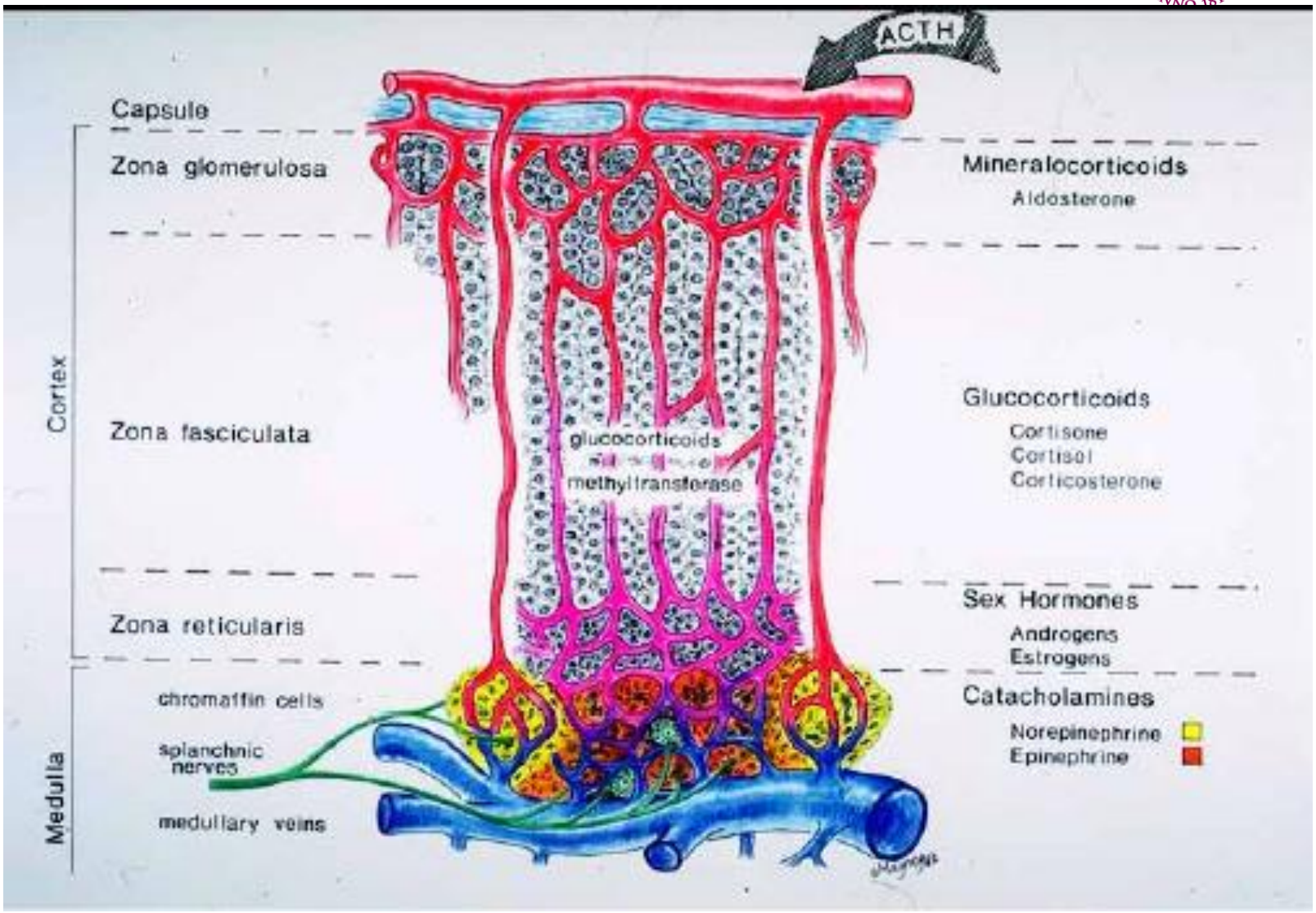
Binjuren

Svetlana Lajic, prof/öl

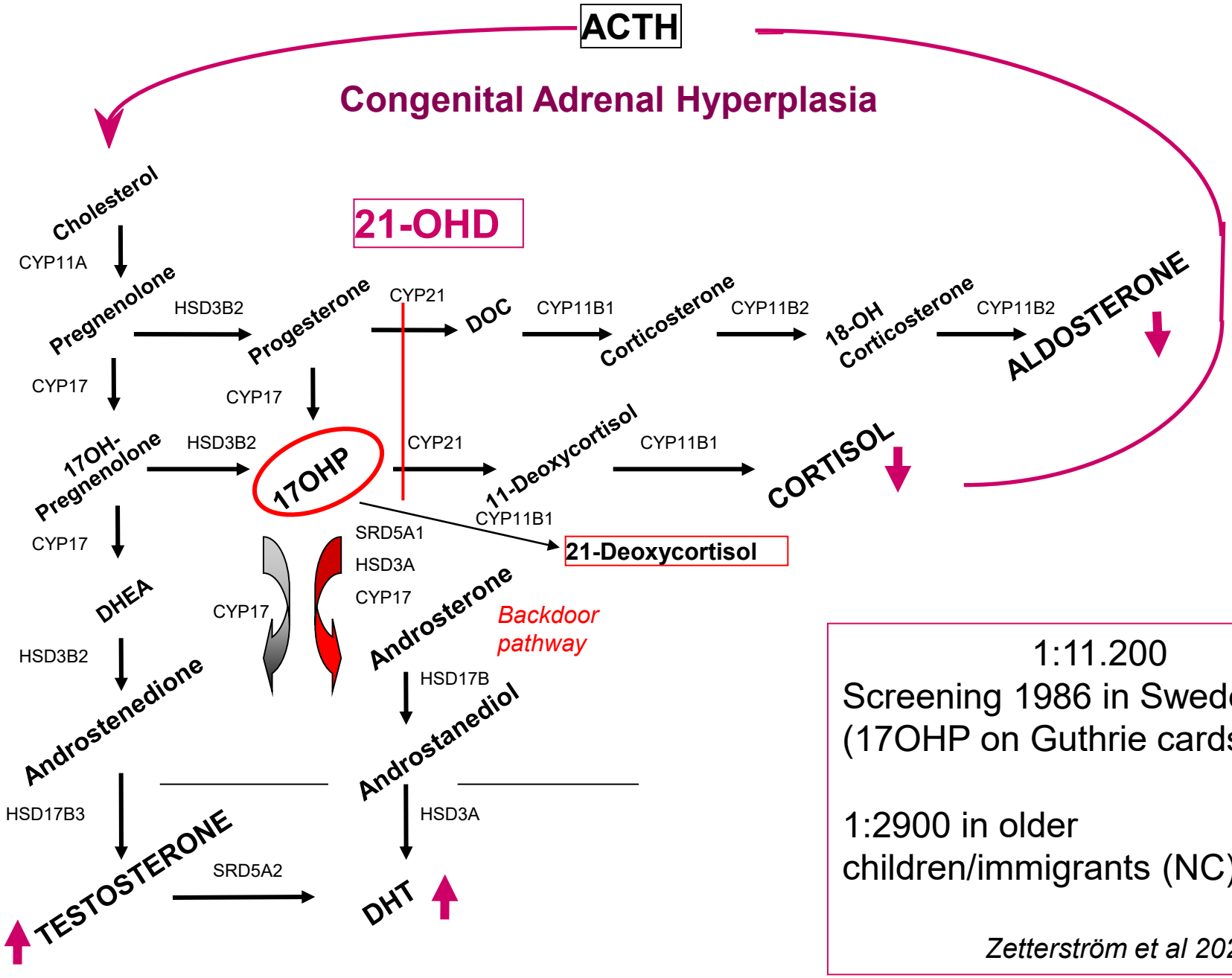
Mottagningen för barnendokrinologi och medfödda metabola sjukdomar,

Astrid Lindgrens barnsjukhus och Drottning Silvias barnsjukhus

Structure of the adrenal gland



Congenital Adrenal Hyperplasia



1:11.200
Screening 1986 in Sweden
(17OHP on Guthrie cards)

1:2900 in older
children/immigrants (NC)

Zetterström et al 2020

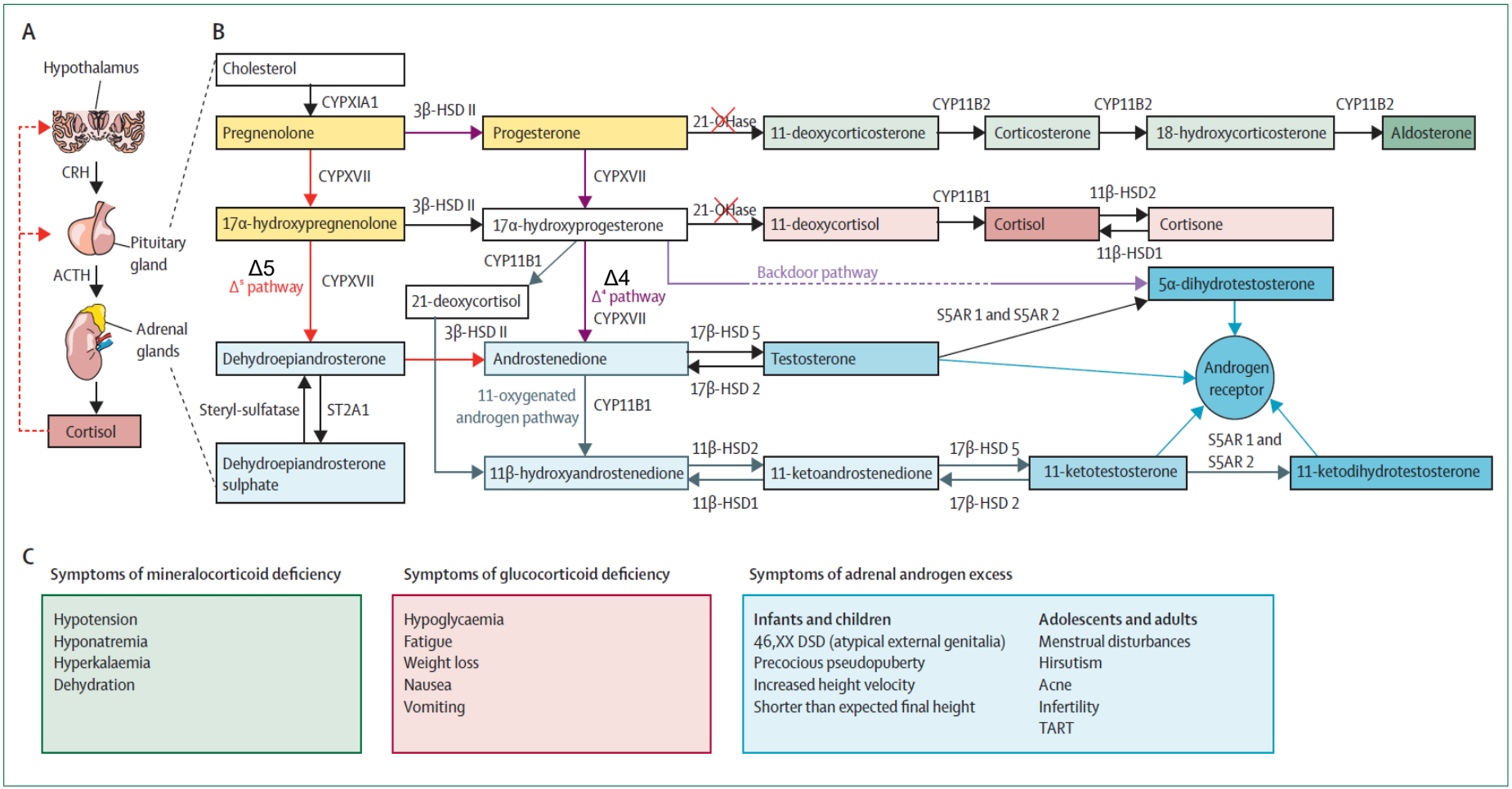


Figure 1: Steroid synthesis pathways in congenital adrenal hyperplasia due to 21-OHase deficiency

Auer et al Lancet 2023

New screening process for 21OHD in Sweden

First tier: Immunoassay for 17OHP from Guthrie cards at 48 h

Cut-off 50 nmol/L for full-term babies; 200 nmol/L for premature (<GW35)

Second tier: LC-MS/MS

17OHP
21-deoxycortisol pathognomonic, if > 2.5 nmol/L, even if low ratio
POS screening

11-deoxycortisol
Cortisol
Androstenedione

RATIO: 17OHP+A4/cortisol

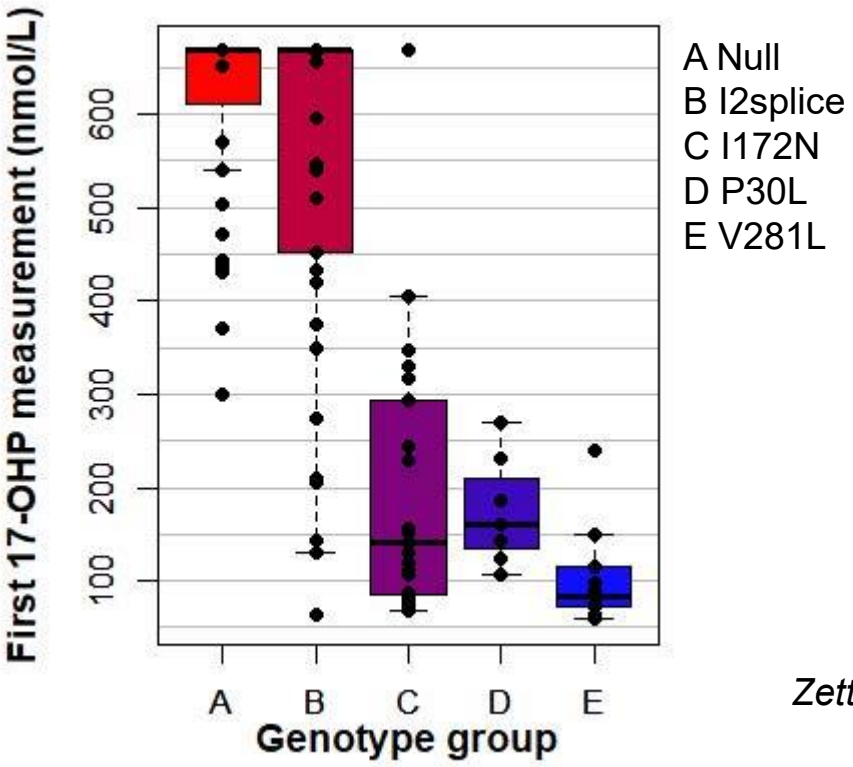
>1 POSITIVE for full-term babies
>1.5 POSITIVE for premature babies

Neonatal Screening for CAH

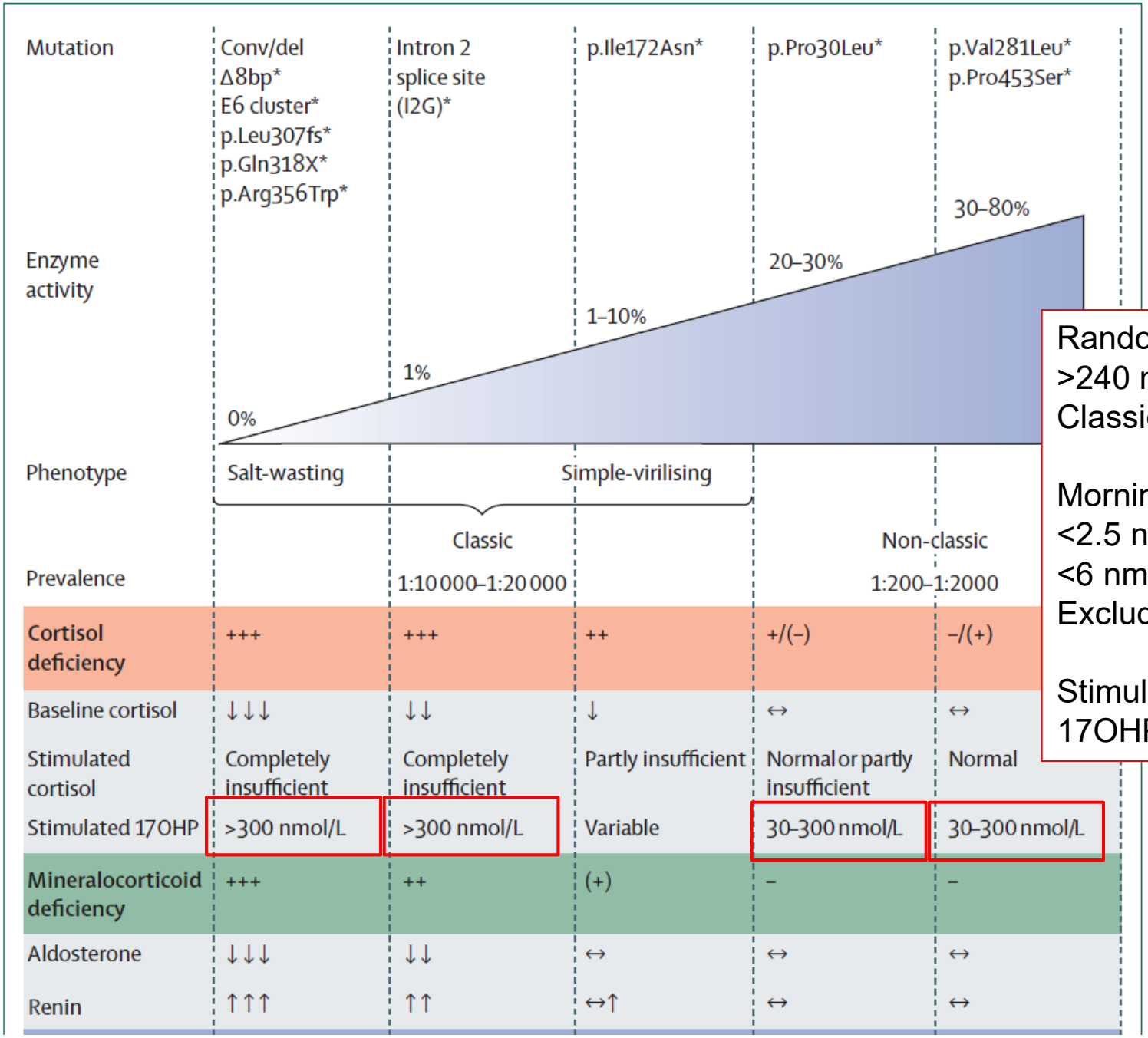
- Neonatal screening saves lives and leads to earlier diagnosis in both sexes.
  (Gidlöf et al Lancet Diab Endo 2013)

- Screening differentiate between genotype groups.

  - **Does neonatal screening improve long-term health?**
  - **Do early diagnosis and treatment improve cognitive outcome?**



Zetterström et al 2020



Random sample
>240 nmol/L 17OHP
Classic CAH

Morning basal 17OHP
<2.5 nmol/L children
<6 nmol/L adults
Exclude 21OHD

Stimulated >30 nmol/L
17OHP, confirm 21OHD

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

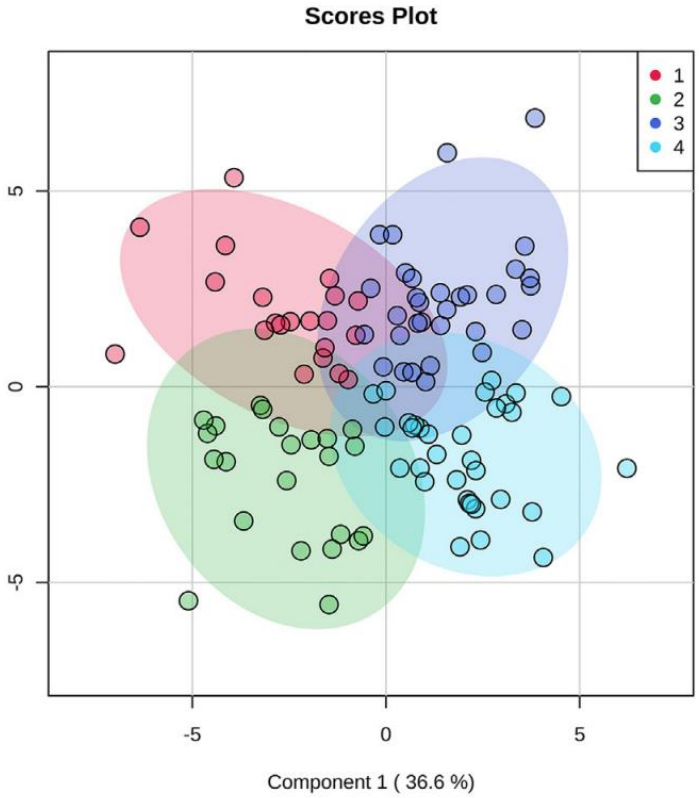
journal homepage: www.metabolismjournal.com

Urinary GC–MS steroid metabotyping in treated children with congenital adrenal hyperplasia.

Clemens Kamrath [a], Michaela F. Hartmann [a], Jörn Pons-Kühnemann [b], Stefan A. Wudy [a,*]

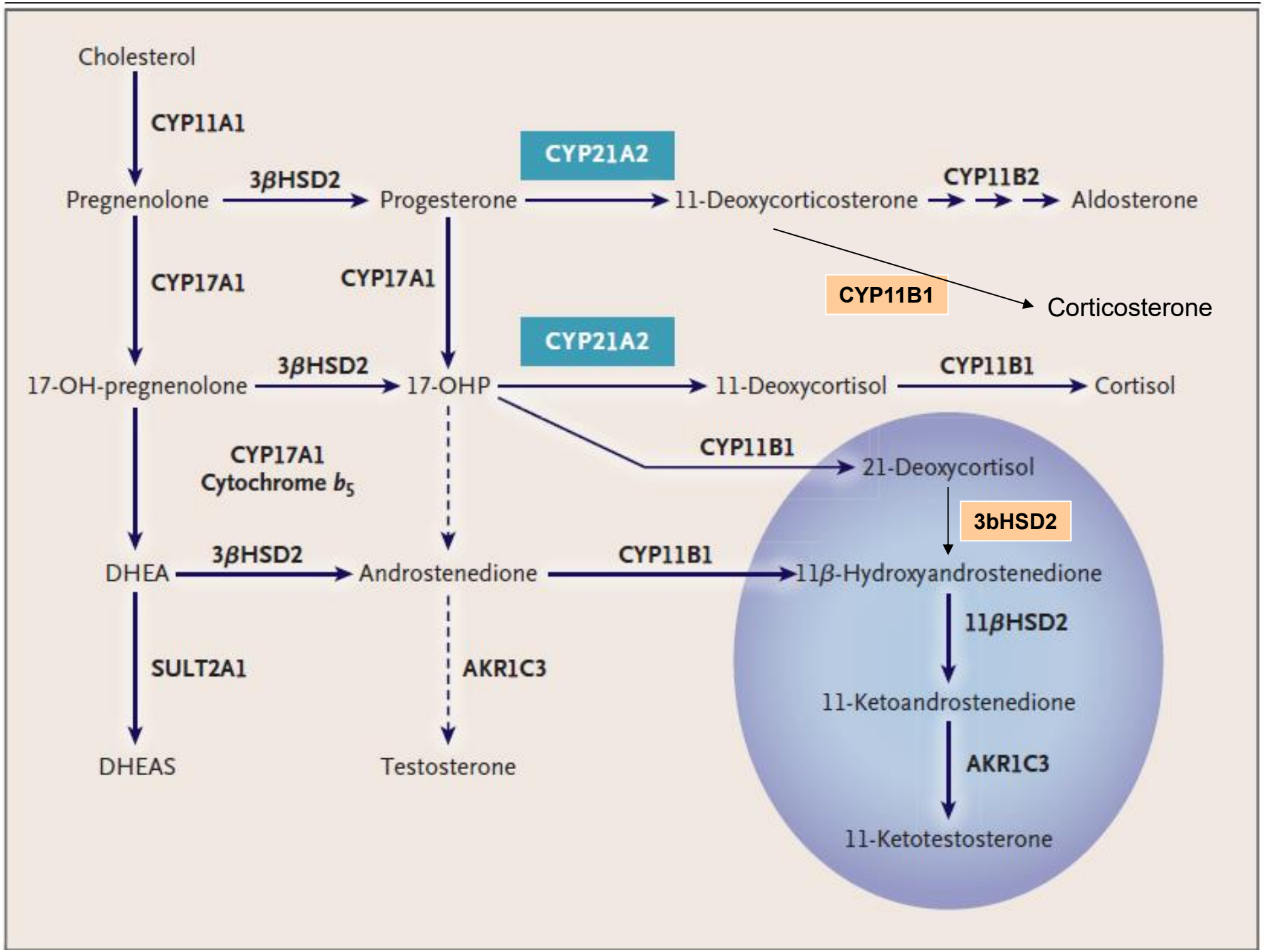
[a] Division of Pediatric Endocrinology & Diabetology, Center of Child and Adolescent Medicine, Justus Liebig University, Giessen, Germany
[b] Medical Statistics, Institute of Medical Informatics, Justus Liebig University, Giessen, Germany

CAH (n=107) 3-7 years, HC+MC
24-h U-steroid profiles
GC-MS
4 metabotypes (Kamrath 2020)



4 metabotypes

1. Adequate control: low cortisol, A, 17OHP
2. Overtreatment: high cortisol, low A, 17OHP
3. Undertreatment: low cortisol, high A, 17OHP
4. Treatment failure: ok cortisol, high A, 17OHP

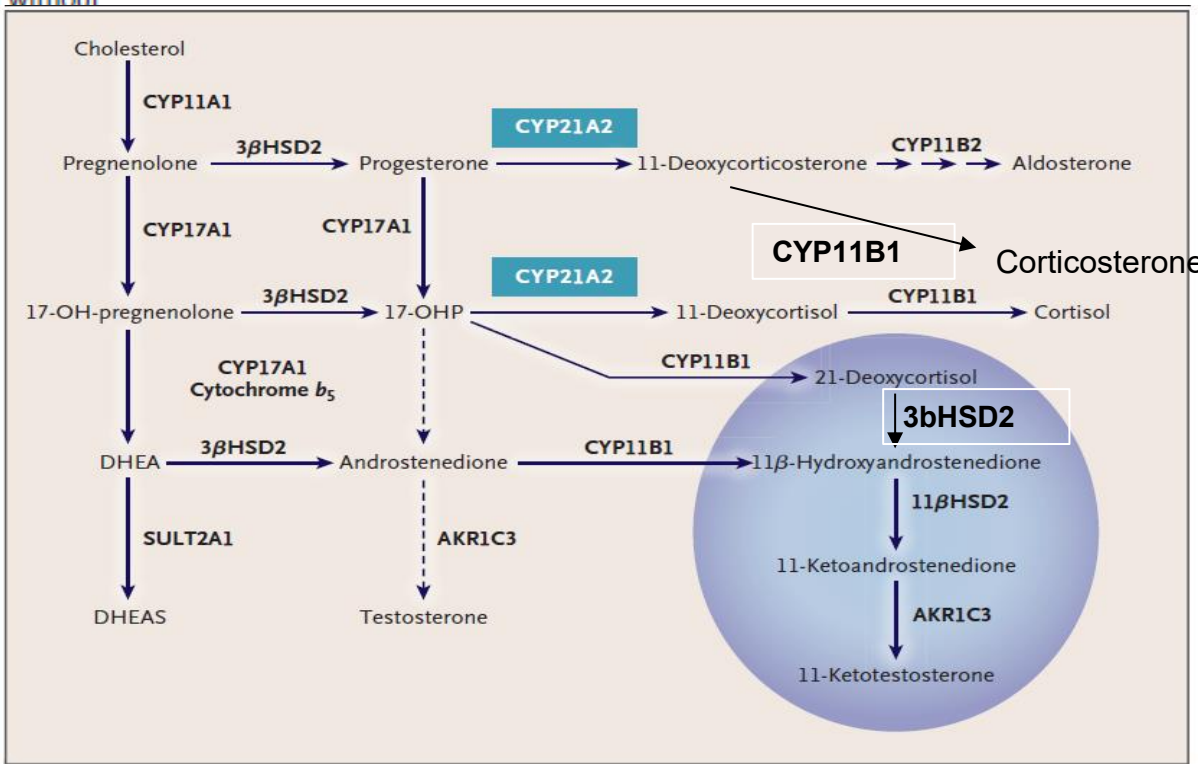

Cholesterol
CYP11A1
Pregnenolone
3βHSD2
Progesterone
CYP21A2
11-Deoxycorticosterone
CYP11B2
Aldosterone
CYP11B1
Corticosterone
CYP17A1
CYP17A1
17-OH-pregnenolone
3βHSD2
17-OHP
CYP21A2
11-Deoxycortisol
CYP11B1
Cortisol
CYP11B1
21-Deoxycortisol
3bHSD2
CYP17A1
Cytochrome b5
DHEA
3βHSD2
Androstenedione
CYP11B1
11β-Hydroxyandrostenedione
11βHSD2
11-Ketoandrostenedione
AKR1C3
11-Ketotestosterone
SULT2A1
AKR1C3
DHEAS
Testosterone

	21-hydroxylase deficiency	11β-hydroxylase deficiency	17α-hydroxylase/ 17,20-lyase deficiency	3β-hydroxy-steroid dehydrogenase type 2 deficiency	P450 oxidoreductase deficiency	Lipoid adrenal hyperplasia	Cholesterol side chain cleavage enzyme deficiency
Affected gene (OMIM number)	*CYP21A2* (201910)	*CYP11B1* (202010)	*CYP17A1* (202110)	*HSD3B2* (201810)	*POR* (201750)	*StAR* (600617)	*CYP11A1* (118485)
Incidence	Classic: 1:10 000 to 1:20 000[25] Non-classic: 1:200[27] to 1:1000[26]	1:100 000[32] in Caucasians, 1:6000[33] in Moroccan Jews* Non-classic: unknown	1:50 000[34] Increased frequency in Brazil*[34,35]	Rare	Rare, 130 cases from 11 countries reported[36]	Rare, mostly Japanese, Korean, and Palestinian populations[37]	Rare, <30 patients, mostly from eastern Turkey[38]
Affected organs	Adrenal glands	Adrenal glands	Adrenal glands and gonads	Adrenal glands and gonads	Adrenal glands, gonads, liver, and skeletal	Adrenal glands and gonads	Adrenal glands and gonads
Disorder of sex development	Classic: 46,XX Non-classic: No	Classic: 46,XX Non-classic: No	46,XY	Classic: 46,XY, 46,XX (rare) Non-classic: No	46,XX, 46,XY (variable)	46,XY Non-classic: 46,XY (variable)	46,XY Non-classic: 46,XY (variable)
Salt wasting	Classic: Yes Non-classic: No	No	No	Yes	No	Classic: yes Non-classic: minimal to none	Classic: Yes Non-classic: minimal to none
Hypertension	No	Yes Non-classic: variable	Yes	No	Yes	No	No
Postnatal virilisation	Classic: yes Non-classic: yes	Classic: Yes Non-classic: Yes	No	Classic: 46,XX Non-classic: 46,XX	No	No	No
Sex steroid deficiency	No	No	Yes	Classic: Yes Non-classic: No	Yes	Yes Non-classic: variable	Yes Non-classic: variable

Auer, Nordenström, Lajic, Reisch *Lancet 2023*

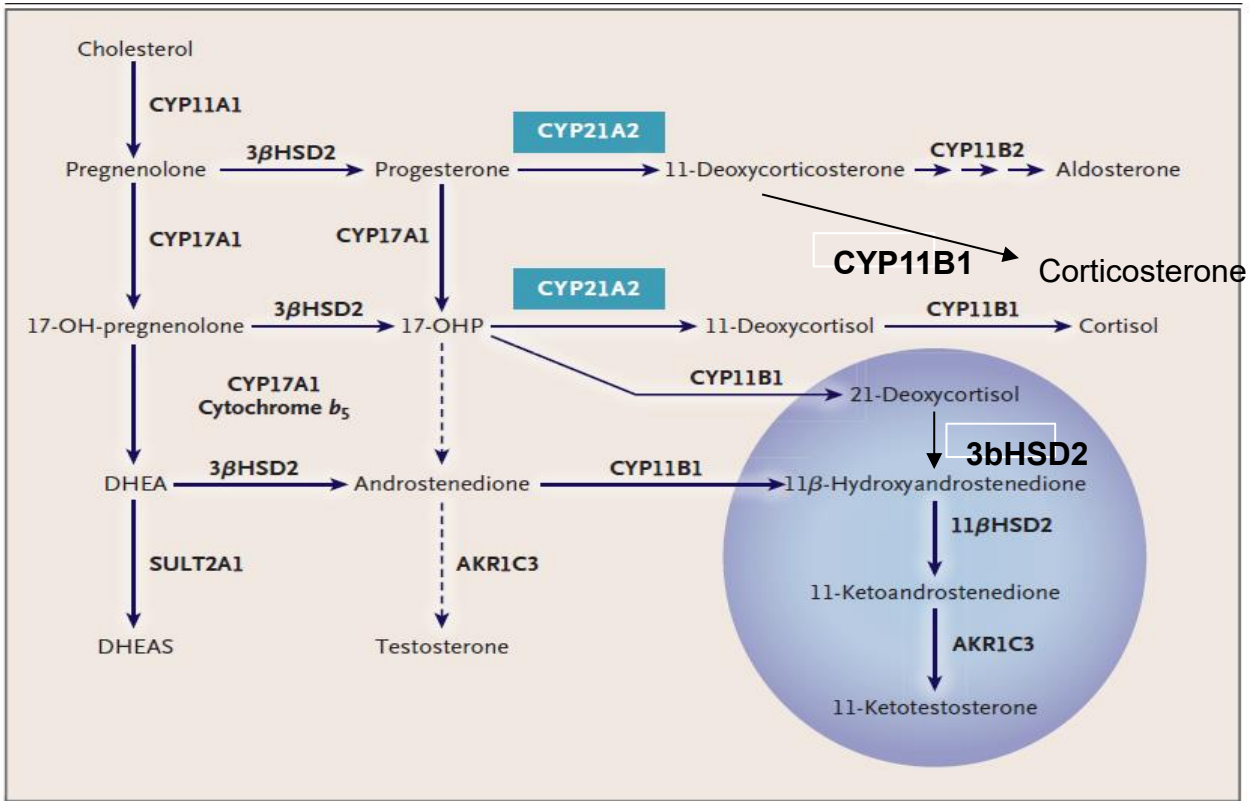
	21-hydroxylase deficiency	11β-hydroxylase deficiency	17α-hydroxylase/ 17,20-lyase deficiency	3β-hydroxy-steroid dehydrogenase type 2 deficiency
Affected gene (OMIM number)	*CYP21A2* (201910)	*CYP11B1* (202010)	*CYP17A1* (202110)	*HSD3B2* (201810)
Incidence	Classic: 1:10 000 to 1:20 000[25] Non-classic: 1:200[27] to 1:1000[26]	1:100 000[32] in Caucasians, 1:6000[33] in Moroccan Jews* Non-classic: unknown	1:50 000[34] Increased frequency in Brazil*[34,35]	Rare
Affected organs	Adrenal glands	Adrenal glands	Adrenal glands and gonads	Adrenal glands and gonads
Disorder of sex development	Classic: 46,XX Non-classic: No	Classic: 46,XX Non-classic: No	46,XY	Classic: 46,XY, 46,XX (rare) Non-classic: No
Salt wasting	Classic: Yes Non-classic: No	No	No	Yes
Hypertension	No	Yes Non-classic: variable	Yes	No
Postnatal virilisation	Classic: yes Non-classic: yes	Classic: Yes Non-classic: Yes	No	Classic: 46,XX Non-classic: 46,XX
Sex steroid deficiency	No	No	Yes	Classic: Yes Non-classic: No

	Clinical presentation	Hormonal profile	Cosyntropin stimulation testing*
21-hydroxylase deficiency **21OHD**	Classic: atypical genitalia (46,XX), neonatal salt wasting (75%), and virilisation <4 year old (46,XY) Non-classic: precocious pubarche, hirsutism, oligomenorrhea/amenorrhea, and female infertility	↑ 17OHP, 21-deoxycortisol, androstenedione, and renin ↓ Cortisol and aldosterone 17OHP 21DOL	17OHP >30 nmol/L (>1000 ng/dL) (several times higher for classic)
11β-hydroxylase deficiency **11bOHD**	Classic: atypical genitalia (46,XX), virilisation <4 years old (46,XY), hypertension, and hypokalaemia Non-classic: precocious pubarche, hirsutism, oligomenorrhea/amenorrhea, female infertility, and with or without hypertension	↑ DOC, 11-deoxycortisol, androstenedione and 17OHP (mild) ↓ Cortisol, aldosterone, corticosterone, and renin 11DOL, 11DOC	11-deoxycortisol >3 times the upper limit of normal (several times higher for classic)



17aOHD högt DOC, corticosterone, prog lågt 17OHPREG, 17OHP

17α-hydroxylase/ 17,20-lyase deficiency	Adolescent female with absence of secondary sexual characteristics, hypertension, and hypokalaemia	↑ DOC, corticosterone (>115 nmol/L, 4000 ng/dL), and progesterone ↓ Cortisol, aldosterone, 17-hydroxypregnenolone, 17OHP, renin, DHEA, and androstenedione	Poor response of 17-hydroxypregnenolone and 17OHP Elevated ratios of DOC to cortisol and corticosterone to sex steroids
3β-hydroxysteroid dehydrogenase type 2 deficiency **3bHSD**	Atypical genitalia (46,XX: rare, mild; 46,XY), neonatal salt wasting Non-classic: precocious pubarche, hirsutism, and oligomenorrhea/ amenorrhea (46,XX); atypical genitalia (46,XY; mild)	↑ 17-hydroxypregnenolone, DHEA, and renin ↓ Cortisol, aldosterone, progesterone, 17OHP, androstenedione, DOC, and 11-deoxycortisol högt 17OHPREG, DHEA	17-hydroxypregnenolone >150 nmol/L (5000 ng/dL) Elevated ratios pregnenolone to progesterone and 17-hydroxypregnenolone to 17OHP



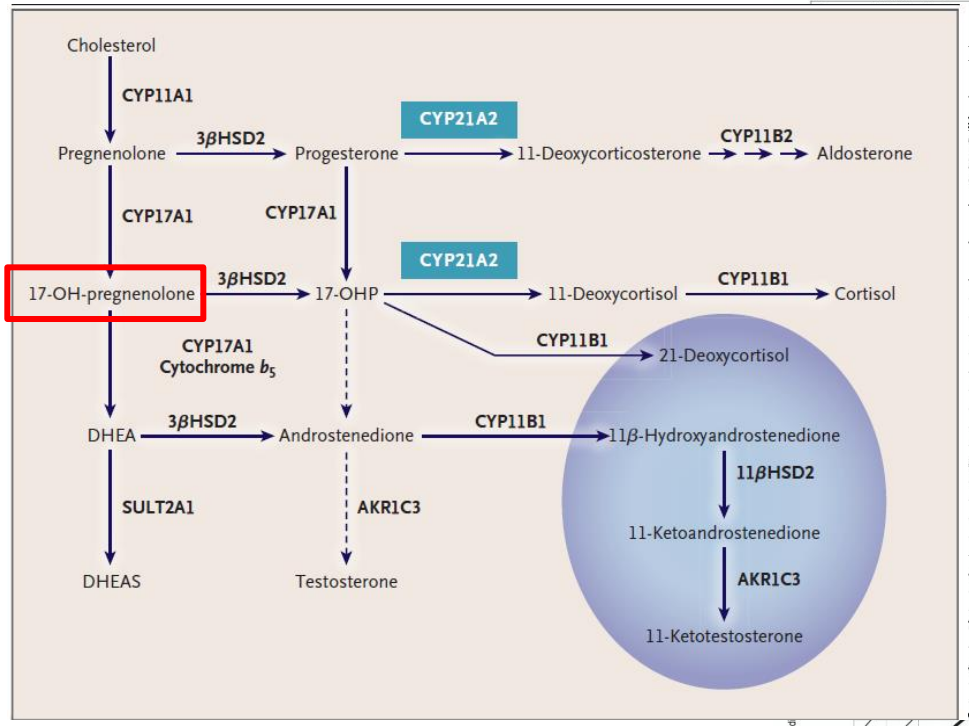
Fall

- Flicka. FV 3690g, FL 51,5, Apgar 9-10-10
- Trögt med amningen, dygn 2 B-glukos 0,0 resp 0,1 stiger till 0,7 mM på 5ml glukos po. Inlägges på neo glukosdropp och tillmatning
- Stigmatiserad? Fyrfingerfåra bilat, bred näsrot, ngt hypoton med ofullständig Moro reflex. Cor blåsljud. Karyotyp. GÅR HEM från NEO.

- Screeninglarm 17-OHP 125 nmol/L. Ej viriliserad. Na 127 mM, K 6 mM.
- Behandling: HC, Florinef, Addex Na.

- PKU prov 2/17OHP >900 nmol/L; S-17OHP 760 nmol/L.
- A4 53 nmol/L, Testo > 55 nmol/L, Kortisol 401 nmol/L, DHEAS 5,8, ACTH 180 pmol/L
- Med behandling 17-OHP sjunker till 50 nmol/L.
- Familjen sätter ut beh med HC/Florinef!

- Virilisering med behåring, över labia majora medialt, sämre vikt- och längdutveckling men pigg.
- Återinsätter medicinering efter långa diskussioner.
- GENOTYPNING: **3 beta HSD!**
- Svår form enl genotypen, men utan prenatal virilisering (?)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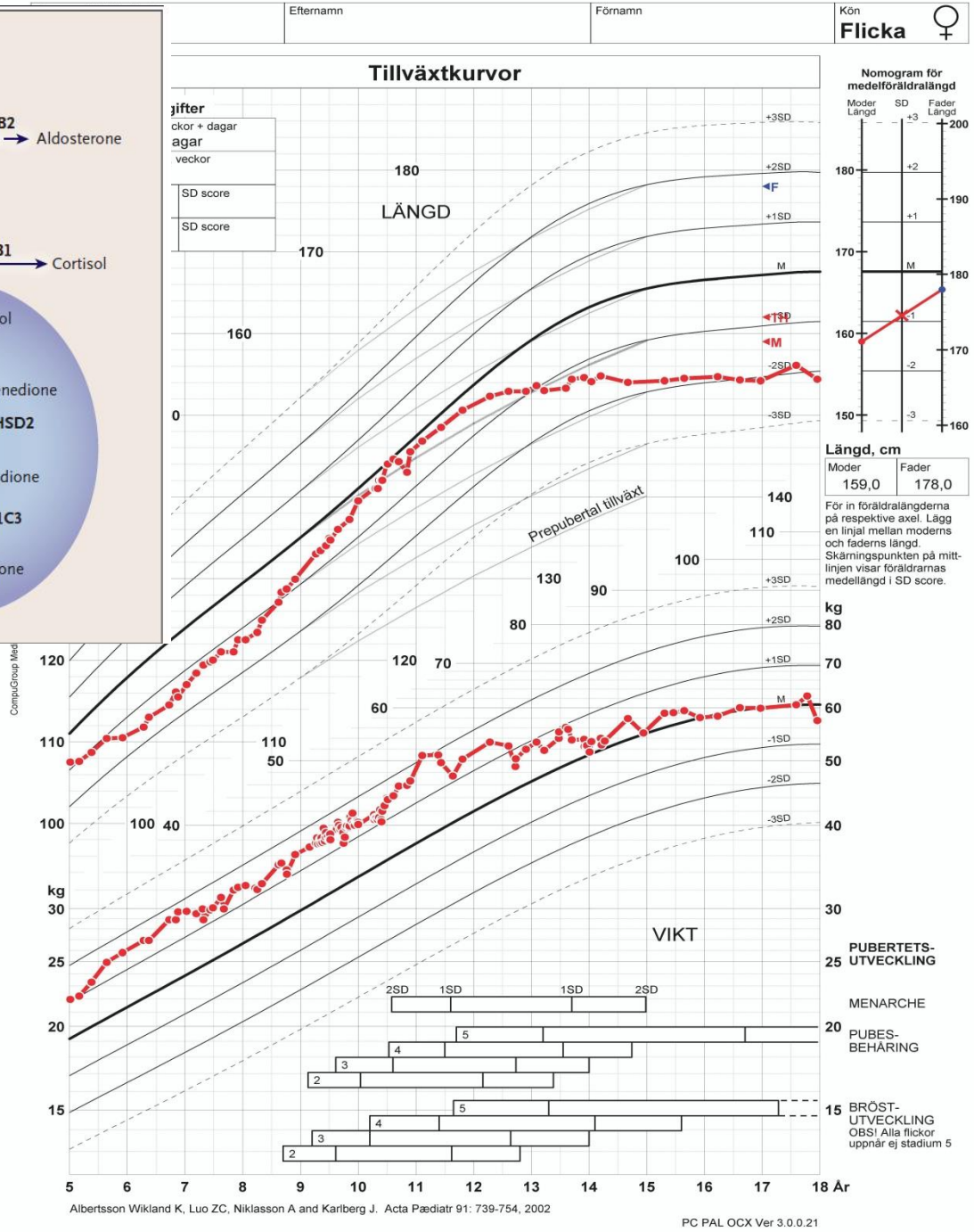
3βHSD2
17-OHP
CYP21A2
11-Deoxycortisol
CYP11B1
Cortisol
CYP17A1
Cytochrome b5
CYP11B1
21-Deoxycortisol
DHEA
3βHSD2
Androstenedione
CYP11B1
11β-Hydroxyandrostenedione
11βHSD2
SULT2A1
AKR1C3
11-Ketoandrostenedione
AKR1C3
DHEAS
Testosterone
11-Ketotestosterone


Efternamn
Förnamn
Kön
Flicka
Tillväxtkurvor
LÄNGD
VIKT
Prepubertal tillväxt
Nomogram för medelföräldralängd
Moder Längd
SD
Fader Längd
Längd, cm
Moder 159,0
Fader 178,0
För in föräldralängderna på respektive axel. Lägg en linjal mellan moderns och faderns längd. Skärningspunkten på mittlinjen visar föräldrarnas medellängd i SD score.
PUBERTETS-UTVECKLING
MENARCHE
PUBES-BEHÅRING
BRÖST-UTVECKLING
OBS! Alla flickor uppnår ej stadium 5
Albertsson Wikland K, Luo ZC, Niklasson A and Karlberg J. Acta Pædiatr 91: 739-754, 2002
PC PAL OCX Ver 3.0.0.21

Ökad hormonproduktion i binjurebarken

Cushings sjukdom - Hypofysadenom

Cushings syndrom – Adrenokortikal tumör

Symtom Cushing hos barn

- Viktökning (som kan vara måttlig)
- Låg eller upphörd längdtillväxt
- Röda kinder
- Ansiktsförändring (kolla familjealbumet!!!)
- Buffalo hump
- Blåmärken; Hudbristningar
- Längdförkortning (kotkompressioner)
- Osteopeni
- Högt blodtryck
- Trötthet, muskulär hypotoni
- Depression, nedsatt primärminnesfunktion; vredesutbrott
- Sömnstörning/sömnlöshet

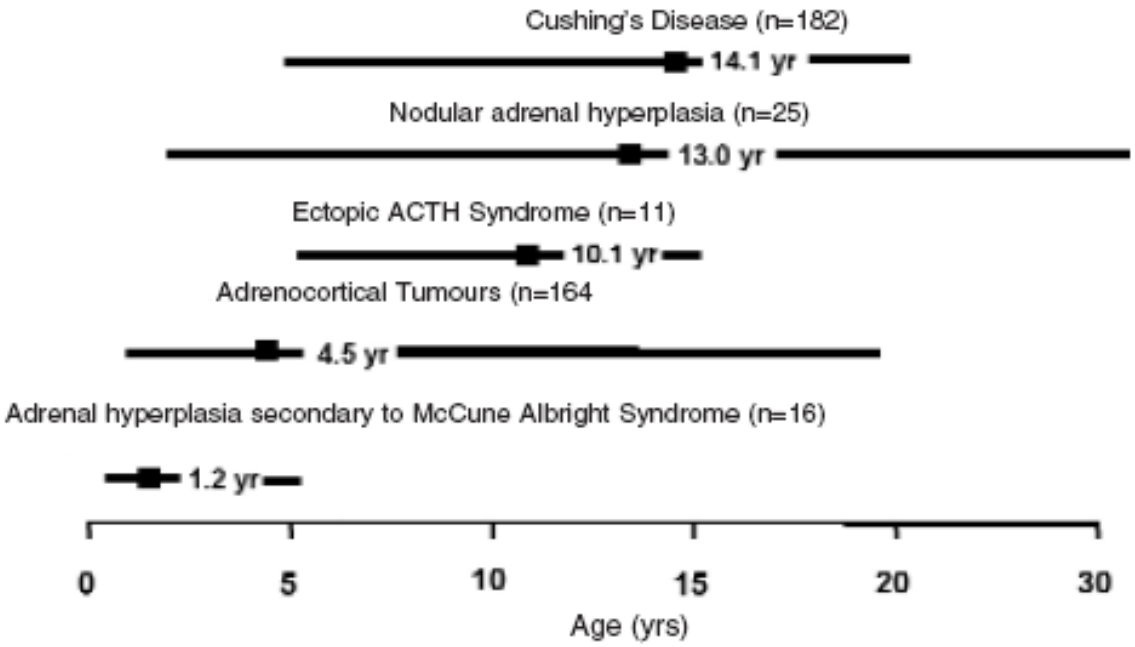
Cushing in childhood

Cushing syndrome in infancy: usually associated with McCune-Albright syndrome; adrenocortical tumors most commonly occur in children under four years of age.

Cushing's disease is the commonest cause of CS after five years of age.

The median age of pituitary Cushing presentation is 14.1 yrs.

Peak incidence for age of different forms of Cushing



Review of 398 pediatric CS cases from the literature showing ages of peak incidence, represented by the boxes

Chan 2007

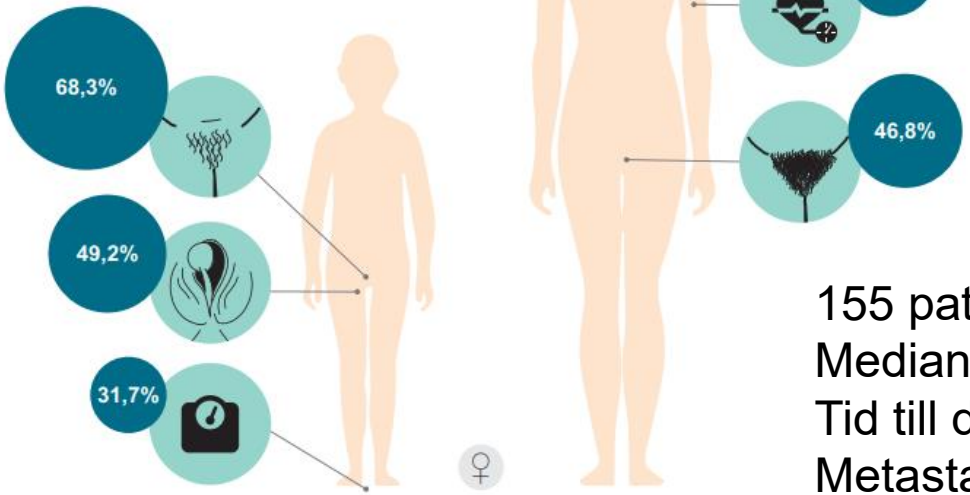
The Endocrine Phenotype Induced by Pediatric Adrenocortical Tumors Is Age- and Sex-Dependent

Marina Kunstreich,[1,2] Desiree Dunstheimer,[1] Pascal Mier,[2] Paul-Martin Holterhus,[3] Stefan A. Wudy,[4] Angela Huebner,[5] Antje Redlich,[2,*] and Michaela Kuhlen[1,*]

JCEM 2024

A

N=63 prepubertala flickor
Pubarche
Klitorishypertrofi
Viktuppgång



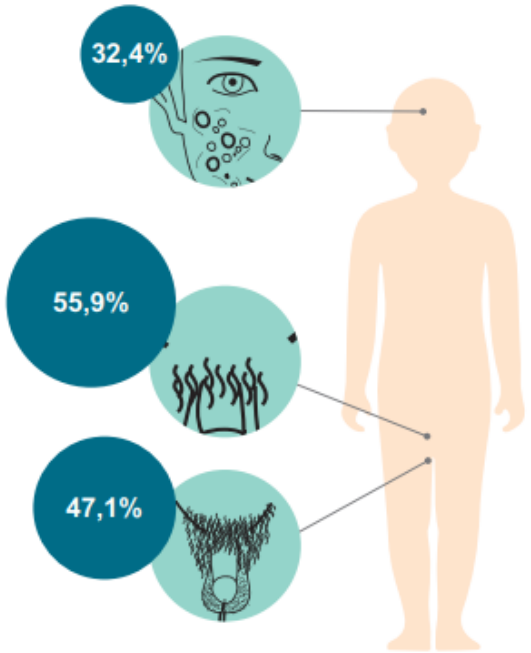
B

N=47 pubertala flickor
Ökad pubesbehåring
Acne
Hypertoni

155 patienter (110 f, 45 m).
Median ålder vid ACT diagnos 4.2 år.
Tid till diagnos 4.8 mån.
Metastaserande sjukdom – klitorishypertrofi, icke met, hypertoni.

C

N=34 prepubertala pojkar
Pubarche
Penistillväxt
Acne



D

N=11 pubertala pojkar
Viktuppgång
Hypertoni
Ökad pubesbehåring
Striae

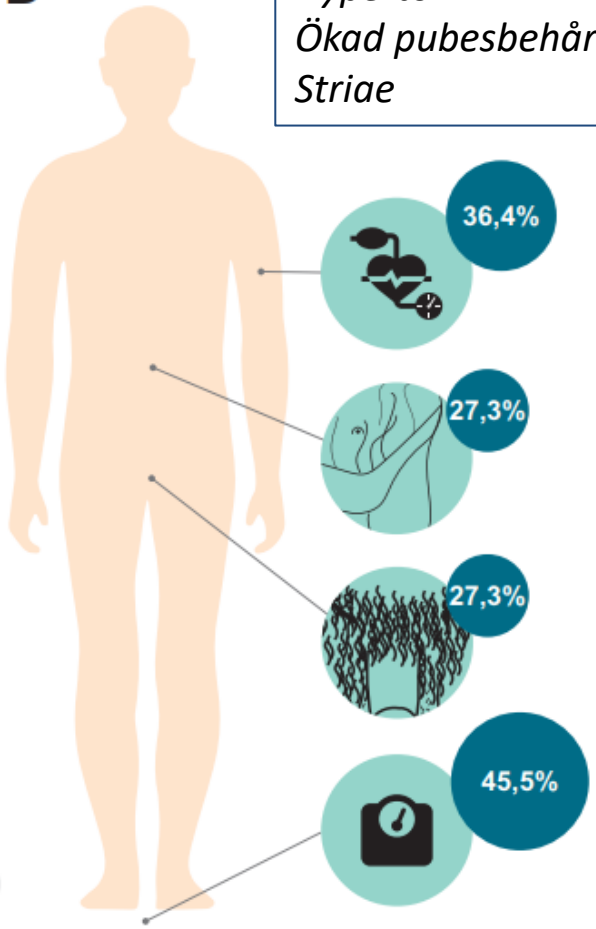


TABLE 1 Hereditary tumor syndromes associated with ACC.

Syndrome	Associated Gene mutations	Major clinical features	Prevalence %-ACC
Li-Fraumeni syndrome	*TP53*	Breast cancer, leukemia, lymphoma, brain tumors, sarcomas, adrenocortical carcinoma	3-7% in adults 50-80% in children
Beckwith-Wiedemann syndrome	*IGF2, CDK1C, H19* locus changes on 11p15	Wilms tumor, hepatoblastoma and neuroblastoma	<1%
Multiple Endocrine Neoplasia 1	*MEN1*	Hyperparathyroidism, pituitary tumors, parathyroid tumors, pancreatic neuroendocrine tumors (PNETs), collagenoma, angiofibroma	1.4%
Lynch syndrome	*MSH2, MSH6, MLH1, PMS2*	Colorectal carcinoma, endometrial carcinoma, ovarian cancer, pancreatic cancer, brain cancer	3%
Familial adenomatous polyposis	*APC*	Colorectal cancer, duodenal carcinoma. Thyroid cancer, desmoid tumor	<1%
Neurofibromatosis type 1	*NF1*	Malignant peripheral nerve sheet tumor, pheochromocytoma, neurofibroma, optic glioma	<1%
Carney complex	*PRKAR1A*	Primary pigmented nodular adrenocortical disease (PPNAD), Sertoli cell tumors, thyroid adenoma, myxoma, pituitary tumors, schwanoma	<1%

Hos barn ACC mest androgenproduktion, funktionella tumörer.

Influence of sex and functional status on the value of serum steroid profiling in discriminating adrenocortical carcinoma from adrenocortical adenoma

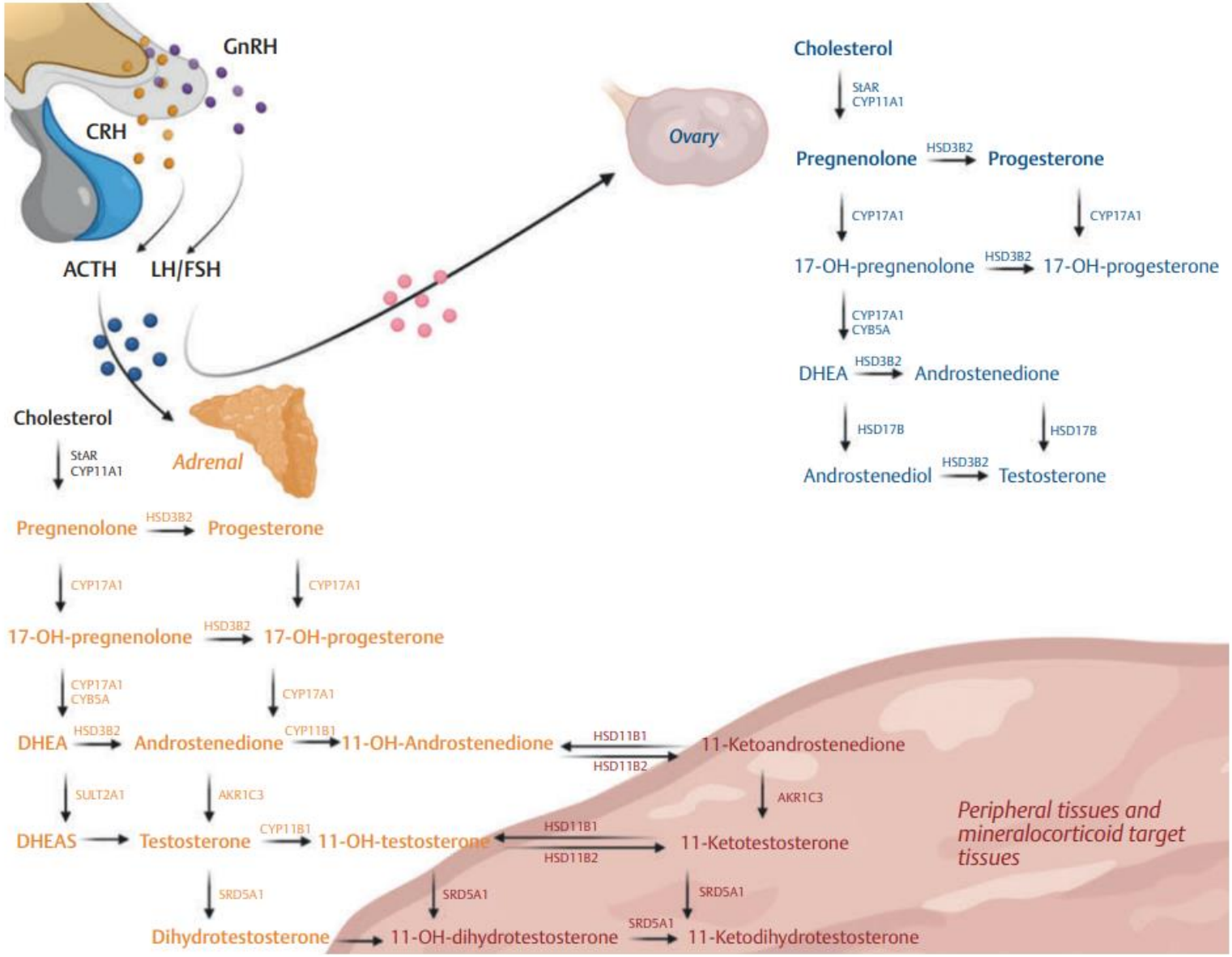
Yan Weng[1†], Ju-Ying Tang[1†], Xiao-Yun Zhang[1†], Diao-Zhu Lin[1], Ying Guo[1], Ying Liang[1], Lin Wang[2], Jing Zhou[1], Li Yan[1], Tian-Xin Lin[3*] and Shao-Ling Zhang[1*]

Frontiers in Endocrinology 2024

31 patients with ACC and 31 matched patients with ACA.
ACC larger tumor diameters, lower (BMI), and higher levels of **11-deoxycortisol, progesterone, and androstenedione** than ACA.

11-deoxycortisol was the only valuable index for discriminating ACC from ACA, regardless of functional status and sex.

Progesterone, DHEA, and DHEAS levels were higher in the functional ACC group than in the non-functional ACC group.


GnRH
CRH
ACTH
LH/FSH
Ovary
Cholesterol
StAR
CYP11A1
Adrenal
Pregnenolone
HSD3B2
Progesterone
CYP17A1
17-OH-pregnenolone
17-OH-progesterone
CYB5A
DHEA
Androstenedione
CYP11B1
11-OH-Androstenedione
HSD11B1
HSD11B2
11-Ketoandrostenedione
SULT2A1
AKR1C3
DHEAS
Testosterone
11-OH-testosterone
11-Ketotestosterone
SRD5A1
Dihydrotestosterone
11-OH-dihydrotestosterone
11-Ketodihydrotestosterone
HSD17B
Androstenediol
Peripheral tissues and mineralocorticoid target tissues


Voff!

Karolinska Institutet

Tack!