

Early-onset Familial Hypoaldosteronism (Aldosterone Synthase Deficiency / CYP11B2 Deficiency)

Comprehensive Disease Characterization Report

Summary

Early-onset Familial Hypoaldosteronism is isolated aldosterone synthase deficiency (ASD), also known as corticosterone methyloxidase (CMO) deficiency types I and II. It is an autosomal recessive inborn error of steroidogenesis caused by biallelic loss-of-function variants in **CYP11B2**, the gene encoding the mitochondrial cytochrome P450 enzyme **aldosterone synthase**. CYP11B2 catalyzes the terminal three steps of aldosterone biosynthesis (11 β -hydroxylation $\rightarrow$ 18-hydroxylation $\rightarrow$ 18-oxidation) in the adrenal **zona glomerulosa**. When the enzyme fails, aldosterone cannot be synthesized while cortisol and sex-steroid synthesis remain fully intact, producing an **isolated mineralocorticoid deficiency**.

Affected neonates and infants present in the first weeks to months of life with a renal **salt-wasting** phenotype: hyponatremia, hyperkalemia, metabolic acidosis, dehydration, recurrent vomiting, feeding difficulty, and failure to thrive. The biochemical hallmark is **high plasma renin activity** with **low (CMO I) or inappropriately normal (CMO II) aldosterone** and **normal cortisol**. The absence of skin hyperpigmentation and the normal cortisol distinguish ASD from both aldosterone-resistance disorders (pseudohypoaldosteronism type 1, PHA1) and from salt-wasting congenital adrenal hyperplasia (CAH). CMO II is further distinguished by a **pathognomonic elevation of the 18-hydroxycorticosterone/aldosterone ratio**.

The disorder is eminently treatable: mineralocorticoid replacement with **fludrocortisone** (with sodium chloride supplementation in infancy) rapidly corrects electrolytes and produces catch-up growth, usually within ~2 months. Prognosis is excellent when recognized early, whereas untreated salt-wasting crises can be lethal in infancy. Remarkably, the clinical phenotype ameliorates with age (increasing dietary salt intake and maturing renal mineralocorticoid sensitivity), so fludrocortisone can frequently be **discontinued by mid-**

childhood even though the enzymatic defect persists biochemically for life. The disease is ultra-rare globally but enriched in consanguineous and founder populations — most notably **~1 in 4,000 births among Jews of Iranian origin**, who carry the founder CYP11B2 haplotype p.R181W + p.V386A.

Disease Identity and Key Identifiers

Early-onset Familial Hypoaldosteronism (MONDO:0035320) is synonymous with **aldosterone synthase deficiency (ASD) / corticosterone methyloxidase deficiency**. Two biochemically defined forms exist:

Form	OMIM	Biochemistry	Enzymatic lesion
CMO I (type 1)	203400	No detectable aldosterone; low/normal 18-OHB	Loss of both 18-hydroxylase and 18-oxidase activity
CMO II (type 2)	610600	Low-normal aldosterone; markedly elevated 18-OHB; high 18-OHB/aldosterone ratio	18-hydroxylase retained, 18-oxidase lost

Common synonyms / alternative names: aldosterone synthase deficiency; corticosterone methyloxidase deficiency types I and II (CMO I/II); corticosterone 18-methyloxidase deficiency; isolated hypoaldosteronism; congenital hypoaldosteronism; familial hypoaldosteronism.

- **Gene:** CYP11B2 (cytochrome P450 family 11 subfamily B member 2), chromosome **8q24.3**
- **Protein:** Aldosterone synthase (UniProt **P19099**)
- **Inheritance:** Autosomal recessive
- **Category:** Mendelian inborn error of steroidogenesis

The disease knowledge here is derived predominantly from **aggregated disease-level resources** (OMIM, Orphanet) and from the primary clinical/genetic literature — single consanguineous kindreds, founder-population cohorts, and a handful of multicenter case series — rather than from large EHR-scale individual-patient datasets.

Key Findings

Finding 1 — CYP11B2 loss of function causes isolated aldosterone deficiency

Biallelic inactivating mutations in CYP11B2 (chr8q24.3, encoding the mitochondrial cytochrome P450 aldosterone synthase) cause an **isolated** defect in aldosterone biosynthesis. The two clinical forms, CMO I (OMIM 203400) and CMO II (OMIM 610600), are distinguished by residual terminal enzyme activity. A critical quantitative principle is that **enzymatic activity must generally fall below ~1% of normal** before aldosterone biosynthesis is measurably impaired, reflecting substantial functional reserve in the pathway. Documented pathogenic variants include p.Gly452Arg, p.Thr185Ile, the compound R173K+E198D+V386A allele, and in-frame deletion of Arg173.

"Pathogenic variants in CYP11B2 result in corticosterone methyloxidase type I deficiency (CMO I), an orphan condition with a potentially lethal electrolyte imbalance in infancy." — PMID: 41229259

"Many mutations have been documented in each of these genes; in general enzymatic activity must be reduced to <1% of normal for aldosterone biosynthesis to be impaired." — PMID: 15134805

"The first, corticosterone methyloxidase type I (CMO I or type 1 deficiency), is characterized by no detectable aldosterone secretion, a low or normal secretion of the steroid 18OHB" — PMID: 9814506

Finding 2 — Clinical presentation: neonatal/infantile salt wasting with a high-renin, low-aldosterone profile

Patients present in the neonatal period or early infancy with failure to thrive, feeding problems, recurrent vomiting and dehydration, severe **hyponatremia**, **hyperkalemia**, and **metabolic acidosis**. The laboratory hallmark is markedly **elevated plasma renin activity** with **low (CMO I)** or **inappropriately normal (CMO II)** plasma aldosterone. Because cortisol synthesis is unaffected, this is an isolated mineralocorticoid defect. The pathognomonic biochemical signature of CMO II is an elevated **18-hydroxycorticosterone/aldosterone ratio**.

"We studied an infant with failure to thrive and persistent hyponatremia despite oral sodium supplementation. Initial analyses revealed highly elevated plasma renin but normal values of plasma aldosterone." — PMID: 22931312

"diagnosed initially in the neonatal period because of severe hyponatremia, hyperkalemia, metabolic acidosis, and failure to thrive" — PMID: 41229259

"presented with failure to thrive and feeding problems at age 6 weeks. Important laboratory findings were low plasma sodium and elevated potassium and renin." — PMID: 9838244

Finding 3 — Diagnosis by steroid profiling and CYP11B2 sequencing; treatment with fludrocortisone is highly effective and often discontinuable

Biochemical diagnosis rests on **multisteroid analysis** demonstrating the pathognomonic elevation of the 18-hydroxycorticosterone/aldosterone ratio (CMO II) together with elevated precursors (11-deoxycorticosterone [DOC], corticosterone, 18-OHDOC). Molecular confirmation is by CYP11B2 sequencing. **Mineralocorticoid replacement with fludrocortisone** ($\pm$ sodium chloride supplementation in infancy) corrects the electrolyte disturbance and produces **catch-up growth**. Because distal-tubular aldosterone responsiveness matures with age and dietary salt intake rises, **treatment can frequently be discontinued** in later childhood without deterioration — in one documented case, stopped at age 9 years without relapse.

"revealing a pathognomonic pattern with a highly elevated ratio of 18-OH-corticosterone to aldosterone" — PMID: 22931312

"Treatment with fludrocortisone resulted in catch-up growth. Discontinuation of treatment at the age of 9 years was later possible without any clinical or biochemical deterioration." — PMID: 22931312

"secrete increased amounts of the steroid precursors DOC, corticosterone, and 18OHDOC, and are subject to salt wasting and poor growth" — PMID: 9814506

Finding 4 — Pathophysiology and differential diagnosis

The isolated nature of the defect (normal cortisol, no hyperpigmentation) is the central clinical discriminator from aldosterone-resistance disorders and from CAH. ASD must be separated from **pseudohypoaldosteronism type 1 (PHA1)** — a *resistance* disorder in which aldosterone is HIGH — and from **21-hydroxylase deficiency CAH** (low cortisol, ambiguous genitalia, hyperpigmentation).

"Aldosterone synthase deficiency (ASD), which is caused by a genetic defect in CYP11B2, involves a deficiency in aldosterone alone." — [PMID: 41905953](#)

"ASD must also be differentiated from another disease, pseudohypoaldosteronism type 1 (PHA1), which involves resistance to aldosterone. PHA1a is caused by a heterozygous defect in NR3C2, which encodes the mineralocorticoid receptor. PHA1b is an autosomal recessive disorder caused by defects in the 3 epithelial sodium channel subunits" — [PMID: 41905953](#)

"Aldosterone is synthesized in the adrenal zona glomerulosa via the action of the mitochondrial cytochrome P450 enzyme aldosterone synthase (CYP11B2) through sequential enzyme reactions." — [PMID: 41229259](#)

Finding 5 — Epidemiology and founder mutations (Jews of Iranian origin, ~1/4,000)

CMO II deficiency is relatively frequent among **Jews of Iranian origin**, with an estimated incidence of **1 in 4,000 births**. Affected individuals are homozygous for **two** CYP11B2 missense variants, **p.R181W** and **p.V386A**, inherited together on a founder haplotype. Functional expression showed that R181W reduces 18-hydroxylase and abolishes 18-oxidase activity while leaving 11 β -hydroxylase intact, whereas V386A causes a small reduction in 18-hydroxycorticosterone production. Critically, individuals homozygous for **R181W alone (n=8)** or **V386A alone (n=3)** were asymptomatic, demonstrating that the two variants act **additively** to produce disease. Globally the disorder is ultra-rare; most other reports are single consanguineous kindreds, consistent with autosomal recessive inheritance.

"CMO-II deficiency is frequent among Jews from Iran (1 in 4000 births)" — [PMID: 8481357](#)

"two candidate mutations, R181W and V386A, were found in the CYP11B2 genes" — [PMID: 1594605](#)

"R181W reduced 18-hydroxylase and abolished 18-oxidase activities but left 11 beta-hydroxylase activity intact, whereas V386A caused a small but consistent reduction in the production of 18-hydroxycorticosterone" — PMID: 1594605

"All individuals affected with CMO-II deficiency were homozygous for both mutations, whereas eight asymptomatic subjects were homozygous for R181W alone and three were homozygous for V386A alone" — PMID: 1594605

Finding 6 — Enzyme biochemistry: a three-step mitochondrial P450 reaction

Aldosterone synthase (CYP11B2, UniProt P19099) is a mitochondrial cytochrome P450 that converts **11-deoxycorticosterone to aldosterone** via three sequential reactions: **11 β -hydroxylation** ($\rightarrow$ corticosterone), **18-hydroxylation** ($\rightarrow$ 18-hydroxycorticosterone), and **18-oxidation** ($\rightarrow$ aldosterone). The enzyme coordinates its substrate at a catalytic **heme** moiety in the substrate-binding pocket (demonstrated structurally with the inhibitor dexfandrostat). Disease variants are characterized functionally in heterologous expression systems (cultured mammalian cells; fission yeast *Schizosaccharomyces pombe*) by measuring residual 11 β -/18-hydroxylase and 18-oxidase activity. CMO I variants abolish all terminal activity (no aldosterone, low 18-OHB), whereas CMO II variants retain 18-hydroxylase but lose 18-oxidase (normal/low aldosterone, high 18-OHB).

"The aldosterone synthase, CYP11B2, catalyses the conversion of 11-deoxycorticosterone to aldosterone, a process that requires three steps: a hydroxylation at position 11 β to form corticosterone, another one at position 18 to produce 18-hydroxycorticosterone, and, finally, an oxidation at position 18 to form aldosterone." — PMID: 21237269

"precisely coordinates with the catalytic heme moiety in the space of the CYP11B2 substrate binding pocket forming a tight and stable complex" — PMID: 37827219

*"the heterologous expression of the mutants of CYP11B2 in fission yeast (*Schizosaccharomyces pombe*) followed by steroid bioconversion assays for the enzymatic characterisation of the investigated mutants" — PMID: 21237269*

Relevant CHEBI entities: aldosterone (CHEBI:27584), corticosterone (CHEBI:16827), 11-deoxycorticosterone (CHEBI:16973), 18-hydroxycorticosterone, potassium(1+) (CHEBI:29103), sodium(1+) (CHEBI:29101).

Finding 7 — Natural history and prognosis (multicenter cohort data)

A multicenter cohort of **16 patients from 12 families (8 female)** quantified the natural history: median age at presentation **3.1 months** (range 0.4–8.1), with poor weight gain the most common presenting symptom (**56.3%**). Median age at starting fludrocortisone was **3.6 months**, and catch-up growth was achieved a median of **2 months** after treatment began. Fludrocortisone was successfully **discontinued in 5/16 patients at a median age of 6.0 years** (range 2.2–7.6). Importantly, reduced aldosterone synthase activity **persisted biochemically** even after discontinuation, confirming that clinical remission reflects compensatory maturation (increasing dietary salt, maturing renal mineralocorticoid sensitivity) rather than resolution of the enzyme defect.

"Catch-up growth was achieved at median 2 months (range: 0.5 to 14.5) after treatment. Fludrocortisone could be stopped in 5 patients at a median age of 6.0 years (range: 2.2 to 7.6)." — PMID: 34415991

"Sixteen patients from 12 families were included (8 females; median age at presentation: 3.1 months, range: 0.4 to 8.1). The most common symptom was poor weight gain (56.3%)." — PMID: 34415991

"Plasma steroid profiles revealed reduced aldosterone synthase activity both at diagnosis and after discontinuation of treatment compared to age-matched controls." — PMID: 34415991

Finding 8 — Variant spectrum and the CYP11B1 homology pitfall

Pathogenic CYP11B2 variants span **all molecular classes** and are enriched in consanguineous populations: missense (p.T185I — most common at **40%** in a Turkish cohort; also p.Y195H, p.F130L, p.G452W, p.G288S, p.G452R, p.R181W, p.V386A, p.E198D), nonsense (p.Q338stop), frameshift (p.Ser344Profs9), splice-site (c.1200+1G>A, c.1122-18G>A), and in-frame deletions (p.E198del, p.I339_E343del, p.K175del, deletion of Arg173). Novel variants continue to be reported in Palestinian, Turkish, Arab, Chinese, Indian, and Polish patients from consanguineous or founder backgrounds. Variants are germline, biallelic (homozygous or compound heterozygous), and loss-of-function, classified pathogenic/likely pathogenic under ACMG criteria with functional/structural support. A key diagnostic caveat: CYP11B2 shares ~95% sequence identity with the neighboring CYP11B1 gene*, creating sequencing pitfalls and risk of chimeric/unequal-crossover alleles.

"We identified 6 novel (p.Y195H, c.1200 + 1G > A, p.F130L, p.E198del, c.1122-18G > A, p.I339_E343del) and 4 previously described CYP11B2 variants. The most common variant (40%) was p.T185I." — PMID: 34415991

"revealed three homozygous pathogenic variants: p.Ser344Profs9, p.G452W in two patients from an extended family, and p.Q338stop"* — PMID: 33438832

"describe potential pitfalls in CYP11B2 sequencing due to its homology to CYP11B1" — PMID: 39700478

Finding 9 — Formal diagnostic criteria separate ASD from PHA1 and CAH

A consensus diagnostic framework (Japanese Intractable Adrenal Disorders Research) defines ASD by: **(clinical)** salt-wasting symptoms — poor feeding, vomiting, dehydration, poor weight gain — **AND absence of skin pigmentation**; plus **(laboratory)** low serum sodium with high serum potassium; low-to-normal plasma aldosterone with high plasma renin activity/active renin concentration; and **no low blood cortisol**. Diagnoses of exclusion include PHA1 and 21-hydroxylase deficiency. This operationalizes the key discriminators: aldosterone is LOW/normal in ASD (deficiency) vs HIGH in PHA1 (resistance); cortisol is normal in ASD vs low in salt-wasting CAH; and there is no hyperpigmentation.

"1) Presents with salt-wasting symptoms (poor feeding, vomiting, dehydration, poor weight gain). 2) No skin pigmentation." — PMID: 41905953

"2) Low to normal plasma aldosterone and high plasma renin activity or high plasma active renin concentration. 3) No low blood cortisol level." — PMID: 41905953

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

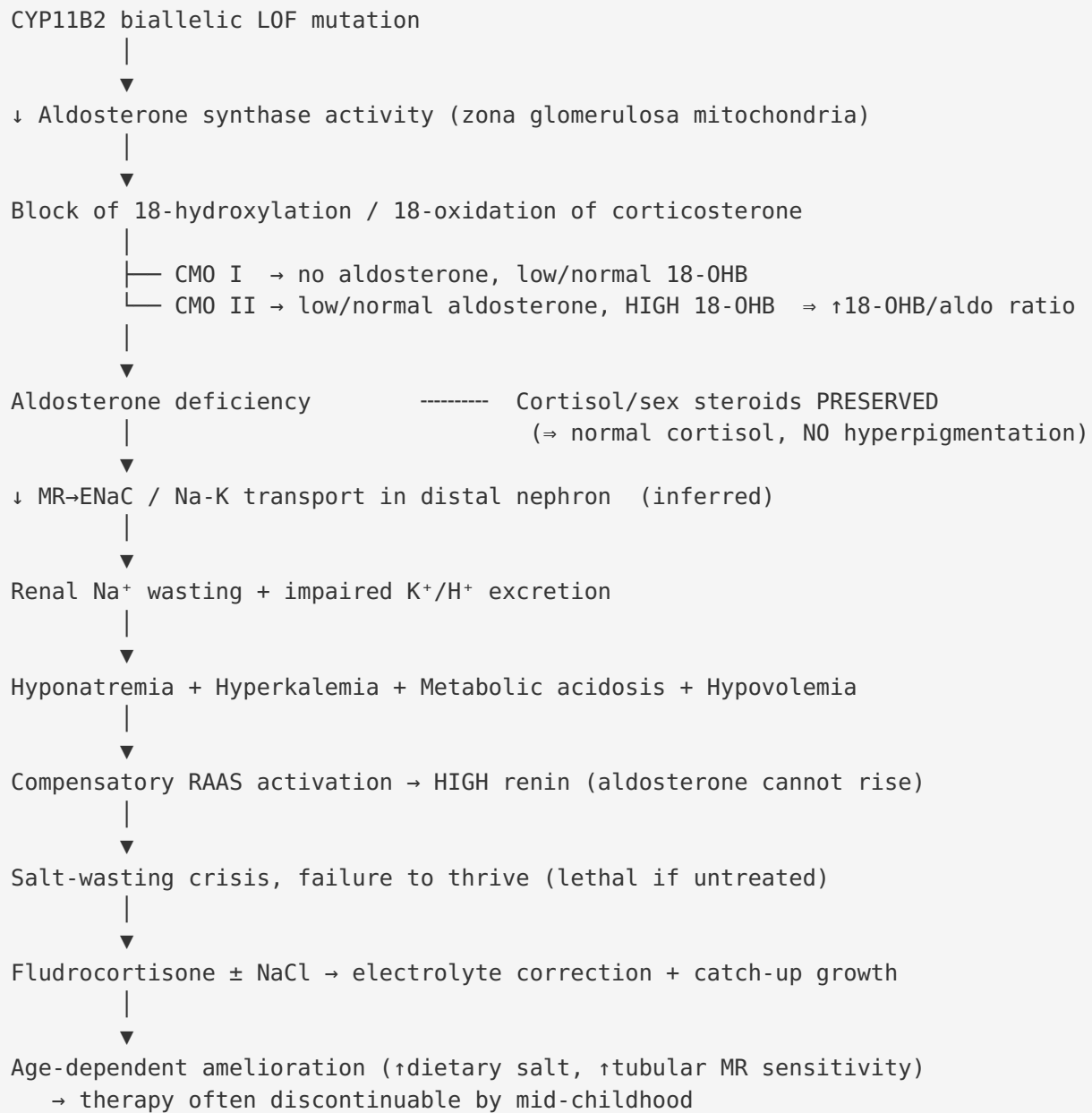
1. A **biallelic loss-of-function CYP11B2 mutation** (germline, homozygous or compound heterozygous) **leads to** deficient or absent aldosterone synthase protein/activity in the adrenal zona glomerulosa.

2. Deficient aldosterone synthase activity **results in** failure of the terminal reactions of aldosterone biosynthesis — specifically 18-hydroxylation and/or 18-oxidation of corticosterone.
3. This **leads to** profound aldosterone deficiency (CMO I: no aldosterone; CMO II: low/inappropriately normal aldosterone with accumulated 18-hydroxycorticosterone — hence the diagnostic high 18-OHB/aldosterone ratio).
4. Loss of circulating aldosterone **results in** loss of mineralocorticoid-receptor–driven ENaC and Na^+/K^+ transport in the aldosterone-sensitive distal nephron (*inferred from the known physiology of MR/ENaC signaling*).
5. Impaired distal sodium reabsorption and potassium/ H^+ secretion **lead to** renal sodium wasting with impaired potassium and acid excretion.
6. This **results in** hyponatremia, hyperkalemia, metabolic acidosis, and hypovolemia.
7. Hypovolemia and hyponatremia **lead to** compensatory activation of the renin–angiotensin system (**hyperreninemia**), which cannot be translated into aldosterone because the enzymatic block is downstream.
8. The net effect **results in** a neonatal/infantile salt-wasting crisis with dehydration, vomiting, and failure to thrive — potentially lethal if untreated.

Branch point (preserved pathway): Because the lesion is specific to the terminal zona-glomerulosa enzyme, **cortisol and sex-steroid synthesis are unaffected**. This branch explains the two defining clinical negatives — **normal cortisol** and **no hyperpigmentation** — which separate ASD from salt-wasting CAH and from primary adrenal insufficiency.

Age-dependent amelioration branch: Over time, **increasing dietary salt intake** and **maturing renal tubular mineralocorticoid sensitivity** compensate for the persistent enzyme deficit, allowing clinical (but not biochemical) remission and discontinuation of therapy by mid-childhood.

Compact pathway diagram



Ontology term suggestions

Domain	Term(s)
Disease (MONDO)	MONDO:0035320 (Early-onset Familial Hypoaldosteronism)
Gene (HGNC)	CYP11B2
Phenotype (HPO)	Hyponatremia (HP:0002902); Hyperkalemia (HP:0002153); Metabolic acidosis (HP:0001942); Failure to thrive (HP:0001508); Dehydration (HP:0001944); Vomiting (HP:0002013); Hypoaldosteronism (HP:0011046); Increased circulating renin level (HP:0000848); Salt craving (HP:0003108)
Biological process (GO)	Aldosterone biosynthetic process (GO:0032342); steroid biosynthetic process (GO:0006694); sodium ion transport (GO:0006814); potassium ion homeostasis (GO:0055075)
Cellular component (GO)	Mitochondrion (GO:0005739); mitochondrial inner membrane (GO:0005743)
Cell type (CL)	Adrenal cortex zona glomerulosa cell; (kidney) principal cell of the collecting duct
Anatomy (UBERON)	Adrenal gland / adrenal cortex (UBERON:0001235); zona glomerulosa (UBERON:0001228); kidney (UBERON:0002113); distal convoluted tubule / collecting duct
Chemical (CHEBI)	Aldosterone (CHEBI:27584); corticosterone (CHEBI:16827); 11-deoxycorticosterone (CHEBI:16973); sodium(1+) (CHEBI:29101); potassium(1+) (CHEBI:29103)
Treatment (NCIT)	Fludrocortisone; sodium chloride supplementation

Section-by-Section Characterization

1. Disease Information

Isolated aldosterone synthase deficiency (CMO I/II), an autosomal recessive inborn error of adrenal steroidogenesis. Identifiers: MONDO:0035320; OMIM 203400 (CMO I) and 610600 (CMO II); gene CYP11B2 (8q24.3); protein UniProt P19099. Synonyms as listed above. Information derived from aggregated disease-level resources and primary clinical literature.

2. Etiology

Causal factor: purely genetic — biallelic loss-of-function CYP11B2 variants. **Genetic risk factors:** founder/consanguineous backgrounds dramatically raise risk (e.g., Iranian-Jewish R181W+V386A haplotype). No established environmental causes; the disease is monogenic. **Protective/modifier factors:** none proven genetically, but *dietary salt intake* and *maturation of renal mineralocorticoid sensitivity* act as powerful acquired modifiers of clinical severity with age. **Gene–environment interaction:** the principal interaction is between the fixed enzymatic deficit and dietary sodium availability — high salt intake offsets renal sodium wasting and underlies age-dependent remission.

3. Phenotypes

Phenotype	Type	HPO	Onset	Frequency / notes
Hyponatremia	Lab abnormality	HP:0002902	Neonatal/infantile	Core feature
Hyperkalemia	Lab abnormality	HP:0002153	Neonatal/infantile	Core feature
Metabolic acidosis	Lab abnormality	HP:0001942	Neonatal/infantile	Common
Failure to thrive / poor weight gain	Clinical sign	HP:0001508	Infantile	56.3% most common presenting symptom (P 34415991)
Recurrent vomiting	Symptom	HP:0002013	Infantile	Common
Dehydration	Clinical sign	HP:0001944	Infantile	Common, can be severe
Elevated plasma renin	Lab abnormality	HP:0000848	Neonatal/infantile	Diagnostic hallmark
Low/inappropriately normal aldosterone	Lab abnormality	HP:0011046	Neonatal/infantile	Core; defines deficiency

Severity: severe in infancy (potentially lethal salt-wasting crises), self-ameliorating with age.

Progression: episodic crises early; overall course improves (clinical remission by mid-childhood).

Quality of life: major in untreated infancy; excellent with timely treatment and after age-related remission.

4. Genetic / Molecular Information

Causal gene: CYP11B2 (8q24.3). **Variant classes:** missense, nonsense, frameshift, splice-site, and in-frame deletions — all germline, biallelic, loss-of-function (see Finding 8). **Allele frequencies:** pathogenic alleles are rare globally but locally common on founder haplotypes (e.g., R181W+V386A in Iranian Jews). **Functional consequence:** loss of function (reduced/absent 18-hydroxylase and/or 18-oxidase activity). **Diagnostic caveat:** ~95% homology with CYP11B1 risks mis-mapping and chimeric alleles. No epigenetic or large chromosomal mechanisms are established for this disorder.

5. Environmental Information

No toxic, infectious, or occupational cause. The one environmentally modifiable factor is **dietary sodium**: low intake unmasks/worsens salt wasting; higher intake (and salt supplementation) mitigates it.

6. Mechanism / Pathophysiology

See the ordered causal chain and diagram above. Upstream: CYP11B2 LOF → zona glomerulosa mitochondrial enzyme failure. Downstream: aldosterone deficiency → distal-nephron sodium wasting → electrolyte derangement → RAAS activation. Preserved branch: intact cortisol/androgen synthesis.

7. Anatomical Structures Affected

- **Primary organ**: adrenal gland, specifically the **adrenal cortex zona glomerulosa** (UBERON:0001228), site of the enzymatic defect.
- **Secondary (functionally affected) organ: kidney** — aldosterone-sensitive distal nephron (distal convoluted tubule, connecting tubule, collecting duct principal cells), where mineralocorticoid action is lost.
- **Body system**: endocrine (adrenal steroidogenesis) and renal/electrolyte-regulatory.
- **Subcellular compartment: mitochondrion** (GO:0005739) — aldosterone synthase is a mitochondrial inner-membrane P450.
- **Lateralization**: bilateral (systemic hormonal deficiency).

8. Temporal Development

Onset: neonatal to early infancy (median presentation ~3.1 months; range 0.4–8.1). **Pattern**: acute salt-wasting crises on a chronic genetic background. **Course**: severe early, then progressive clinical amelioration with age. **Remission**: treatment can be discontinued in a substantial fraction (5/16; median 6.0 years) — a treatment-withdrawable clinical remission despite persistent biochemical deficit. **Critical period**: infancy is the window of vulnerability (crisis risk) and of therapeutic opportunity.

9. Inheritance and Population

Inheritance: autosomal recessive. **Penetrance:** essentially complete for biallelic LOF genotypes, though expressivity varies (CMO I vs II; allele-dependent). **Epidemiology:** ultra-rare globally; ~1/4,000 births among Jews of Iranian origin (founder effect). **Founder effect:** R181W+V386A compound haplotype. **Consanguinity:** major driver — most non-founder cases arise in consanguineous Palestinian, Turkish, Arab, Chinese, Indian kindreds. **Sex ratio:** no strong sex bias (cohort 8/16 female). **Carrier frequency:** elevated in founder/consanguineous populations; heterozygotes are asymptomatic.

10. Diagnostics

Laboratory: serum electrolytes ($\downarrow$ Na⁺, $\uparrow$ K⁺, acidosis); **plasma renin activity (high); plasma aldosterone (low/inappropriately normal); multisteroid profiling** showing elevated DOC, corticosterone, 18-OHDOC, and the **pathognomonic high 18-OHB/aldosterone ratio** (CMO II); **normal cortisol**. **Genetic testing:** CYP11B2 single-gene sequencing or targeted adrenal/steroidogenesis gene panels; WES/WGS for atypical cases — with careful handling of CYP11B1 homology. **Clinical criteria:** salt-wasting symptoms + no skin pigmentation + the laboratory profile above (Finding 9). **Differential diagnosis:** PHA1 (high aldosterone, resistance), salt-wasting CAH / 21-hydroxylase deficiency (low cortisol, virilization, hyperpigmentation), secondary PHA (renal/urologic disease, UTI/reflux). **Screening:** cascade/carrier testing in affected families and founder populations.

11. Outcome / Prognosis

Excellent with early recognition and mineralocorticoid replacement: normal growth and development, catch-up growth within ~2 months. **Mortality:** untreated infantile salt-wasting crises can be fatal. **Morbidity:** minimal once treated. **Prognostic factors:** timeliness of diagnosis and treatment; CMO subtype. Long-term, many patients achieve treatment-free clinical remission while retaining a subclinical enzyme defect.

12. Treatment

Mainstay: fludrocortisone (synthetic mineralocorticoid; NCIT: Fludrocortisone), $\pm$ **sodium chloride supplementation** in infancy. Corrects electrolytes, restores volume, enables catch-up growth. **Pharmacogenomics / advanced/gene/cell/RNA therapies:** none established or required — the disorder is managed effectively by hormone replacement. **Treatment strategy:** initiate in infancy, titrate to electrolytes/renin/growth, and attempt **supervised**

discontinuation in mid-childhood once salt tolerance and renal sensitivity mature. **Adverse events:** standard mineralocorticoid excess risks (hypertension, hypokalemia) if overdosed — monitored by electrolytes and blood pressure.

13. Prevention

No primary prevention (monogenic). **Secondary prevention:** early detection and prompt fludrocortisone prevent crises and failure to thrive. **Genetic counseling / screening:** autosomal recessive counseling, carrier and cascade testing in founder/consanguineous families; prenatal/preimplantation options where a familial variant is known. **Tertiary prevention:** electrolyte monitoring and salt management to prevent recurrent crises.

14. Other Species / Natural Disease

Human disease (NCBI Taxon 9606). Murine models of aldosterone synthase deficiency (**aldosterone synthase-deficient mice**) are used experimentally to study renal potassium/sodium handling (e.g., tissue-kallikrein and NCC studies). Orthologous gene: mouse *Cyp11b2*. No prominent naturally occurring companion-animal counterpart is established in the reviewed literature.

15. Model Organisms

Mouse is the principal model: aldosterone synthase (*Cyp11b2*)-deficient mice recapitulate aldosterone-independent physiology and have been used to dissect distal-nephron potassium handling and renal adaptation (e.g.,

P 20624970

used aldosterone synthase-deficient mice to show aldosterone-independent control of tissue kallikrein). **In vitro:** heterologous expression in cultured mammalian cells and **fission yeast** (*S. pombe*) enables steroid-bioconversion assays to functionally classify CYP11B2 variants (

P 21237269

Applications: variant functional characterization, steroidogenesis pathway dissection, renal electrolyte physiology. **Limitations:** rodent adrenal zonation and steroid profiles differ from humans; in vitro systems isolate enzymatic activity but not whole-organism salt handling.

Evidence Base

PMID	Title (abbrev.)	Supports
15134805	<i>Aldosterone synthase deficiency and related disorders</i>	<1% residual activity threshold; overview
9814506	<i>Isolated ASD caused by E198D and V386A</i>	CMO I vs II biochemistry; elevated precursors
41229259	<i>ASD with coexisting celiac disease</i>	Orphan, lethal infantile electrolyte imbalance; zona glomerulosa mitochondrial synthesis
22931312	<i>Homozygous CYP11B2 in infant with CMO II</i>	High renin/normal aldosterone; 18-OHB/aldo ratio; fludrocortisone + discontinuation at 9y
9838244	<i>Homozygous deletion of Arg-173, CMO II</i>	Infantile onset; hyponatremia, hyperkalemia, high renin
41905953	<i>Congenital aldosterone deficiency and its resistance</i>	Isolated deficiency; PHA1 differential; formal diagnostic criteria
8481357	<i>11β-hydroxylase/CMO-II in Jews of Morocco/Iran</i>	1/4,000 incidence in Iranian Jews
1594605	<i>CYP11B2 mutations causing CMO II</i>	R181W + V386A founder variants; additive two-variant requirement; functional data
21237269	<i>S. pombe system for CMO-causing mutations</i>	Three-step enzymatic mechanism; yeast functional assay
37827219	<i>CYP11B2 inhibition by dexfadostat</i>	Heme/substrate-pocket active-site structure
34415991	<i>Catch-up growth and discontinuation of fludrocortisone in ASD</i>	Cohort demographics; catch-up growth; discontinuation; persistent biochemical defect; variant spectrum
33438832	<i>CYP11B2 deficiency in Palestinian infants</i>	Frameshift/missense/nonsense variants; consanguinity; genetic heterogeneity
39700478	<i>Cracking the code of ASD: genetics and biochemistry</i>	CYP11B1 homology sequencing pitfall

Supporting/contextual literature also reviewed:

P 32539318

(CMO II novel mutations), 41426917 (ASD type I novel variant, neonate), 37332400 (CMO1 case reports), 35848593 (novel CYP11B2 variant), 15179565 and 22764468 (differential diagnosis: selective hypoaldosteronism vs PHA1), 38324138 and 38027139 (chimeric CYP11B1/CYP11B2 alleles), 41709876 (rare CAH subtypes including ASD), 6507399 (Iranian-Jewish CMO II child). Several RAAS/renal-physiology and mouse-model papers (e.g., 20624970, 23447069, 20049674) provide mechanistic context for aldosterone action and model-organism applications.

Limitations and Knowledge Gaps

1. **Small evidence base.** The disorder is ultra-rare; most data come from single kindreds, founder cohorts, and one 16-patient multicenter series. There are no large-scale prevalence, incidence, or outcome datasets outside founder populations.
2. **Downstream nephron step is inferred.** The loss of MR→ENaC signaling in the distal nephron is drawn from general mineralocorticoid physiology rather than disease-specific tissue studies in ASD patients.
3. **Genotype–phenotype relationships are incompletely resolved.** The boundary between CMO I and CMO II is biochemical and allele-dependent, and some variants produce intermediate phenotypes; residual-activity thresholds are approximate.
4. **Quality-of-life and long-term outcome data are sparse.** Formal QoL instruments (EQ-5D, SF-36, PROMIS) have not been applied; long-term adult outcomes after childhood remission are under-characterized.
5. **No omics-scale molecular profiling** (transcriptomic/proteomic/metabolomic) specific to ASD adrenal tissue was identified; mechanism rests on enzymology and steroid biochemistry.
6. **Diagnostic homology pitfall** (CYP11B2/CYP11B1 ~95% identity) may cause under- or misdiagnosis in laboratories not using homology-aware methods.

Proposed Follow-up Experiments / Actions

1. **Build an international ASD registry** capturing genotype, steroid profiles (including 18-OHB/aldosterone ratio), treatment course, age at discontinuation, and long-term adult outcomes to firm up natural history and penetrance/expressivity.
 2. **Systematic functional classification** of all reported CYP11B2 variants in a standardized assay (e.g., *S. pombe* or mammalian expression) to produce a quantitative residual-activity ladder predicting CMO I vs II vs intermediate phenotypes.
 3. **Homology-aware diagnostic protocols** (long-read sequencing, MLPA/CNV analysis) to resolve CYP11B1/CYP11B2 chimeras and prevent misclassification; validate against known founder haplotypes.
 4. **Prospective QoL and growth outcome study** using standardized instruments, including after treatment discontinuation, to document remission durability and any late relapse risk.
 5. **Mechanistic confirmation of the distal-nephron step** in patient-derived or model systems (e.g., renal organoids/iPSC-derived tubular cells) to move the MR→ENaC step from inferred to demonstrated.
 6. **Carrier-screening evaluation** in founder/consanguineous populations (Iranian-Jewish, Palestinian, Turkish, Arab cohorts) to quantify carrier frequency and inform genetic counseling and prenatal/preimplantation options.
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Report compiled from 9 confirmed findings and 38 reviewed papers over 5 investigation iterations. Evidence types span human clinical case reports/series, in vitro functional expression assays, structural biology, and model-organism studies.
