyosis or leiomyoma	From 5 years
	Familial hypocalciuric hypercalcemia type 1 (FHH1)	*CASR*	3q13.3–q21.1	Impaired calcium sensing/signalling; loss of function; AD, rarely AR	Lifelong mild hypercalcemia with inappropriately normal or mildly elevated PTH and low urinary calcium	Homozygous or compound heterozygous *CASR* variants may cause neonatal severe hyperparathyroidism with severe hypercalcemia,	Possible from birth, according to clinical context

					excretion; FeCa usually low	bone demineralisation and failure to thrive	
Isolated/familial hypercalcemia	Familial hypocalciuric hypercalcemia type 2 (FHH2)	*GNA11*	19p13.3	Impaired calcium sensing/signalling; loss of function; AD	Similar FHH phenotype with persistent hypercalcemia and low urinary calcium excretion	Usually, isolated biochemical phenotype	Possible from birth, according to clinical context
	Familial hypocalciuric hypercalcemia type 3 (FHH3)	*AP2S1*	19q13.32	Impaired calcium sensing/signalling; loss of function; AD	Similar FHH phenotype; may be more symptomatic in some families	Possible pancreatitis reported	Possible from birth, according to clinical context
Isolated familial PHPT	Familial isolated hyperparathyroidism (FIHP)	*GCM2*	6p24.2	Proto-oncogene; gain of function; AD with incomplete penetrance	Familial isolated PHPT, often multiglandular and/or recurrent	Usually, no syndromic manifestations	Approximately 5 years before the age at diagnosis of the index case

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; FeCa: fractional excretion of calcium; FHH, familial hypocalciuric hypercalcemia; FIHP, familial isolated hyperparathyroidism; HPT-JT, hyperparathyroidism-jaw tumor syndrome; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumor; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

10. Conclusion

Monogenic and hereditary endocrine forms of hypertension are rare when considered individually, but they are highly relevant because many of them are clinically relevant and amenable to targeted management. The main challenge for clinicians is to recognize the warning signs: early-onset, severe or resistant hypertension; suppressed renin associated with potassium or acid–base disturbances; PPGL at any age; familial or pediatric primary aldosteronism; bilateral adrenal Cushing syndrome; gigantism or young-onset acromegaly; and early, recurrent, multiglandular or syndromic primary hyperparathyroidism. Although modern NGS panels have made genetic screening more accessible, their results must always be interpreted in the context of a careful endocrine assessment and complementary technique such as MLPA, long-range PCR, copy-number analysis or tumor sequencing should be used when indicated. The goal is not to genetically investigate every patient with hypertension, but to identify those in whom a molecular diagnosis will meaningfully change treatment, surveillance and family counselling. In selected patients, genetic screening has therefore become an essential tool of precision in the management of endocrine hypertension.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The present research work does not contain any studies performed on animal/human subjects by any of the authors

Statement of informed consent

No human participants, animals, or identifiable patient data were involved.

References

[1] World Health Organization. Hypertension [Internet]. Geneva: WHO; 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension

[2] **Young** WF Jr, Calhoun DA, Lenders JWM, Stowasser M, Textor SC. Screening for endocrine hypertension: an Endocrine Society scientific statement. Endocr Rev. 2017;38(2):103-22. doi:10.1210/er.2017-00054.

[3] **Mancia** G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension. J Hypertens. 2023;41(12):1874-2071. doi:10.1097/HJH.0000000000003480.

[4] **Bhadada** SK, Sudhayakumar A. Endocrine hypertension: from basic science to clinical practice. Indian J Med Res. 2023;158(3):325-6. doi:10.4103/ijmr.ijmr_1061_23.

[5] **Papadopoulou-Marketou** N, Koch CA, Poulios E, et al. Overview of endocrine hypertension. In: Feingold KR, Adler RA, Ahmed SF, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [updated 2026 Mar 31]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278980/

[6] **Raina** R, Krishnappa V, Das A, Amin H, Radhakrishnan Y, Nair NR, et al. Overview of monogenic or Mendelian forms of hypertension. Front Pediatr. 2019;7:263. doi:10.3389/fped.2019.00263.

[7] **Burrello** J, Monticone S, Buffolo F, Tetti M, Veglio F, Williams TA, et al. Is there a role for genomics in the management of hypertension? Int J Mol Sci. 2017;18(6):1131. doi:10.3390/ijms18061131.

[8] **Park** SJ, Shin JI. Diagnosis and treatment of monogenic hypertension in children. Yonsei Med J. 2023;64(2):77-86. doi:10.3349/ymj.2022.0316.

[9] **Garovic** VD, Hilliard AA, Turner ST. Monogenic forms of low-renin hypertension. Nat Clin Pract Nephrol. 2006;2(11):624-30.

[10] **Lu** YT, Fan P, Zhang D, Zhang Y, Meng X, Zhang QY, et al. Overview of monogenic forms of hypertension combined with hypokalemia. Front Pediatr. 2021;8:543309. doi:10.3389/fped.2020.543309.

[11] **Levanovich** PE, Diaczok A, Rossi NF. Clinical and molecular perspectives of monogenic hypertension. Curr Hypertens Rev. 2020;16(2):91-107. doi:10.2174/1573402115666190409115330.

[12] **Richards** S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the ACMG and AMP. Genet Med. 2015;17(5):405-24. doi:10.1038/gim.2015.30.

[13] **Wallace** SE, Bean LJH. Educational Materials — Genetic Testing: Current Approaches. 2017 Mar 14 [Updated 2025 Nov 20]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279899/

[14] **Neumann** HPH, Young WF Jr, Eng C. Pheochromocytoma and paraganglioma. N Engl J Med. 2019;381(6):552-65. doi:10.1056/NEJMra1806651.

[15] **Muth** A, Crona J, Gimm O, et al. Genetic testing and surveillance guidelines in hereditary pheochromocytoma and paraganglioma. J Intern Med. 2019;285(2):187-204. doi:10.1111/joim.12869.

[16] **Lenders** JWM, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915-42.

[17] **Jhawar** S, Arakawa Y, Kumar S, et al. New insights on the genetics of pheochromocytoma and paraganglioma and its clinical implications. Cancers (Basel). 2022;14(3):594.

[18] **Fishbein** L, Leshchiner I, Walter V, et al. Comprehensive molecular characterization of pheochromocytoma and paraganglioma. Cancer Cell. 2017;31(2):181-93.

[19] **Haute Autorité de Santé**. Pheochromocytomas and paragangliomas: National Diagnostic and Care Protocol (PNDS) [Internet]. Saint-Denis La Plaine: HAS; 2021. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2021-10/pheochromocytomes_et_paragangliomes_pnds.pdf

[20] **NGS in PPGL Study Group; Toledo** RA, Burnichon N, Cascon A, Benn DE, Bayley JP, Welander J, et al. Consensus statement on next-generation-sequencing-based diagnostic testing of hereditary phaeochromocytomas and paragangliomas. Nat Rev Endocrinol. 2017;13(4):233-47. doi:10.1038/nrendo.2016.185.

[21] **Buffet** A, Burnichon N, Favier J, Gimenez-Roqueplo AP. An overview of 20 years of genetic studies in pheochromocytoma and paraganglioma. Best Pract Res Clin Endocrinol Metab. 2020;34(2):101416.

[22] **Maass** PG, Aydin A, Luft FC, Schächterle C, Weise A, Stricker S, et al. PDE3A mutations cause autosomal dominant hypertension with brachydactyly. Nat Genet. 2015;47(6):647-53. doi:10.1038/ng.3302.

[23] **Ercu** M, Marko L, Schachterle C, Tsvetkov D, Cui Y, Maghsodi S, et al. Phosphodiesterase 3A and arterial hypertension. Circulation. 2020;142(2):133-49.

[24] **Adler** GK, Stowasser M, Correa RR, et al. Primary aldosteronism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2025;110(9):2453-95.

[25] **Mulatero** P, Monticone S, Deinum J, et al. Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement. J Hypertens. 2020;38(10):1919-28.

[26] **Funder** JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(5):1889-916. doi:10.1210/jc.2015-4061.

[27] **Mulatero** P, Scholl UI, Williams TA, et al. Familial hyperaldosteronism: an Endo-ERN clinical practice guideline. Eur J Endocrinol. 2024;190(4):G1-G13.

[28] **Zennaro** MC, Jeunemaitre X. SFE/SFHTA/AFCE consensus on primary aldosteronism, part 5: genetic diagnosis of primary aldosteronism. Ann Endocrinol (Paris). 2016;77(3):214-9. doi:10.1016/j.ando.2016.02.006.

[29] **Perez-Rivas** LG, Williams TA, Reincke M. Inherited forms of primary hyperaldosteronism: new genes, new phenotypes and proposition of a new classification. Exp Clin Endocrinol Diabetes. 2019;127(2-03):93-9. doi:10.1055/a-0713-0629.

[30] **Monticone** S, Buffolo F, Tetti M, Veglio F, Pasini B, Mulatero P. Genetics in endocrinology: the expanding genetic horizon of primary aldosteronism. Eur J Endocrinol. 2018;178(3):R101-11. doi:10.1530/EJE-17-0946.

[31] **Lifton** RP, Dluhy RG, Powers M, Rich GM, Cook S, Ulick S, et al. A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature. 1992;355(6357):262-5. doi:10.1038/355262a0.

[32] **Litchfield** WR, New MI, Coolidge C, Lifton RP, Dluhy RG. Evaluation of the dexamethasone suppression test for the diagnosis of glucocorticoid-remediable aldosteronism. J Clin Endocrinol Metab. 1997;82(11):3570-3. doi:10.1210/jcem.82.11.4381.

[33] **Scholl** UI, Stolting G, Schewe J, et al. CLCN2 chloride channel mutations in familial hyperaldosteronism type II. Nat Genet. 2018;50(3):349-54.

[34] **Choi** M, Scholl UI, Yue P, et al. K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. Science. 2011;331(6018):768-72.

[35] **Geller** DS, Zhang J, Wisgerhof MV, Shackleton C, Kashgarian M, Lifton RP. A novel form of human Mendelian hypertension featuring nonglucocorticoid-remediable aldosteronism. J Clin Endocrinol Metab. 2008;93(8):3117-23. doi:10.1210/jc.2008-0594.

[36] **Scholl** UI, Stolting G, Nelson-Williams C, et al. Recurrent gain-of-function mutation in calcium channel CACNA1H causes early-onset hypertension with primary aldosteronism. eLife. 2015;4:e06315.

[37] **Scholl** UI, Goh G, Stölting G, de Oliveira RC, Choi M, Overton JD, et al. Somatic and germline CACNA1D calcium channel mutations in aldosterone-producing adenomas and primary aldosteronism. Nat Genet. 2013;45(9):1050-4. doi:10.1038/ng.2695.

[38] **Zilbermint** M, Xekouki P, Faucz FR, et al. Primary aldosteronism and ARMC5 variants. J Clin Endocrinol Metab. 2015;100(6):E900-9. doi:10.1210/jc.2014-4167.

[39] **Rassi-Cruz** M, Maria AG, Faucz FR, London E, Vilela LAP, Santana LS, et al. Phosphodiesterase 2A and 3B variants are associated with primary aldosteronism. Endocr Relat Cancer. 2021;28(1):1-13. doi:10.1530/ERC-20-0384.

[40] **Williams** TA, Monticone S, Schack VR, Stindl J, Burrello J, Buffolo F, et al. Somatic ATP1A1, ATP2B3, and KCNJ5 mutations in aldosterone-producing adenomas. Hypertension. 2014;63(1):188-95. doi:10.1161/HYPERTENSIONAHA.113.01733.

[41] **Speiser** PW, Arlt W, Auchus RJ, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(11):4043-88.

[42] **Tosun** BG, Guran T. Congenital adrenal hyperplasia and hypertension. In: Pappachan JM, Fernandez CJ, editors. Endocrine hypertension: from basic science to clinical practice. 1st ed. Elsevier; 2023. p. 113-25. doi:10.1016/B978-0-323-96120-2.00015-7.

[43] **Nimkarn** S, New MI. Steroid 11beta-hydroxylase deficiency congenital adrenal hyperplasia. Trends Endocrinol Metab. 2008;19(3):96-9.

[44] **Khandelwal** P, Deinum J. Monogenic forms of low-renin hypertension: clinical and molecular insights. Pediatr Nephrol. 2022;37(7):1495-509. doi:10.1007/s00467-021-05246-x.

[45] **Asirvatham** AR, Balachandran K, Jerome P, Venkatesan V, Koshy T, Mahadevan S. Clinical, biochemical and genetic characteristics of children with congenital adrenal hyperplasia due to 17α-hydroxylase deficiency. J Pediatr Endocrinol Metab. 2020;33(8):1051-6. doi:10.1515/jpem-2020-0050.

[46] **Auchus** RJ. Steroid 17-hydroxylase and 17,20-lyase deficiencies, genetic and pharmacologic. J Steroid Biochem Mol Biol. 2017;165(Pt A):71-8. doi:10.1016/j.jsbmb.2016.02.002.

[47] **Tetti** M, Monticone S, Burrello J, et al. Liddle syndrome: review of the literature and description of a new case. Int J Mol Sci. 2018;19(3):812.

[48] **Hanukoglu** I, Hanukoglu A. Epithelial sodium channel family: phylogeny, structure-function, tissue distribution, and associated inherited diseases. Gene. 2016;579(2):95-132. doi:10.1016/j.gene.2015.12.061.

[49] **Lu** YT, Zhang D, Zhang QY, et al. Apparent mineralocorticoid excess: comprehensive overview of molecular genetics. J Transl Med. 2022;20:500.

[50] **Palermo** M, Quinkler M, Stewart PM. Apparent mineralocorticoid excess syndrome: an overview. Arq Bras Endocrinol Metabol. 2004;48(5):687-96. doi:10.1590/S0004-27302004000500015.

[51] **Nicolaides** NC, Charmandari E. Glucocorticoid resistance. Experientia Suppl. 2019;111:85-102. doi:10.1007/978-3-030-25905-1_6.

[52] **Nicolaides** NC, Charmandari E. Chrousos syndrome: from molecular pathogenesis to therapeutic management. Eur J Clin Invest. 2015;45(5):504-14. doi:10.1111/eci.12426.

[53] **Garg** AK, Parajuli P, Mamillapalli CK. Pregnancy complicated by hypertension and hypokalemia. Am J Kidney Dis. 2020;76(4):A21-2. doi:10.1053/j.ajkd.2020.04.012.

[54] **Riepe** FG. Clinical and molecular features of type 1 pseudohypoaldosteronism. Horm Res. 2009;72(1):1-9. doi:10.1159/000224334.

[55] **Lacroix** A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet. 2015;386(9996):913-27. doi:10.1016/S0140-6736(14)61375-1.

[56] **Martinerie** L, Bouligand J, North MO, Bertherat J, Assié G, Espiard S, et al. Consensus statement by the French Society of Endocrinology and French Society of Pediatric Endocrinology & Diabetology for the diagnosis of Cushing's syndrome: genetics of Cushing's syndrome. Ann Endocrinol (Paris). 2024;85(4):284-93. doi:10.1016/j.ando.2024.01.005.

[57] **Stratakis** CA. Cushing syndrome caused by adrenocortical tumors and hyperplasias: corticotropin-independent Cushing syndrome. Endocr Dev. 2008;13:117-32. doi:10.1159/000134829.

[58] **Kamilaris** CDC, Stratakis CA. Genetics and genomics of Cushing syndrome and primary aldosteronism. Front Endocrinol (Lausanne). 2021;12:632543.

[59] **Hernandez-Ramirez** LC, Stratakis CA. Genetics of Cushing syndrome. Endocrinol Metab Clin North Am. 2018;47(2):275-97.

[60] **Hannah-Shmouni** F, Stratakis CA. A gene-based classification of primary adrenocortical hyperplasias. Horm Metab Res. 2020;52(3):133-41. doi:10.1055/a-1107-2972.

[61] **Assié** G, Libé R, Espiard S, Rizk-Rabin M, Guimier A, Luscap W, et al. ARMC5 mutations in macronodular adrenal hyperplasia with Cushing's syndrome. N Engl J Med. 2013;369(22):2105-14.

[62] **Kamilaris** CDC, Hannah-Shmouni F, Stratakis CA. Adrenocortical tumorigenesis: lessons from genetics. Best Pract Res Clin Endocrinol Metab. 2020;34(3):101428. doi:10.1016/j.beem.2020.101428.

[63] **Lecoq** AL, Stratakis CA, Viengchareun S, Chaligné R, Tosca L, Deméocq V, et al. Adrenal GIPR expression and chromosome 19q13 microduplications in GIP-dependent Cushing's syndrome. JCI Insight. 2017, Sep 21;2(18):e92184. doi: 10.1172/jci.insight.92184.

[64] **Carney** JA, Young WF, Stratakis CA. Primary bimorphic adrenocortical disease: cause of hypercortisolism in McCune-Albright syndrome. Am J Surg Pathol. 2011;35:1311-26.

[65] **Espiard** S, Vantyghem MC, Assié G, Cardot-Bauters C, Raverot G, Brucker-Davis F, et al. Frequency and incidence of Carney complex manifestations: a prospective multicenter study with a three-year follow-up. J Clin Endocrinol Metab. 2020;105(3):dgaa002. doi: 10.1210/clinem/dgaa002.

[66] **Ma** ZY, Song ZJ, Chen JH, Wang YF, Li SQ, Zhou LF, et al. Recurrent gain-of-function USP8 mutations in Cushing's disease. Cell Res. 2015;25:306-17.

[67] **Hayashi** K, Inoshita N, Kawaguchi K, Ardisasmita AI, Suzuki H, Fukuhara N, et al. The USP8 mutational status may predict drug susceptibility in corticotroph adenomas of Cushing's disease. Eur J Endocrinol. 2016;174:213-26.

[68] **Chen** J, Jian X, Deng S, Ma Z, Shou X, Shen Y, et al. Identification of recurrent USP48 and BRAF mutations in Cushing's disease. Nat Commun. 2018;9(1):3171. doi:10.1038/s41467-018-05275-5.

[69] **Vergès** B, Boureille F, Goudet P, Murat A, Beckers A, Sassolas G, et al. Pituitary disease in MEN type 1: data from the France-Belgium MEN1 multicenter study. J Clin Endocrinol Metab. 2002;87:457-65.

[70] **Chasseloup** F, Pankratz N, Lane J, Faucz FR, Keil MF, Chittiboina P, et al. Germline CDKN1B loss-of-function variants cause pediatric Cushing's disease with or without an MEN4 phenotype. J Clin Endocrinol Metab. 2020;105:1983-2005.

[71] **Kiefer** FW, Winhofer Y, Iacovazzo D, Korbonits M, Wolfsberger S, Knosp E, et al. PRKAR1A mutation causing pituitary-dependent Cushing disease in a patient with Carney complex. Eur J Endocrinol. 2017;177:K7-12.

[72] **De Kock** L, Sabbaghian N, Plourde F, Srivastava A, Weber E, Bouron-Dal Soglio D, et al. Pituitary blastoma: a pathognomonic feature of germ-line DICER1 mutations. Acta Neuropathol. 2014;128:111-22.

[73] **Roussel-Gervais** A, Couture C, Langlais D, Takayasu S, Balsalobre A, Rueda BR, et al. The CABLES1 gene in glucocorticoid regulation of pituitary corticotrope growth and Cushing disease. J Clin Endocrinol Metab. 2016;101:513-22.

[74] **Bogusławska** A, Korbonits M. Genetics of acromegaly and gigantism. J Clin Med. 2021;10(7):1377. doi:10.3390/jcm10071377.

[75] **Cardoso** LM, Marques P, Pereira MT, Agapito A, Almeida R, Amaral S, et al, The Pituitary Study Group of the Portuguese Society of Endocrinology, Diabetes and Metabolism; Diagnosis and Management of Acromegaly: A Consensus Statement of the Pituitary Study Group of the Portuguese Society of Endocrinology, Diabetes and Metabolism. *Endocrinol Insights* 14 April 2025; 20 (1): 29–58. https://doi.org/10.1159/000541671

[76] **Brue** T, Rahabi H, Barry A, Barlier A, Bertherat J, Borson-Chazot F, et al. Position statement on the diagnosis and management of acromegaly: the French National Diagnosis and Treatment Protocol. Ann Endocrinol (Paris). 2023;84(6):697-710. doi:10.1016/j.ando.2023.08.003.

[77] **Beckers** A, Aaltonen LA, Daly AF, Karhu A. Familial isolated pituitary adenomas and pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein gene. Endocr Rev. 2013;34(2):239-77. doi:10.1210/er.2012-1013.

[78] **Trivellin** G, Daly AF, Faucz FR, Yuan B, Rostomyan L, Larco DO, et al. Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. N Engl J Med. 2014;371(25):2363-74. doi:10.1056/NEJMoa1408028.

[79] **Beckers** A, Lodish MB, Trivellin G, Rostomyan L, Lee M, Faucz FR, et al. X-linked acrogigantism syndrome: clinical profile and therapeutic responses. Endocr Relat Cancer. 2015;22(3):353-67. doi:10.1530/ERC-15-0038.

[80] **Thakker** RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al.; Endocrine Society. Clinical practice guidelines for multiple endocrine neoplasia type 1. J Clin Endocrinol Metab. 2012;97(9):2990-3011. doi:10.1210/jc.2012-1230.

[81] **Goudet** P, Cadiot G, Barlier A, Baudin E, Borson-Chazot F, Brunaud L, et al. French guidelines from the GTE, AFCE and ENDOCAN-RENATEN for the screening, diagnosis and management of multiple endocrine neoplasia type 1. Ann Endocrinol (Paris). 2024;85(1):2-19. doi:10.1016/j.ando.2023.09.003.

[82] **Del Rivero** J, Gangi A, Annes JP, Jasim S, Keller J, Lundholm MD, et al. American Association of Clinical Endocrinology consensus statement on management of multiple endocrine neoplasia type 1. Endocr Pract. 2025;31(4):403-18. doi:10.1016/j.eprac.2025.02.001.

[83] **Hannah-Shmouni** F, Stratakis CA. Growth hormone excess in neurofibromatosis. Genet Med. 2019;21:1254-5.

[84] **Romanet** P, Coppin L, Molin A, Santucci N, Le Bras M, Odou MF, et al. Role of genetics in primary hyperparathyroidism. Primary Hyperparathyroidism Consensus 2024. French Society of Endocrinology; 2024.

[85] **Chevalier** B, Coppin L, Romanet P, Cuny T, Maiza JC, Abeillon J, et al. Beyond MEN1, when to think about MEN4? Retrospective study on 5600 patients in the French population and literature review. J Clin Endocrinol Metab. 2024;109(7):e1482-93. doi:10.1210/clinem/dgae055.

[86] **Thakker** RV. Genetics of parathyroid tumors. J Intern Med. 2016;280(6):574-83. doi:10.1111/joim.12523.

[87] **Höppner**, J.; Sinningen, K.; Raimann, A.; Obermayer-Pietsch, B.; Grasemann, C. Disorders of the Calcium Sensing Signaling Pathway: From Familial Hypocalciuric Hypercalcemia (FHH) to Life Threatening Conditions in Infancy. *J. Clin. Med.* 2022, *11*, 2595. https://doi.org/10.3390/jcm11092595