Hypertension-picking the odd one out

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Monogenic hypertension – the odd one out

"…genetic forms of hypertension stem from gain- or loss-of-function mutations within the mineralocorticoid, glucocorticoid, or sympathetic pathways"

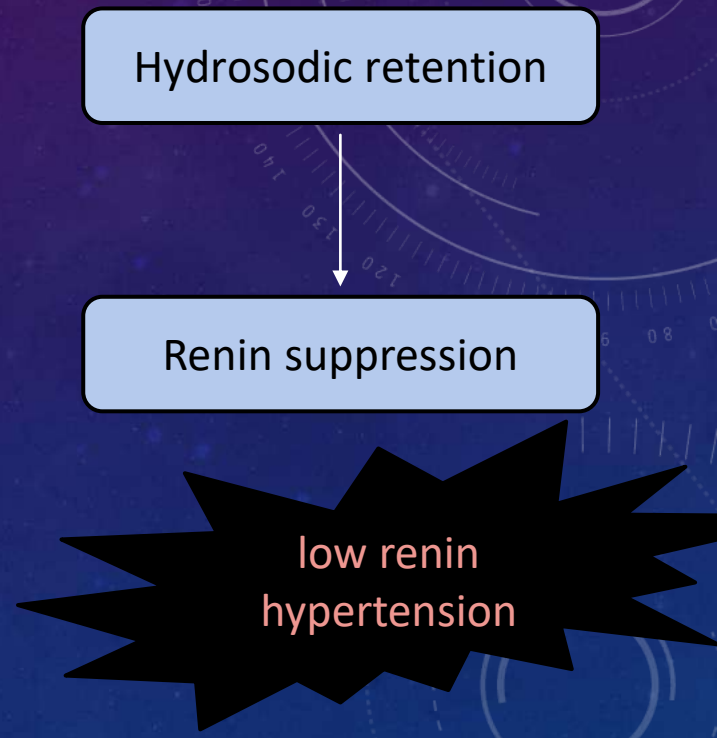
Three mechanisms of hypertension

(1) excessive sodium ion reabsorption by hyperactive channels

(2) hyperstimulation of mineralocorticoid

receptors due to alterations in steroid synthesis

(3) excess mineralocorticoid synthesis causing volume expansion

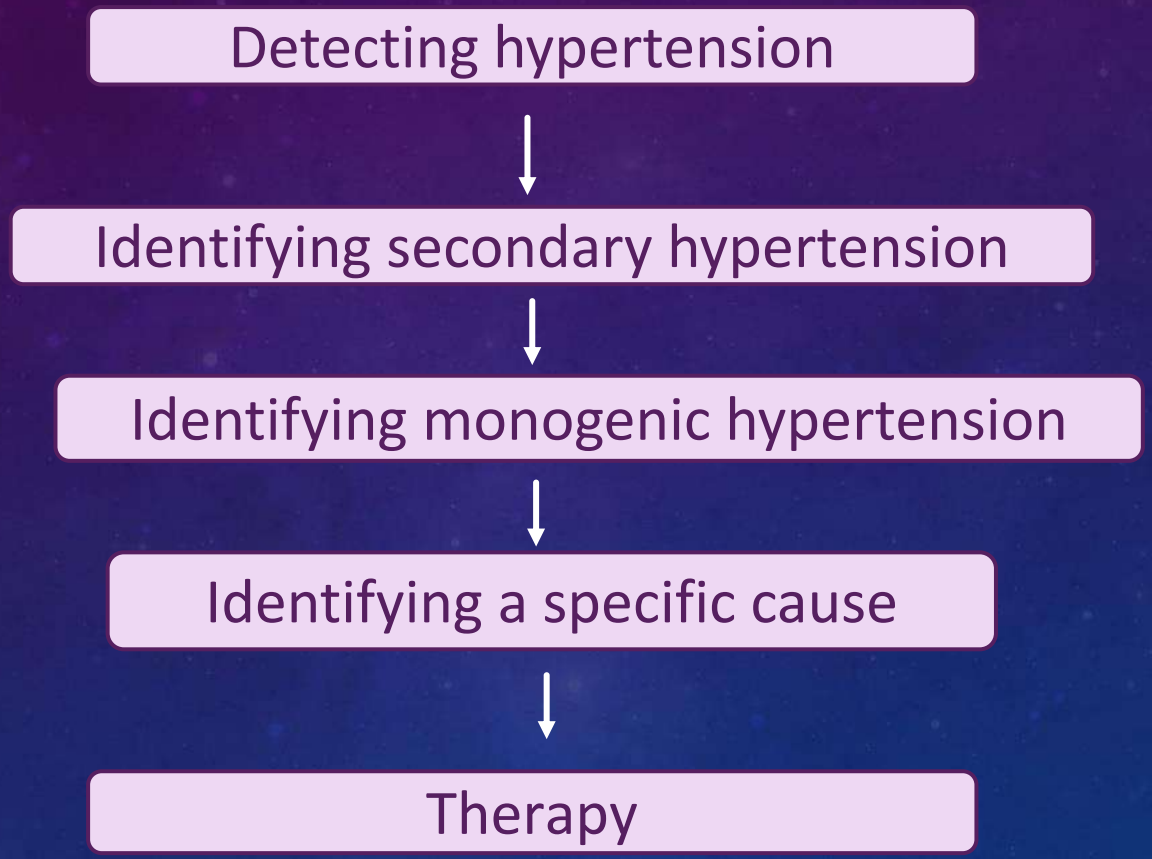


Front Pediatr. 2019 Jul 1;7:263. doi:10.3389/fped.2019.00263.

Front. Pediatr (2019) 7:263

May account for approximately
1.8% of childhood hypertension
Pediatr Nephrol. 2011 Mar;26(3):441-7

Learning objectives



Not included

- Familial phaeochromocytoma
- Hypertension-brachydactyly syndrome

Childhood hypertension: overview

TABLE 3 Updated Definitions of BP Categories and Stages

For Children Aged 1–13 y	For Children Aged ≥13 y
Normal BP: <90th percentile	Normal BP: <120/<80 mm Hg
Elevated BP: ≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	Elevated BP: 120/<80 to 129/<80 mm Hg
Stage 1 HTN: ≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mm Hg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mm Hg
Stage 2 HTN: ≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg (whichever is lower)	Stage 2 HTN: ≥140/90 mm Hg

AAP, 2017

"Symptoms and signs specifically related to hypertension are rare in childhood and usually only evident if hypertension is severe"

McCrindlle, B. W. Nat. Rev. Cardiol. 7, 155–163 (2010)

Estimated prevalence

Overall: 4.04.00% (95% CI, 2.10%-6.48%)

Prehypertension: 9.67% (95% CI, 7.26%-12.38%)

Stage 1: 4.00% (95% CI, 2.10%-6.48%)

Stage 2: 0.95% (95% CI, 0.48%-1.57%)

-Song et al, 2019

When should BP be measured?

- Once a year in children ≥3 years (grade C, moderate recommendation)
- At every visit in children ≥3 years if
  - obesity,
  - taking medications that increase BP,
  - renal disease
  - a history of aortic arch obstruction/coarctation of aorta
  - diabetes

  (grade C, moderate recommendation)

AAP Clinical Practice Guideline, 2017

- In children < 3 years if
  - h/o prematurity, VLBW or other complications requiring intensive care
  - congenital heart disease
  - recurrent UTI, haematuria or proteinuria
  - known renal or urological malformations
  - family h/o congenital renal disease
  - solid organ transplant
  - malignancy or bone marrow transplant
  - treatment with drugs known to increase BP
  - other systemic disease associated with hypertension e.g. tuberous sclerosis, neurofibromatosis
  - evidence of raised intracranial pressure

  (grade C, moderate recommendation)

When to suspect secondary hypertension

- Young child
- Very high BP (stage 2)
- Diastolic hypertension
- Resistant hypertension
- Clinical features of underlying disorder

AAP 2017: Children ≥ 6 years do not need extensive evaluation for 2° htn if they have positive fam h/o, are overweight or obese and do not have h/o and physical findings suggestive of a 2° cause of htn

Current Hypertension Reviews, 2019, 15, 1-8

TABLE 14 Examples of Physical Examination Findings and History Suggestive of Secondary HTN or Related to End Organ Damage Secondary to HTN

Body System	Finding, History	Possible Etiology
Vital signs	Tachycardia	Hyperthyroidism
		PCC
		Neuroblastoma
	Decreased lower extremity pulses; drop in BP from upper to lower extremities	Coarctation of the aorta
Eyes	Proptosis	Hyperthyroidism
	Retinal changes[a]	Severe HTN, more likely to be associated with secondary HTN
Ear, nose, throat	Adenotonsillar hypertrophy	SDB
	History of snoring	Sleep apnea
Height, weight	Growth retardation	Chronic renal failure
	Obesity (high BMI)	Cushing syndrome
	Truncal obesity	Insulin resistance syndrome
Head, neck	Elfin facies	Williams syndrome
	Moon facies	Cushing syndrome
	Thyromegaly, goiter	Hyperthyroidism
	Webbed neck	Turner syndrome

Skin	Pallor, flushing, diaphoresis	PCC
	Acne, hirsutism, striae	Cushing syndrome
		Anabolic steroid abuse
	Café-au-lait spots	Neurofibromatosis
	Adenoma sebaceum	Tuberous sclerosis
	Malar rash	Systemic lupus
	Acanthosis nigricans	T2DM
Hematologic	Pallor	Renal disease
	Sickle cell anemia	
Chest, cardiac	Chest pain	Heart disease
	Palpitations	
	Exertional dyspnea	
	Widely spaced nipples	Turner syndrome
	Heart murmur	Coarctation of the aorta
	Friction rub	Systemic lupus (pericarditis)
		Collagen vascular disease
	Apical heave[a]	LVH
Abdomen	Abdominal mass	Wilms tumor
		Neuroblastoma
		PCC
	Epigastric, flank bruit	RAS
	Palpable kidneys	Polycystic kidney disease
		Hydronephrosis
		Multicystic dysplastic kidney

Genitourinary	Ambiguous or virilized genitalia	Congenital adrenal hyperplasia
	Urinary tract infection	Renal disease
	Vesicoureteral reflux	
	Hematuria, edema, fatigue	
	Abdominal trauma	
Extremities	Joint swelling	Systemic lupus
		Collagen vascular disease
	Muscle weakness	Hyperaldosteronism
		Liddle syndrome
Neurologic, metabolic	Hypokalemia, headache, dizziness, polyuria, nocturia	Reninoma
	Muscle weakness, hypokalemia	Monogenic HTN (Liddle syndrome, GRA, AME)

TABLE 10 Screening Tests and Relevant Populations

Patient Population	Screening Tests
All patients	Urinalysis
	Chemistry panel, including electrolytes, blood urea nitrogen, and creatinine
	Lipid profile (fasting or nonfasting to include high-density lipoproteina and total cholesterol)
	Renal ultrasonography in those <6 y of age or those with abnormal urinalysis or renal function
In the obese (BMI >95th percentile) child or adolescent, in addition to the above	Hemoglobin A1c (accepted screen for diabetes)
	Aspartate transaminase and alanine transaminase (screen for fatty liver)
	Fasting lipid panel (screen for dyslipidemia)
Optional tests to be obtained on the basis of history, physical examination, and initial studies	Fasting serum glucose for those at high risk for diabetes mellitus
	Thyroid-stimulating hormone
	Drug screen
	Sleep study (if loud snoring, daytime sleepiness, or reported history of apnea)
	Complete blood count, especially in those with growth delay or abnormal renal function

Adapted from Wiesen J, Adkins M, Fortune S, et al. Evaluation of pediatric patients with mild-to-moderate hypertension: yield of diagnostic testing. *Pediatrics*. 2008;122(5). Available at: www.pediatrics.org/cgi/content/full/122/5/e988.

What suggests a monogenic cause?

- Family history of severe hypertension of early onset
- Muscle weakness
- Short stature
- Early/delayed puberty
- Abnormal potassium levels
- Metabolic acidosis or alkalosis
- Low renin activity

Eur J Pediatr (2012) 171:1433–1439

Pediatr Nephrol. 2022 Jul;37(7):1495-1509.

When should PRA be measured?

- No mention in AAP and JNC guidelines
- When monogenic hypertension is suspected
- May predict elevated BP and hypertension

Clin Exp Hypertens. 2019;41(4):330-335

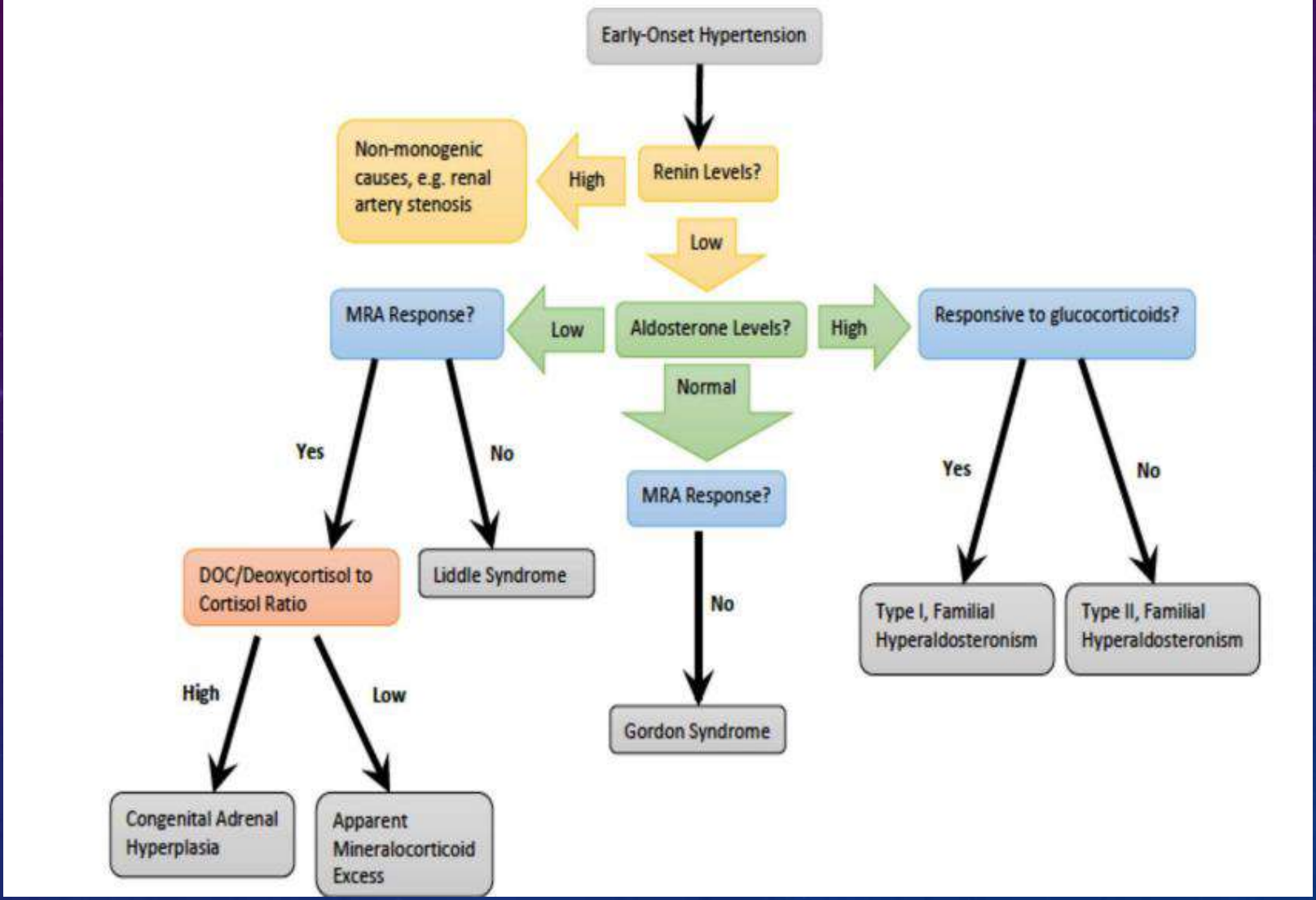
- Low PRA may predict poor response to AHTs

Am J Hypertens. 2019 Jun 11;32(7):668-675

Am J Hypertens. 2019 Jun 11;32(7):668-675

Further evaluation depends on aldosterone levels

Classification



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Assessing plasma renin activity

- Usually LC/MS-MS
- Liaison with lab
- Vacutainer – usually EDTA
- Volume: min 1 ml
- Separate and freeze plasma as soon as possible
- Rapid freezing to prevent cryoactivation of protein to renin
- Note time of day, position of patient

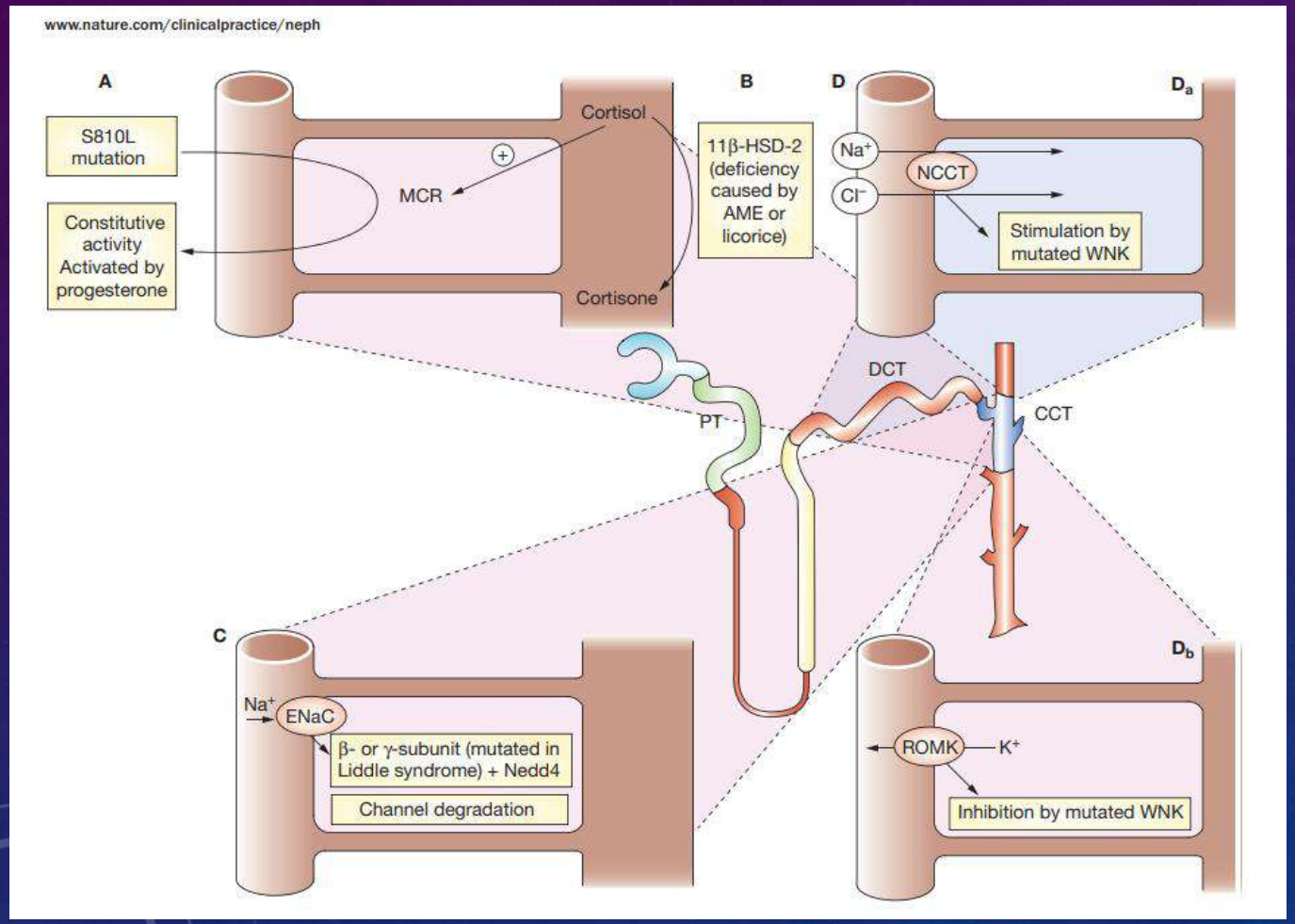
Drugs that tend to increase PRA levels:

- Diuretics (including spironolactone)
- Dihydropyridine calcium channel blockers
- Angiotensin converting enzyme (ACE) inhibitors
- Angiotensin receptor antagonists

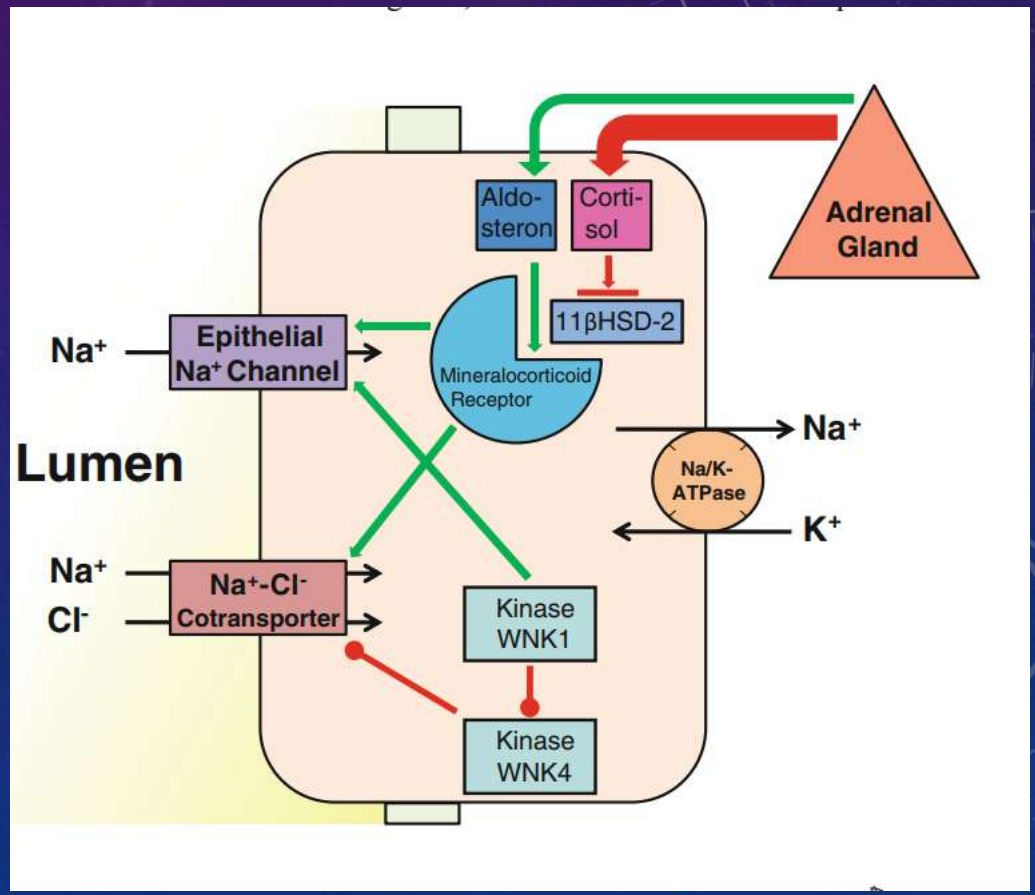
Drugs that tend to decrease PRA levels:

- Beta-blockers
- Clonidine
- Alpha-methyldopa
- Nonsteroidal anti-inflammatory agents

Overview of monogenic hypertension



Nat Clin Pract Nephrol. 2006 Nov;2(11):624-30



Eur J Pediatr (2012) 171:1433–1439

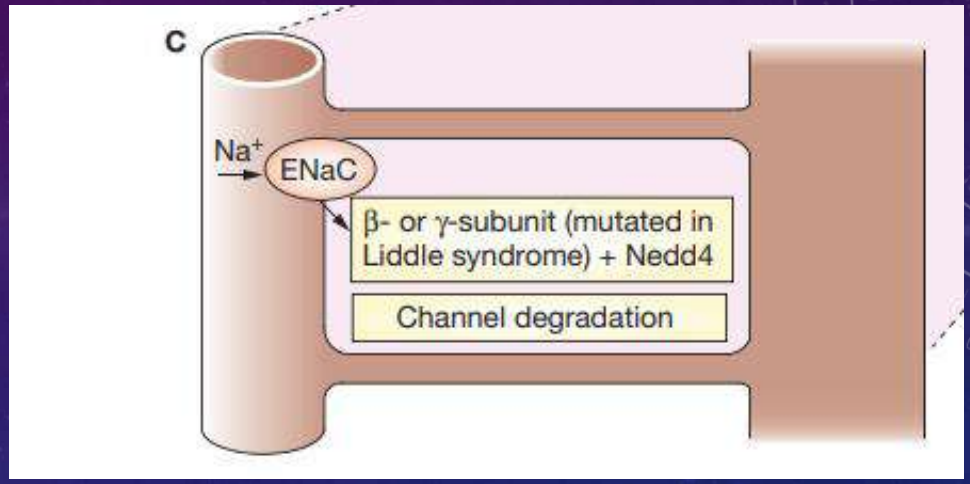
Liddle syndrome

Epidemiology

- 30 case reports till 2019; but genetic variations consistent with Liddle syndrome more common
  - 1.5% on genetic testing in a Chinese population
  - 6% prevalence among hypertensive US veterans

Pathogenesis

- Mutation in *SCNN1B* and *SCNN1G* encoding beta and gamma subunits of ENaC
- Disruption of proline rich carboxy terminal
- Loss of affinity to Nedd4-2, a regulator



Nat Clin Pract Nephrol. 2006 Nov;2(11):624-30

- Sodium retention – fluid retention and hypertension
- Potassium loss
- Proton secretion

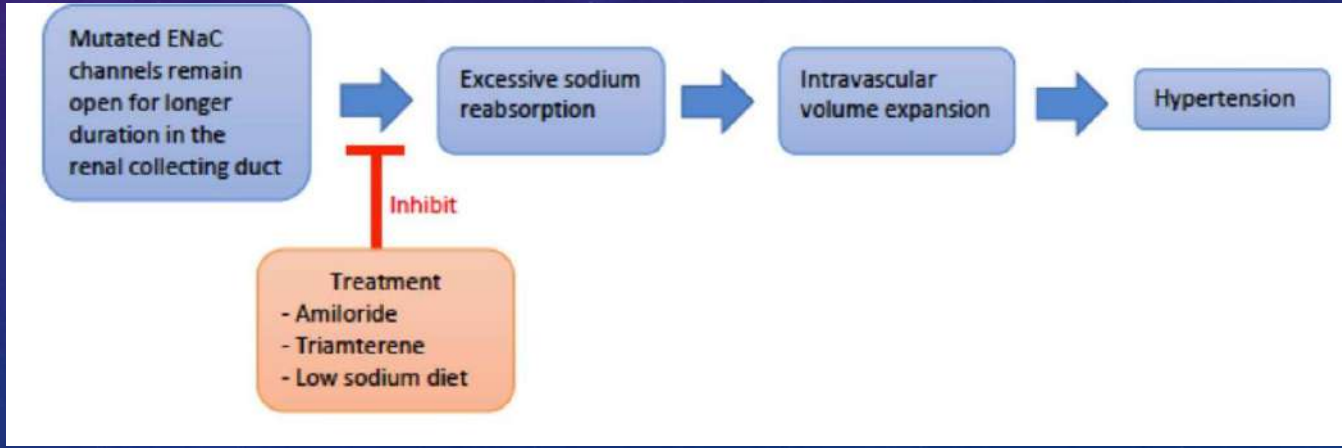
Liddle syndrome

Clinical features

- AD inheritance, fam h/o early onset hypertension
- Early onset in the index patient
- Hypokalemia, metabolic alkalosis
- No response to spironolactone
- Workup: low renin, low aldosterone, random aldosterone: renin < 30

Treatment

- Low sodium diet
- ENaC antagonist: amiloride



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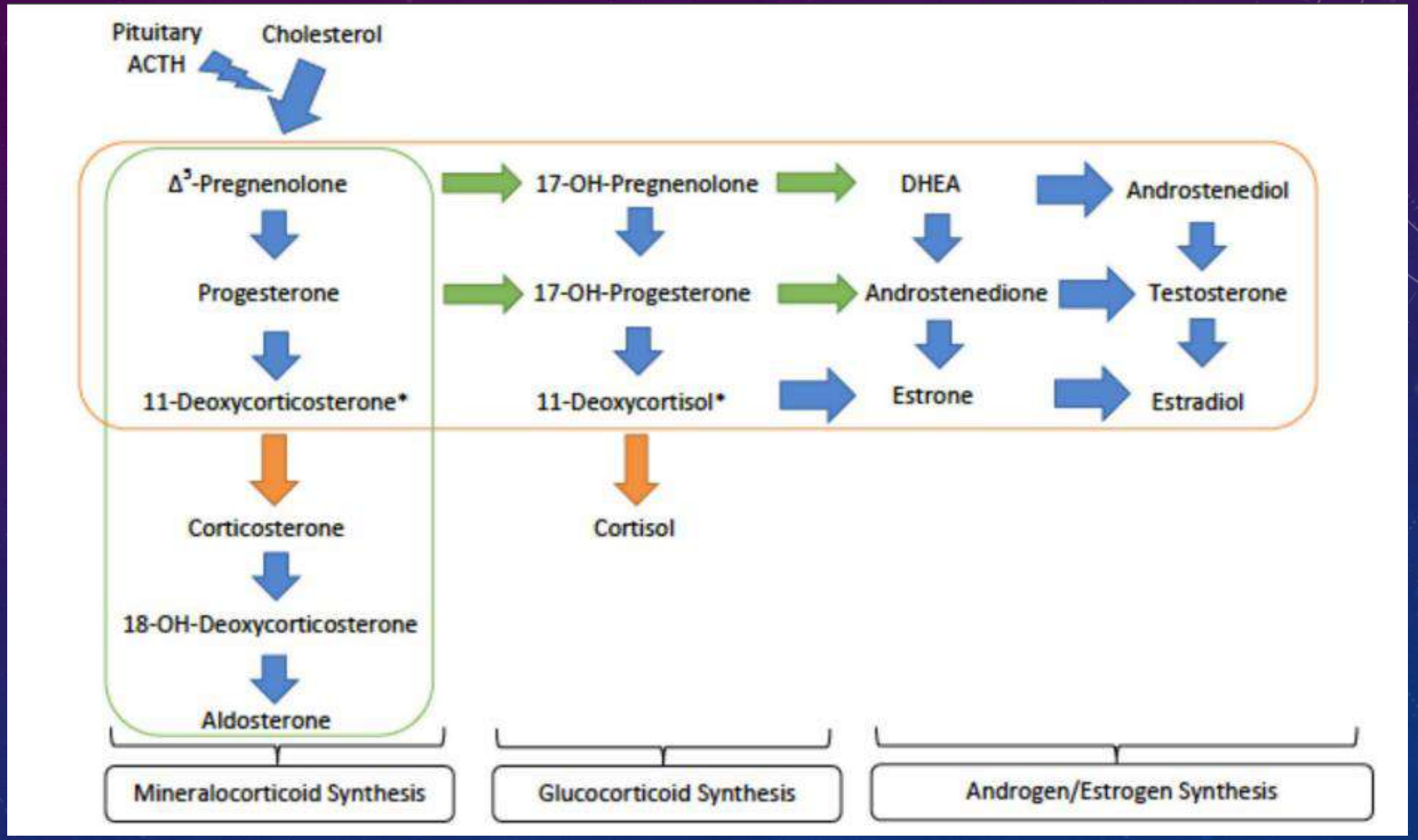
Steroidogenesis: recap



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Congenital adrenal hyperplasia

11β hydroxylase deficiency: CAH type IV

Epidemiology

- Rare: accounts for 5-8% CAH, can be upto 15% in middle eastern populations

Pathogenesis

- Mutation in *CYP11B1* encoding 11β hydroxylase
- Deficiency of cortisol - stimulation of ACTH
- Accumulation of 11 deoxycorticosterone & 11 deoxycortisol – mineralocorticoid activity

Clinical features

- DSD: virilization in female, precocious puberty in males
- Early onset hypertension

17α hydroxylase deficiency: CAH type V

Epidemiology

- Rare: exact prevalence unclear

Pathogenesis

- Mutation in *CYP17A1* encoding P450C17α
- Deficiency of cortisol - stimulation of ACTH
- Deficiency of sex steroids
- deoxycortisol – mineralocorticoid activity

Clinical features

- DSD: delayed puberty in females, males may have female phenotype
- Early onset hypertension

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Congenital adrenal hyperplasia

11β hydroxylase deficiency: CAH type IV

Diagnosis

- Blood levels of adrenal hormones
- Genetic testing of *CYP11B1*

Treatment

- Oral hydrocortisone to suppress ACTH
- Spironolactone, amiloride, CCBs

17α hydroxylase deficiency: CAH type V

Diagnosis

- Steroid analysis upon ACTH-stimulation: ↑ levels of pregnenolone and progesterone relative to 17α-pregnenolone & 17α-progesterone
- Genetic testing of *CYP17A1*

Treatment

- Oral hydrocortisone to suppress ACTH
- Spironolactone, amiloride, CCBs
- Sex hormone replacement therapy

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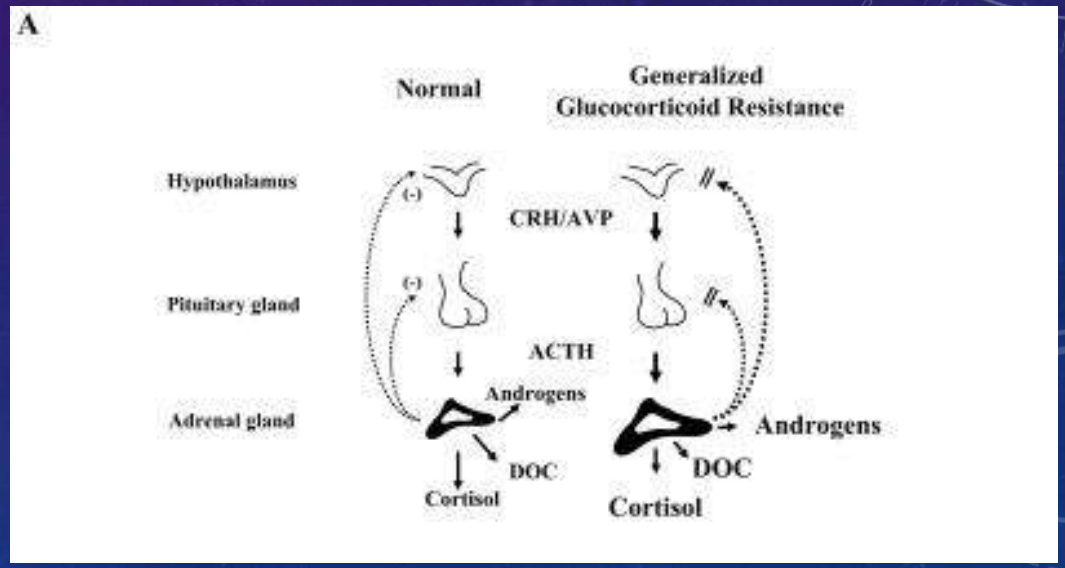
Primary glucocorticoid resistance

- Loss of function mutation in *NR3C1* encoding the glucocorticoid receptor
- Absence of negative feedback loop to suppress ACTH
  Reduction in activity of 11βHSD2 (like AME)
- Adrenal hyperplasia, hypertension, hirsutism
- Elevated urinary free cortisol
- Serum cortisol >50 nmol/L after overnight

dexamethasone suppression test

without clinical features of Cushing syndrome

- Treatment: high dose dexamethasone



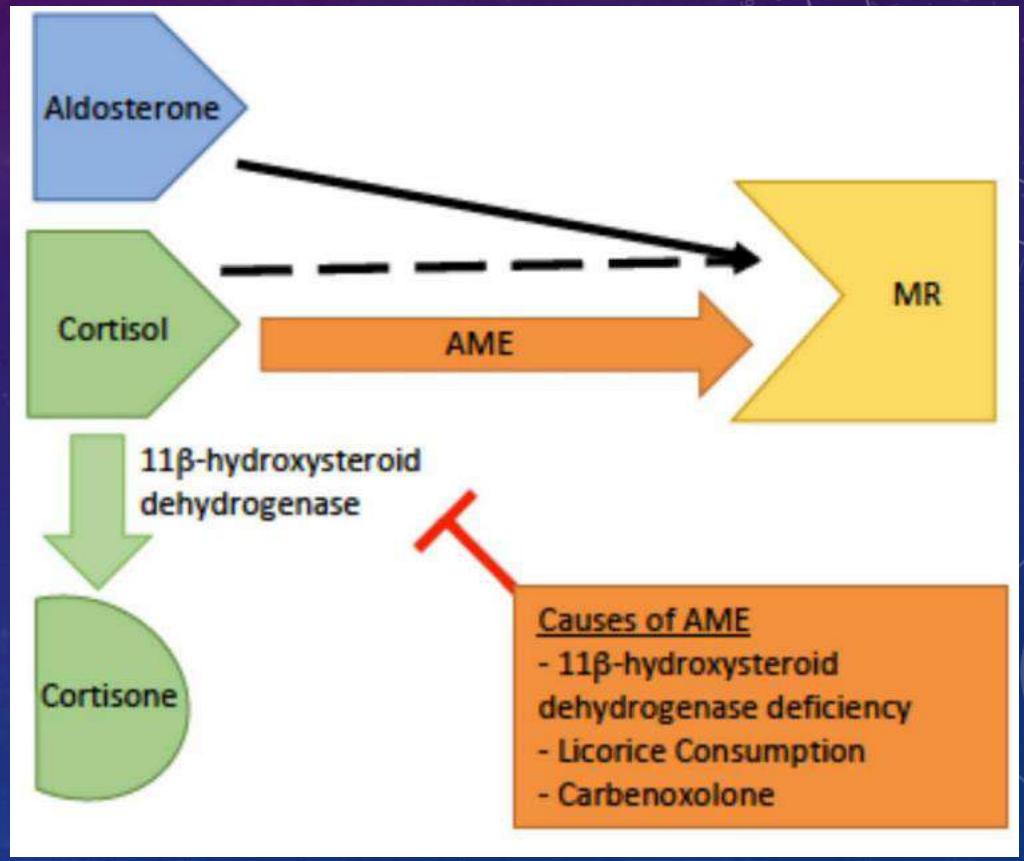
Apparent mineralocorticoid excess (Ulick syndrome)

Epidemiology

- Unclear, reported in multiple ethnic populations

Pathogenesis

- Loss of function mutation in *HSD11B2* encoding 11β-hydroxysteroid dehydrogenase type 2
- Also caused by excess liquorice consumption
- Cortisol not inactivated in the CCT



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Apparent mineralocorticoid excess (Ulick syndrome)

Clinical features

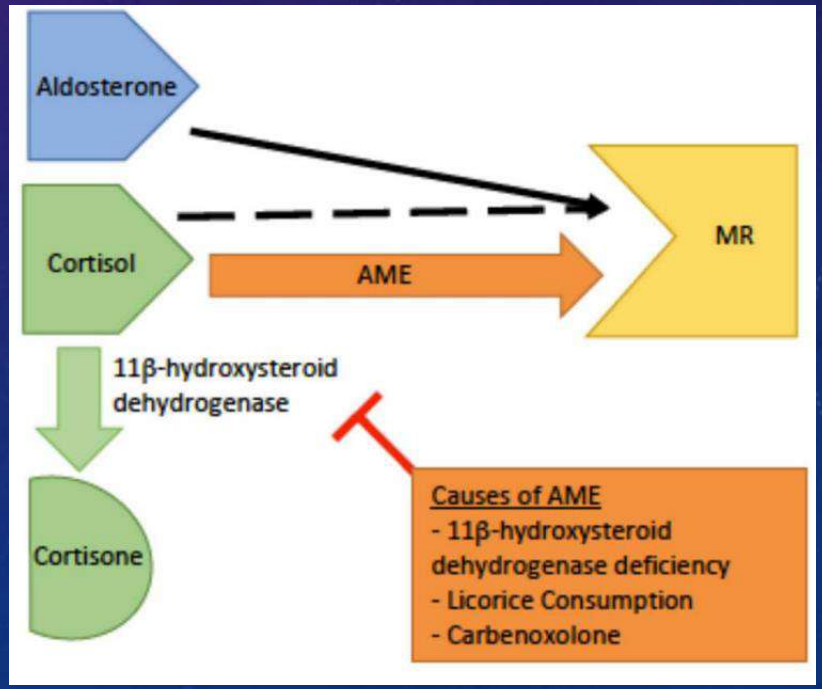
- IUGR/low birth weight (76-100%)
- Early onset hypertension – may be severe with sequelae
- Hypokalemia, metabolic alkalosis
- Hypercalciuria/nephrocalcinosis (50-75%)
- Secondary NDI

Workup

- Low renin, low aldosterone
- Elevated urinary cortisol to cortisone ratio (1.3–10; normal 0.5) & tetrahydrocortisol (THF) + 5αTHF to tetrahydrocortisone (THE) (2.4–55; normal 1–1.3)

Treatment

- Low sodium diet
- MR antagonists: spironolactone/eplerenone
- Add-on: amiloride
- Glucocorticoids for elevated ACTH



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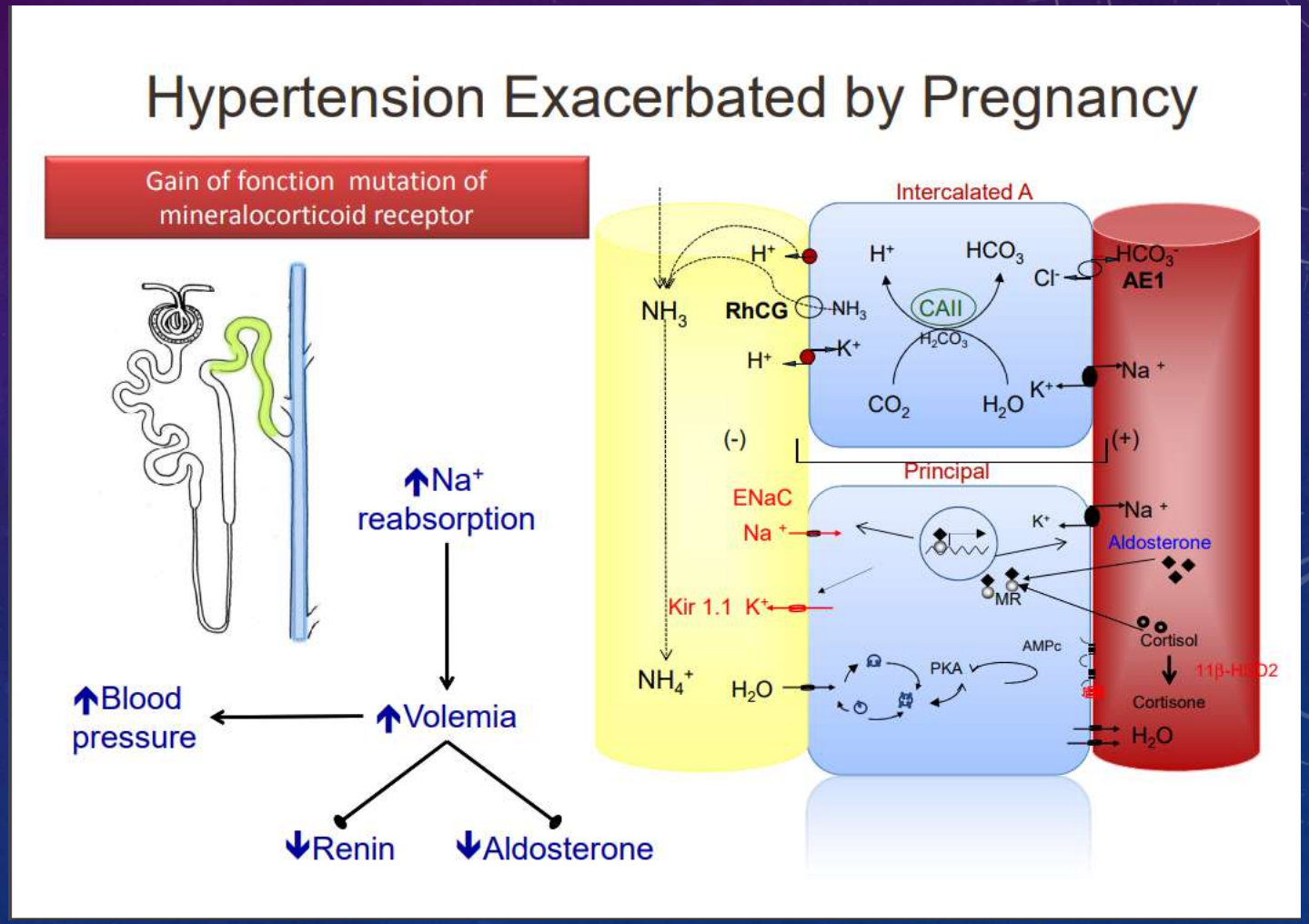
Geller syndrome

Heterozygous gain of function p.Ser810Leu mutation

Mineralocorticoid receptor

- Constitutively active
- Altered specificity to steroid hormones



Vargas, ERKD

Geller syndrome

Epidemiology

- 1st report in 200, < 10 cases reported

Clinical features

- AD inheritance
- Htn before age 20 yrs
- Exacerbated by pregnancy

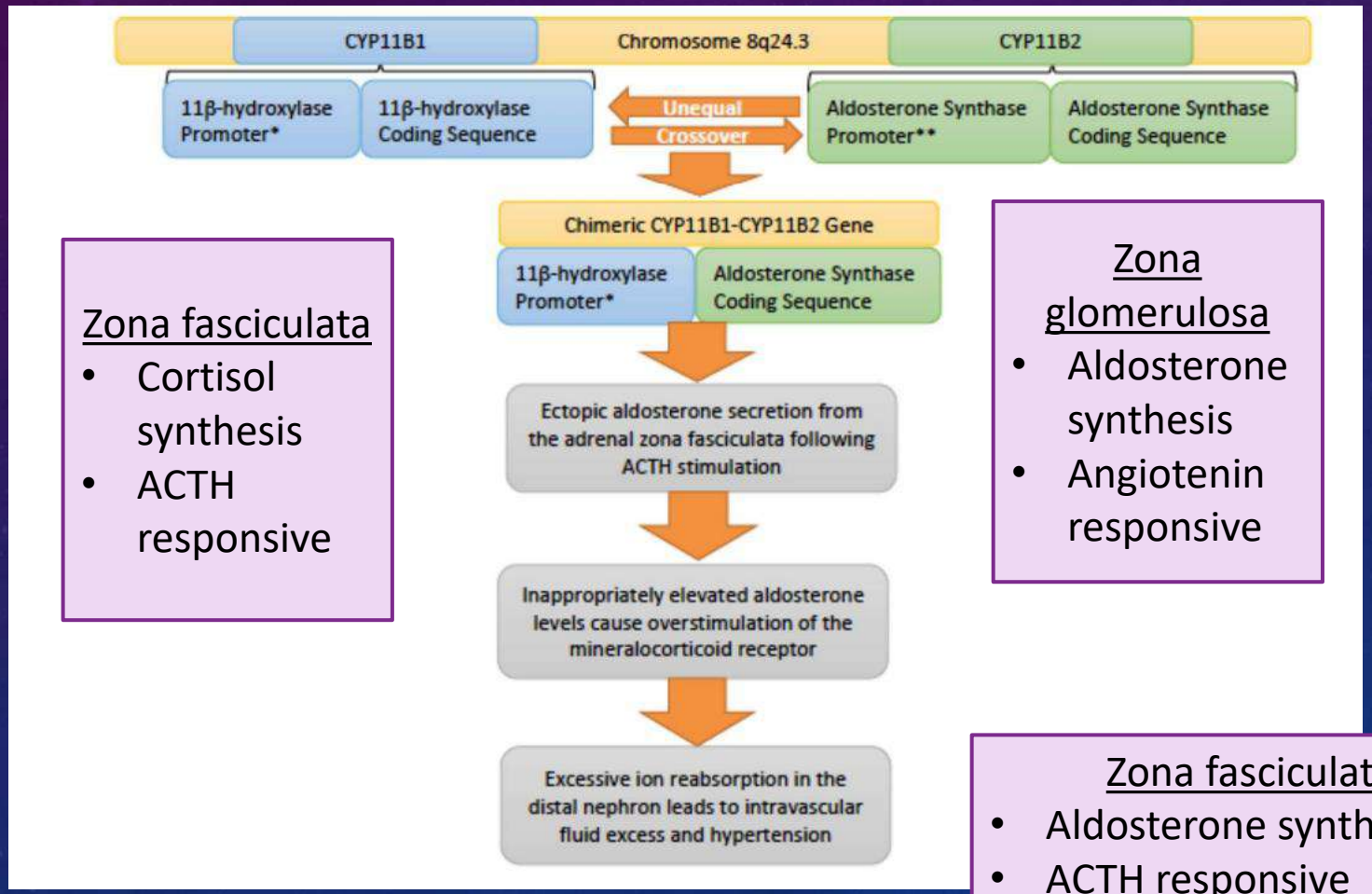
Workup

- PRA ↓, aldosterone low
- Potassium may surprisingly be normal
- Genetic testing

Therapy

- Early delivery
- Spironolactone: contraindicated
- ? Role of fineferone

Glucocorticoid-Remediable Aldosteronism/ Familial Hyperaldosteronism Type 1



<u>Zona fasciculata</u>
- Cortisol synthesis
- ACTH responsive

<u>Zona glomerulosa</u>
- Aldosterone synthesis
- Angiotenin responsive

<u>Zona fasciculata</u>
- Aldosterone synthesis
- ACTH responsive

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Glucocorticoid-Remediable Aldosteronism/ Familial Hyperaldosteronism Type 1

Epidemiology

- Prevalence unclear

Clinical features

- AD inheritance, not seen in blacks
- Onset in early childhood/infancy (80%< 1 yr)
- High incidence of complications – cerebral aneurysms & intracranial hemorrhage
- Hypokalemia – usually mild

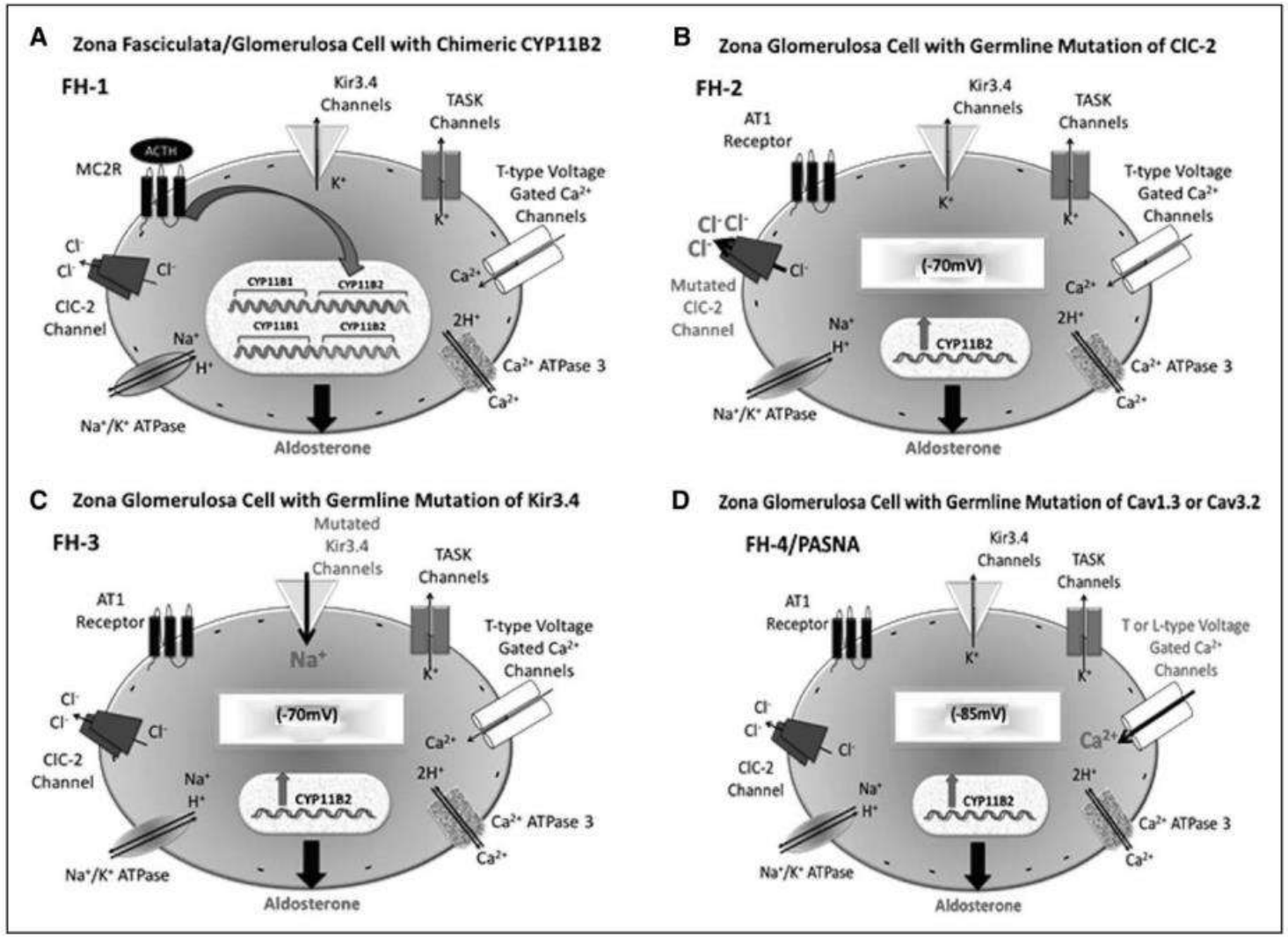
Workup

- PRA ↓, aldosterone normal, random aldosterone: renin > 30
- Urinary steroid analysis
- Genetic testing
- Dexamethasone suppression test, adrenal imaging, and adrenal-vein sampling: obsolete

Therapy

- Glucocorticoids – dexamethasone lowest dose - at bedtime
- Spironolactone/amiloride: add on

Familial Hyperaldosteronism



Hypertension. 2018;71:1010-1014

Familial Hyperaldosteronism

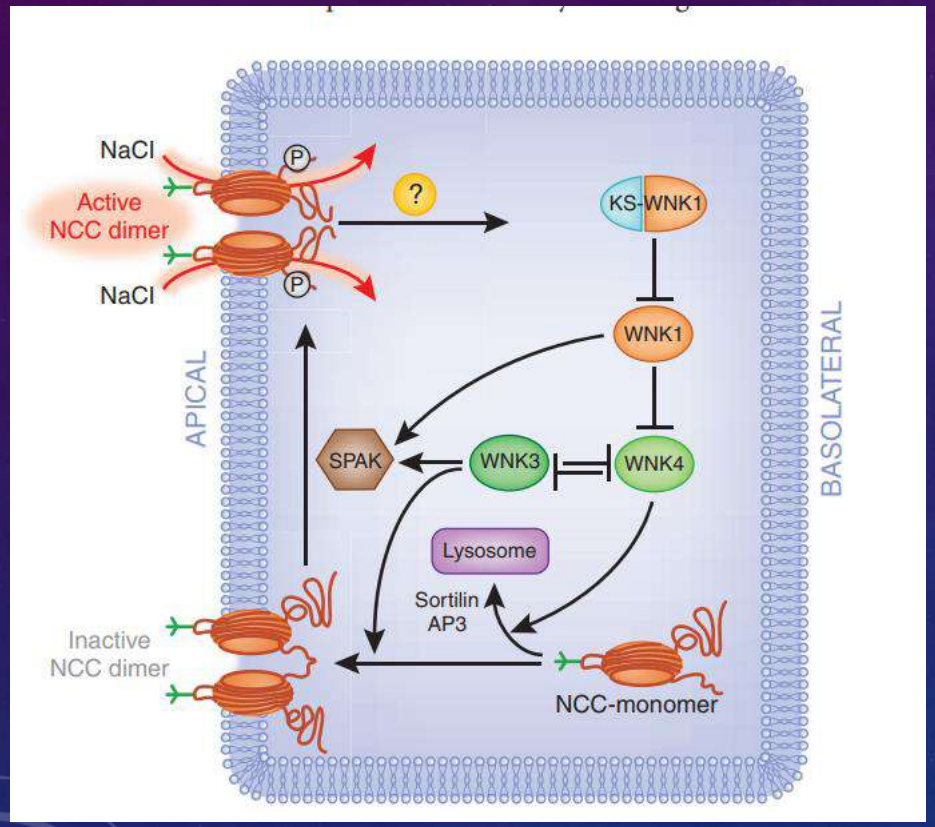
Table. Clinical and Molecular Classification of FH

Type	Subtype	Prevalence, %*	Cytogenetic Location	Gene Mutation	CT Findings	Treatment	Drug-Resistant Hypertension	Clinical Features
FH-1		0.5–1	8q24	*CYP11B2*/*CYP11B1* Chimeric	BAH or APA	Low-dose dexamethasone	Yes (with drugs other than dexamethasone)	Early-onset PA, hybrid steroids, cerebrovascular events
FH-2		5	3q27	*CLCN2* (R172Q, M22K, G24D, S865R, Y26N)	BAH or APA or no adrenal abnormalities	MRA	No	Early-onset PA
FH-3	Type A	0.3	11q23	*KCNJ5* (T158A, I157S, E145Q)	BAH	Bilateral adrenalectomy	Yes	Severe early-onset PA
	Type B	0.3	11q23	*KCNJ5* (G151E, Y152C)	No	MRA	No	Mild PA
FH-4		NA	16p13	*CACNA1H* (M1549V, S196L, P2083L, V1951E)	Little or no adrenal abnormalities	MRA	No	Early-onset PA, mental retardation, social and development disorders
FH-5 (PASNA)		NA	3p14.3	*CACNA1D* (I770M, G403D)	No adrenal abnormalities	Calcium channel blockers	No	Early-onset PA, seizures, neurological abnormalities

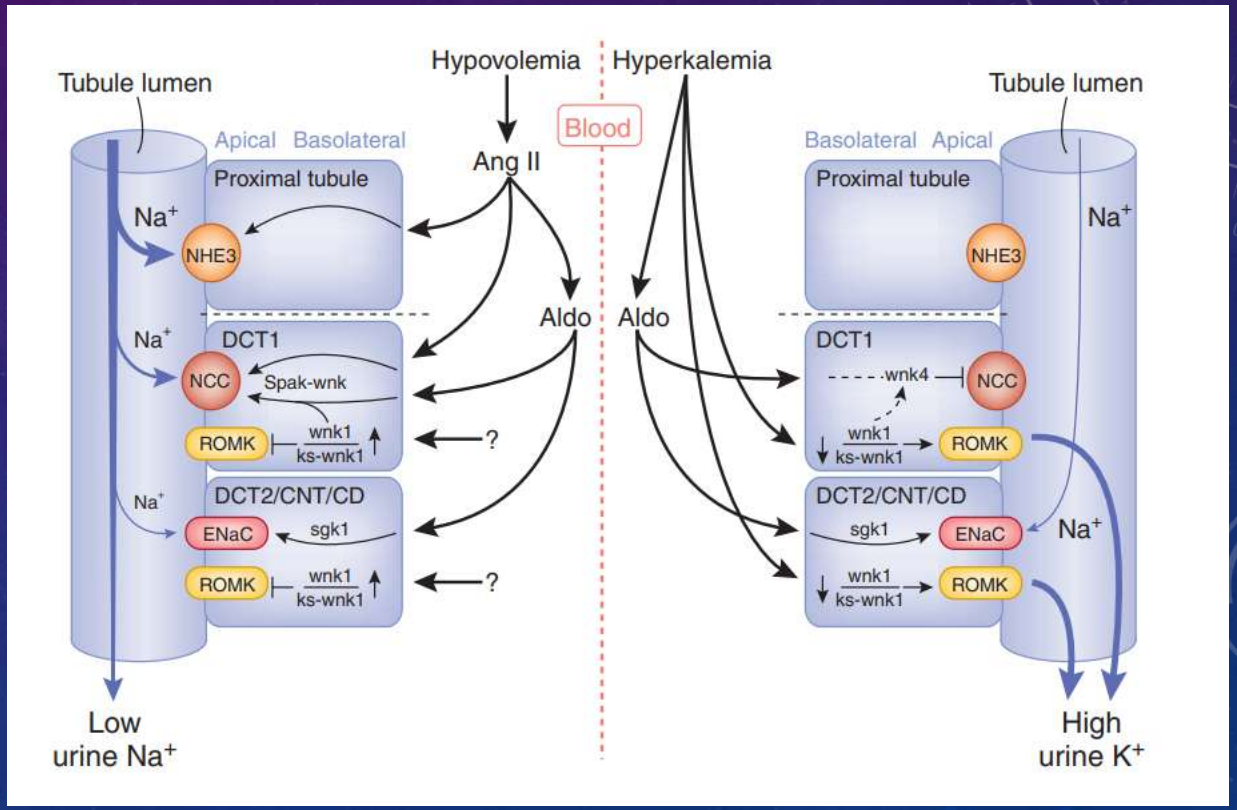
Hypertension. 2018;71:1010-1014

Gordon syndrome/ Familial Pseudohypoaldosteronism Type 2

Regulation of NCC

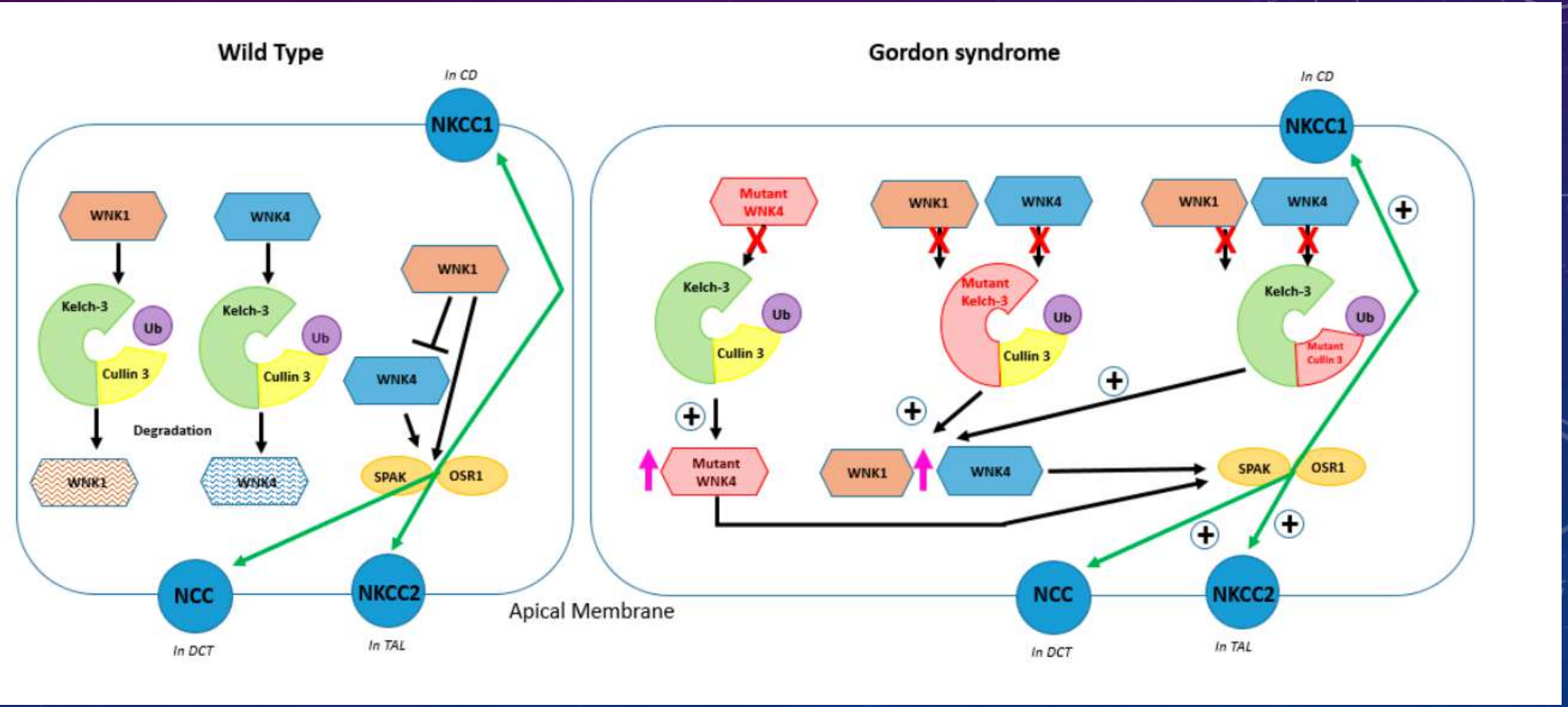


The aldosterone paradox



J Am Soc Nephrol 22: 605–614

Gordon syndrome/ Familial Pseudohypoaldosteronism Type 2



Genes 2019, 10, 986; doi:10.3390/genes10120986

Gordon syndrome/ Familial Pseudohypoaldosteronism Type 2

Table 1. Phenotype–genotype correlations in Gordon syndrome.

	WNK1	*WNK4*	*KLHL3*	*CUL3*
Hypertension	Least severe phenotype and metabolic disorder often precedes hypertension	Metabolic disorder often precedes hypertension	Recessive mutations are more severe and diagnosed at an earlier age than dominant mutations	Most severe phenotype. Presents at youngest age (>90% had hypertension <age 18.
Hyperkalaemia	Least severe	Yes	Dominant mutations had significantly higher serum K^+ than recessive mutations	Most severe Presents at youngest age
Metabolic Acidosis	Least severe	Yes	Yes	Most severe
Other features		Hypercalciuria Hypocalcaemia Decreased bone mineral density Renal calcium stones		Fertility likely affected in de novo mutations. Growth impairment most likely

Genes 2019, 10, 986; doi:10.3390/genes10120986

Gordon syndrome/ Familial Pseudohypoaldosteronism Type 2

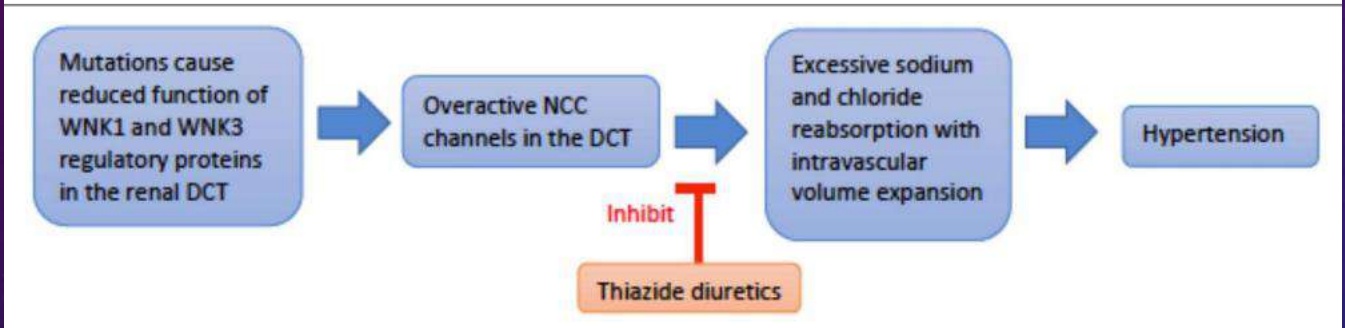


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TABLE 4. Types of Gordon syndrome

Disease	Inheritance	Cytogenetic loci	Gene
Gordon syndrome (pseudohypoaldosteronism type II)	Autosomal dominant (type II A)	1q31-1q42	–
	Autosomal dominant (type II B)	17q21.2	*WNK4*
	Autosomal dominant (type II C)	12p13.33	*WNK1*
	Autosomal dominant or recessive (type II D)	5q31.2	*KLHL3*
	Autosomal dominant (type II E)	2q36.2	*CUL3*

Clinical features

- Early onset hypertension
- Short stature, ID, dental abnormalities, muscle weakness

Workup

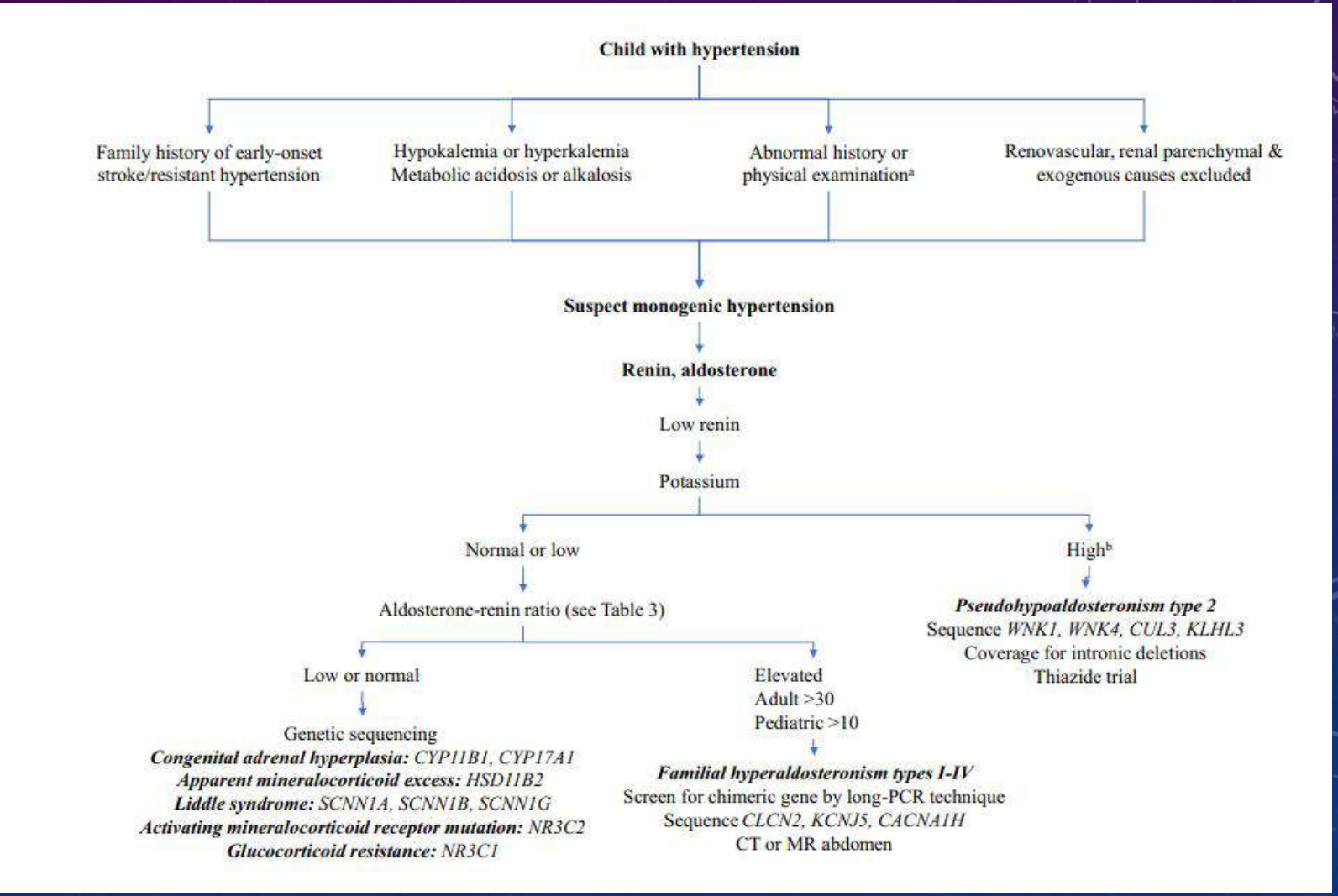
- Hyperchloremic metabolic acidosis
- Hyperkalemia
- Low FeNa

Treatment

- Low sodium diet
- Thiazide diuretics

So how do you pick the odd one out?

- Measure BP where indicated: all children > 3 yrs once a year; others where indicated
- Basic workup
- Identify secondary hypertension
- Identify low renin hypertension



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Thank you