Review
17-Hydroxylase deficiency

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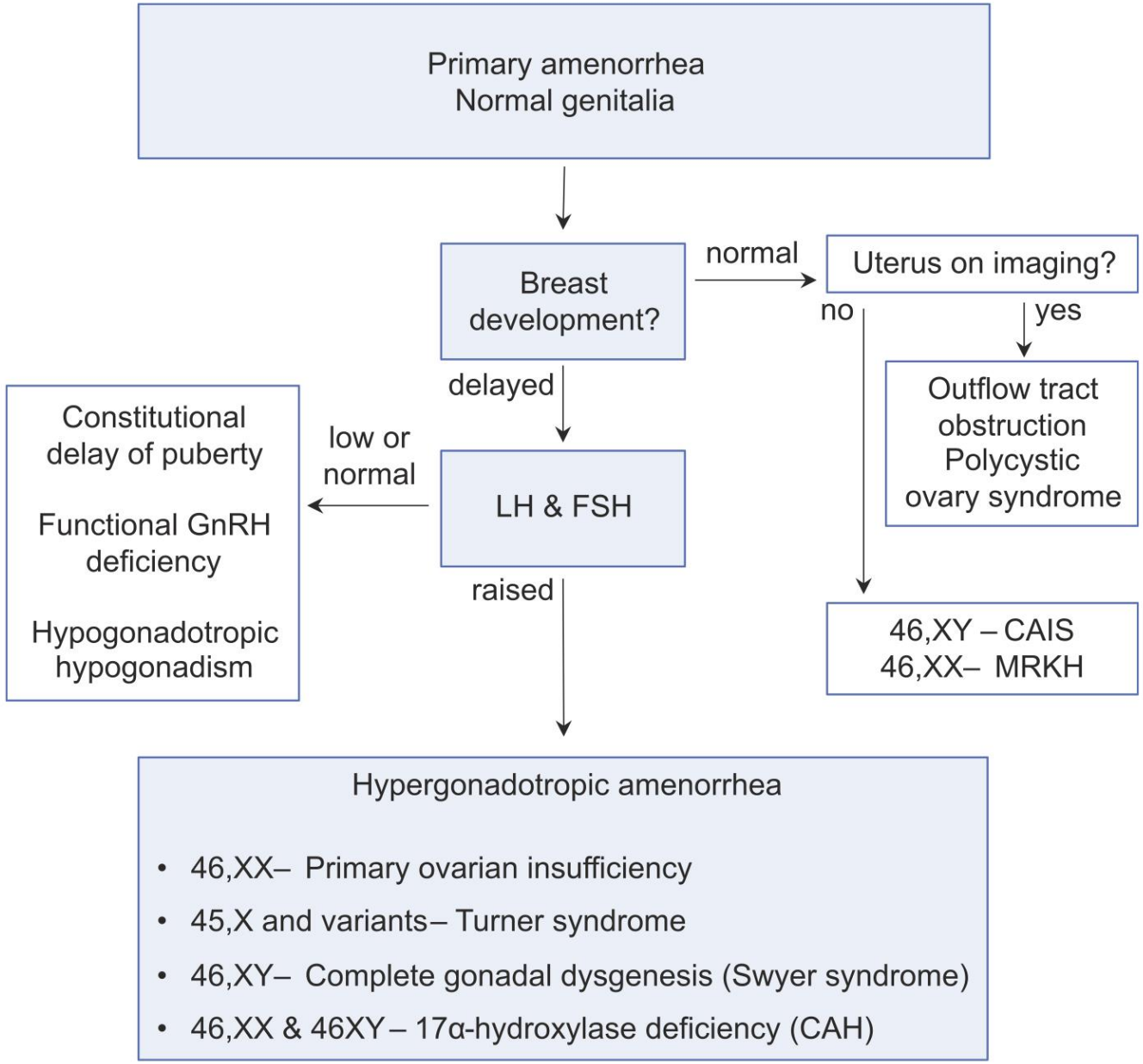
14/7/66

Primary amenorrhea



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History

- The initial case of 17OHD was described by Biglieri et al. in 1966.
- He described a 35-year-old 46, XX woman presented with primary amenorrhea, hypertension, hypokalemia, prepubertal breasts, and absent axillary and pubic hair.

17-Hydroxylation Deficiency in Man *

EDWARD G. BIGLIERI, MARY ANNE HERRON, AND NORMA BRUST

(From the Medical Services, San Francisco General Hospital, and the Department of Medicine, University of California School of Medicine, San Francisco, Calif.)

Journal of Human Hypertension 2018, 32:150–157
Journal of Clinical Investigation Vol. 45, No. 12, 1966

Prevalence

- 17OHD is an uncommon form of CAH, representing only 1% of cases.
- More than 150 cases have been described in the literature to date.
- Occurs in 1/100,000 live births (more common in Brazil and Japan)
- Many 46, XX patients are misdiagnosed with gonadal dysgenesis and 46, XY patients are misdiagnosed with androgen insensitivity (despite low androgen levels).
- The disease is more common in consanguinity. (AR inheritance)

Journal of Human Hypertension 2018, 32:150–157

Prevalence

- The second most common form of CAH varies with country and ethnic background.
  - In Brazil, 17 hydroxylase/17,20-lyase deficiency is the second most common
  - 11-hydroxylase deficiency is most common in the Middle East.
  - In Japan and Korea, both congenital lipoid adrenal hyperplasia and P450-oxidoreductase deficiency are more common than in the rest of the world.

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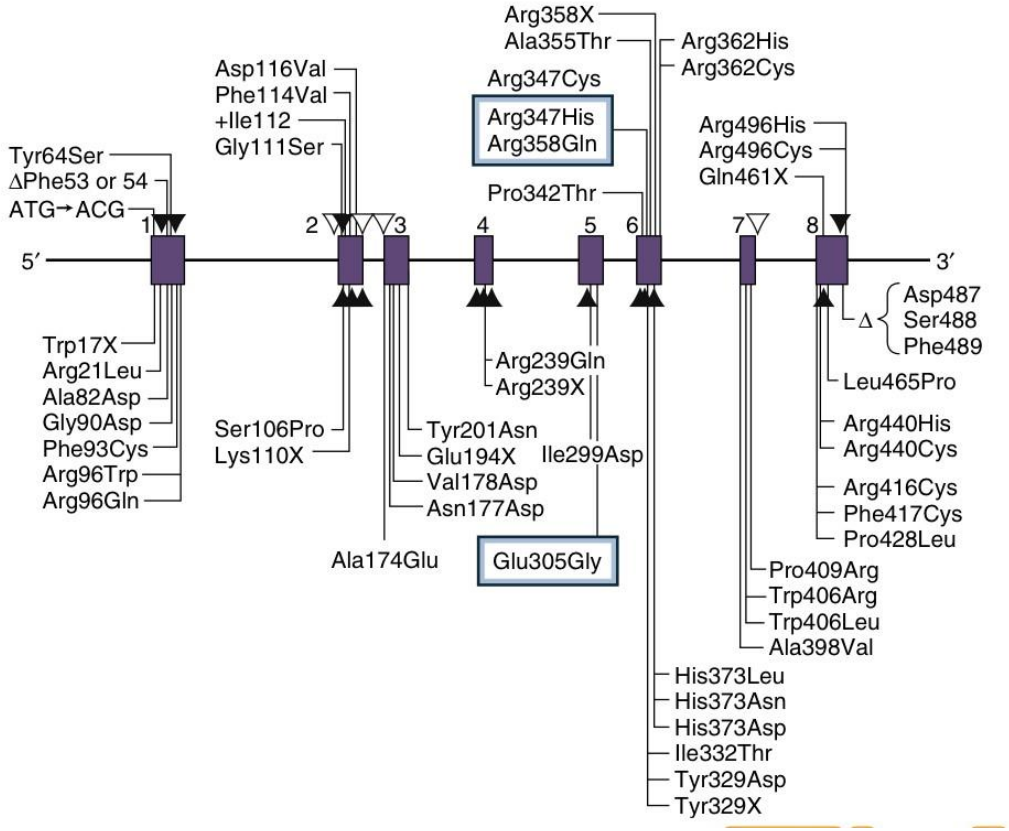
Genetics

- Mutation in CYP17A1 located on chromosome 10q24.3. (OMIM 202110)
- Over 100 mutations have been described including missense, frameshift, splicing, insertion, and deletion mutations.
- This mutation is expressed both in the adrenals and gonads



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Genetics

- The most commonly mutated residues include
  - **Exon 6**
    - Tyr329 (to Asp, X, or frameshift TAC→AA with 418X)
    - Arg362 (to Cys or His)
    - His373 (to Leu, Asn, or Asp)
  - **Exon 7** : Trp406 (to Arg)
  - **Exon 8** : deletion of Asp487-Ser488-Phe489 or a CATC duplication within Asp487-Ser488

J Steroid Biochem Mol Biol. 2017 January ; 165(Pt A): 71–78.
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Genetics

- The CYP17A1 gene encodes a microsomal enzyme (P450c17) that catalyzes both 17-hydroxylase and 17,20-lyase activities that is expressed in the adrenals and gonads.

- Defects in P450c17 action can result in two different forms of CAH.
  - Combined 17-hydroxylase/17,20-lyase deficiency (most often)
  - Isolated 17,20-lyase deficiency (very rare case)

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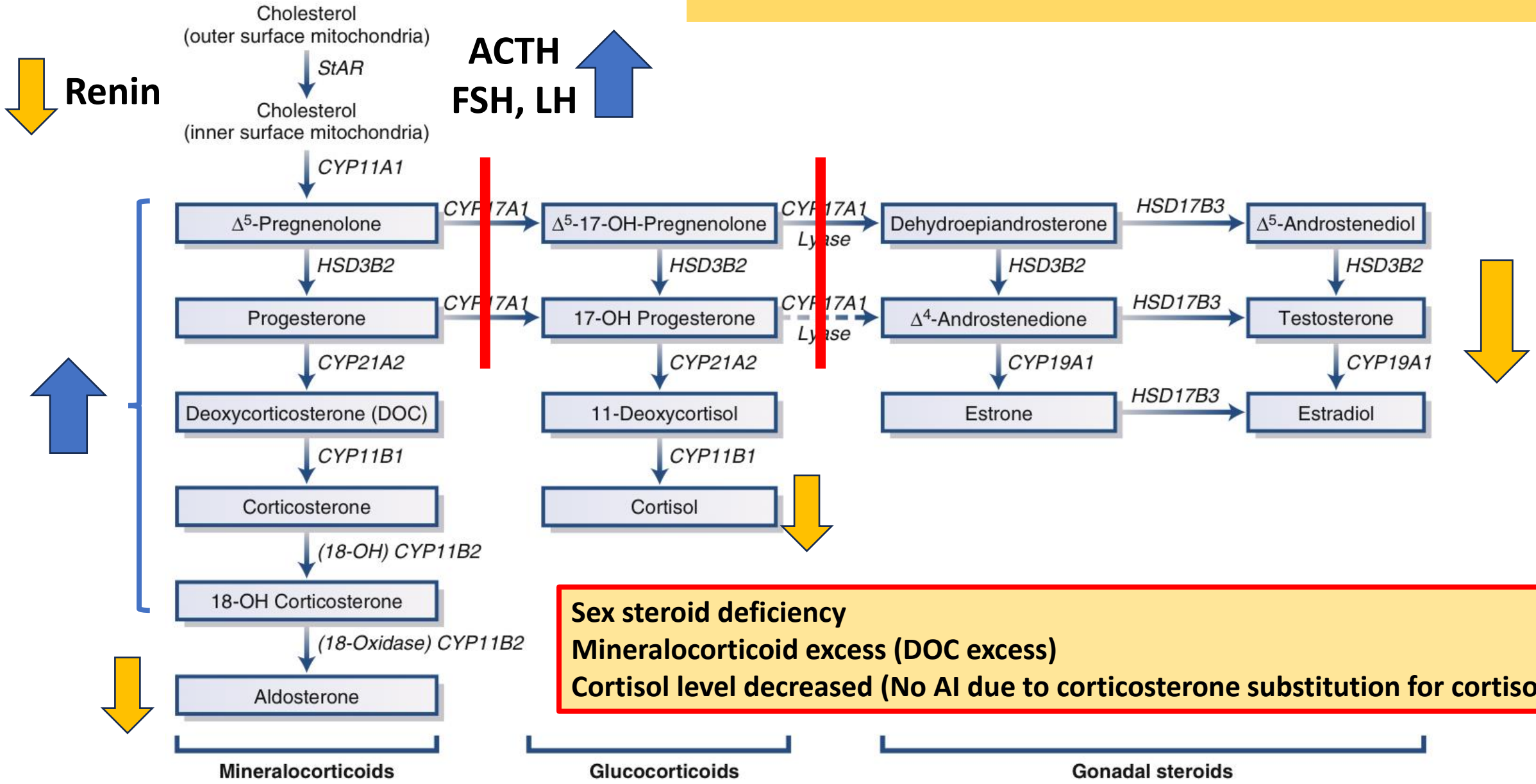
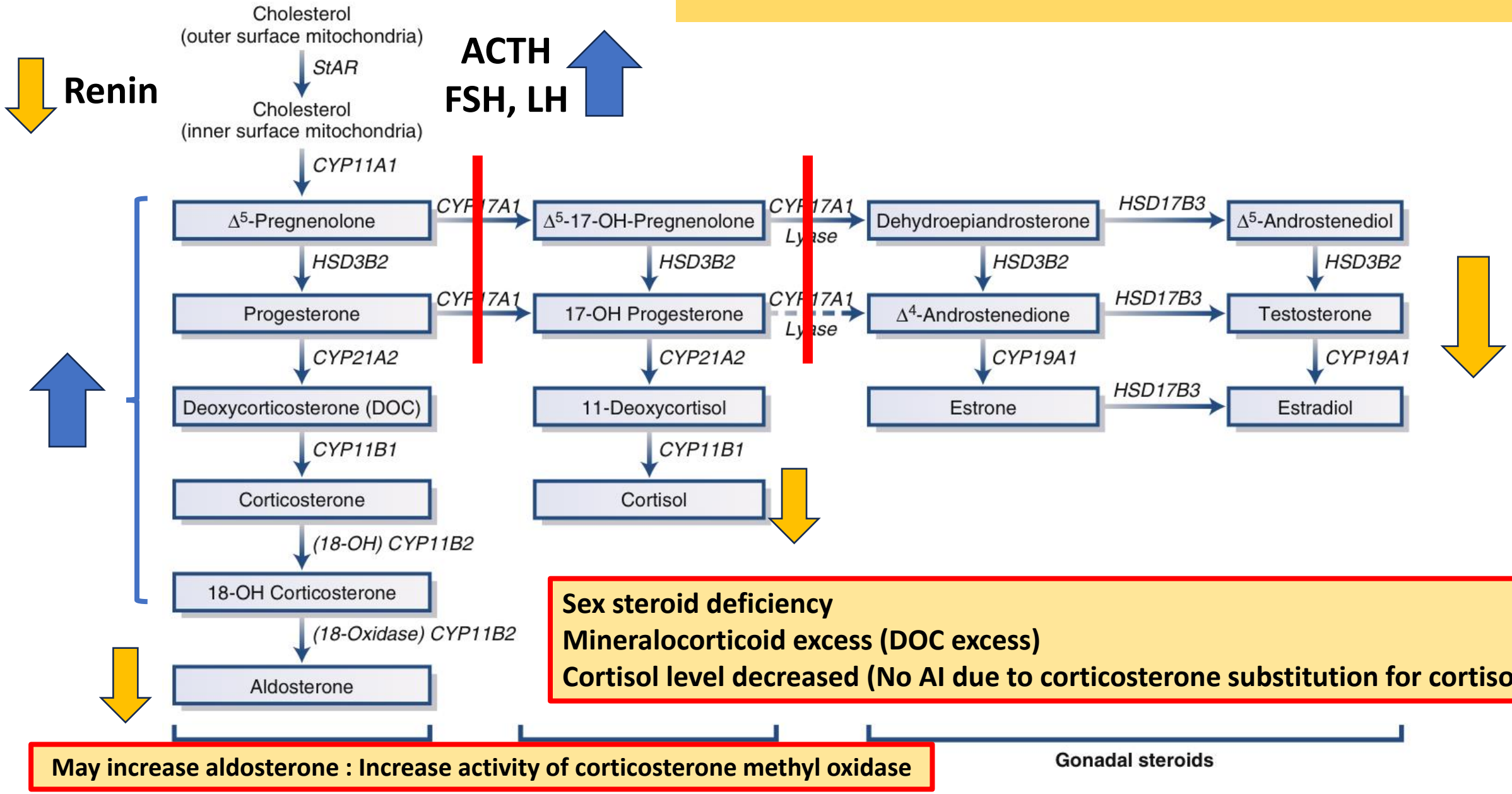
Combined 17-hydroxylase/17,20-lyase deficiency



Sex steroid deficiency
Mineralocorticoid excess (DOC excess)
Cortisol level decreased (No AI due to corticosterone substitution for cortisol)

Combined 17-hydroxylase/17,20-lyase deficiency



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May increase aldosterone : Increase activity of corticosterone methyl oxidase

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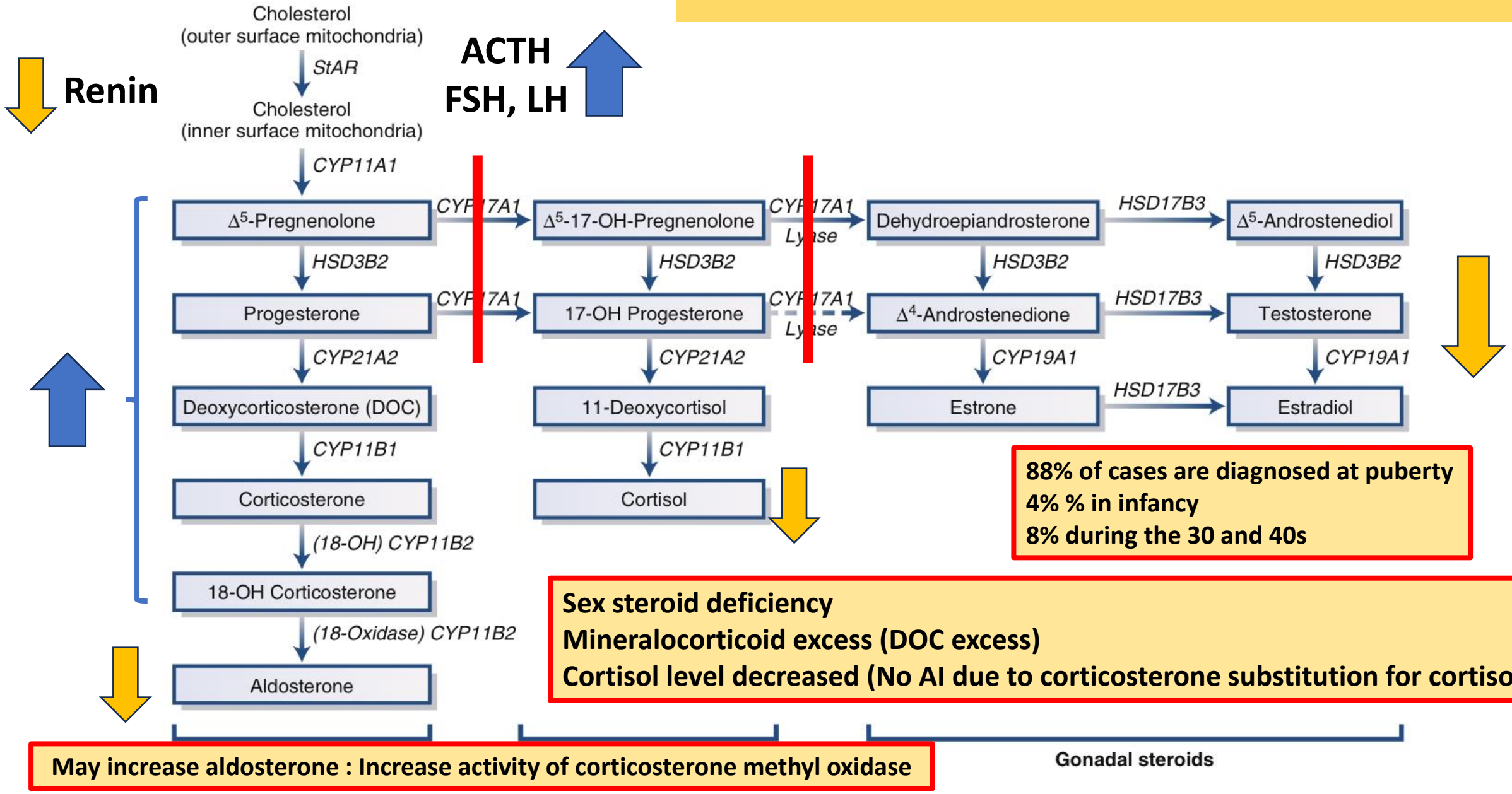

88% of cases are diagnosed at puberty
4% % in infancy
8% during the 30 and 40s

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Clinical manifestations

- Hypertension and/or hypokalemia are often present but variably ascertained prior to evaluation of the amenorrhea and pubertal failure.

- Bone age is frequently delayed because of decreased sex steroid production, and prolonged linear growth can lead to tall stature.

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Clinical manifestations

	46,XX	46,XY
Breast	Not developed	Not developed (Some gynecomastia)
Pubic & Axillary hair	Absent or sparse	Absent or sparse
Gonad	Ovary (large & painful ovarian cysts are common)	-Testis (inguinal canal, intraabdominal, labioscrotal fold) -Inguinal hernia
Internal genitalia	Mullerian	Wolffian (Hypoplastic)
External genitalia	Female	Female (Blind vaginal pouch)
FSH, LH	High	High
Estrogen	Low	Low
Bone age	Delayed (Tall stature)	Delayed (Tall stature)
Blood pressure	HT with hypokalemic metabolic alkalosis	HT with hypokalemic metabolic alkalosis
Adrenal insufficiency	No clinical AI (But low cortisol level)	No clinical AI (But low cortisol level)

Imaging & Pathology

- Patients may have bilateral macronodular adrenal hyperplasia or normal adrenal glands on CT.

- At the tissue level, the adrenal glands show marked hyperplasia of the ZF and ZR with nearly normal ZG.

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Clinical information	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years old)	12	6	6	6	1
Social gender	Female	Female	Female	Female	Female
External genital	Female	Female	Female	Female	Female
Breast (Tanner grade)	1	1	1	1	1
Height (cm) (SD)	142 (<−1 SD)	–	–	136 (2 SD)	–
Blood pressure (mmHg)	138/94	136/98	124/83	169/103	Normal
Karyotype	46, XY	46, XY	46, XX	46, XY	46, XY
Pelvic ultrasound					
Uterus	Not find	Not find	33 × 3.2 × 2.6 mm	Not find	Not find
Ovaries	Not find	Not find	Unclear	Not find	Not find
Testis	Not find	Not find	Not find	Not find	In bilateral groin
Pelvic MRI (uterus and ovaries)	Not find	–	–	–	–
Adrenal MRI	–	–	–	Left adrenal nodular	–
Adrenal CT	No abnormality	–	–	Left adrenal nodular	–
Adrenal ultrasonography	No abnormality	No abnormality	No abnormality	No abnormality	No abnormality

Diagnosis

- Lack of secondary sex characteristics at puberty.
- Plasma concentrations of
  - High level : corticotropin, DOC, corticosterone, and progesterone
  - Low level : 17-OHP, cortisol, and gonadal steroids
- Low-renin hypertension and hypokalemic alkalosis.

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Management

- Replacement therapy with physiologic doses of glucocorticoids

  (Prednisolone 2-5 mg/day, Dexamethasone 0.25-1.0 mg/day or equivalent dose)
  - Suppresses DOC and corticosterone secretion
  - Normalizes serum potassium levels, blood pressure, and plasma renin and aldosterone levels.

- The alternative treatment is a mineralocorticoid antagonist, such as spironolactone or eplerenone, or a combination of low-dose glucocorticoid plus enough mineralocorticoid antagonist to control the blood pressure and potassium.

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Management

- Multidisciplinary approach

- Most 17OHD cases are reared as females and have female gender identity, and thus estrogen replacement is introduced at the age of normal puberty and up titrated, with cyclic progestin in 46, XX patients.
- Ovulation induction has led to term pregnancies in 46, XX cases.

- Gonadectomy is usually performed in 46,XY patients who have a female gender identity and can consent.

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Thank you