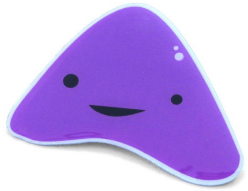
Mahidol University
Faculty of Medicine Siriraj Hospital

SiENDO
Division of Endocrinology and Metabolism
Faculty of Medicine Siriraj Hospital



Reviews in internal medicine R3

Reproductive and growth disorders

Taweesak Wannachalee, MD

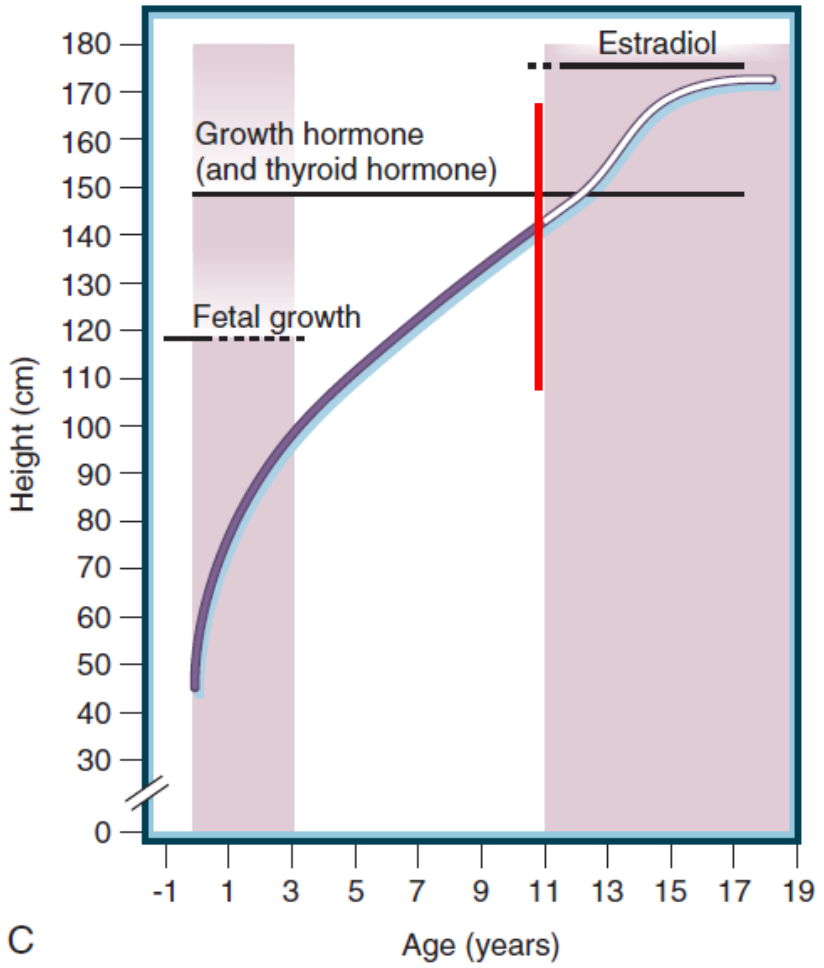
23-11-2024


SiENDO

Physiology of growth

Nutrition
GH
Thyroid hormone

Sex steroids
- Increase GH
and IGF-1



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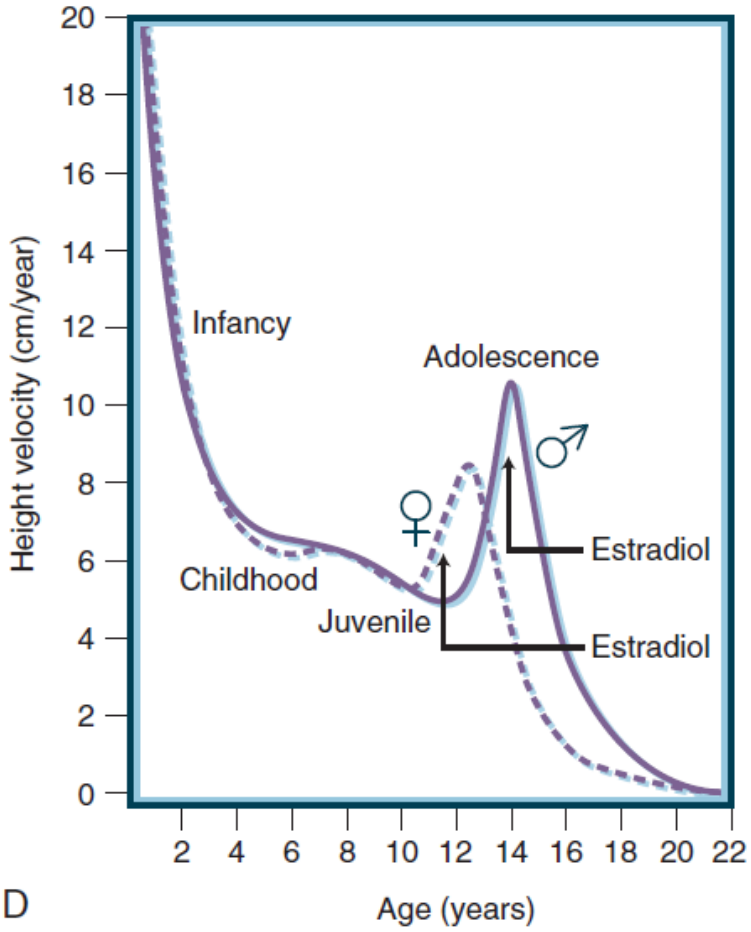

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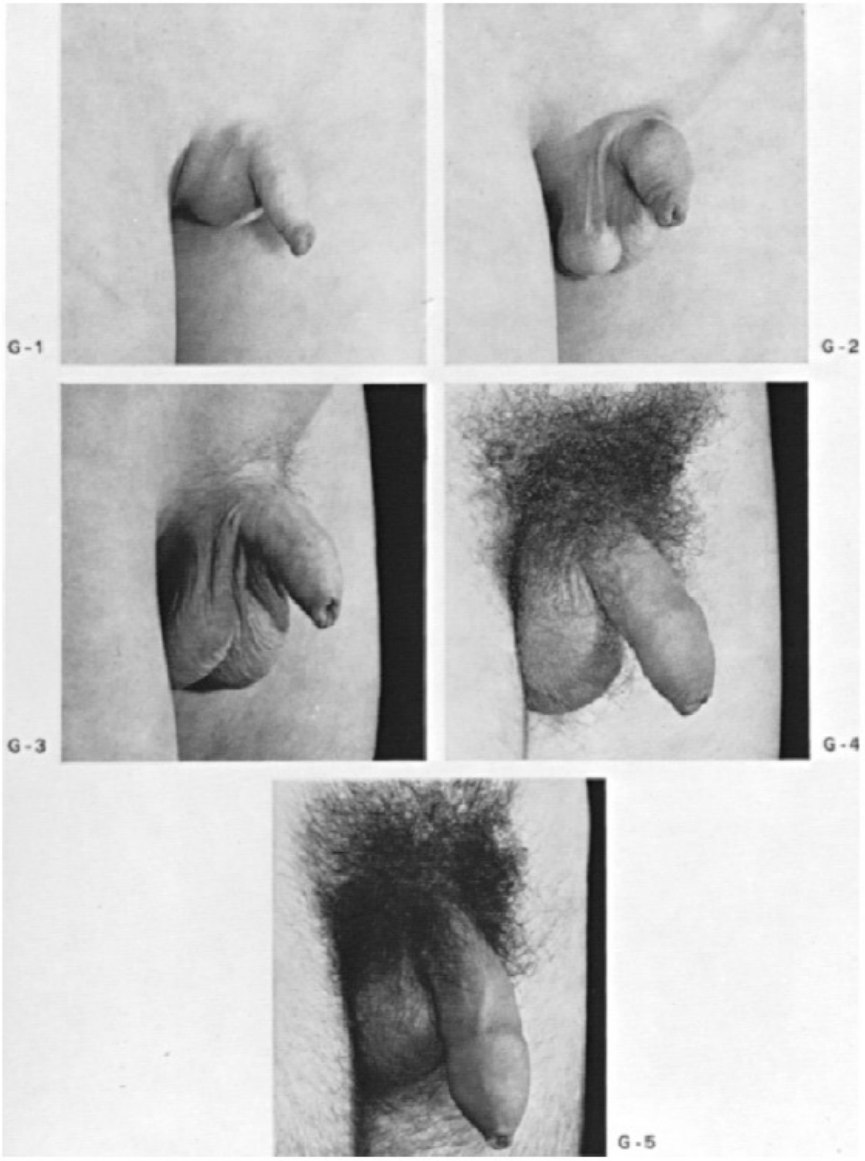
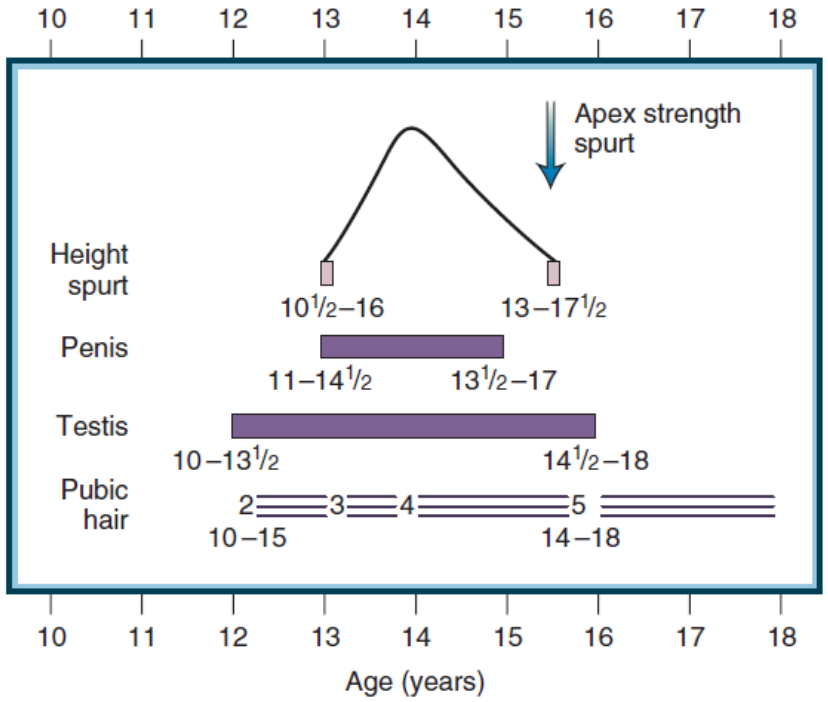
Physiology of growth



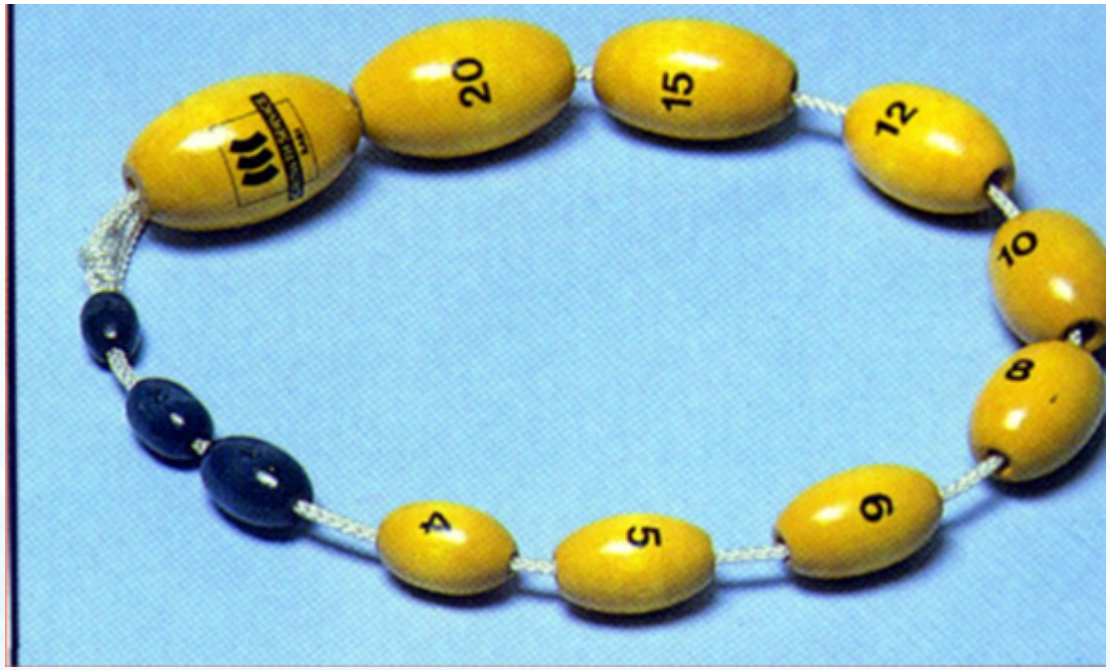
Male

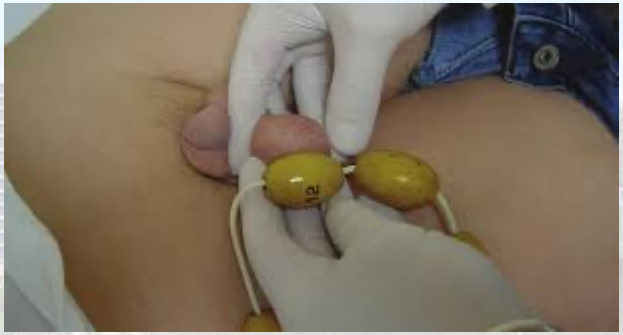


Puberty : Boy

Testicular enlargement 4 mL or 2.5 cm

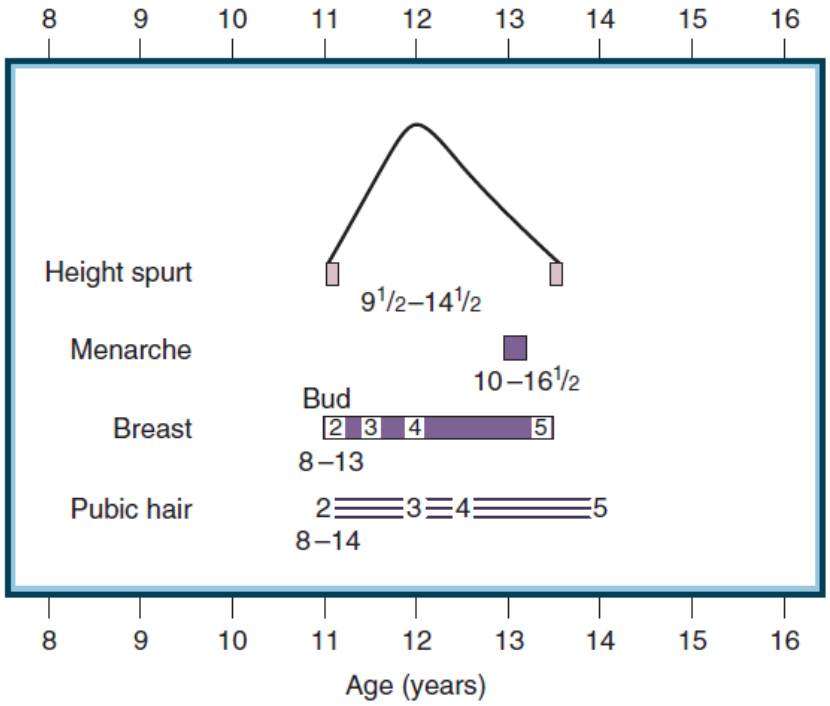
Prader orchidometer

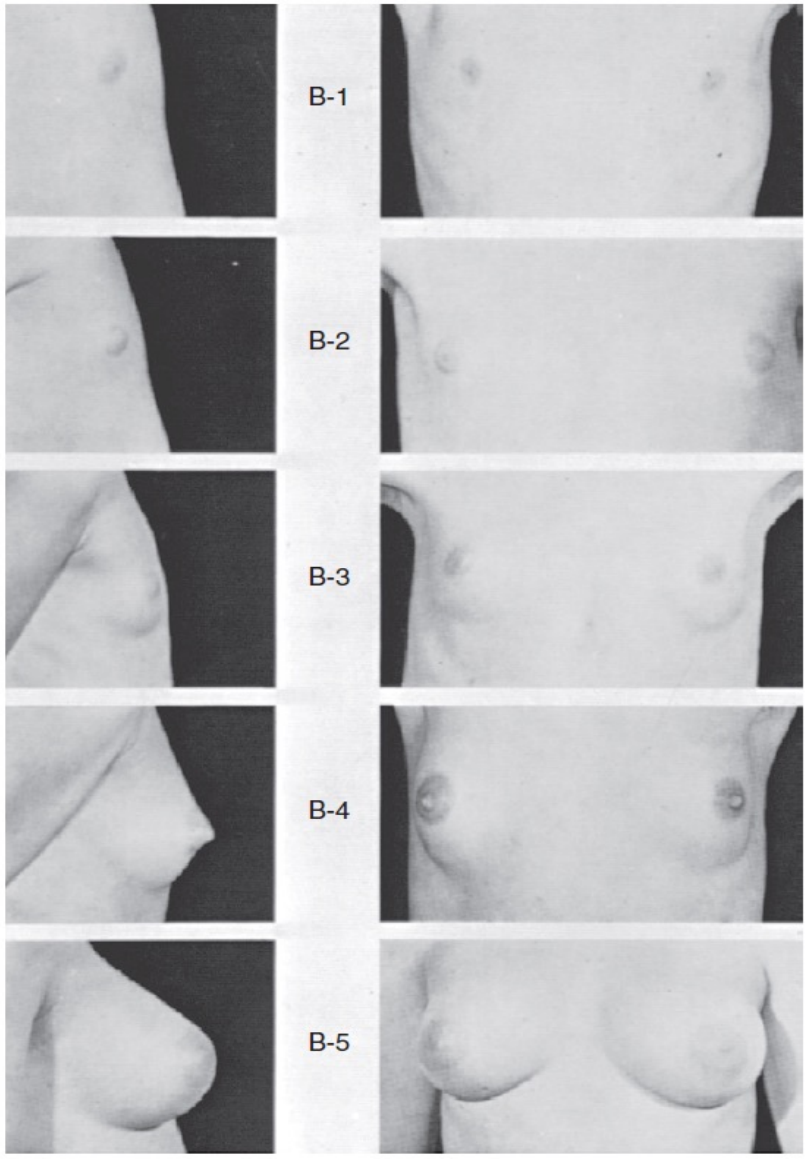




Physiology of growth

Female





Puberty : Girl

Breast bud

Short stature

Definition

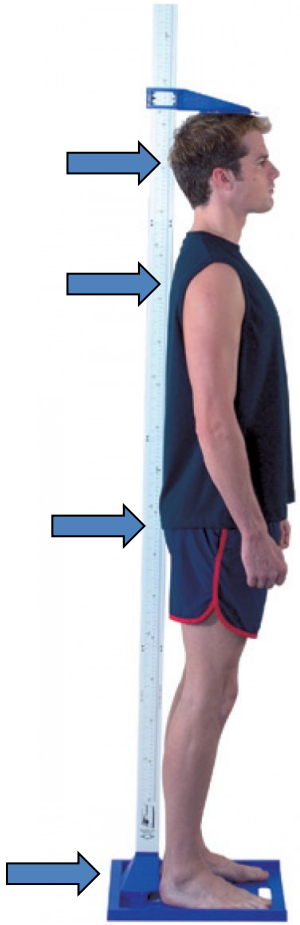
- ✓Height < 2 SD below the mean age
- ✓Height < 3rd percentile for chronological age

Important information

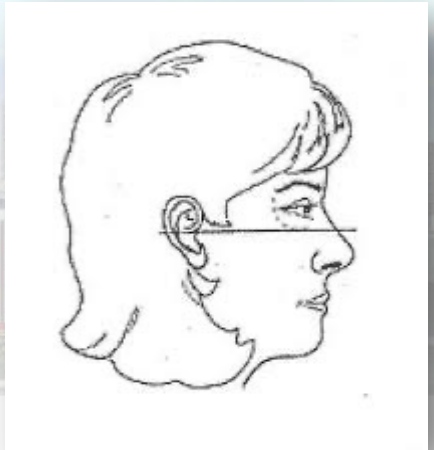
- ✓Accurate height measurement
- ✓Previous growth record
- ✓Height velocity
- ✓Mid-parental height
- ✓Upper:Lower segment ratio
- ✓Bone age

Accurate height measurement

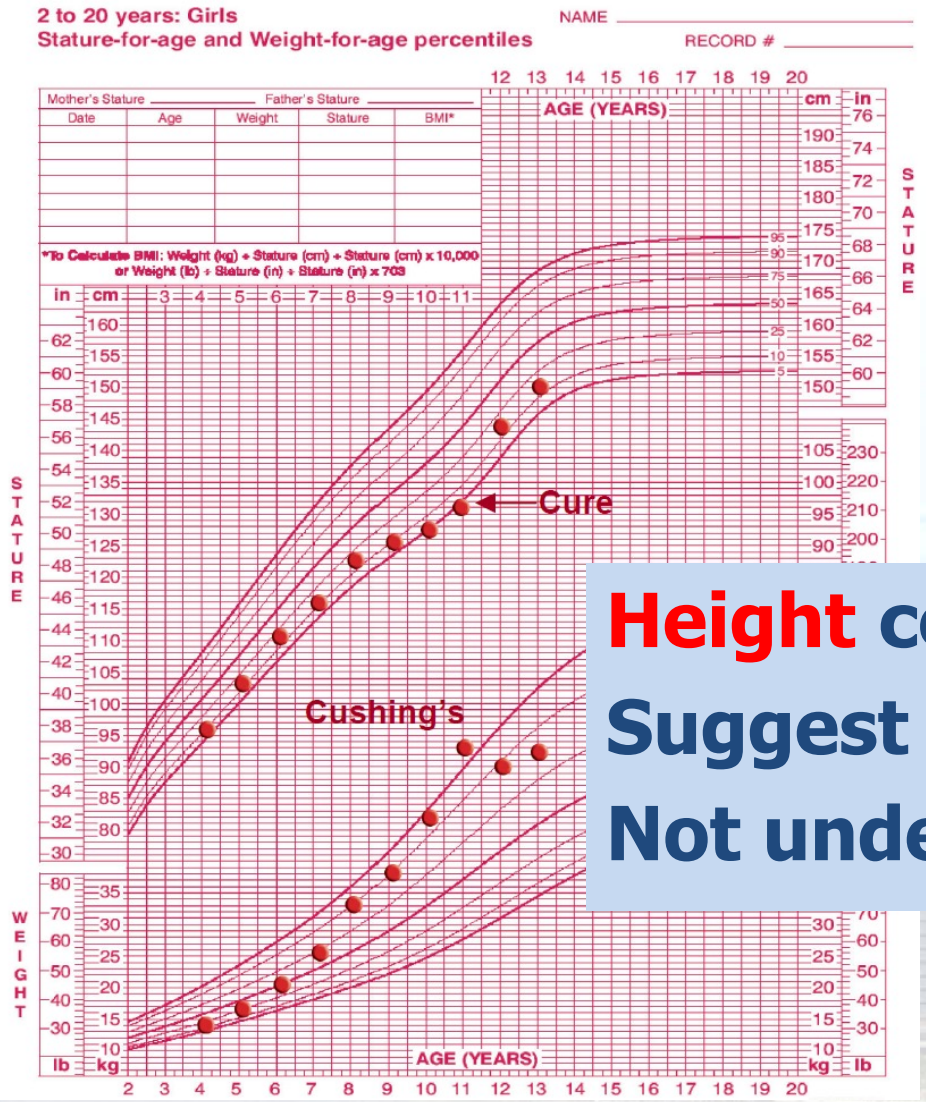
Harpenden stadiometer



- ✓ **Without foot wear**
- ✓ Heels, buttocks, scapula and occiput touching the wall
- ✓ Lower border of the eye socket in the same horizontal plane as external auditory meatus (**Frankfurt plane**)
- ✓ Looking straight ahead



Previous growth record



- ✓Cushing's syndrome
- ✓Growth hormone deficiency
- ✓Hypothyroidism
- ✓Albright's hereditary osteodystrophy

Height centile < Weight centile

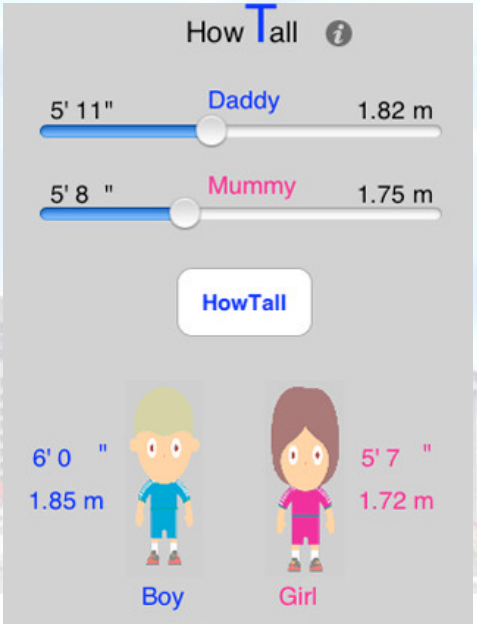
Suggest endocrine causes

Not undernutrition ★★★

Mid-parental height

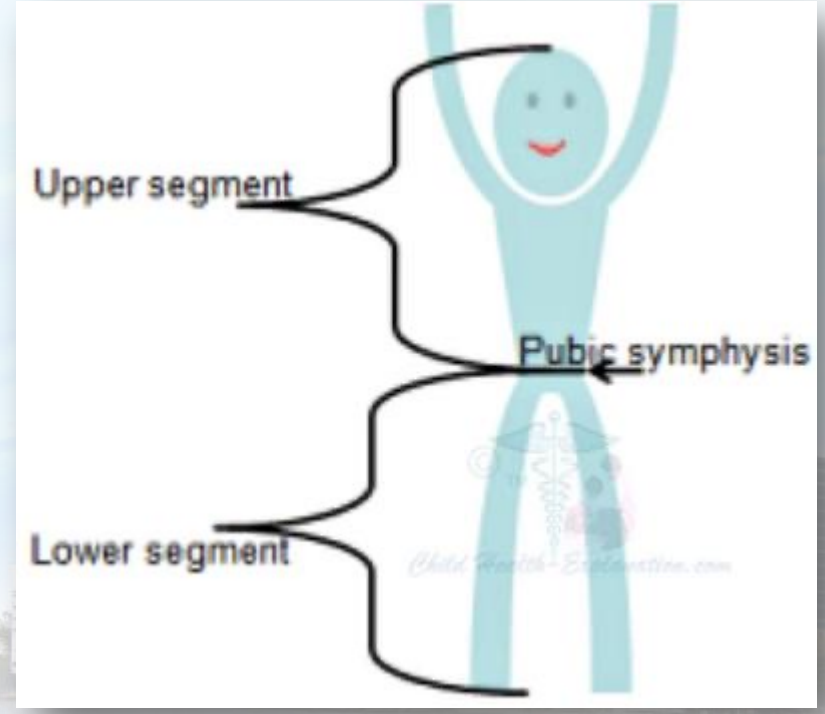
Girl = $\frac{\text{Father's height + Mother's height} - 13}{2}$ ± 5-8 cm

Boy = $\frac{\text{Father's height + Mother's height} + 13}{2}$ ± 5-8 cm



U:L segment ratio

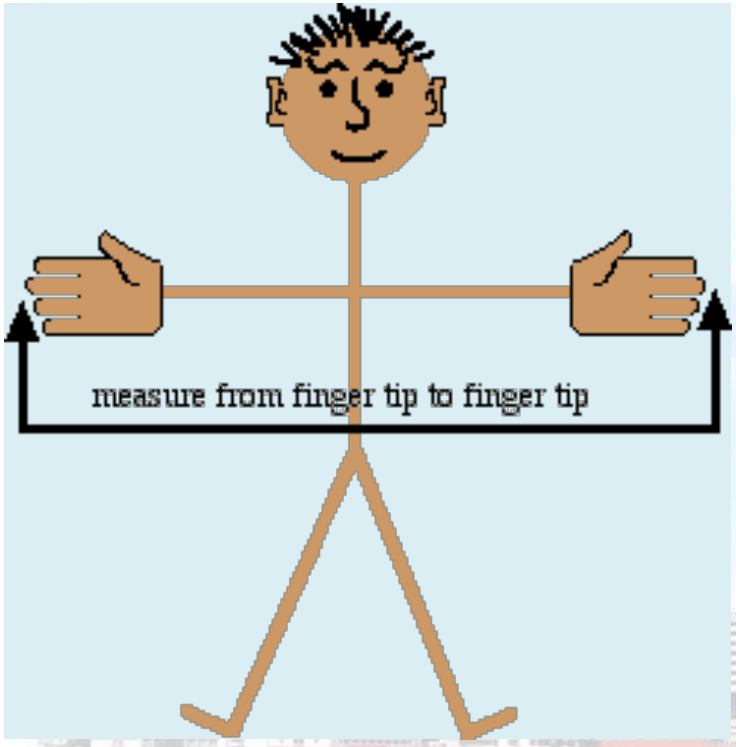
- **Lower segment** = วัดจาก upper border ของ pubic symphysis ถึงพื้น
- **Upper segment** = Height – Lower segment
- First step : Height measurement



Age	U/L segment
Birth	1.7
6 mo	1.6
1 yr	1.5
2 yr	1.4
3 yr	1.3
4 yr	1.25
5 yr	1.2
10 yr	**1.0**

Arm span

- วัดจากปลายนิ้วกลางข้างหนึ่งไปสู่ปลายนิ้วกลางอีกข้างหนึ่ง เมื่อเหยียดแขนออกไปทั้งสองข้างขนานกับพื้น

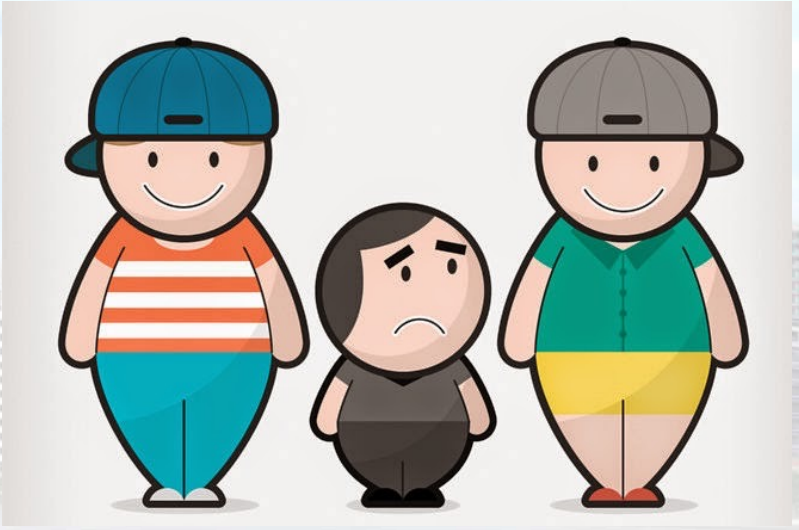


Boy age 10-11yr **arm span < height**
Man **arm span – height= 5.3cm**

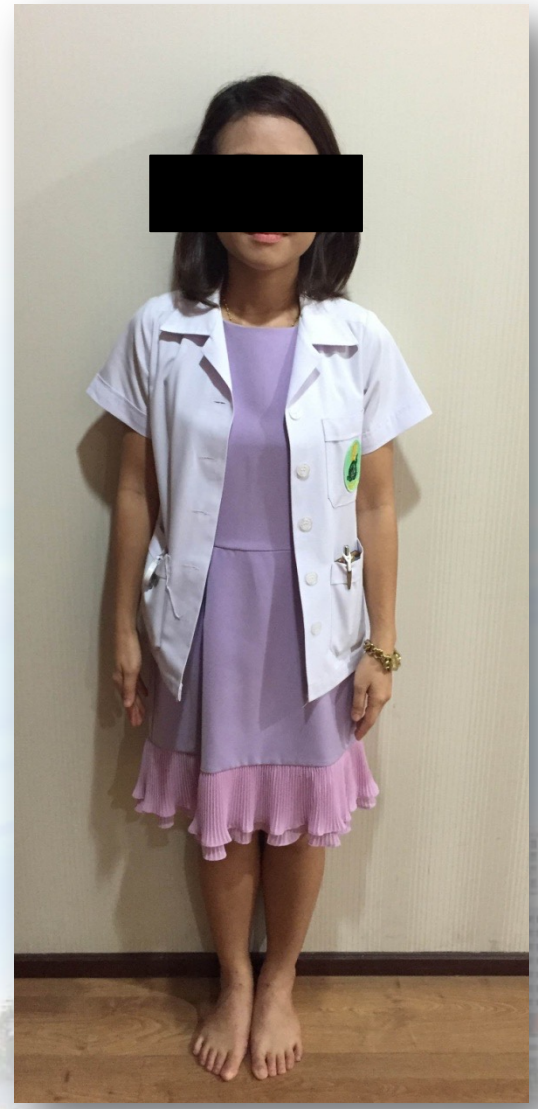
Girl age 11-14yr **arm span < height**
Woman **arm span – height = 1.2cm**

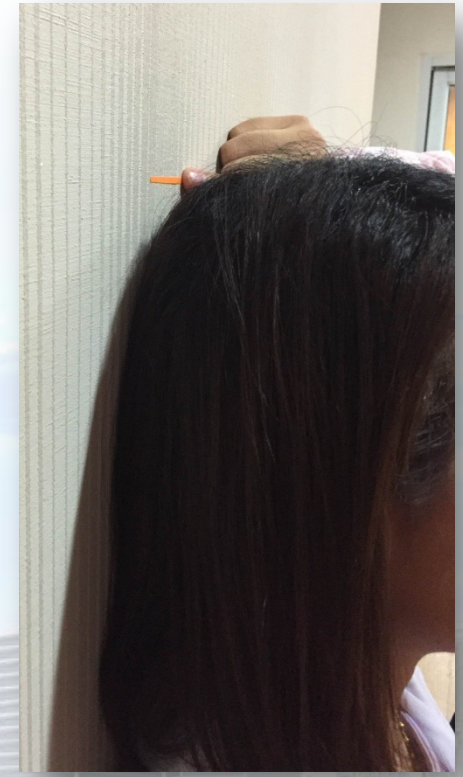
When to concern : short stature

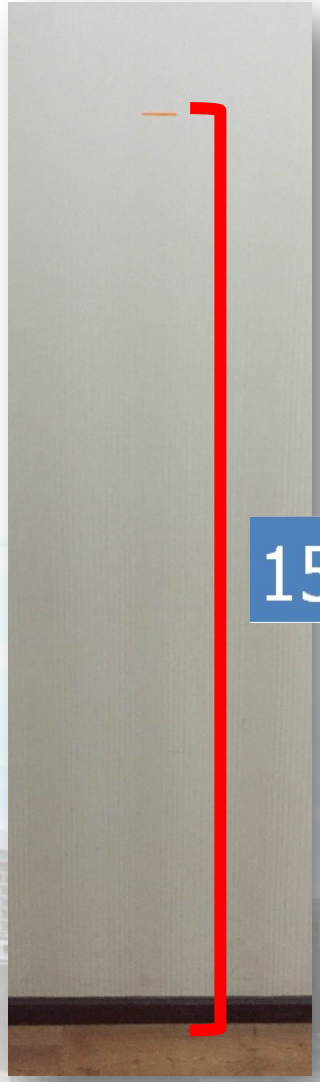
- Severe short stature
- Poor height velocity
- Dysmorphic features
- Signs and symptoms of systemic illness
- Height centile < MPH centile



Height measurement

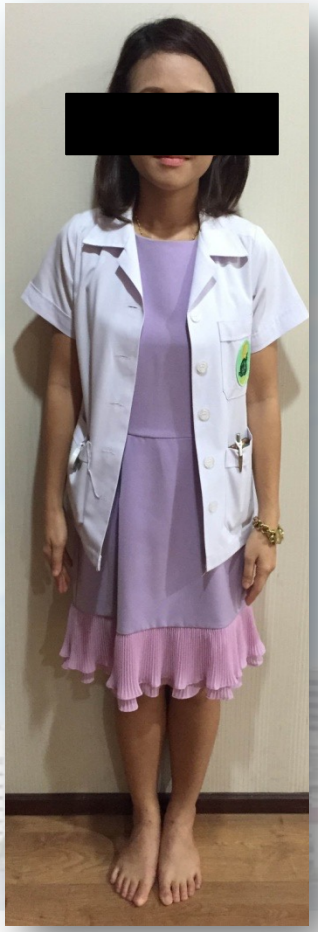






Upper : Lower segment ratio

Height – Lower segment = Upper segment

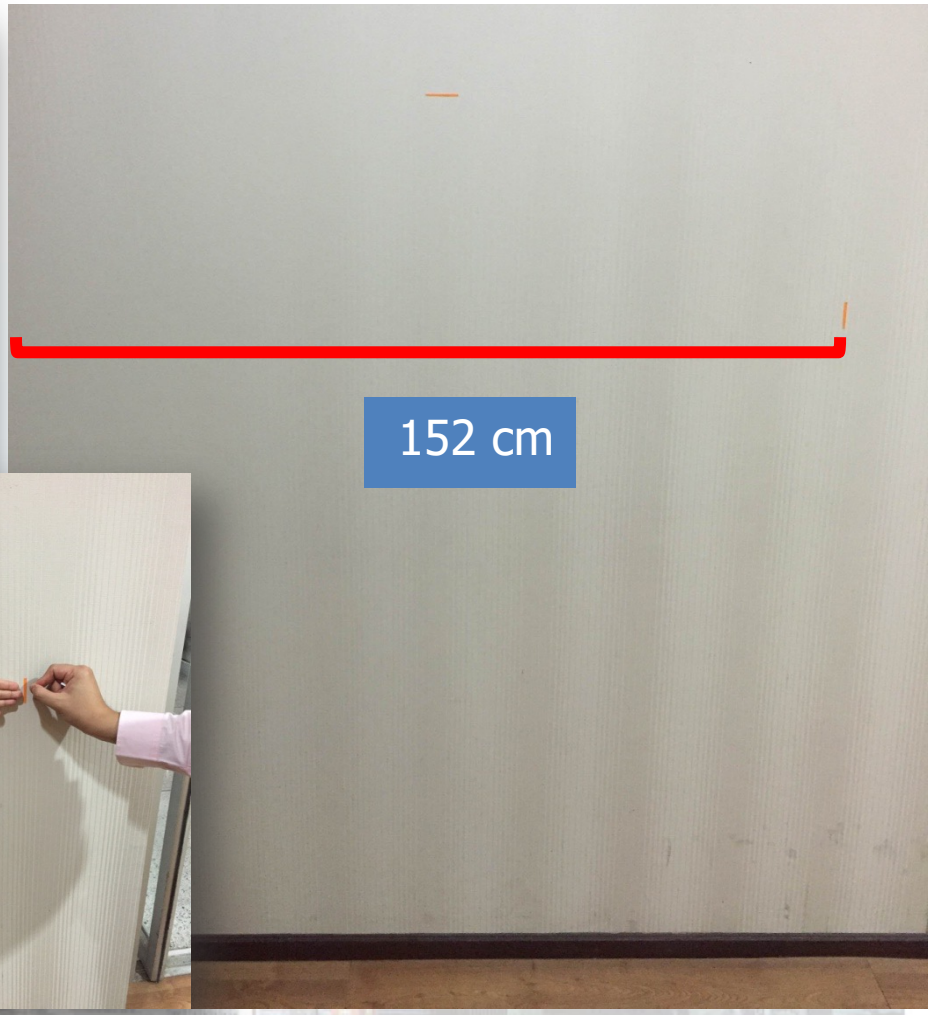


Pubic symphysis

75 cm

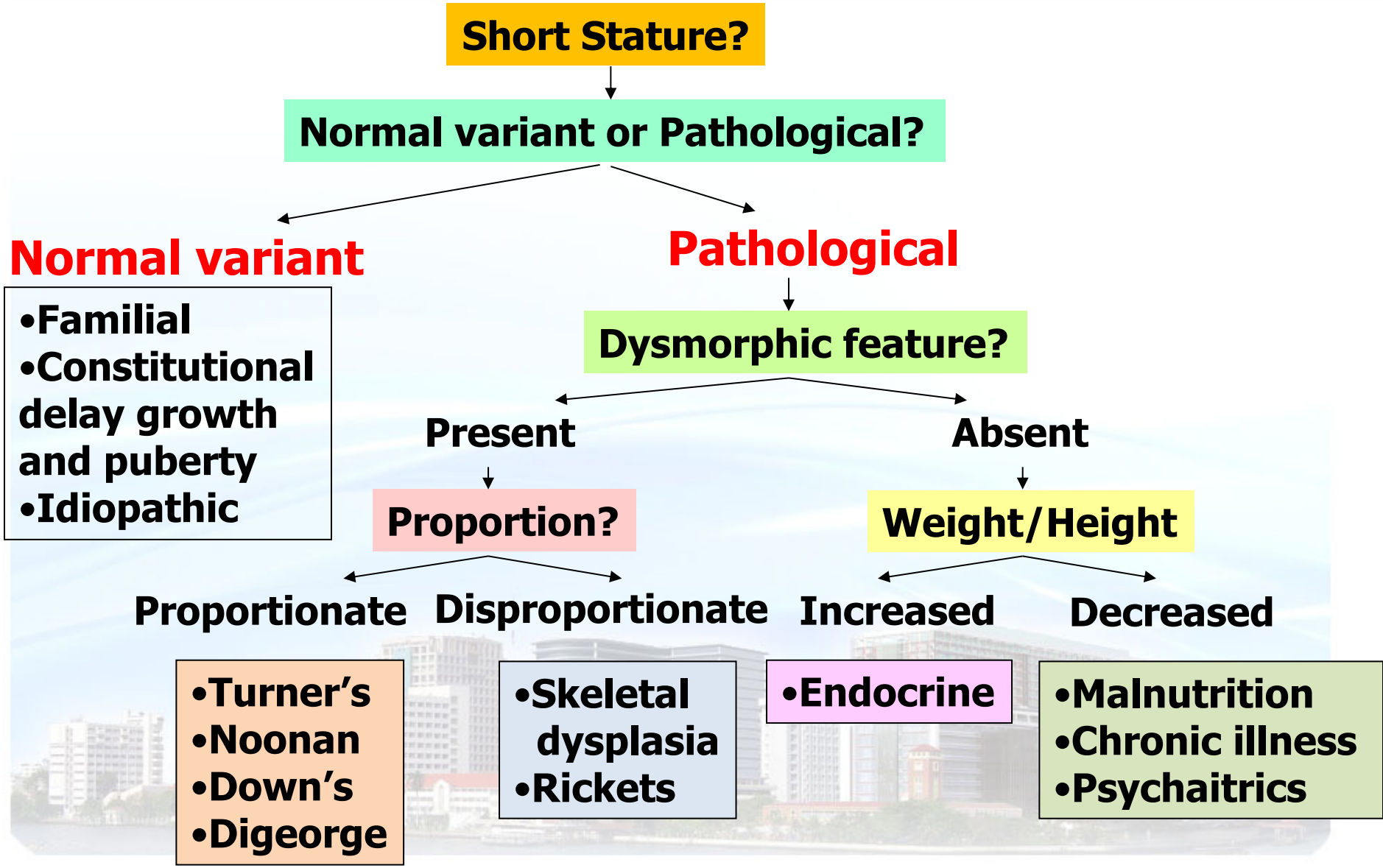
150-75 = 75 cm
Upper : Lower = 75:75 = 1:1

Arm span



Arm span > Height 2 cm (<5 cm)

Practical approach: Short stature



Practical approach: Short stature

Short Stature?

↓

Normal variant or Pathological?

Normal variant

- **Familial**
- **Constitutional delay growth and puberty**
- **Idiopathic**

Pathological

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When to concern : short stature

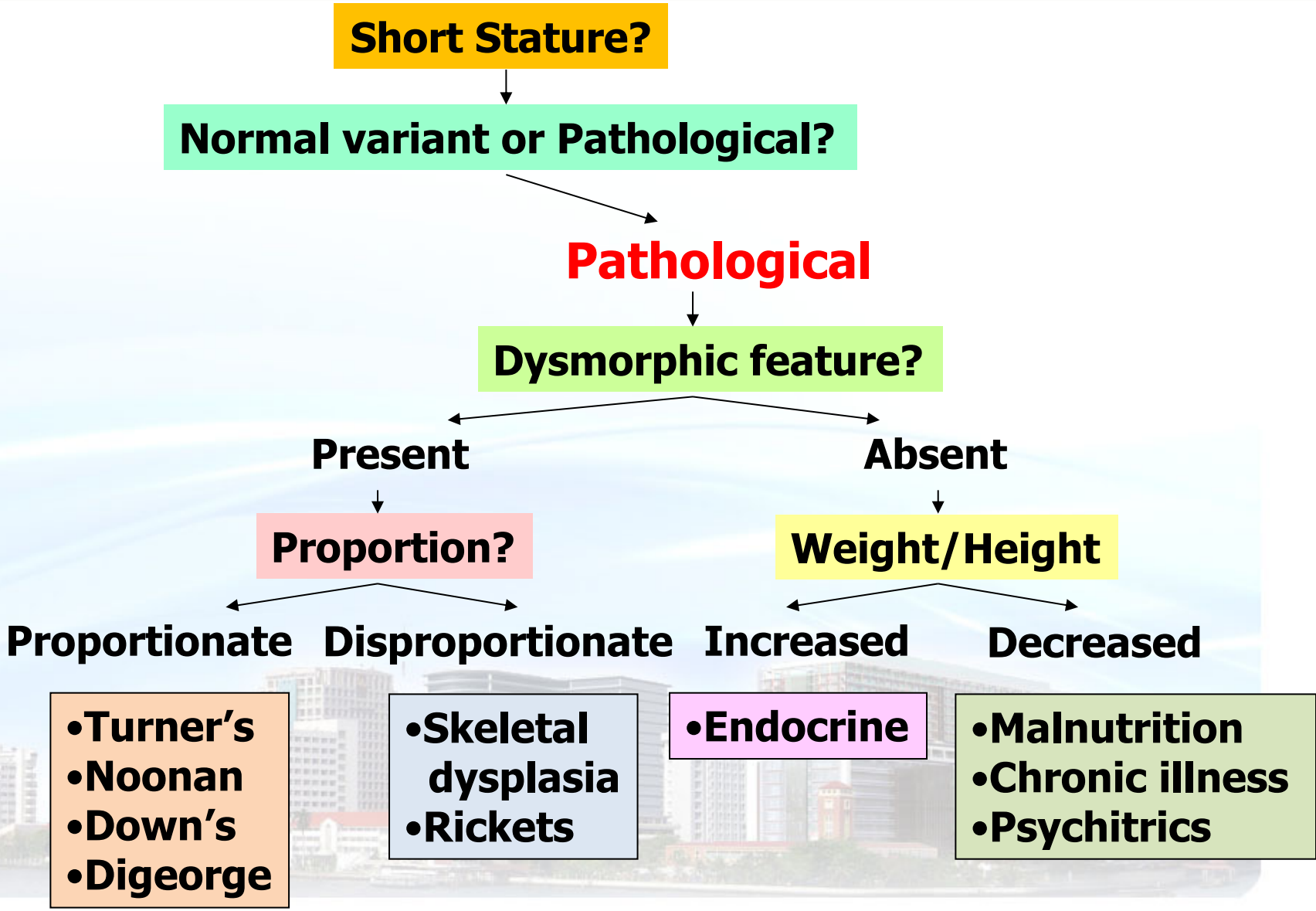
- Severe short stature
- Poor height velocity
- Dysmorphic features
- Signs and symptoms of systemic illness
- Height centile < MPH centile

Differential features of FSS and CDGP

Features	Familial Short Stature	Constitutional delay GP
Parent's stature	Small one or both	Average
Parent's puberty	Usual timing	Delayed
Birth length	Normal	Normal
(0-2yrs)	Normal	Normal to slow
Growth (puberty)	Normal	Slow
Bone age	Normal	Delayed
Timing of puberty	Normal	Delayed
Puberty growth rate	Lower range	Diminished
Adult height	Short	Normal

Peter J Simm. Child and adolescent growth disorder. Australian Family physician.2005;34:731-6

Practical approach: Short stature



Short Stature

Normal variant
- CDGP
- FSS

Pathological

Idiopathic

Disproportionate

Proportionate

Short Limbs
- Skeletal dysplasia
- Rickets

Short Trunk
- Scoliosis

Prenatal Onset
- IUGR
- Syndromes
- Chromosome dis

Postnatal Onset
- Malnutrition
- Chronic disease
- Drugs
- Psychological
- Endocrine disease

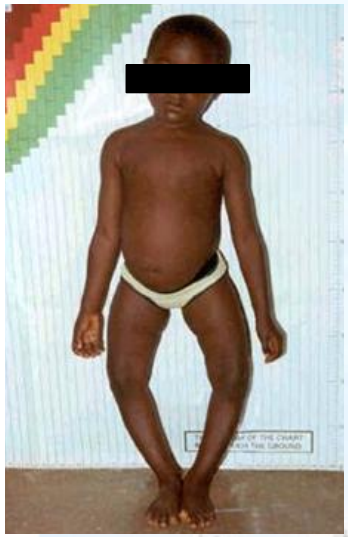
Disproportionate

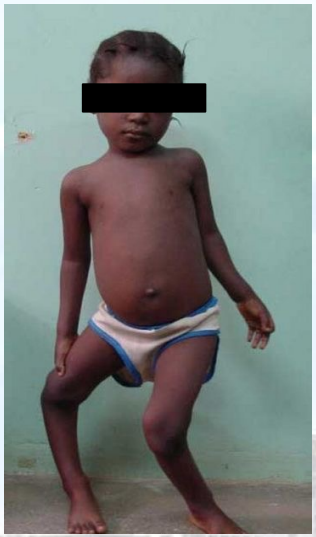
Short Limbs
-Skeletal dysplasia
- Rickets

U>L

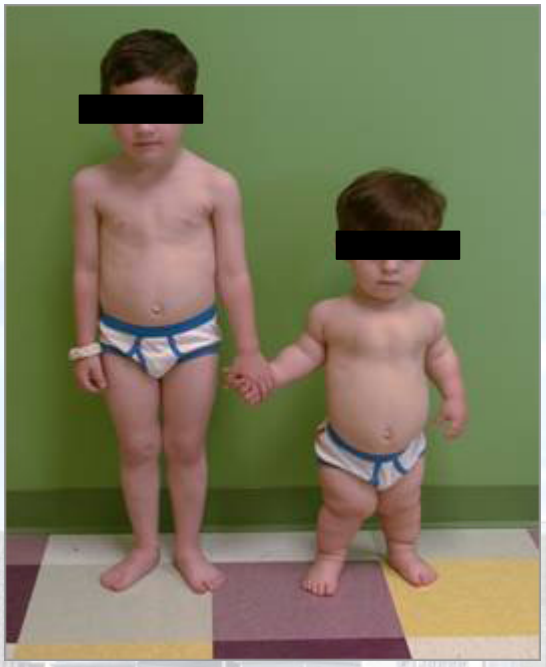
L>U

Short Trunk
- Scoliosis

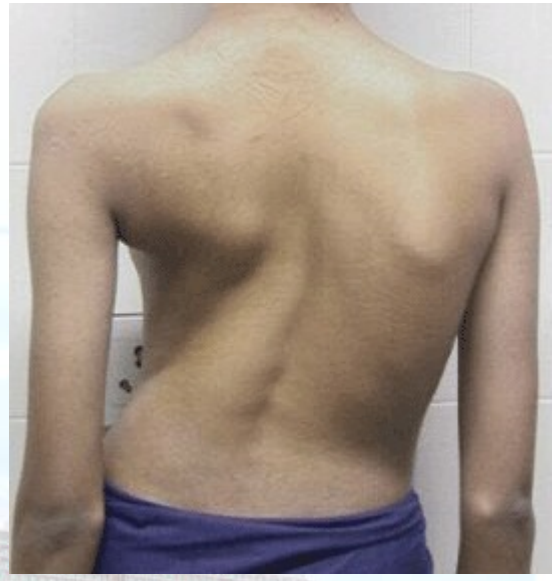




Rickets



Achondroplasia



Proportionate

Prenatal Onset
- IUGR
- Syndromes
- Chromosome dis

Postnatal Onset
- Malnutrition
- Chronic disease
- Drugs
- Psychological
- Endocrine disease

Proportionate

Prenatal Onset
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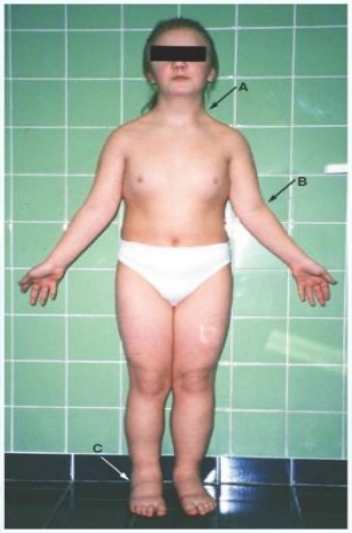
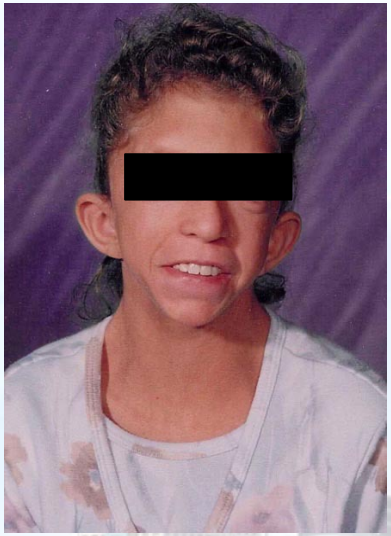
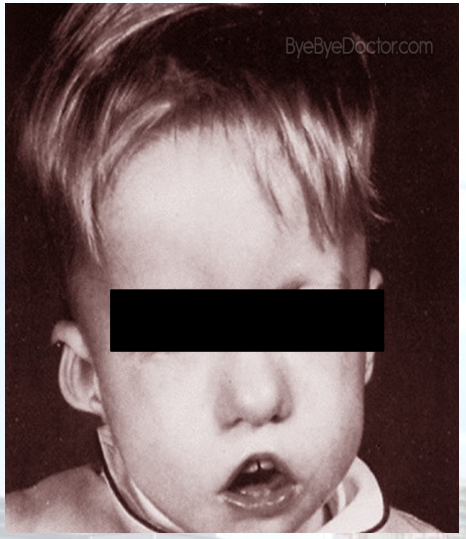


Turner syndrome

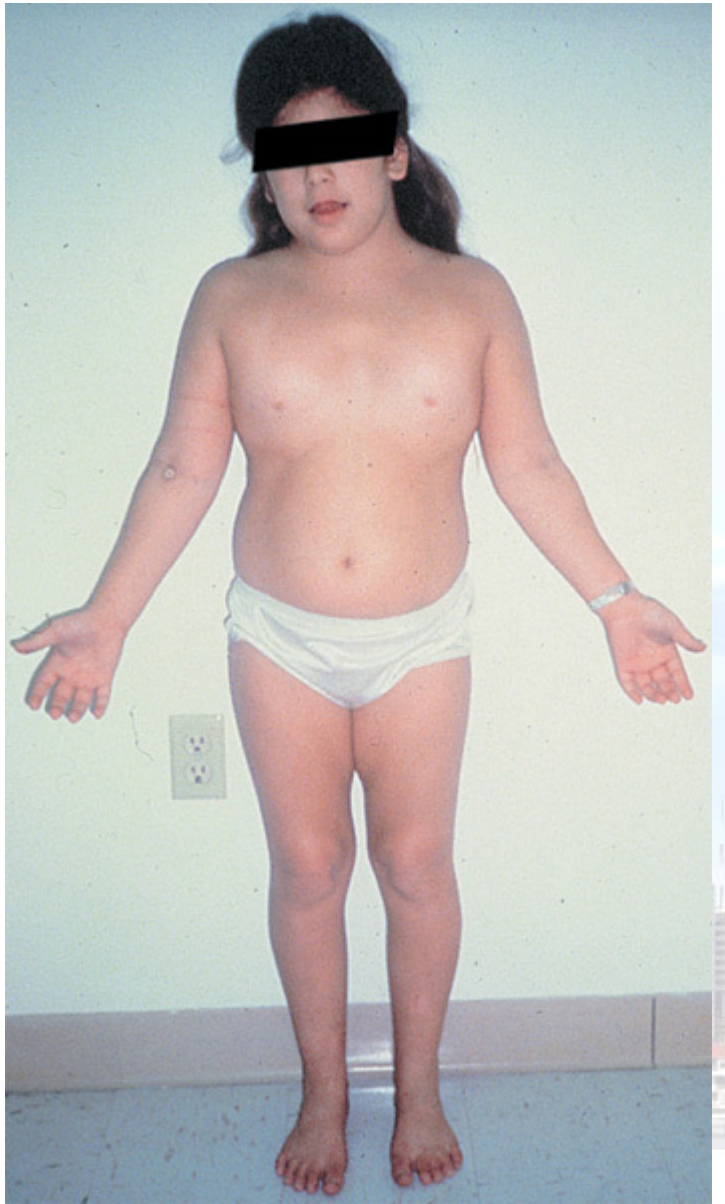


Noonan syndrome



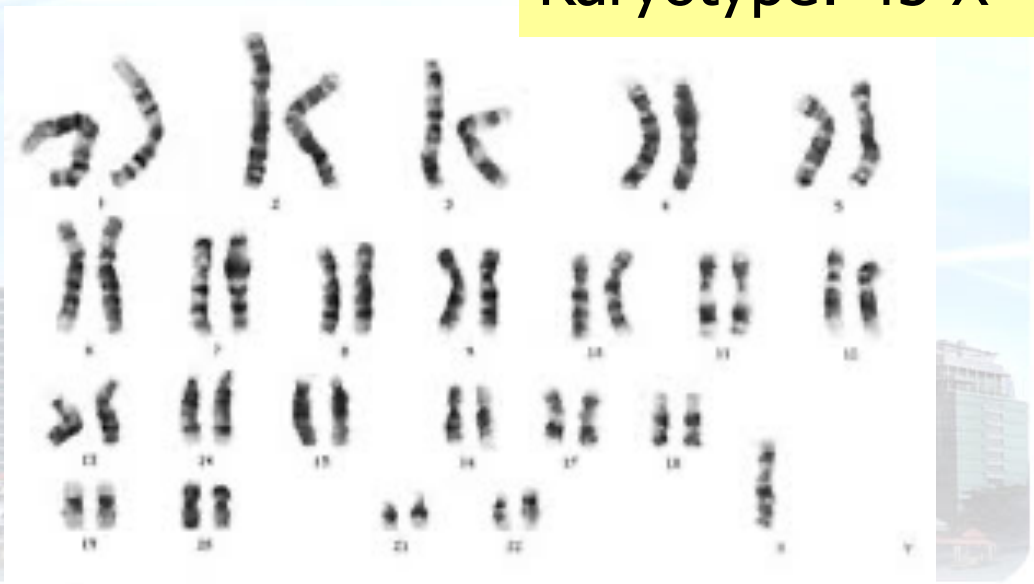
Digeorge syndrome

Turner's syndrome



- ✓ Important cause of **short stature** in girls and **primary amenorrhea** in young women
- ✓ Loss of part or all of an X-chromosome

Karyotype: 45 X

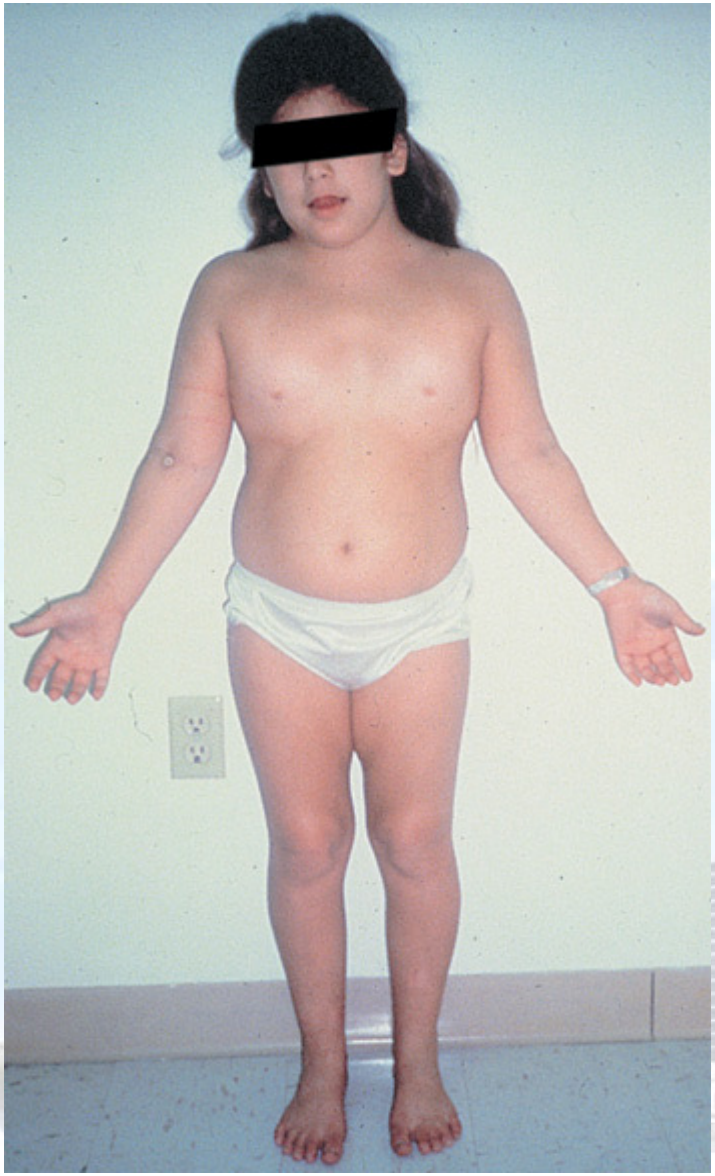


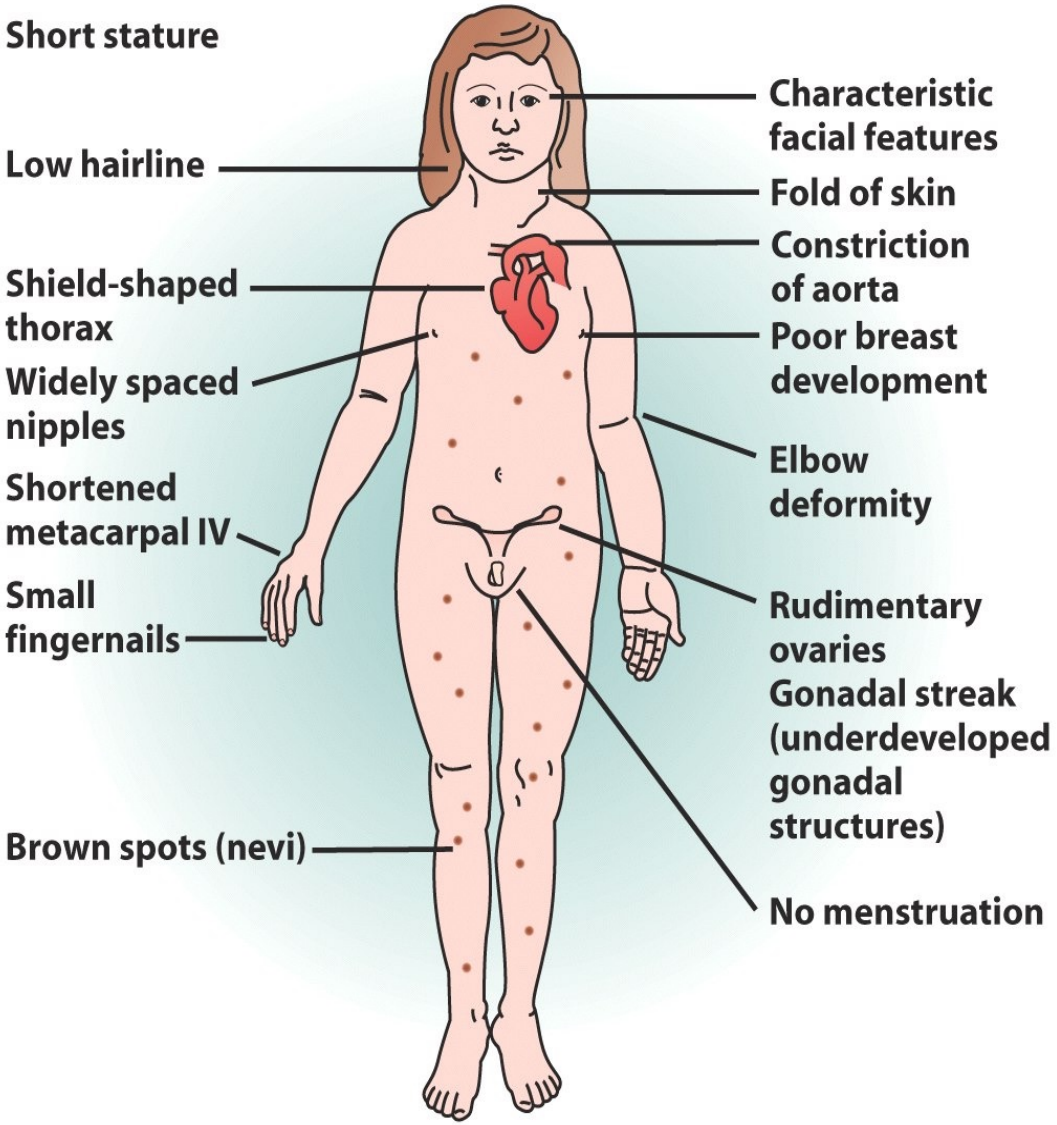
Turner's syndrome: Karyotype

- 1:2,500-5,000 female live births
- Karyotype: the only method of confirming TS diagnosis

Karyotype	No.	%	Phenotype
45,X	95	48	Most severe phenotype. Highest incidence of structural cardiac and renal abnormalities.
46,Xi(Xq)	36	18	Structural abnormalities uncommon. Increased risk of autoimmunity, particularly thyroiditis and IBD, and deafness.
45,X/46,XX	21	11	Least severe phenotype. Increased mean height. Spontaneous puberty and menses in up to 40%.
46,Xr(X)	19	10	Spontaneous menses in 33%. Congenital abnormalities uncommon. Cognitive dysfunction in those with a small ring chromosome.
45,X/46,XY	11	6	Increased risk of gonadoblastoma.
45,X/46,X,idic(Y)	2	1	Increased risk of gonadoblastoma.
46,XXp-	3	1.5	Similar phenotype to 45,X monosomy.
46,XXq-	6	3	Variable phenotype.
other	3	1.5	

Turner's syndrome



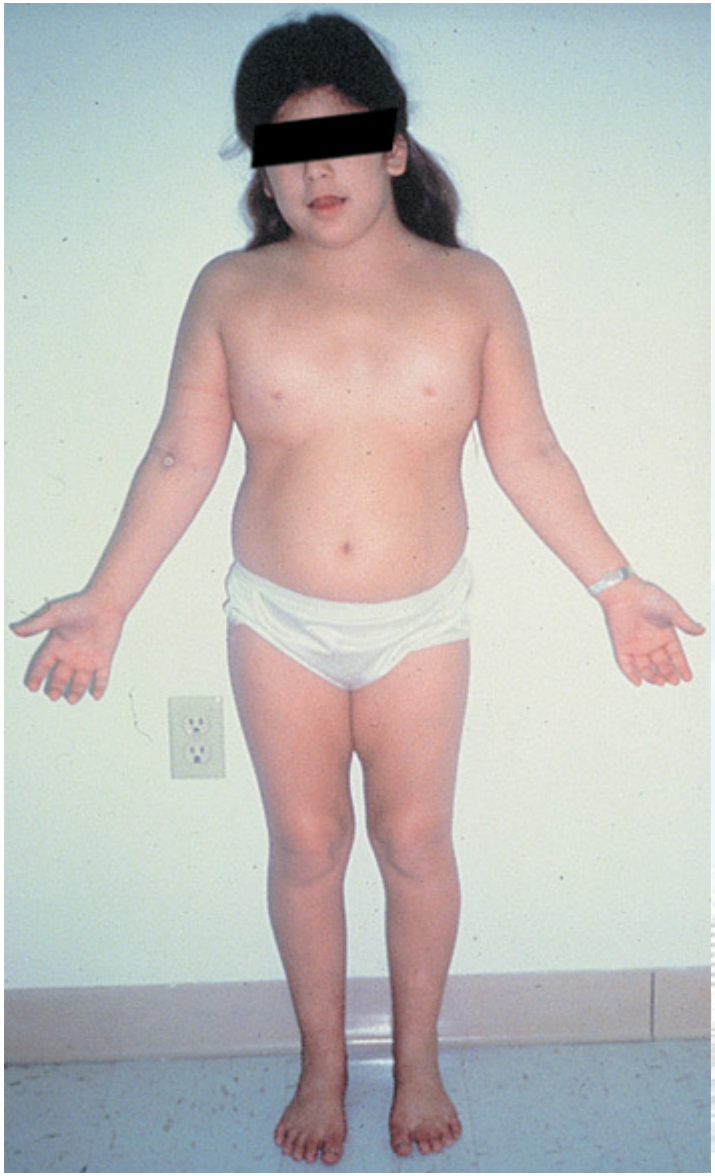


Clinical features of Turner's syndrome

Feature	Frequency (%)
Short stature	98
Gonadal failure	95
Micrognathia	60
Cubitus valgus	47
Low posterior hairline	42
Short neck	40
High arched palate	38
Short fourth metacarpal	37
Multiple naevi	25
Webbed neck	25
Lymphedema of hands and feet	22
Nail dysplasia	13
Scoliosis	11
Madelung deformity	7

Primary: elevated FSH,LH and low E2

Turner's syndrome



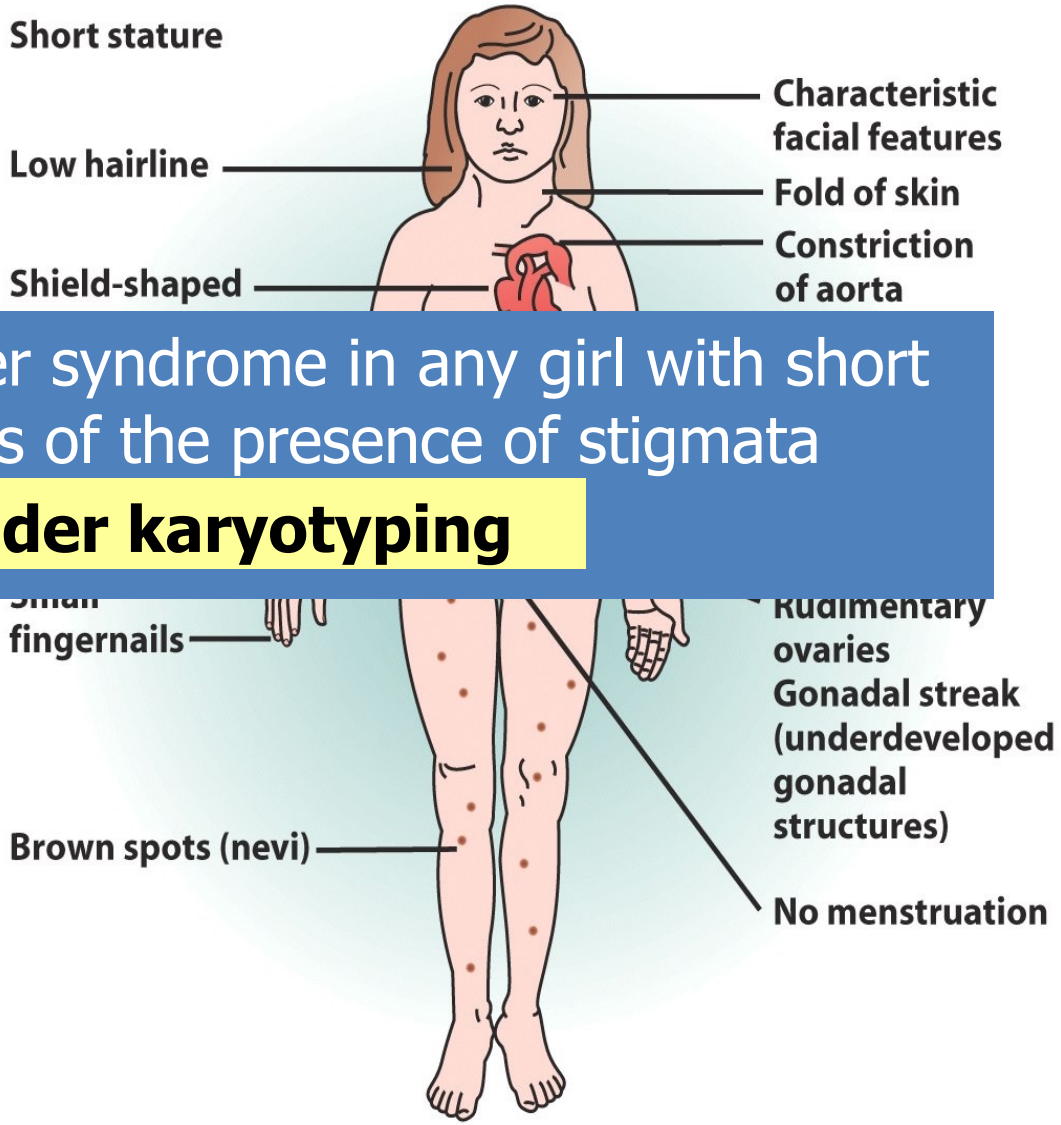
Cardiac abnormalities

	No. (%)[a]
Total no. of patients assessed	1,126
Structural abnormalities	
Bicuspid aortic valve	132 (12)
Coarctation of aorta	103 (9)
Aortic stenosis/regurgitation	38 (3.4)
Partial anomalous venous drainage of the pulmonary veins	26 (2.3)
Other	17 (1.5)
Total	316 (28)

Other abnormalities

- ✓ Hypothyroidism
- ✓ Osteoporosis
- ✓ Insulin resistance & T2DM
- ✓ Kidney abnormalities
- ✓ Hearing loss

Turner's syndrome



Always think of turner syndrome in any girl with short stature regardless of the presence of stigmata

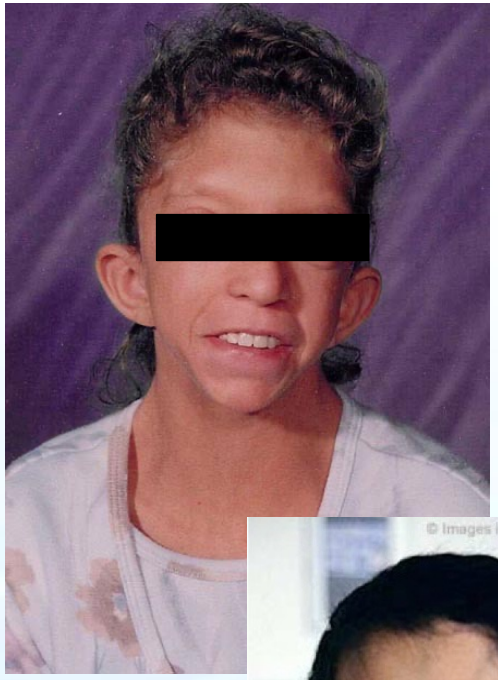
Consider karyotyping

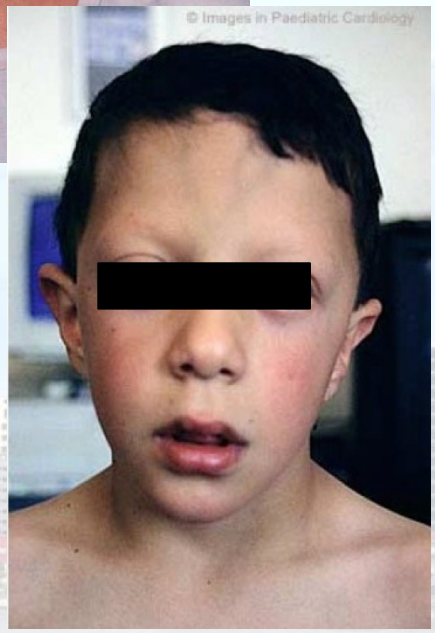
Turner's syndrome : Follow up

Baseline
Karyotype
Renal and pelvic ultrasound
Echocardiography
Thyroid autoantibodies
Gonadotropins
Annual
Physical examination (BMI, blood pressure, CVS, *etc.*)
Thyroid function
Fasting lipids
Fasting blood glucose
Liver function
Renal function
3–5 Yearly
Echocardiography
Bone densitometry
Audiogram

BMI, Body mass index; CVS, cardiovascular system.

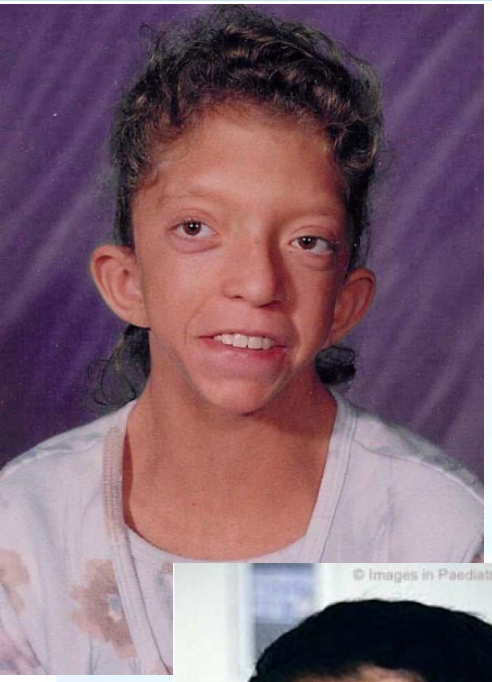
Noonan syndrome

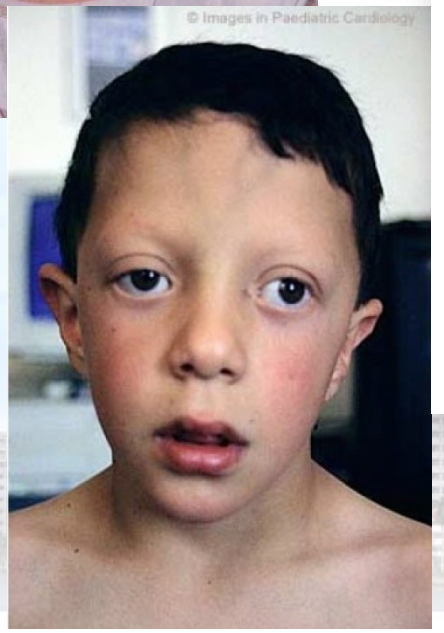




- **Autosomal dominant** that affects both males and females
- One of the most common genetic syndromes associated with **congenital heart disease**

Noonan syndrome: features





Short stature

- Up to 83% of patients have short stature[1]

Characteristic facial features[3]

- Broad, high forehead
- Hypertelorism
- Low-set, posteriorly rotated ears with a thick helix
- High-arched palate
- Micrognathia
- High-arched eyebrows[1]
- Short neck with excess nuchal skin
- Epicanthal folds
- Downward-slanting palpebral fissures
- Low posterior hairline

Congenital heart defects[3]

- Pulmonary valve stenosis
- Hypertrophic obstructive cardiomyopathy
- Atrial and ventricular septal defects
- Persistent ductus arteriosus

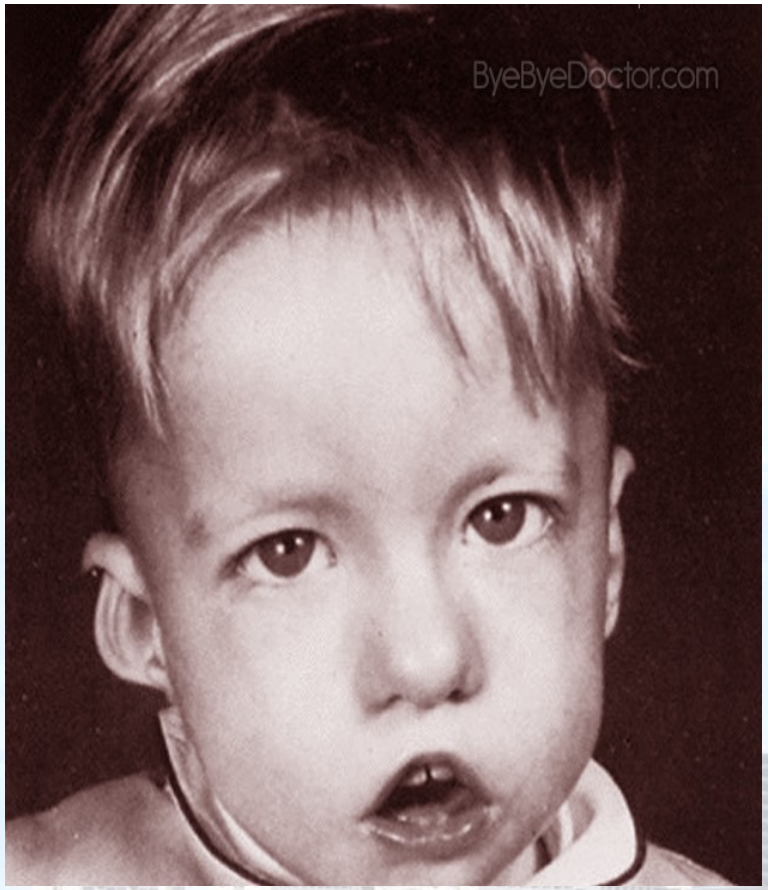
Other clinical manifestations[3-5]

- Pectus carinatum, pectus excavatum
- Scoliosis
- Cryptorchidism
- Lymphatic abnormalities
- Coagulopathy
- Cognitive/learning disabilities
- Ophthalmological issues
- Arnold-Chiari malformation
- Seizures

Noonan syndrome

Characteristic	Turner's syndrome	Noonan's syndrome
Incidence	1:1500-2500 female live birth	1:1000-2500 live birth
2nd sex characteristic	No/Incomplete	Normal
Webbed neck	Posterior	Anterior
IQ	Normal	Mild MR
Family history	Positive	AD
CVS	Coarction of aorta Bicuspid AV	PS, HOCM, PDA, ASD, VSD
Chromosomal study	45,x/mosaic	46,XY 46,XX

Digeorge syndrome



- 22q11.2 deletion syndrome
- The features of this syndrome vary widely

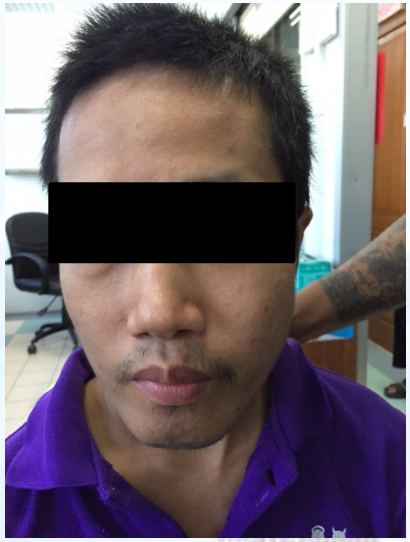
Facial abnormalities:

- **Hypertelorism**
- **Micrognathia**
- **short philtrum with fish-mouth appearance**
- **antimongoloid slant**
- **telecanthus**

Otolaryngic

- **low-set ears, with defective pinna**
- **cleft palate**

Case presentation



Total calcium 6.8 mg/dL
Phosphorus 4.9 mg/dL
Serum Cr 0.85 mg/dL

A 24-year-old man
Presented with
refractory seizure

Approach to hypocalcemia

Hypocalcemia

Serum phosphorus

High serum phosphorus

- Phosphorus loading
- Hypomagnesemia
- Hypoparathyroidism
  - postsurgical(neck)

- Chronic renal failure
- Hypoparathyroidism
  - hereditary
  - infiltrative disease
- Pseudohypoparathyroid

Normal serum phosphorus

- Critical illness :
  gram negative sepsis
- Acute pancreatitis
- Massive Blood transfusion

- Malabsorption
- Osteoblastic metastasis

Low serum phosphorus

- Hungry bone syndrome after parathyroidectomy

- Vitamin D deficiency
- Malabsorption
- Medication : Phenytoin

Acute

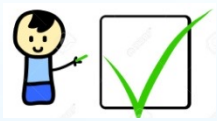
Chronic

Case presentation

Hypocalcemia

Total calcium 6.8 mg/dL
Phosphorus 4.9 mg/dL
Serum Cr 0.85 mg/dL

Serum phosphorus



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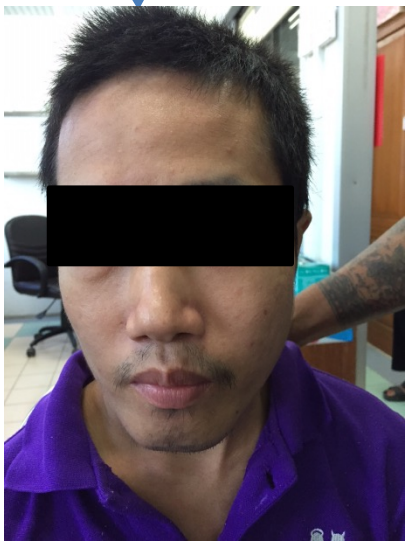
N



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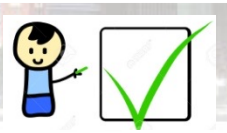
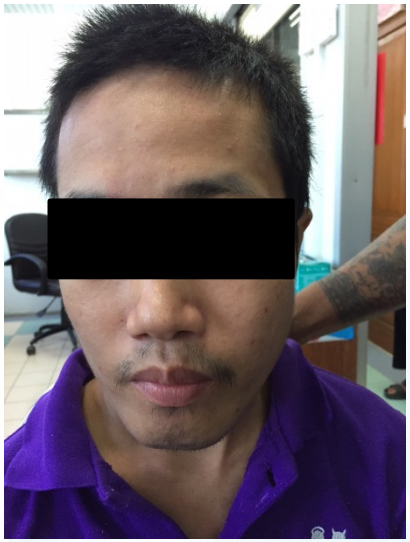


Acute

Chronic

Back to this patient



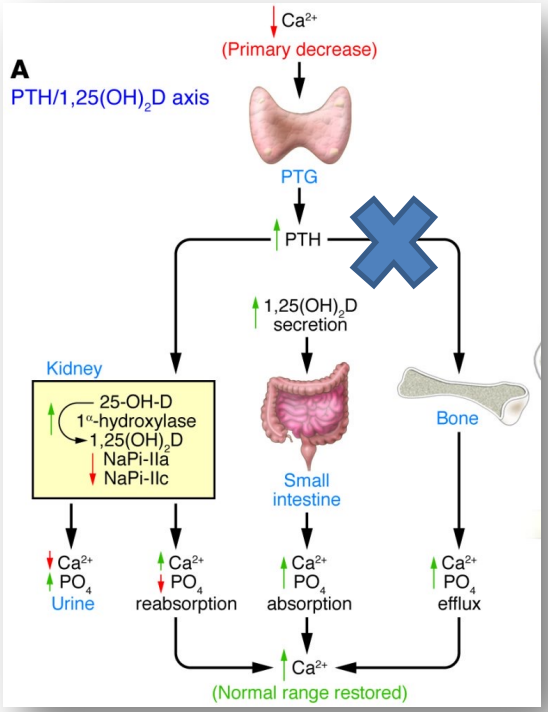
Chronic hypocalcemia with hyperphosphatemia

- Chronic renal failure
- Hypoparathyroidism
  - hereditary
  - infiltrative disease
- Pseudohypoparathyroidism

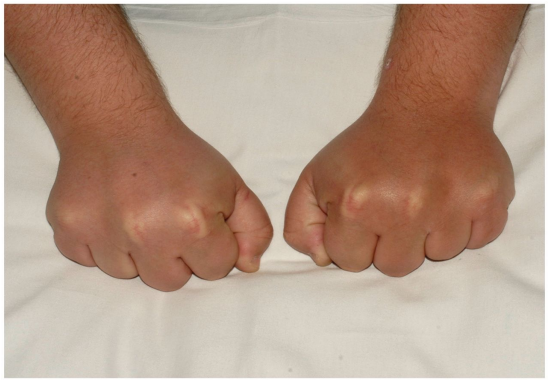
Serum creatinine 0.85

Hypoparathyroidism vs PseudohypoPTH

Hypoparathyroidism



Resistance to PTH action



AHO features

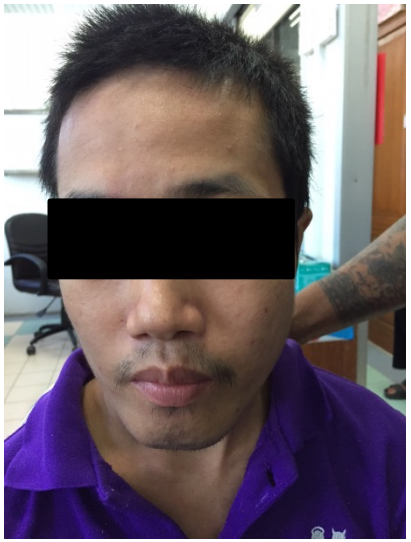
Short stature, obesity

Rounded face,

Short 4th MCP

	Serum calcium	Serum phosphorus	PTH level
Hypoparathyroidism	↓	↑	↓
PseudohypoPTH	↓	↑	↑

Back to this patient



Chronic hypocalcemia with hyperphosphatemia

- Chronic renal failure
- Hypoparathyroidism
  - hereditary
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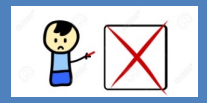
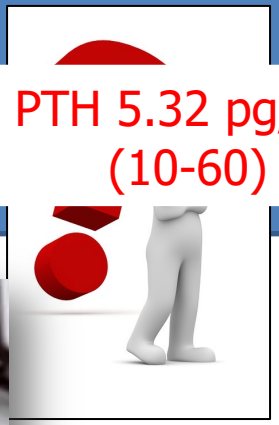
Serum creatinine 0.85

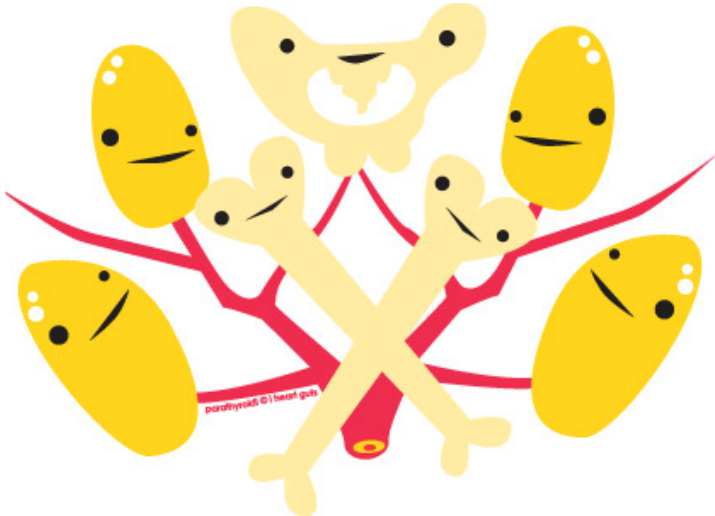


PTH 5.32 pg/mL
(10-60)



Hypoparathyroidism : Causes

1. Genetic syndromes: Digeorge syndrome
   PTH gene mutation
2. Autoimmune disorders: isolated, APS1
3. Infiltrative disease: Hemochromatosis,
   Wilson disease, metastatic cancer
4. Post surgery, irridiation
5. Hypomagnesemia

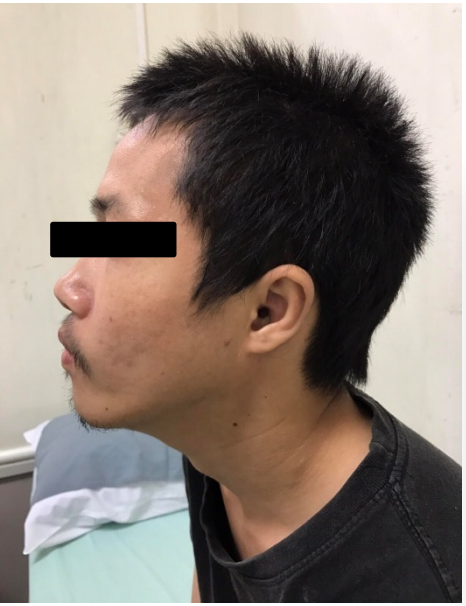


A thorough history taking and physical examination

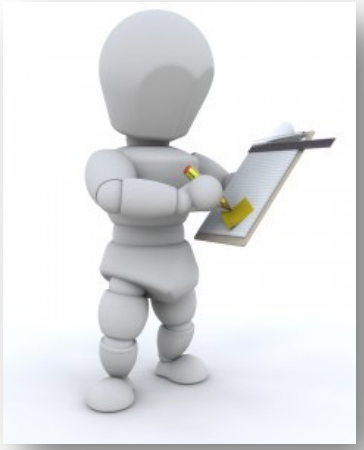
Developmental delay and mild mental retardation

History of Chronic otitis media with left mastoiditis S/P mastoidectomy: **CMI defect**

Abnormal facies: long face, bulbous nose, low set ear, small earlobes



Chronic hypoparathyroidism: onset since birth



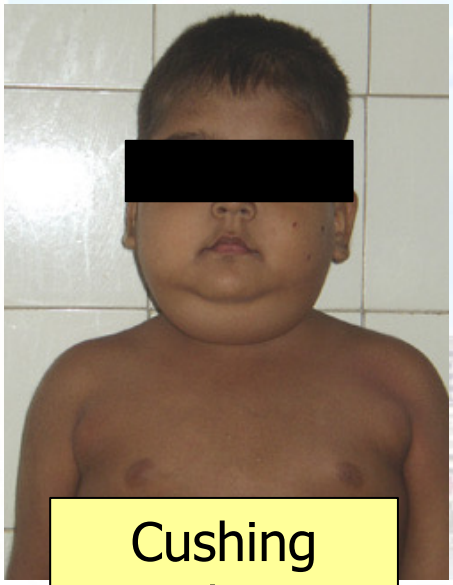
Chromosome 22q11.2 deletion syn
Velocardiofacial syndrome
DiGeorge syndrome

Proportionate

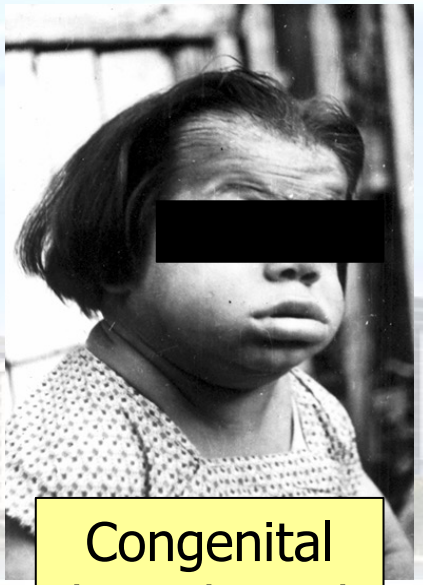
Prenatal Onset
- **IUGR**
- **Syndromes**
- **Chromosome dis**

Postnatal Onset
- **Malnutrition**
- **Chronic disease**
- **Drugs**
- **Psychological**
- **Endocrine disease**

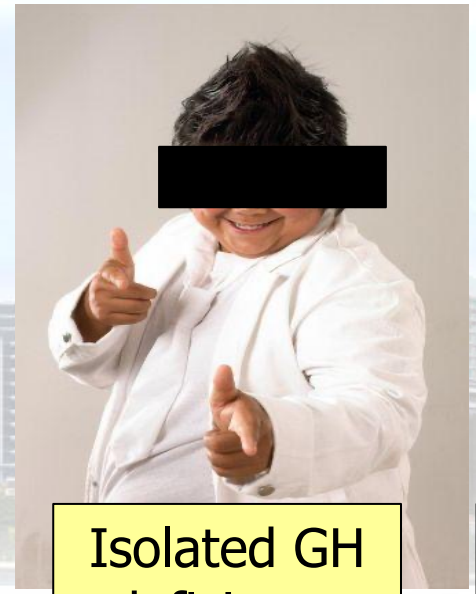
Endocrine diseases: เตี้ย+อ้วน



Cushing syndrome



Congenital hypothyroid



Isolated GH deficiency

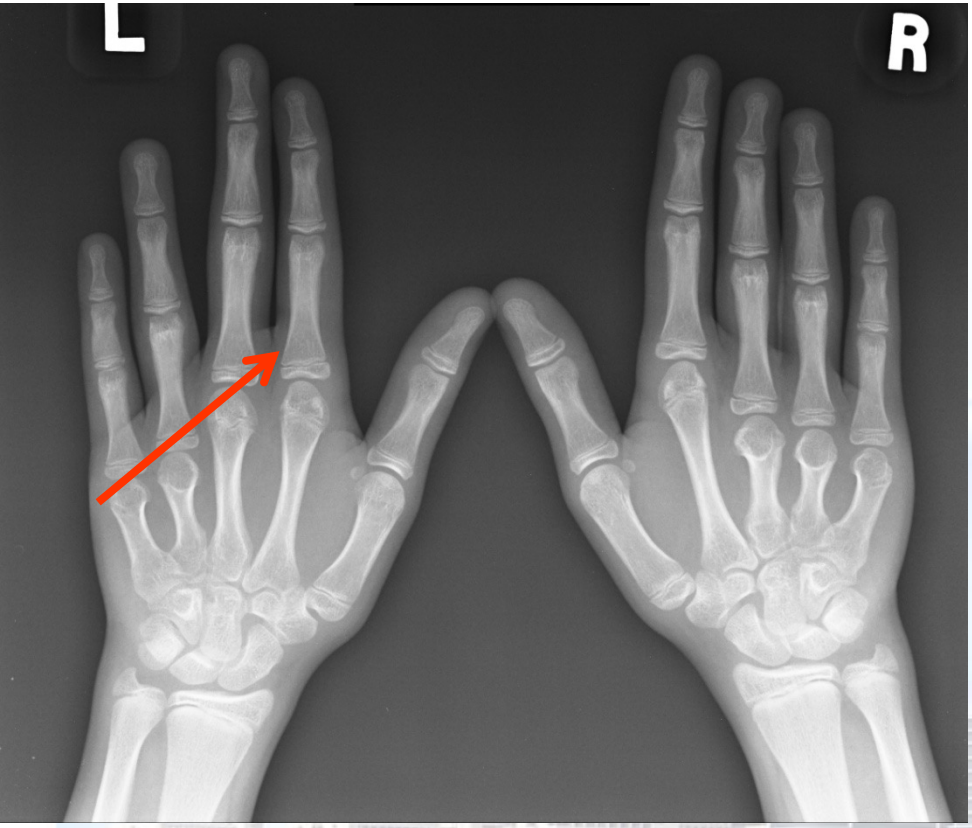
Albright's hereditary osteodystrophy

Albright's Hereditary Osteodystrophy

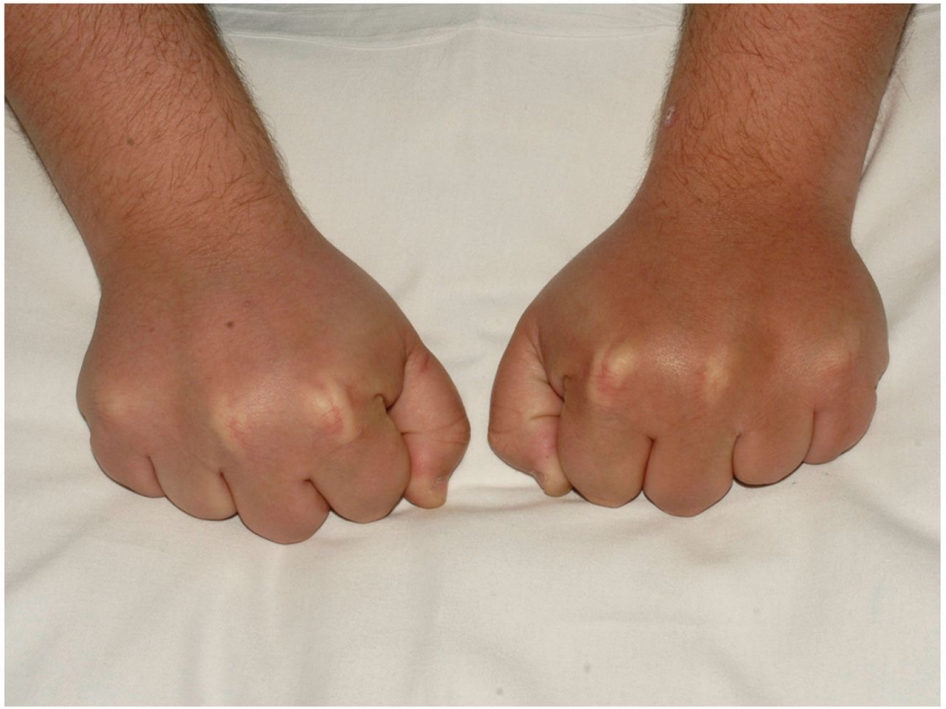
- A lack or responsiveness to PTH (**PTH resistance**)
  Low cal, High Po_4, High PTH
- Short stature, **Short 4th, 5th MCP**, round face, mild mental retardation
- PseudohypoPTH type 1A and pseudopseudohypoPTH

Condition		Appearance	PTH levels	Calcitriol	Calcium	Phosphates	Imprinting
Hypoparathyroidism		Normal	Low	Low	Low	High	Not applicable
Pseudohypoparathyroidism	Type 1A	Skeletal defects	High	Low	Low	High	Gene defect from mother (GNAS1)
	Type 1B	Normal	High	Low	Low	High	Gene defect from mother (GNAS1 and STX16)
	Type 2	Normal	High	Low	Low	High	?
Pseudopseudohypoparathyroidism		Skeletal defects	Normal	Normal	Normal[9]	Normal	gene defect from father

Albright's Hereditary Osteodystrophy



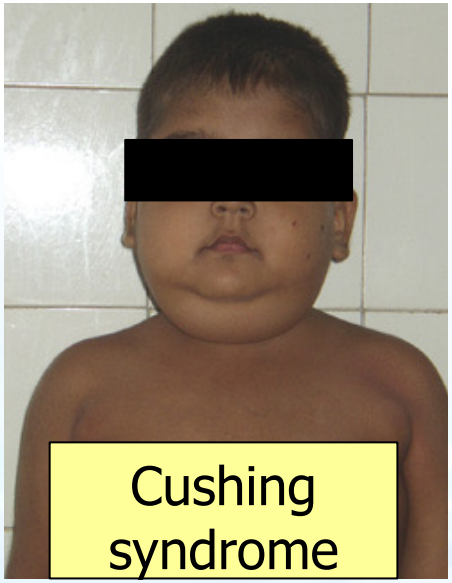
Short 4th, 5th MCP



Knuckle-dimple sign

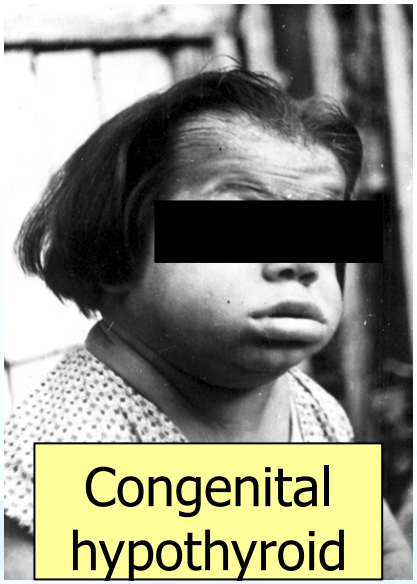
Proportionate: Endocrine disease

Endocrine disease: เตี้ย+อ้วน



Cushing syndrome

- ✓Signs of cushing syndrome



Congenital hypothyroid

- ✓84% thyroid agenesis
- ✓ Mental retardation
- ✓ Cretinous features

Isolated GH deficiency

- ✓Decreased growth rate after the age of 6 months
- ✓ Small voice, frontal bossing
- ✓ younger-appearance than chronological age

Proportionate

Prenatal Onset
- **IUGR**
- **Syndromes**
- **Chromosome dis**

เตี้ย+ผอม

Weight for Height ↓

Weight for Height ↑

เตี้ย+อ้วน

Postnatal Onset
- **Malnutrition**
- **Chronic disease**
- **Drugs**
- **Psychological**
- **Endocrine disease**

Undernutrition
Systemic illness

-RS: Asthma
-CVS: Congenital heart disease
-GI: Malabsorption
-Renal: **RTA**, renal failure
-Neuro: Brain tumors
-Hemato: **Thalassemia**
-Autoimmune diseases

Short Stature

Normal variant
- CDGP
- FSS

Pathological

Idiopathic

Disproportionate

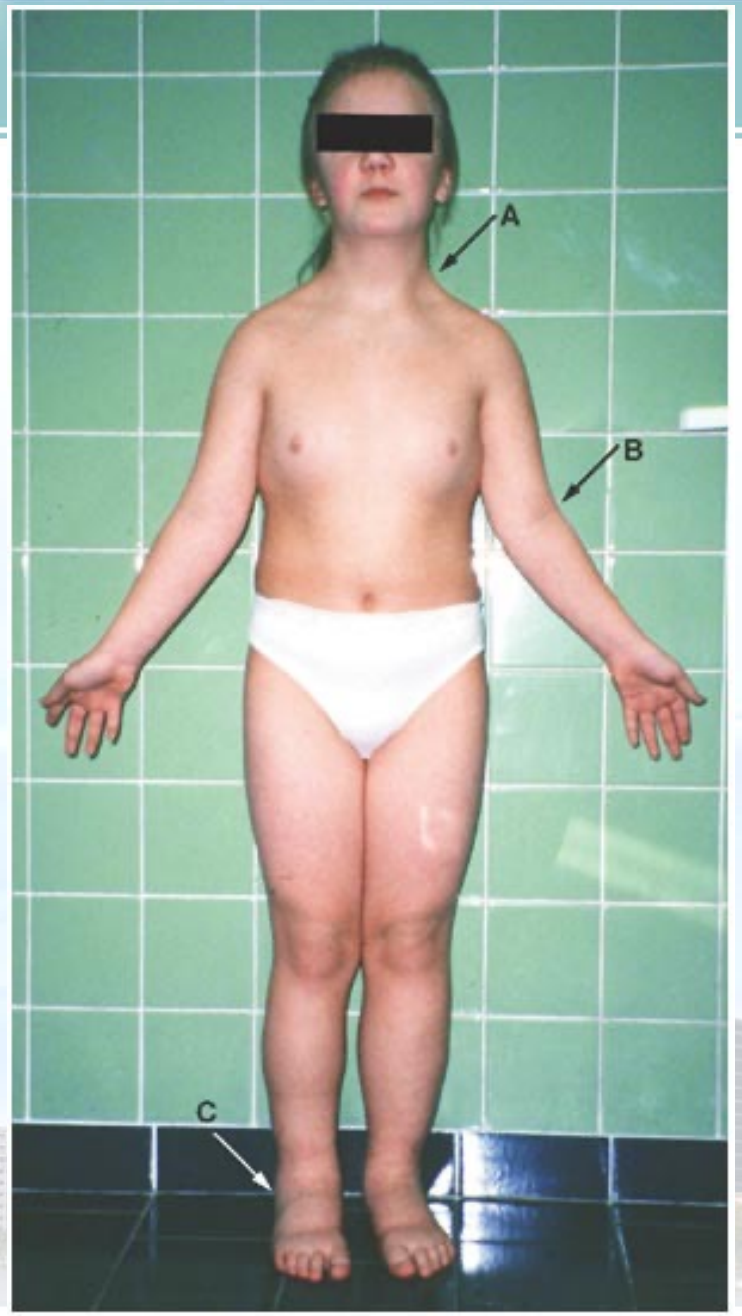
Proportionate

Short Limbs
- Skeletal dysplasia
- Rickets

Short Trunk
- Scoliosis

Prenatal Onset
- IUGR
- Syndromes
- Chromosome dis

Postnatal Onset
- Malnutrition
- Chronic disease
- Drugs
- Psychological
- Endocrine disease



- จงตรวจร่างกายระบบที่เกี่ยวข้อง และให้การวินิจฉัย
- จงตรวจร่างกายระบบที่เกี่ยวข้องกับการ differential diagnosis สาเหตุของ short stature

Short stature

- Height, **Body weight, BMI**
- U/L ratio
  - lower segment: measure from supra pubis symphysis to the floor
  - upper-to-lower ratio should be close to 1
  - If > 1: hypochondroplasia or achondroplasia
- Arm span
- Request growth curve

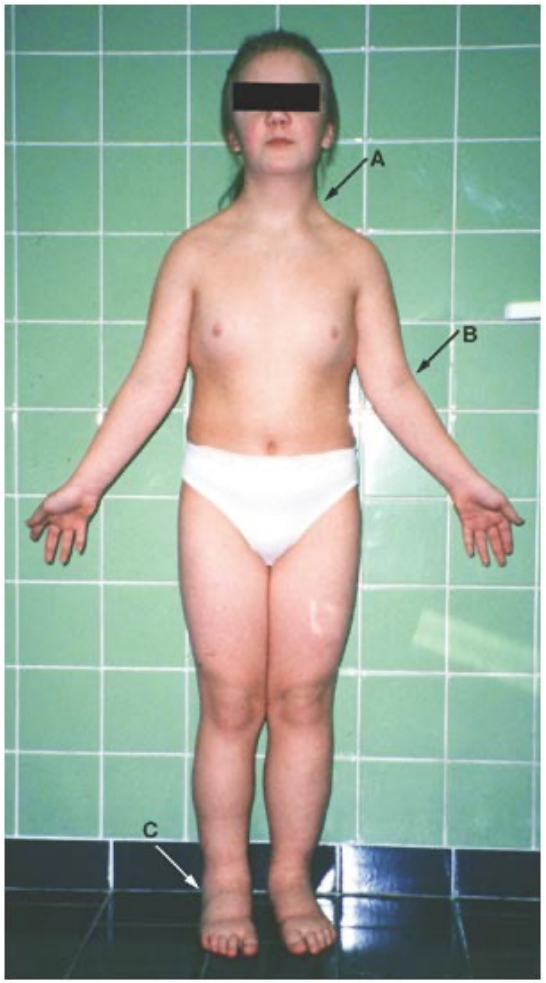
Turner syndrome
Achondroplasia
Cushing syndrome
AHO
Thalassemia
GH deficiency

Short stature

- Vital sign: **Blood pressure**
- GA:
  - Signs of chronic disease: CRF, liver disease, thalassemia, congenital ♡ disease
  - Signs of endocrine disease: Cushing syndrome, AHO, GH deficiency
  - Signs of malnutrition
  - Signs of Turner's syndrome

Turner syndrome
Achondroplasia
Cushing syndrome
AHO
Thalassemia
GH deficiency

Short stature



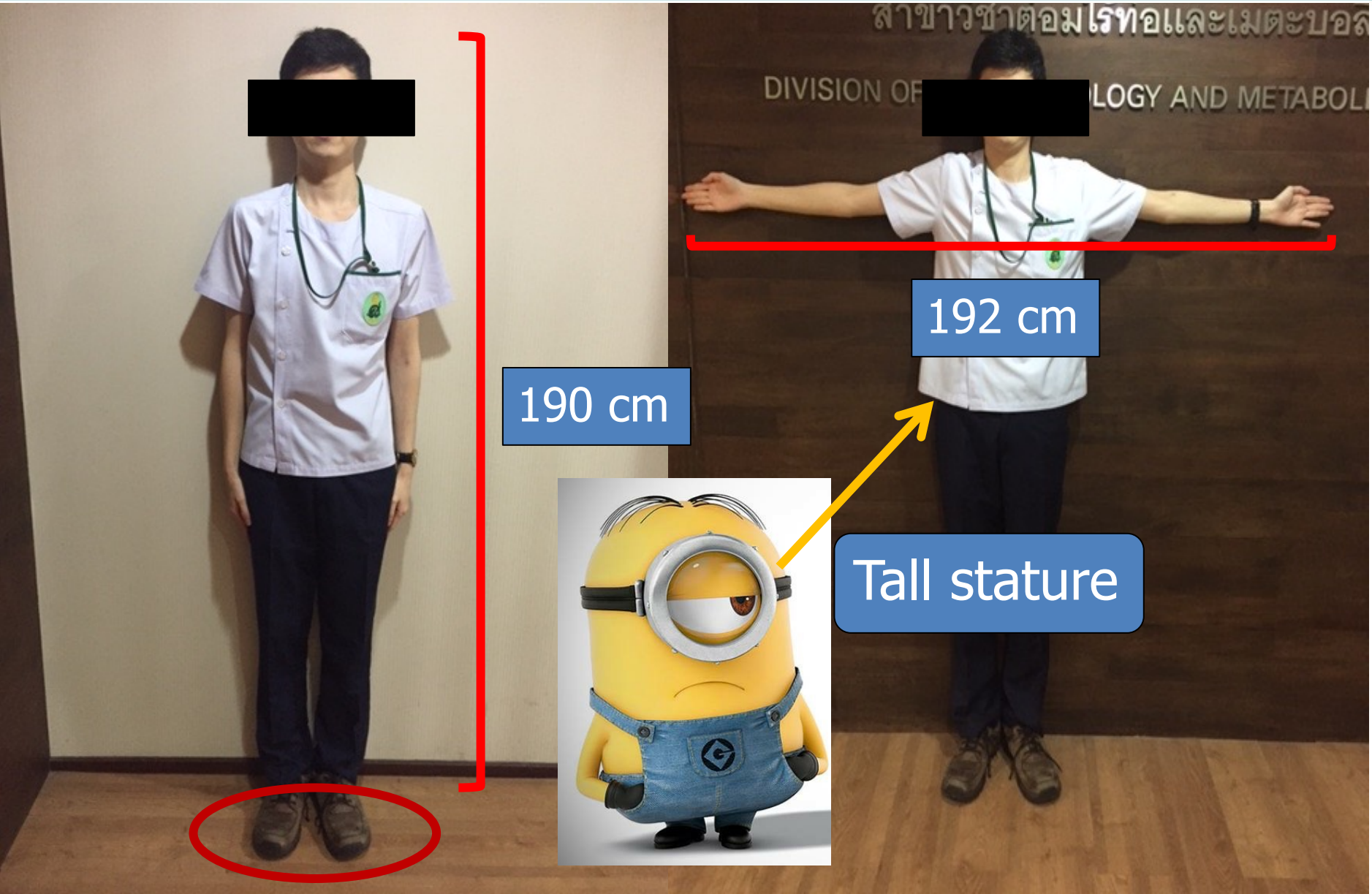
- Signs of turner's syndrome
  - webbed neck
  - Low hairline in the back
  - Low-set ears, High arch palate
  - cubitus valgus
  - shield chest
  - multiple pigmented nevi
  - Swollen hands and feet

Turner syndrome
Achondroplasia
Cushing syndrome
AHO
Thalassemia
GH deficiency

Short stature

- **Secondary sex characteristics: breast, hair, genitalia**
- Thyroid
  - Hypothyroidism
  - Turner's syndrome
- CVS
  - Murmur
- Abdomen: Hepatosplenomegaly
- NS
  - VF, VA
- **Short 4th MCP**

Turner syndrome
Achondroplasia
Cushing syndrome
AHO
Thalassemia
GH deficiency


DIVISION OF
LOGY AND METABOL
192 cm
190 cm
Tall stature

Tall stature

Definition

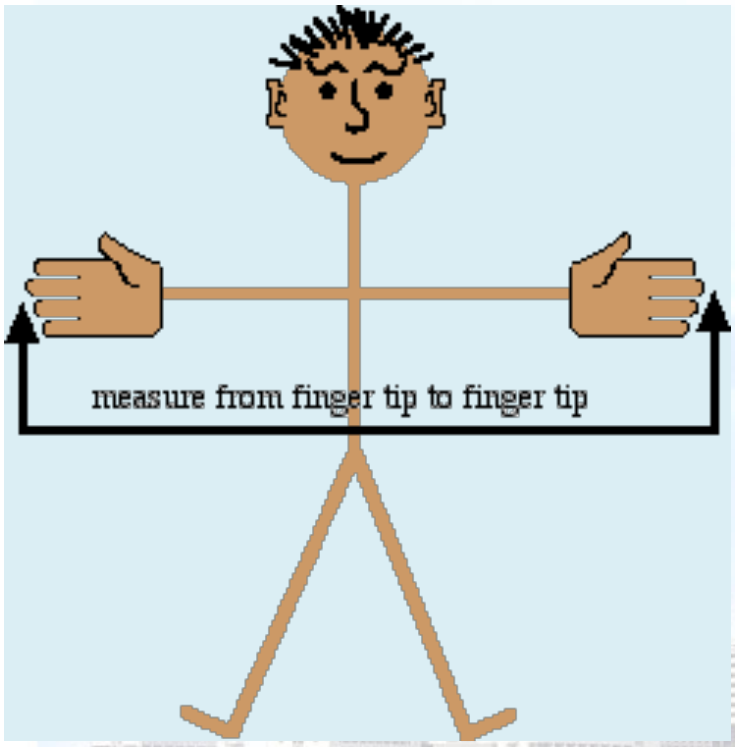
- ✓Height > 2 SD above the mean age
- ✓Height > 2 SD above mid-parental height

Important information

- ✓Accurate height measurement
- ✓Previous growth record
- ✓Height velocity
- ✓Mid-parental height
- ✓Upper:Lower segment ratio
- ✓Bone age
- ✓Secondary sex characteristics

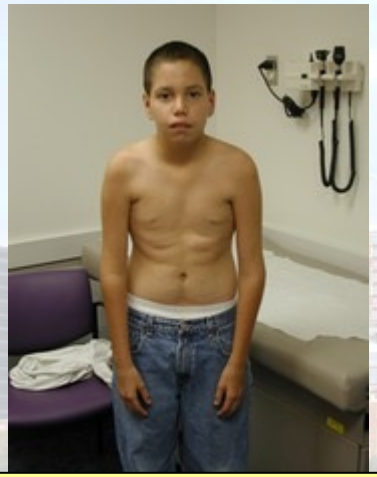
Arm span

- วัดจากปลายนิ้วกลางข้างหนึ่งไปสู่ปลายนิ้วกลางอีกข้างหนึ่ง เมื่อเหยียดแขนออกไปทั้งสองข้างขนานกับพื้น



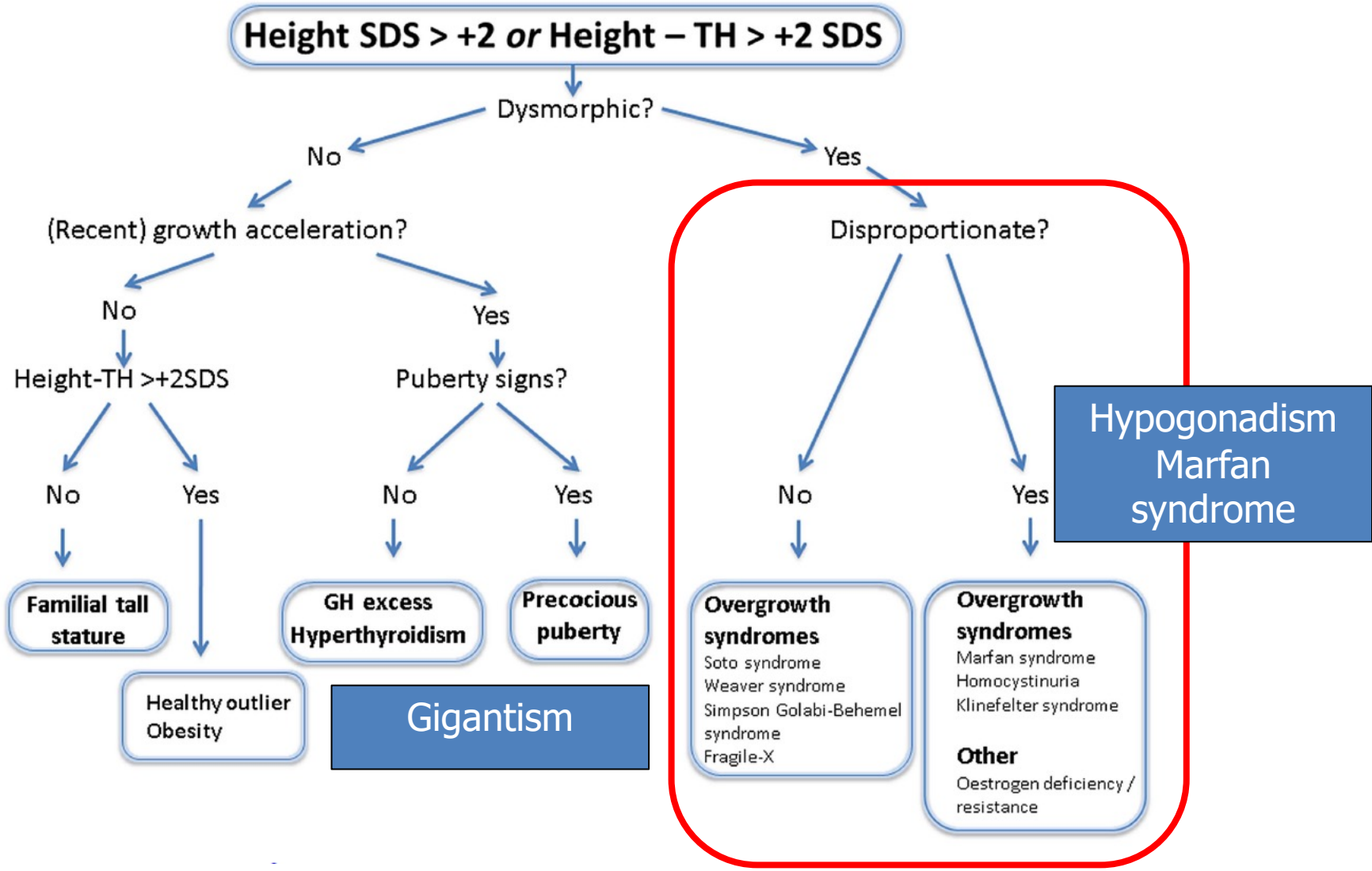
Boy age 10-11yr **arm span < height**
Man **arm span – height= 5.3cm**

Girl age 11-14yr **arm span < height**
Woman **arm span – height = 1.2cm**



Arm span > Height 5 cm --> suspected eunuchoid appearance

Tall stature



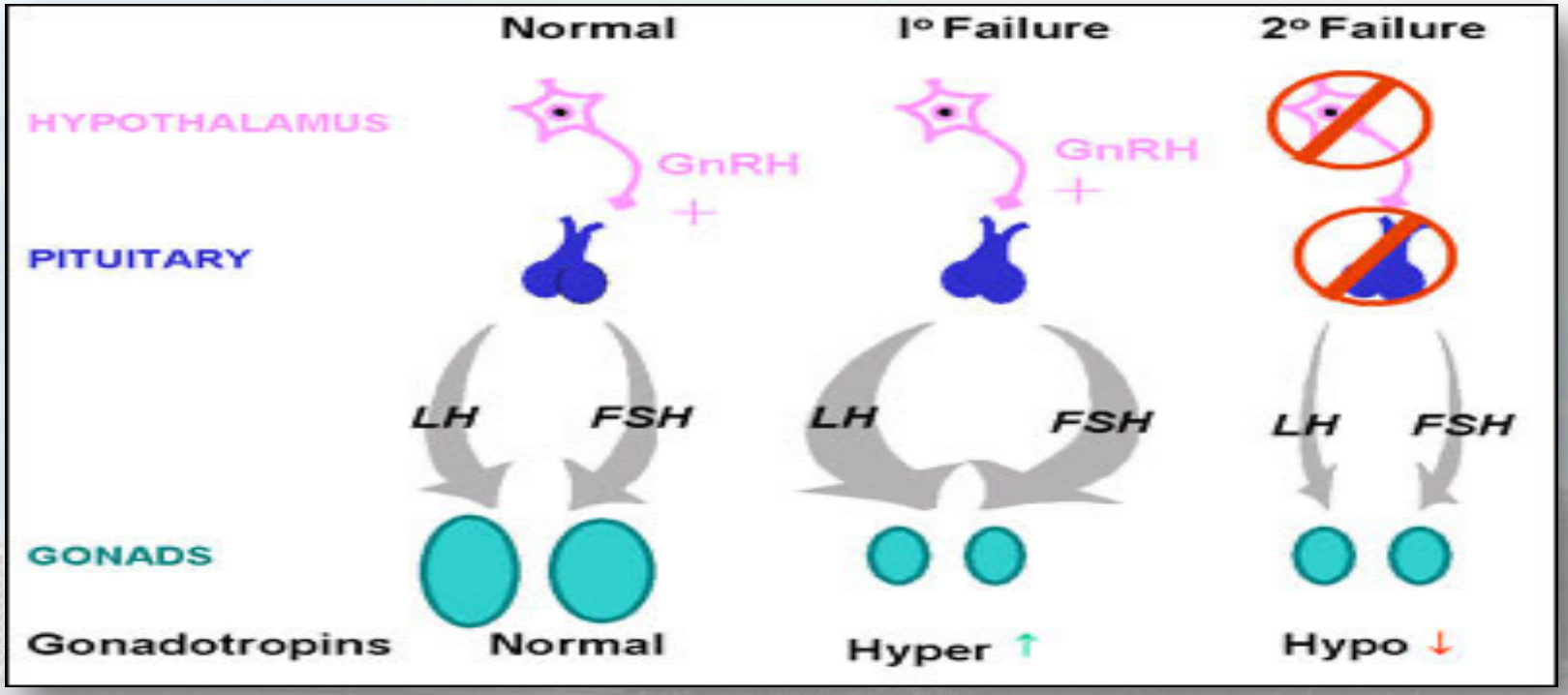
Male hypogonadism : Definition

- A decrease in either of the **two major functions** of the testes:
  - sperm production
  - testosterone production
- Can result from disease
  - Testis (Primary hypogonadism)
  - Pituitary or Hypothalamus (Secondary hypogonadism)

	Primary hypogonadism	Secondary hypogonadism
Testosterone And/or sperm count	Low	Subnormal
FSH/LH	High	Normal/Low

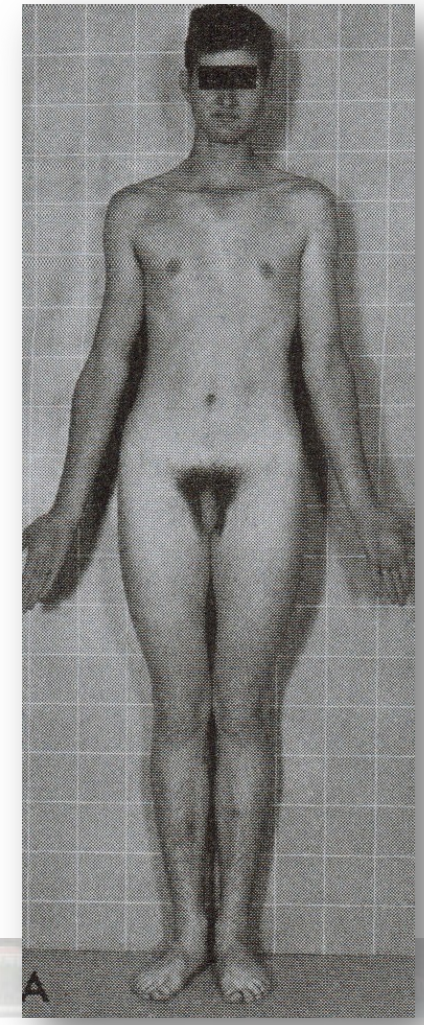
Symptoms

- **Primary or secondary hypogonadism**
  - 1’ (testis): มีอาการของ testosterone deficiency อย่างเดียว
  - 2’ : มีอาการของ testosterone deficiency ร่วมกับขาด hormone อื่น ๆ ด้วย เช่น thyroid, cortisol, GH



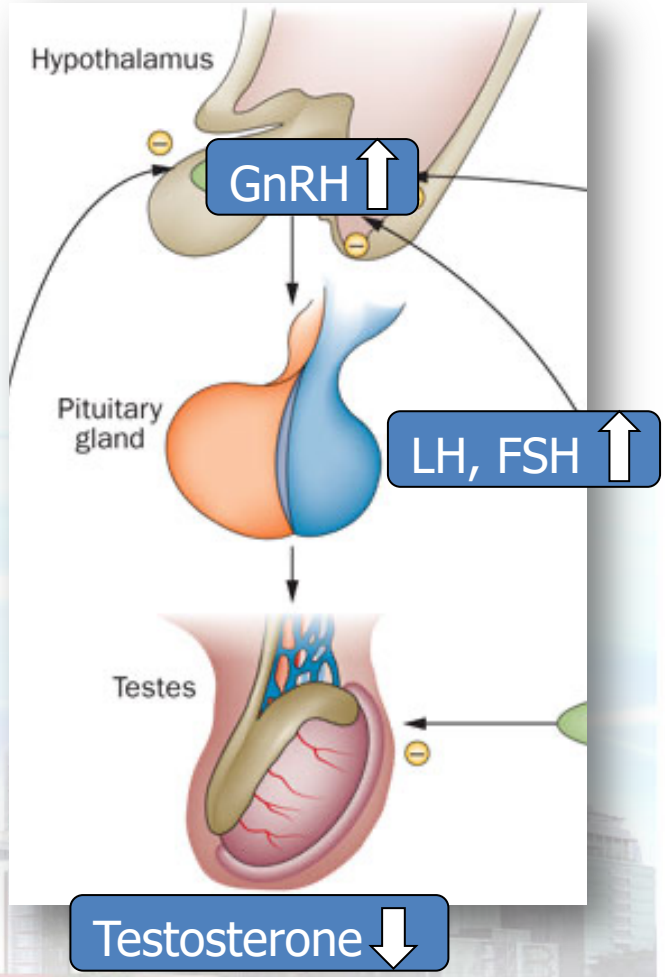
Eunuchoid habitus

- Lack of adult male hair distribution – sparse axillary pubic hair, lack of temporal hair recession
- High-pitched voice
- Infantile genitalia
  - small penis/testes/scrotum
- Poor muscular development
- ↑ fat deposition in the pectoral region/hip/thigh/lower abdomen
- **Eunuchoid proportion**
  - arm span > high span **5 cm**
  - upper/lower segment ratio < 1



Primary hypogonadism

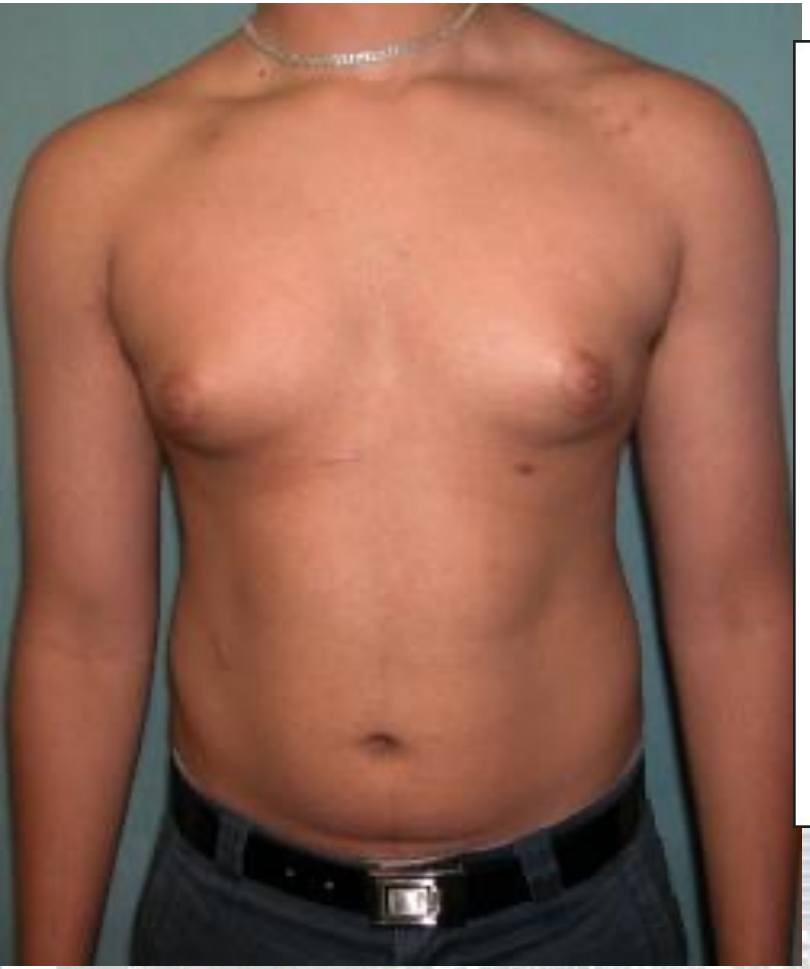
- **Prepubertal onset**
  - Klinefelter's syndrome
- **Postpubertal onset**
  - Mumps orchitis
  - Autoimmune orchitis
  - Trauma, radiation, surgery

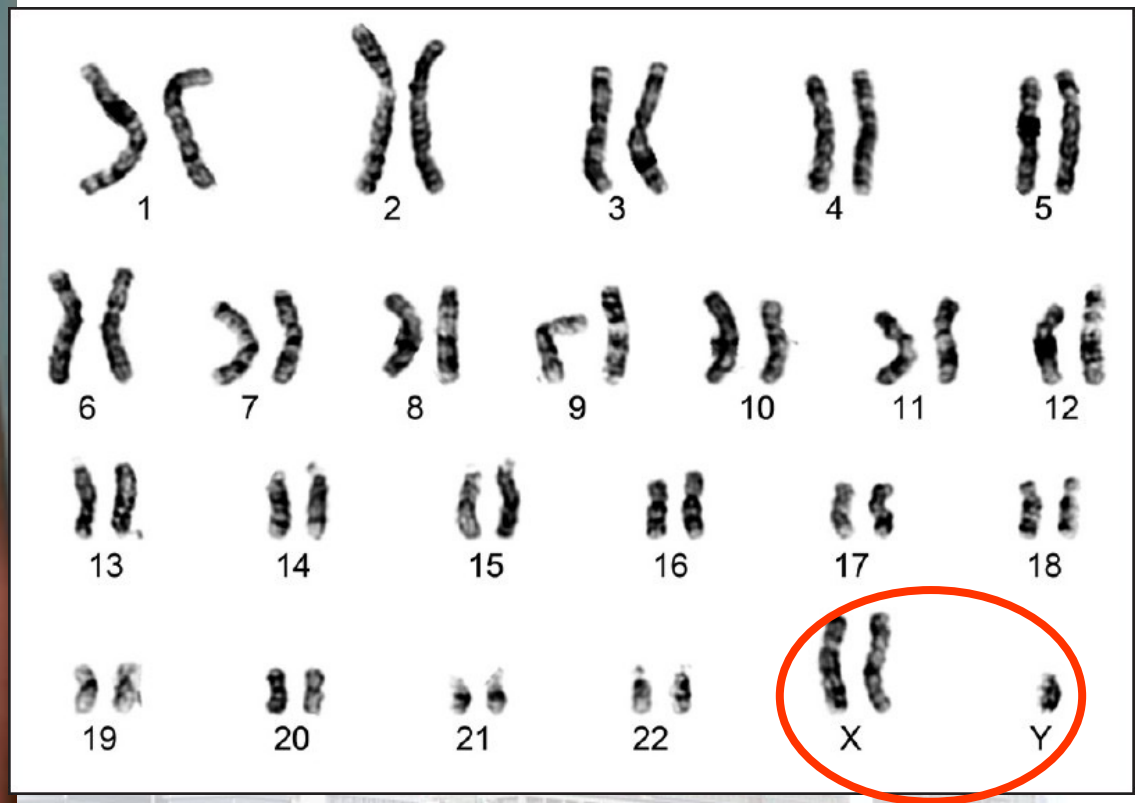


Secondary hypogonadism

Prepubertal onset	Postpubertal onset
•**Kallmann's syndrome** •Idiopathic hypogonadotropic hypogonadism •Pituitary tumor (Craniopharyngioma) •Uremia •Severe systemic illness •Cranial radiation •Hyperprolactinemia	•Acquired idiopathic hypogonadotropic hypogonadism •**Pituitary macroadenoma** •Uremia •Severe systemic illness •Cranial radiation •Hyperprolactinemia •Hemochromatosis •Cushing's syndrome •Cirrhosis •Morbid obesity

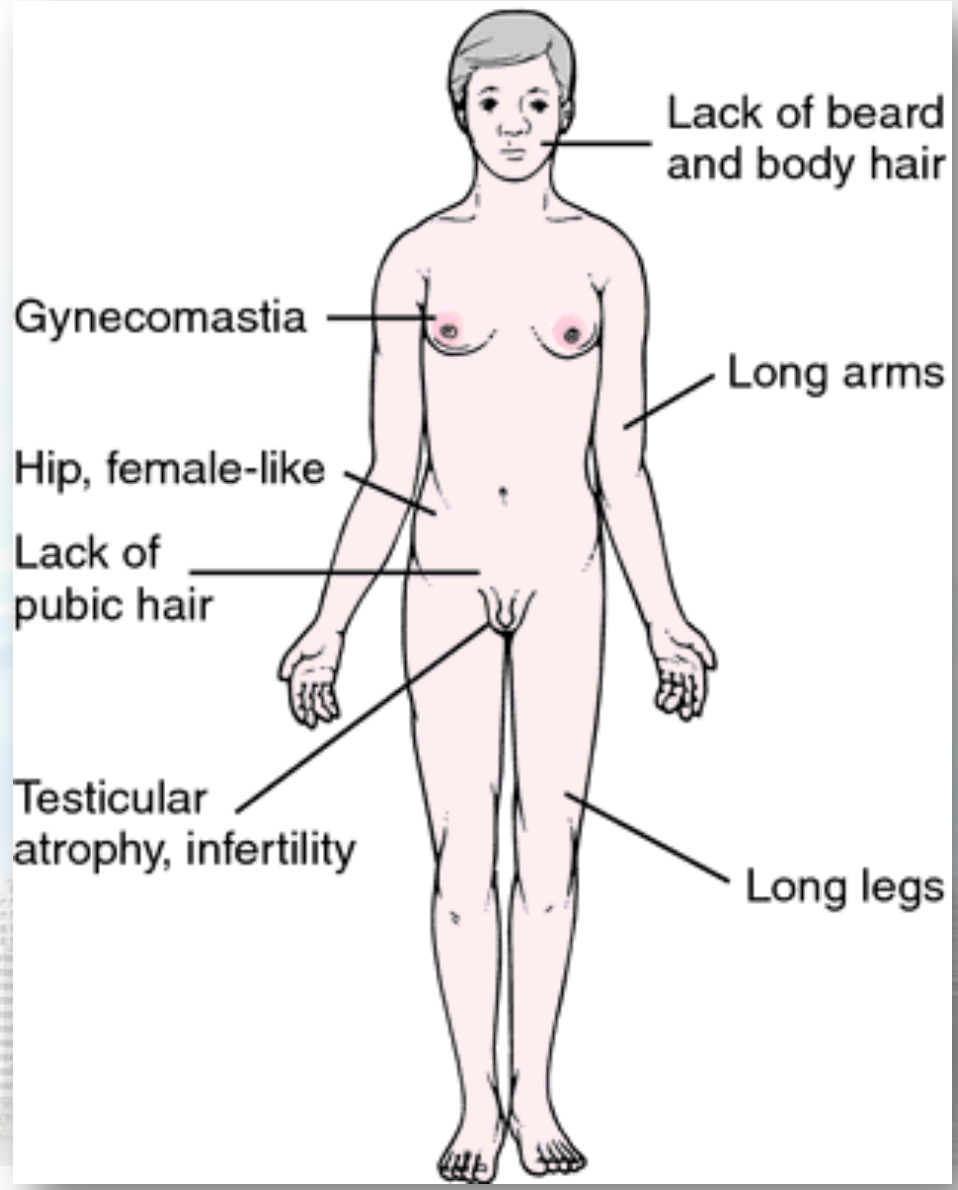
What is the most likely diagnosis?



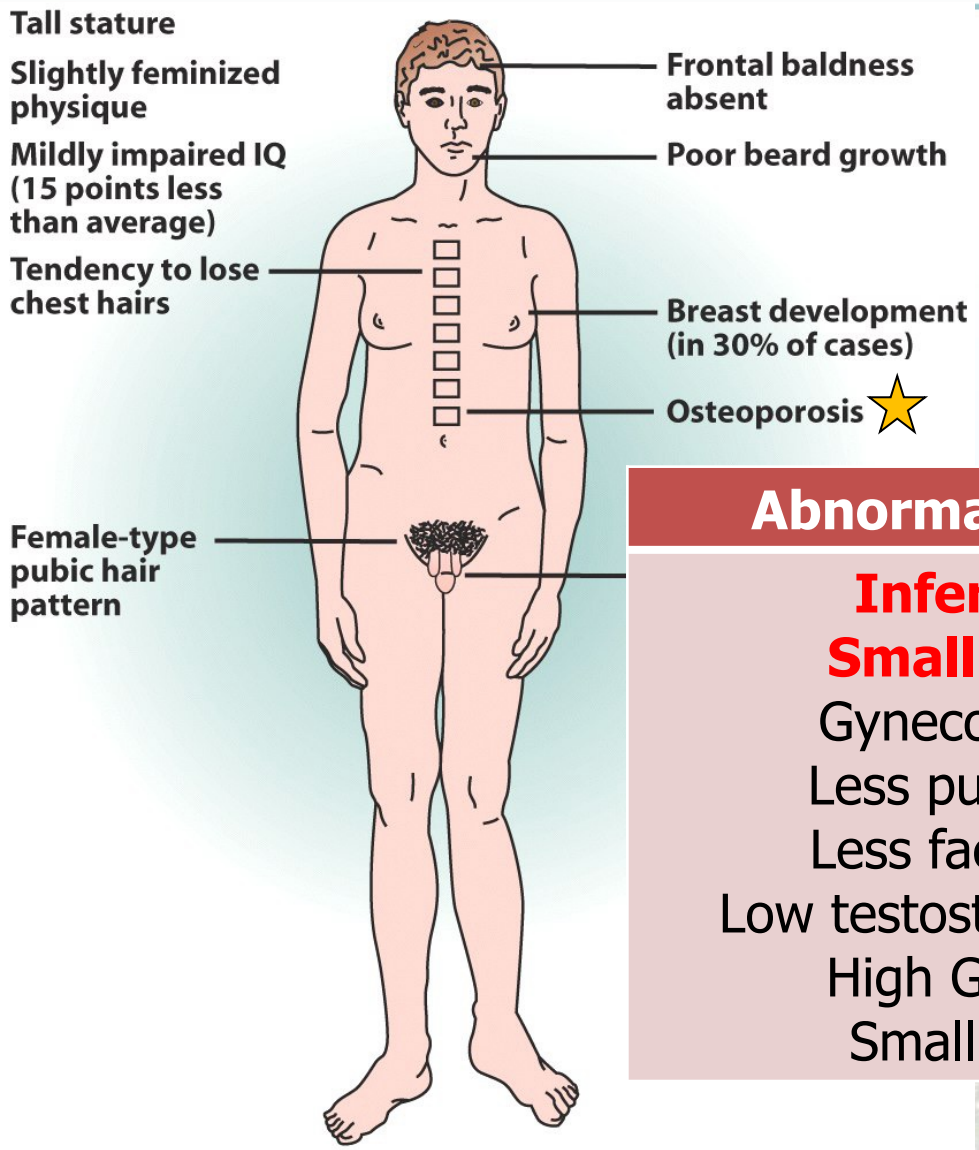


47XXY Klinefelter's syndrome

Klinefelter's syndrome

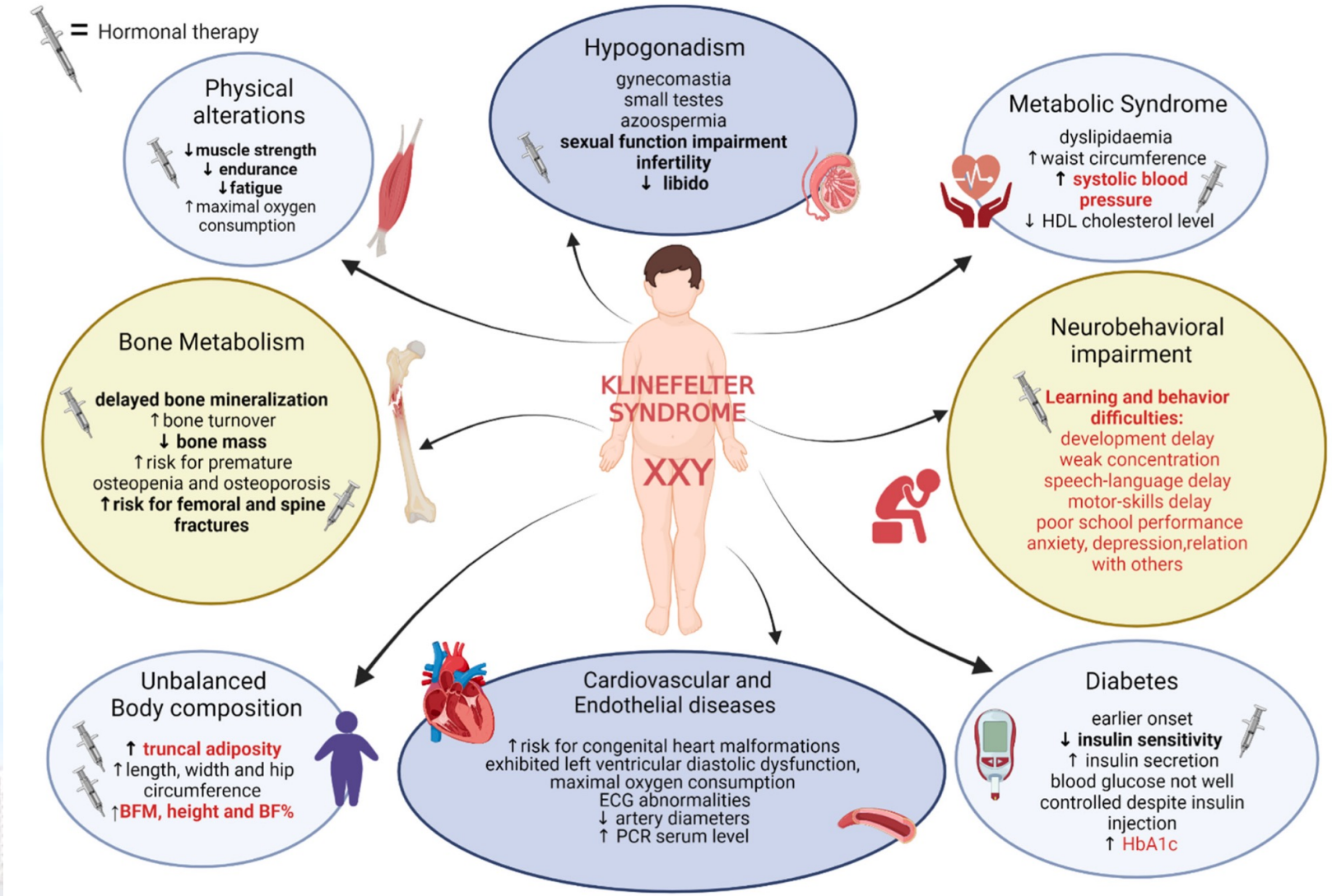


Klinefelter's syndrome

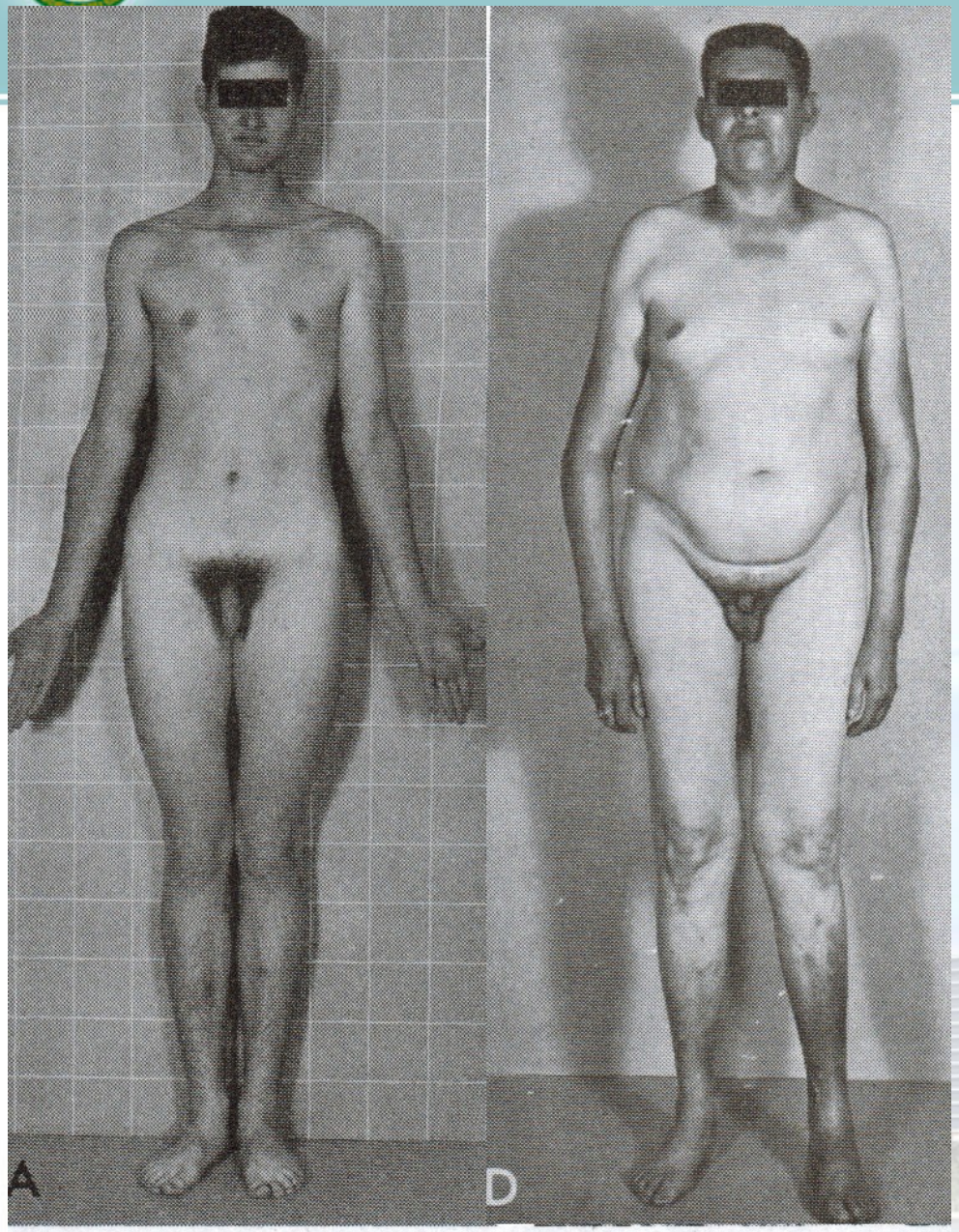


Abnormal finding	%
Infertility	**99 – 100**
Small testis	**99 – 100**
Gynecomastia	50 -75
Less pubic hair	30 – 60
Less facial hair	60 – 80
Low testosterone level	65 – 85
High Gn level	90 – 100
Small penis	10 – 25

Characteristics of KS



Nutrients **2022**, *14*, 2107



- Tall stature, Infertile

  LH <0.5

  FSH <0.5

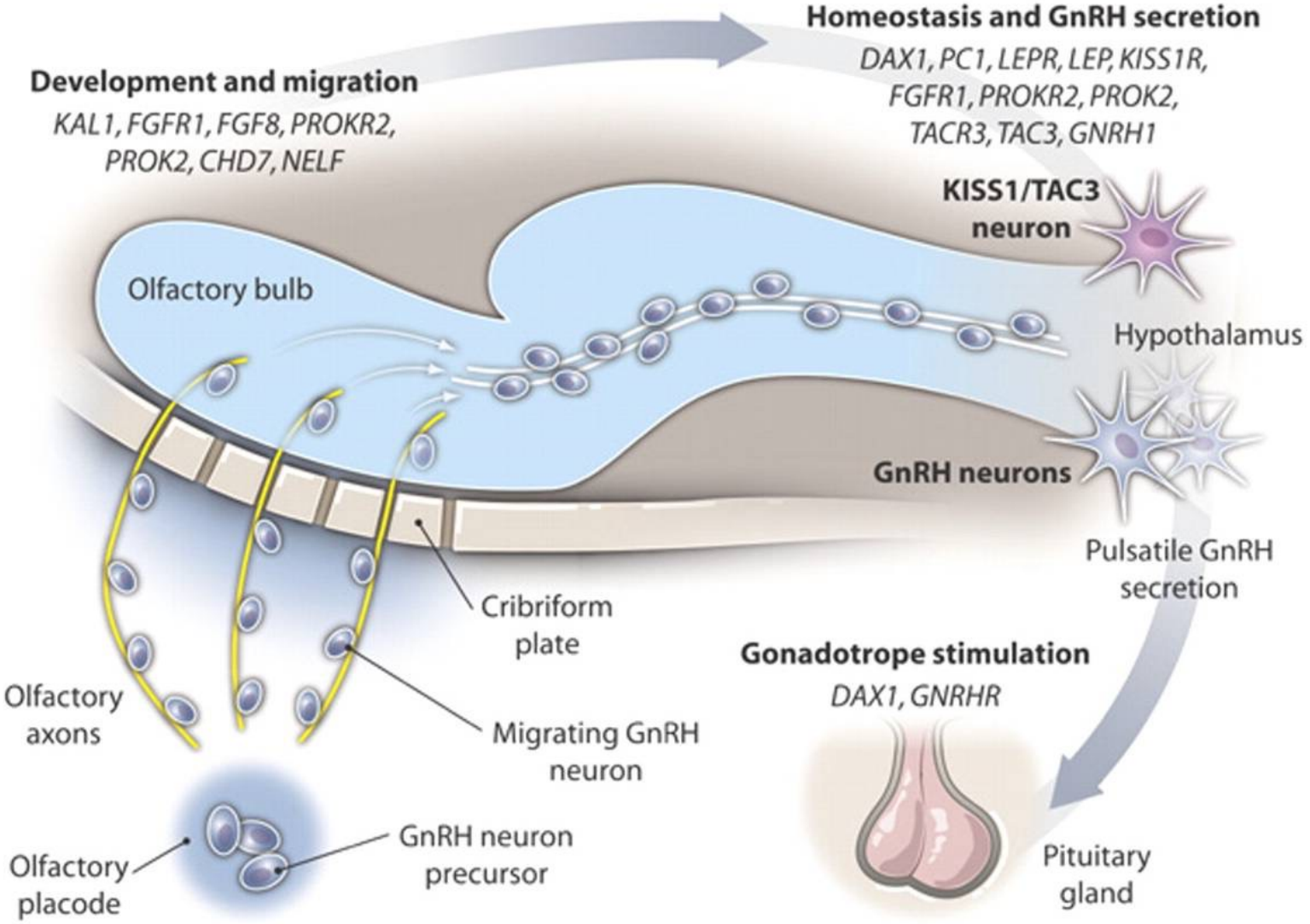
  testosterone <0.025

  Anosmia

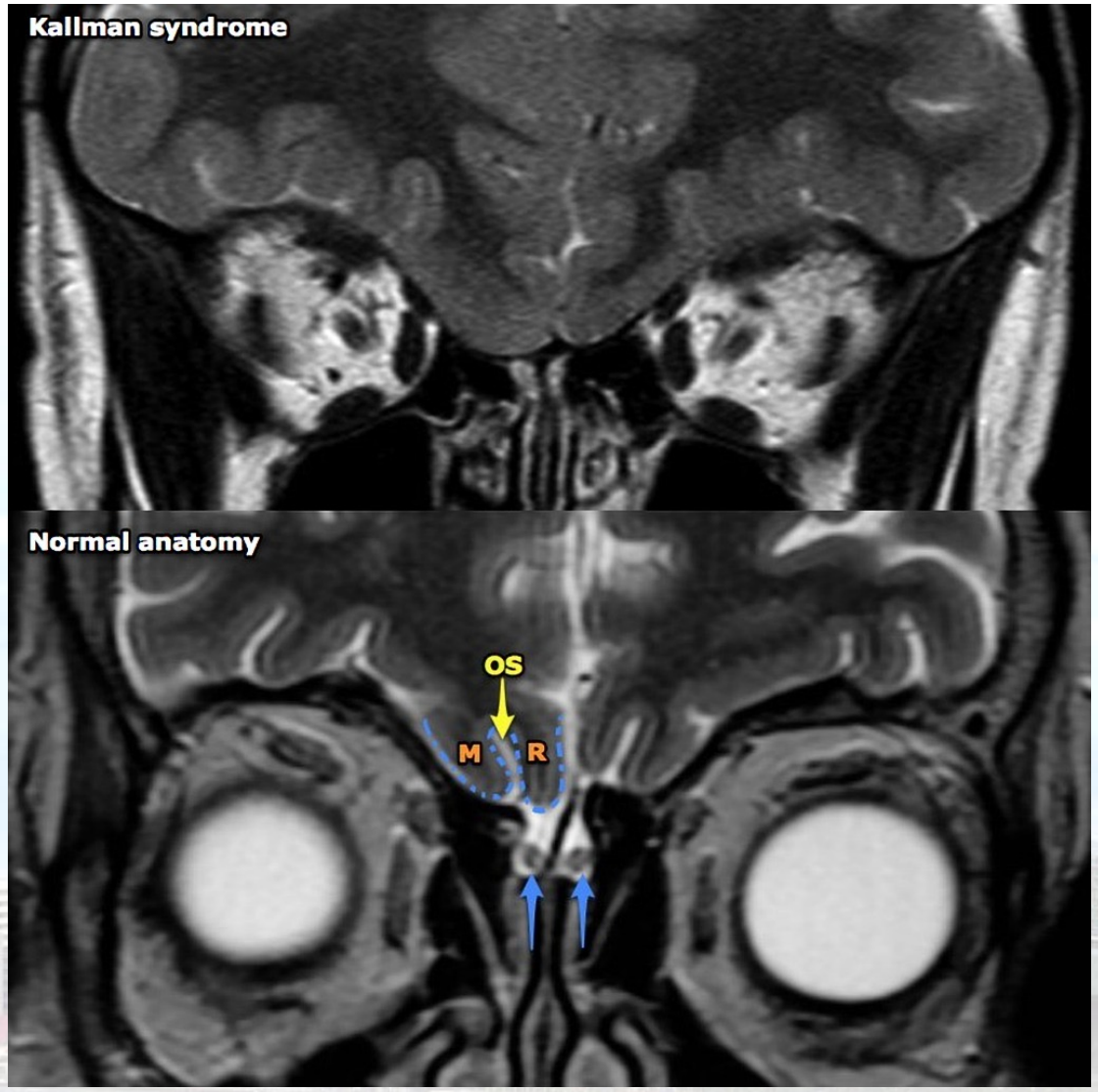
- What is the most likely diagnosis?

Kallmann syndrome

Isolated Hypogonadotrophic Hypogonadism


Homeostasis and GnRH secretion
DAX1, PC1, LEPR, LEP, KISS1R, FGFR1, PROKR2, PROK2, TACR3, TAC3, GNRH1
Development and migration
KAL1, FGFR1, FGF8, PROKR2, PROK2, CHD7, NELF
KISS1/TAC3 neuron
Olfactory bulb
Hypothalamus
GnRH neurons
Pulsatile GnRH secretion
Cribriform plate
Gonadotrope stimulation
DAX1, GNRHR
Olfactory axons
Migrating GnRH neuron
Olfactory placode
GnRH neuron precursor
Pituitary gland

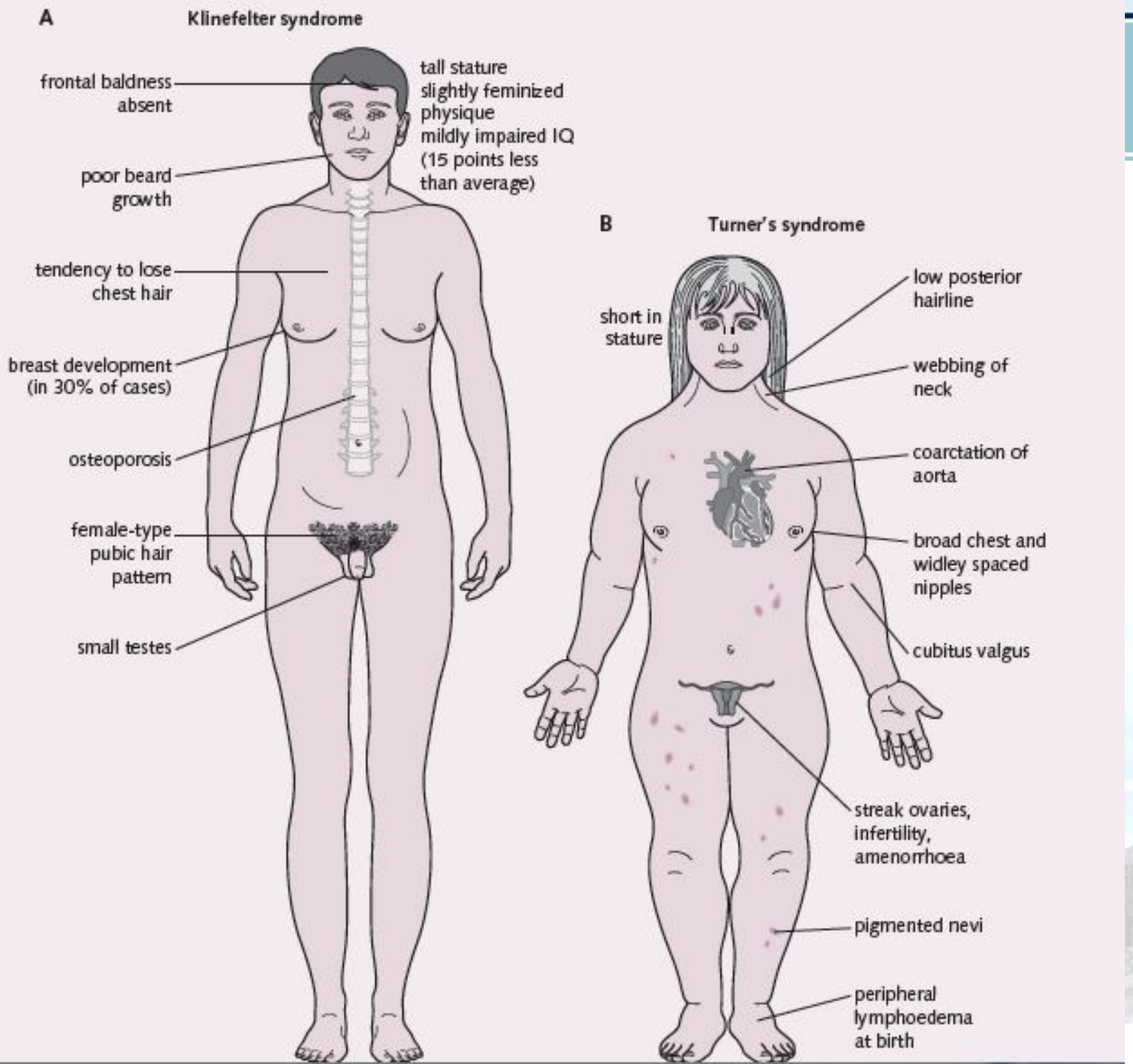
MRI: Kallman syndrome



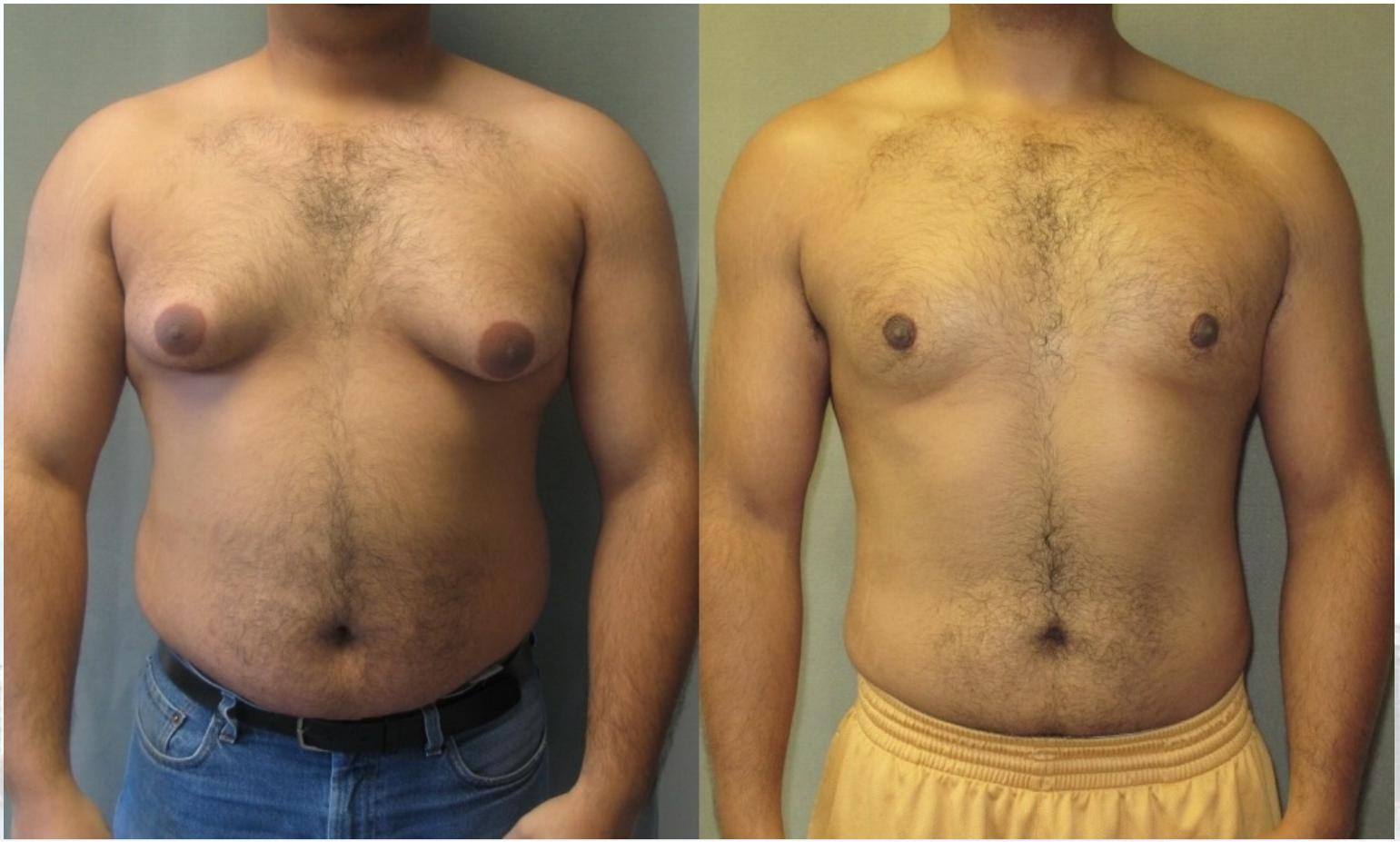
	Klinefelter	Kallmann
Inheritance	-	Most (2/3) : sporadic (new mutation) , others : AD, AR, X-linked
Gynecomastia	Common	Rare (usu s/e of androgen replacement)
Testis	Small, **firm**	Small, **rubbery** or atrophic
Stature	Normal – tall Long leg	Normal No pubertal growth spurt Long arms and legs
Gn levels	**High**	**Usually undetectable**
GnRH test LH response	Hyperresponse at puberty	Prepubertal or no response
Plasma gonadal steroids	Low or normal	Low
Olfaction	**Normal**	**Anosmia or hyposmia**

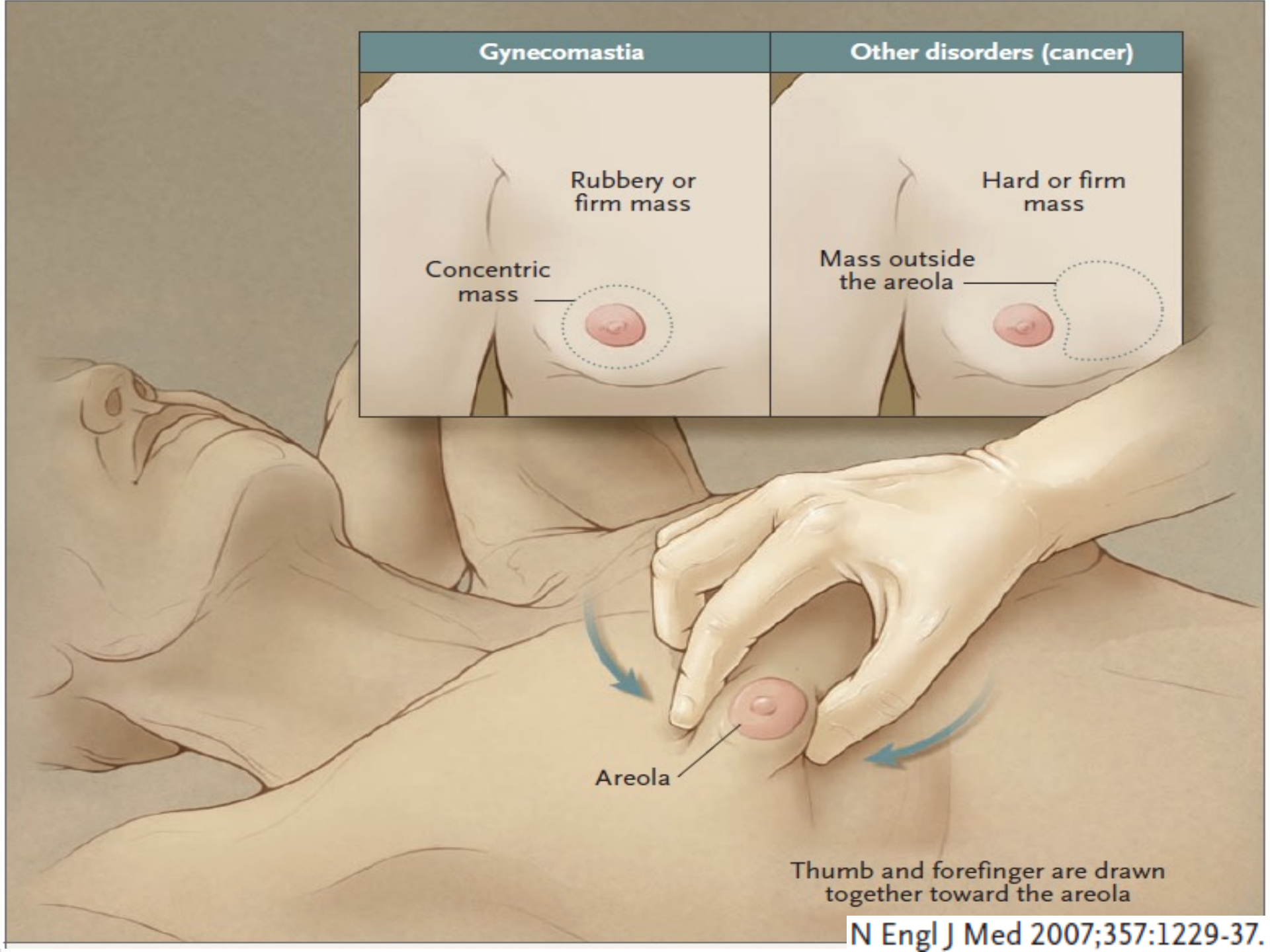
	Klinefelter	Kallmann
Incidence	1:1,000 live male birth	1: 10,000 in male 1:50000 in female
Karyotype	47XXY or variants -48 XXXY -46XY, 46 XXY mosaicism -46XX male	Normal
Associated congenital anomalies		Midline facial defect, red-green color blindness, urogenital tract anomalies, synkinesis, neurosensory hearing loss
Intellectual function	Many with impairment Psychosocial abnormality marked lack of insight poor judgment impaired ability to learn from adverse experience Deficit in the ability to sustain attention	

	Klinefelter	Kallmann
Morbidities and mortality	Pulmonary diseases chronic bronchitis Bronchiectasis emphysema Cancers **germ cell tumors** (particularly extragonadal tumors involving the mediastinum) **breast cancer** possibly non-Hodgkin lymphoma varicose veins, leading to leg ulcers SLE, probably due to the extra X chromosome Diabetes mellitus	Congenital heart diseases Neuropsychiatric problems


A
Klinefelter syndrome
frontal baldness absent
poor beard growth
tendency to lose chest hair
breast development (in 30% of cases)
osteoporosis
female-type pubic hair pattern
small testes
tall stature
slightly feminized physique
mildly impaired IQ (15 points less than average)
B
Turner's syndrome
short in stature
low posterior hairline
webbing of neck
coarctation of aorta
broad chest and widley spaced nipples
cubitus valgus
streak ovaries, infertility, amenorrhoea
pigmented nevi
peripheral lymphoedema at birth

Gynaecomastia





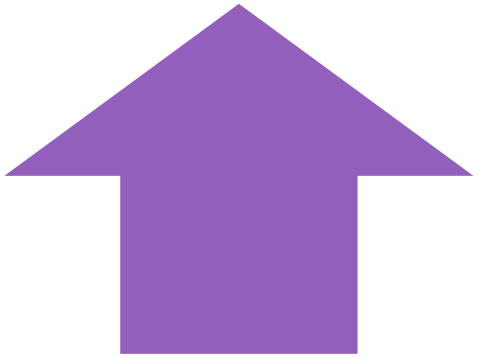
N Engl J Med 2007;357:1229-37.

Gynecomastia: pathogenesis

Imbalance of estrogen and androgen

Free androgen

Free estrogen



Approach to gynaecomastia

True gynaecomastia

Lipomastia	Breast cancer

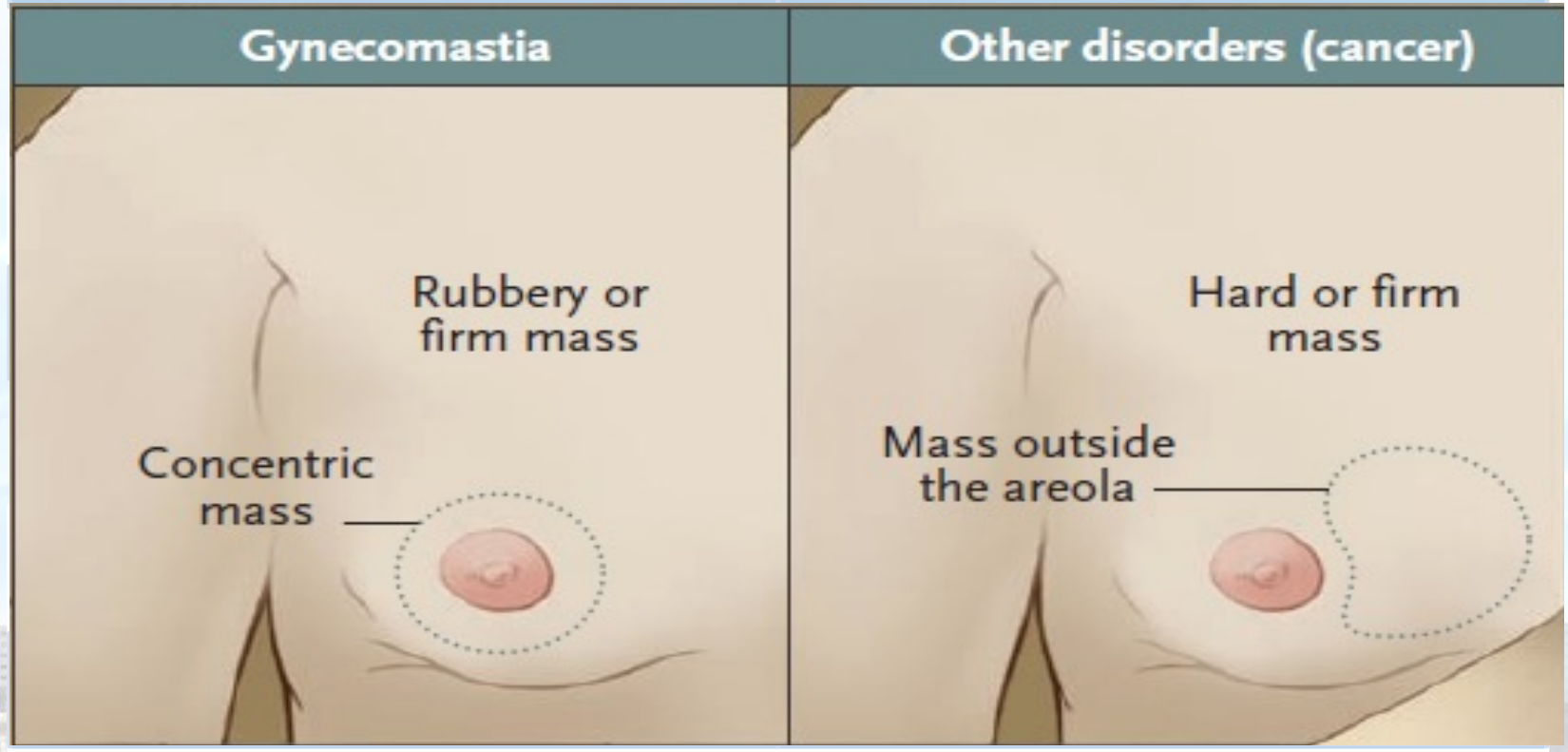


TABLE 2. Drugs commonly implicated in gynecomastia

- Drugs that increase serum estrogens
  - Estrogens, including topical preparations
  - Aromatizable androgens
  - hCG
- Drugs with estrogen-like activity
  - Digitoxin
- Drugs that decrease serum testosterone or dihydrotestosterone
  - GnRH agonists/antagonists
  - Leydig cell damage or inhibition
    - Ketoconazole, metronidazole
    - High-dose spironolactone
    - Cancer chemotherapy
  - Finasteride or dutasteride
- Androgen receptor blockers
  - Flutamide, bicalutamide
  - Spironolactone
  - Cimetidine
  - Marijuana
- Increased serum prolactin
  - Antipsychotic agents
  - Metoclopramide
  - Verapamil
- Other—mechanism uncertain
  - Isoniazid
  - Amiodarone
  - Antidepressants
  - Human GH
  - Highly active antiretroviral therapy (HAART)
  - Proton pump inhibitors

Cause of gynecomastia

I. Estrogen excess
   A. Exogenous estrogens: therapeutic or unintentional exposure, including exposure to aromatizable androgens (*e.g.* athletes)
   B. Endogenous estrogens
      1. Increased secretion from testis (Leydig cell or Sertoli cell tumors, stimulation of normal Leydig cells by LH or hCG)
      2. Increased secretion from adrenals (feminizing adrenocortical tumors)
      3. Increased aromatization of androgens to estrogens (aging, obesity, alcoholic cirrhosis, hyperthyroidism, drugs, hCG-secreting tumors, aromatase excess syndrome)

II. Androgen deficiency: primary or secondary hypogonadism due to disease, trauma, radiation, or drugs

III. Altered serum androgen/estrogen ratio (puberty, aging, refeeding gynecomastia, hepatic cirrhosis, renal failure and dialysis, hyperthyroidism, drugs)

IV. Decreased androgen action
   A. Androgen receptor antagonists (spironolactone, cimetidine, bicalutamide, flutamide)
   B. Absent or defective androgen receptors
   C. Expansion of CAG repeats in the androgen receptor gene (Kennedy disease)

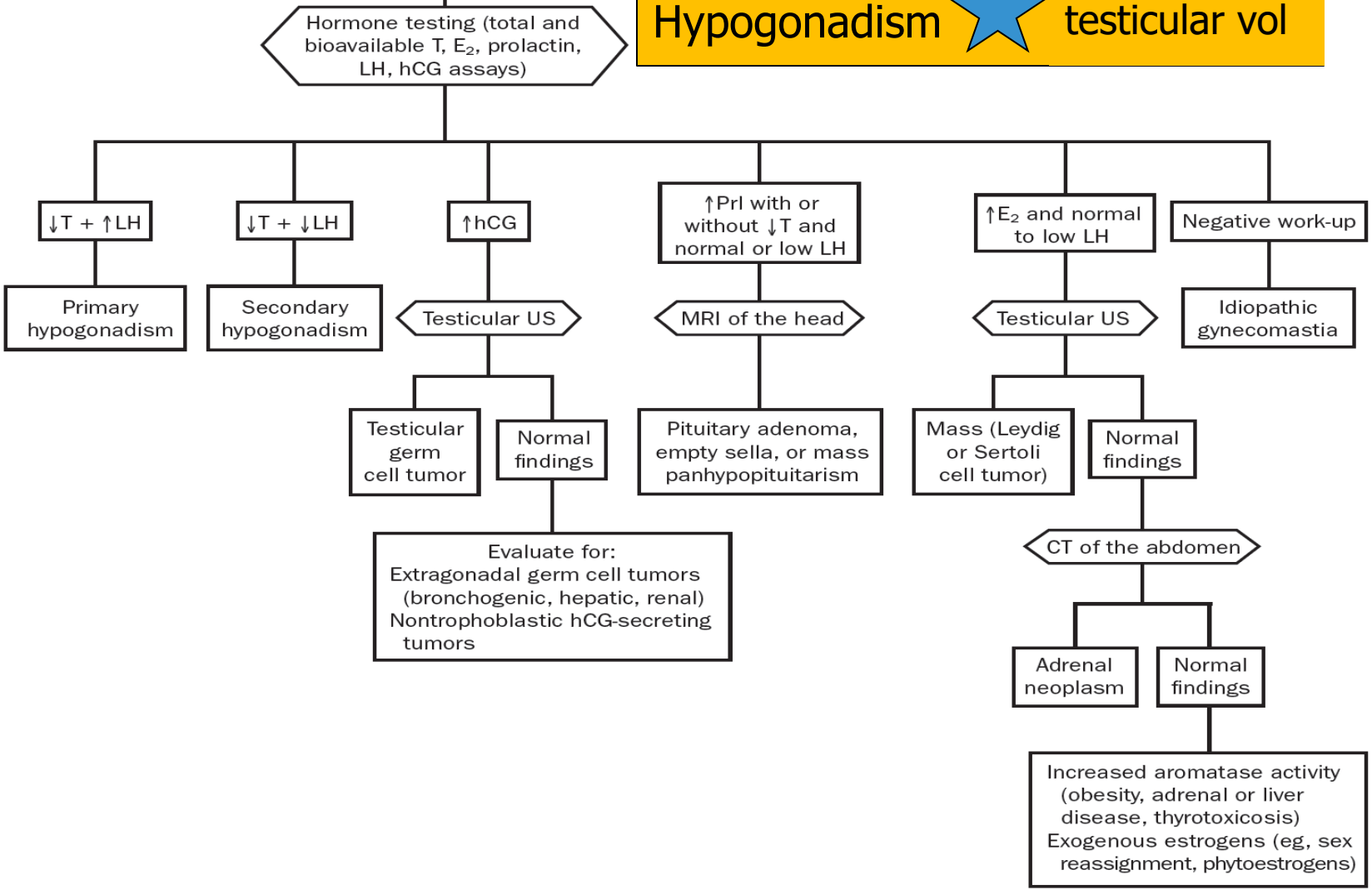
↑ Estrogen

↓ Androgen

Approach to gynecomastia

Exclude common disease

Cirrhosis, Renal failure
Hyperthyroid
Hypogonadism ★ testicular vol



Case

17 year-old female presented with

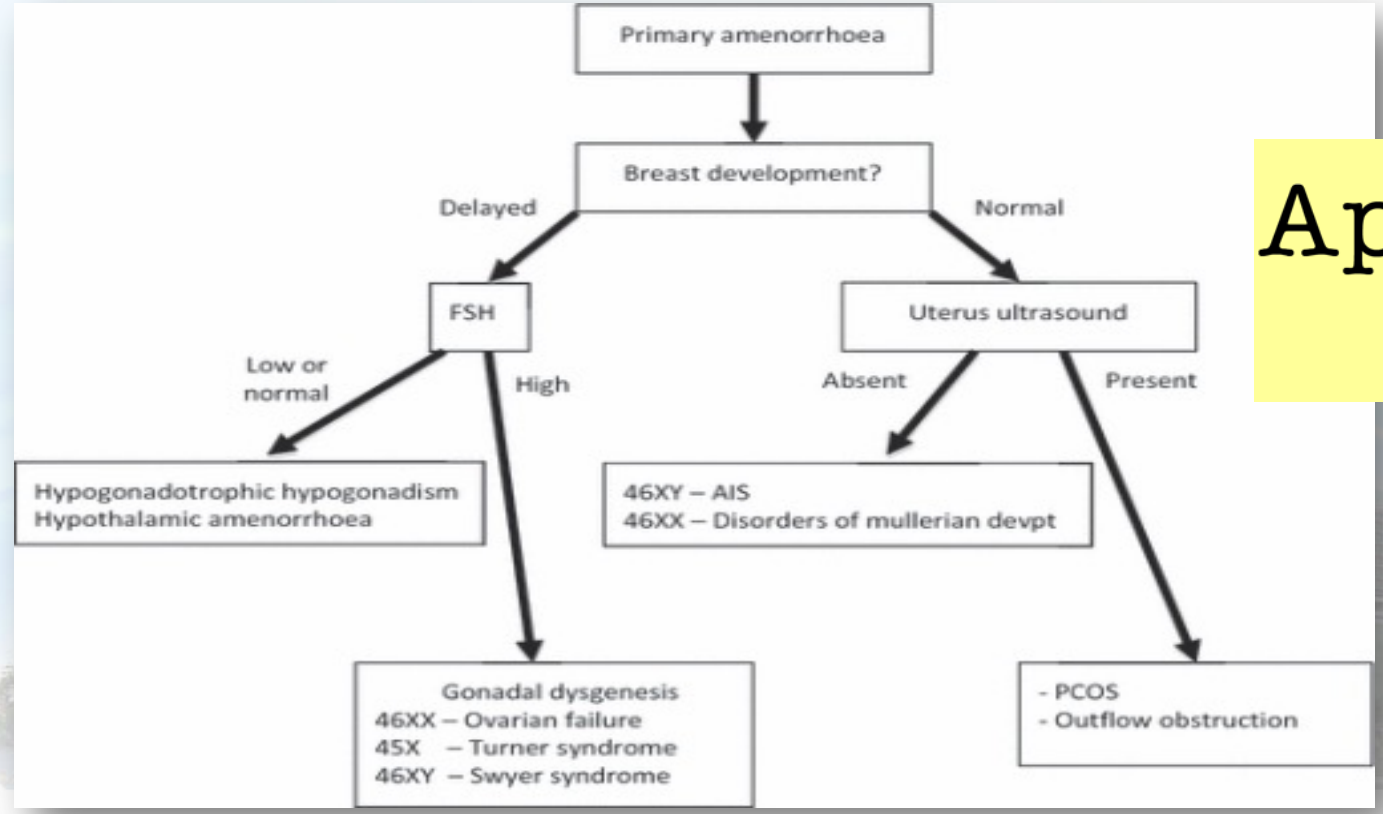
Case

17 year-old female presented with

Definition of amenorrhea

Primary amenorrhea

- ✓ No menarche by age 14, No 2° sex characteristics
- ✓ No menarche by age 16, Normal 2° sex characteristics



Mineralocorticoids excess

Hypertension (hypokalemic metabolic alkalosis)

Plasma aldosterone concentration (PAC)
Plasma renin activity (PRA)

PAC ↑ (≥ 10 ng/dL)
PRA ↓ <1 or DRC < 8-12
ARR ≥ 20-30

PAC ↑
PRA ↑

PAC ↓
PRA ↓

Primary Aldosteronism (PA)

- Aldosterone-producing adenoma (APA)
- Idiopathic hyperaldosteronism (IHA) or bilateral PA
- Glucocorticoid remediable aldosteronism (GRA)

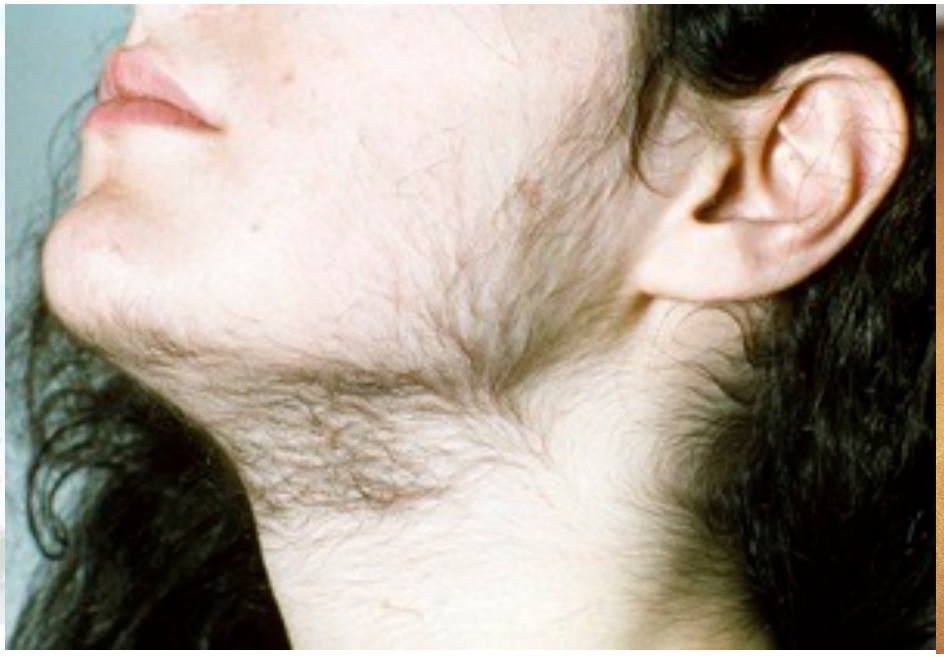
Secondary Aldosteronism

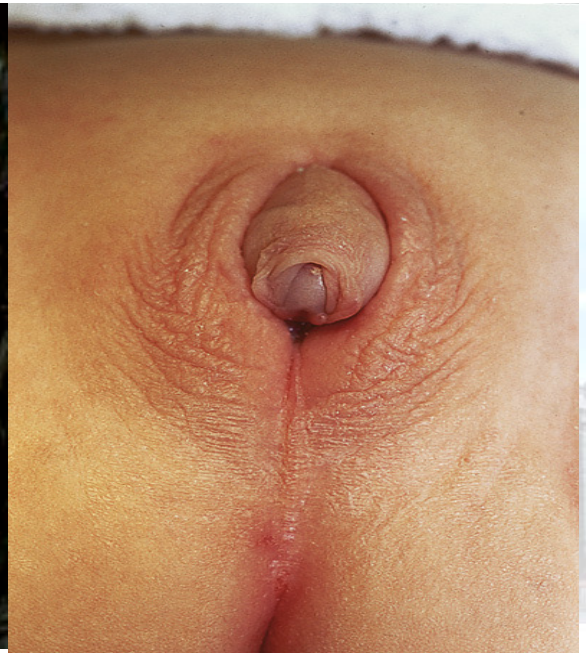
- Renal artery stenosis (RAS)
- Reninoma
- Malignant HT
- Ineffective circulatory volume

Other mineralocorticoid excess

- Cushing syndrome
- CAH (11- and 17-OH deficiency)
- Liddle's syndrome

Congenital adrenal hyperplasia (CAH)





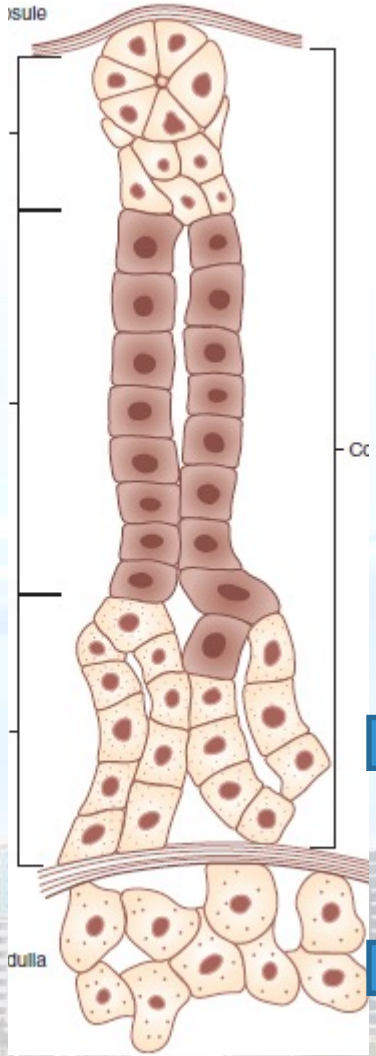
Adrenal gland

Glomerulosa → **A**ldosterone

Fasciculata → **C**orticosteroid

Reticularis → **S**ex steroids

Medulla → Catecholamines

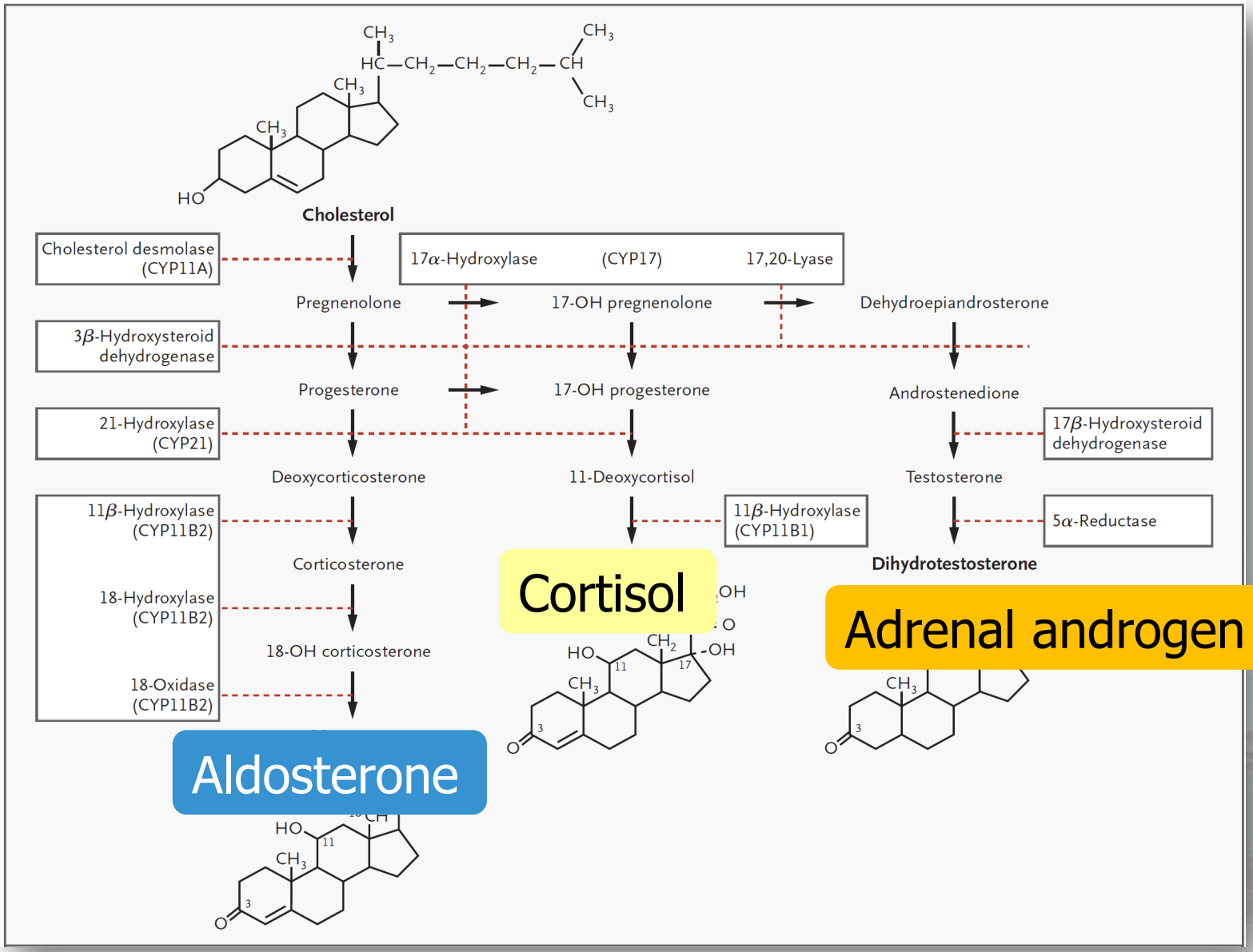


CORTEX

Congenital adrenal hyperplasia

- Autosomal recessive
- **Primary adrenal insufficiency**
- Most common type : **21-OH deficiency**
- Hypertension : 11 & 17 OH deficiency
  low aldosterone, low renin

Adrenal steroidogenesis

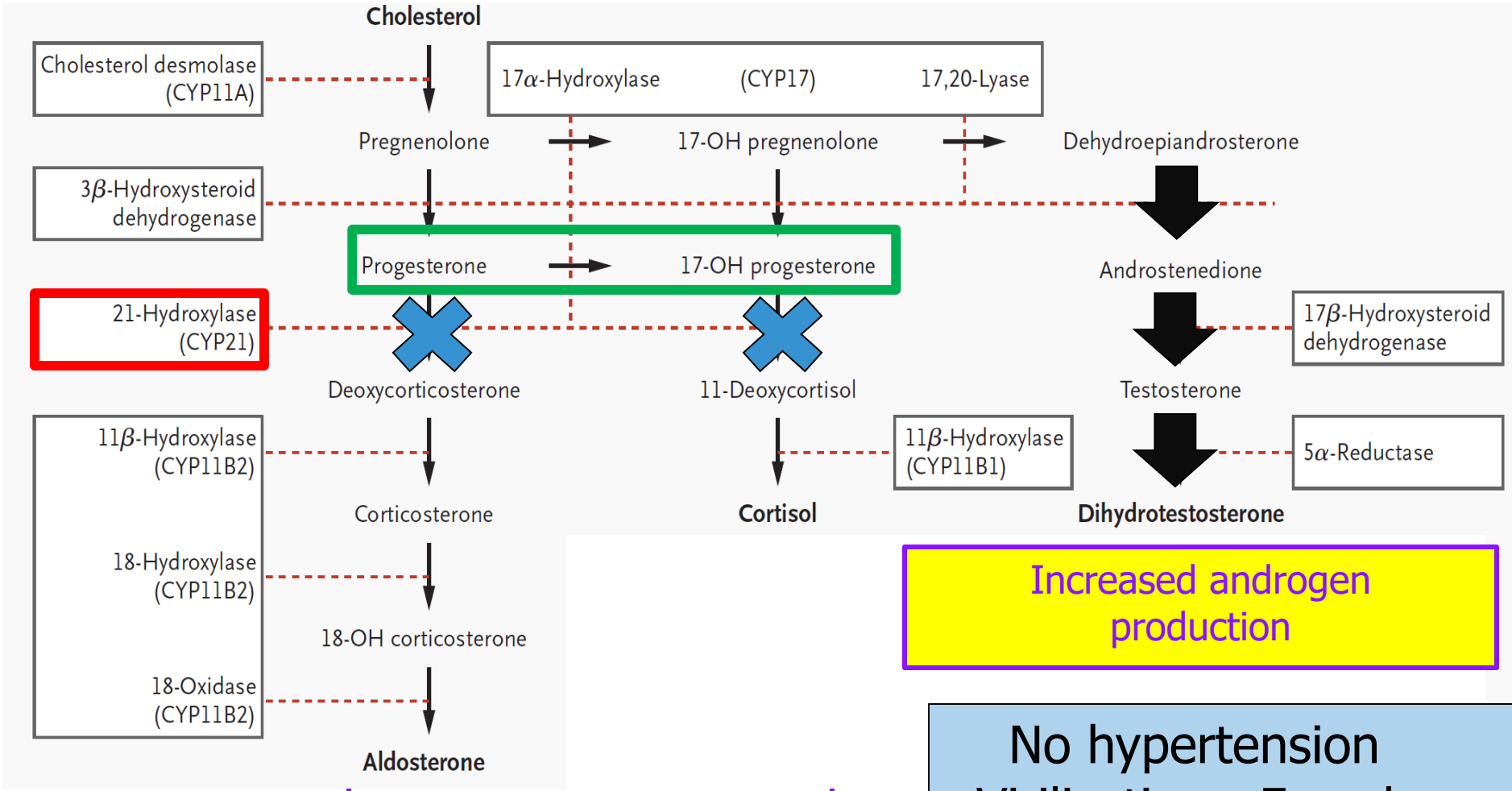


RULE : HIV

1 อยู่หน้ามี HT

1 อยู่หลังมี virilization

21 OH deficiency

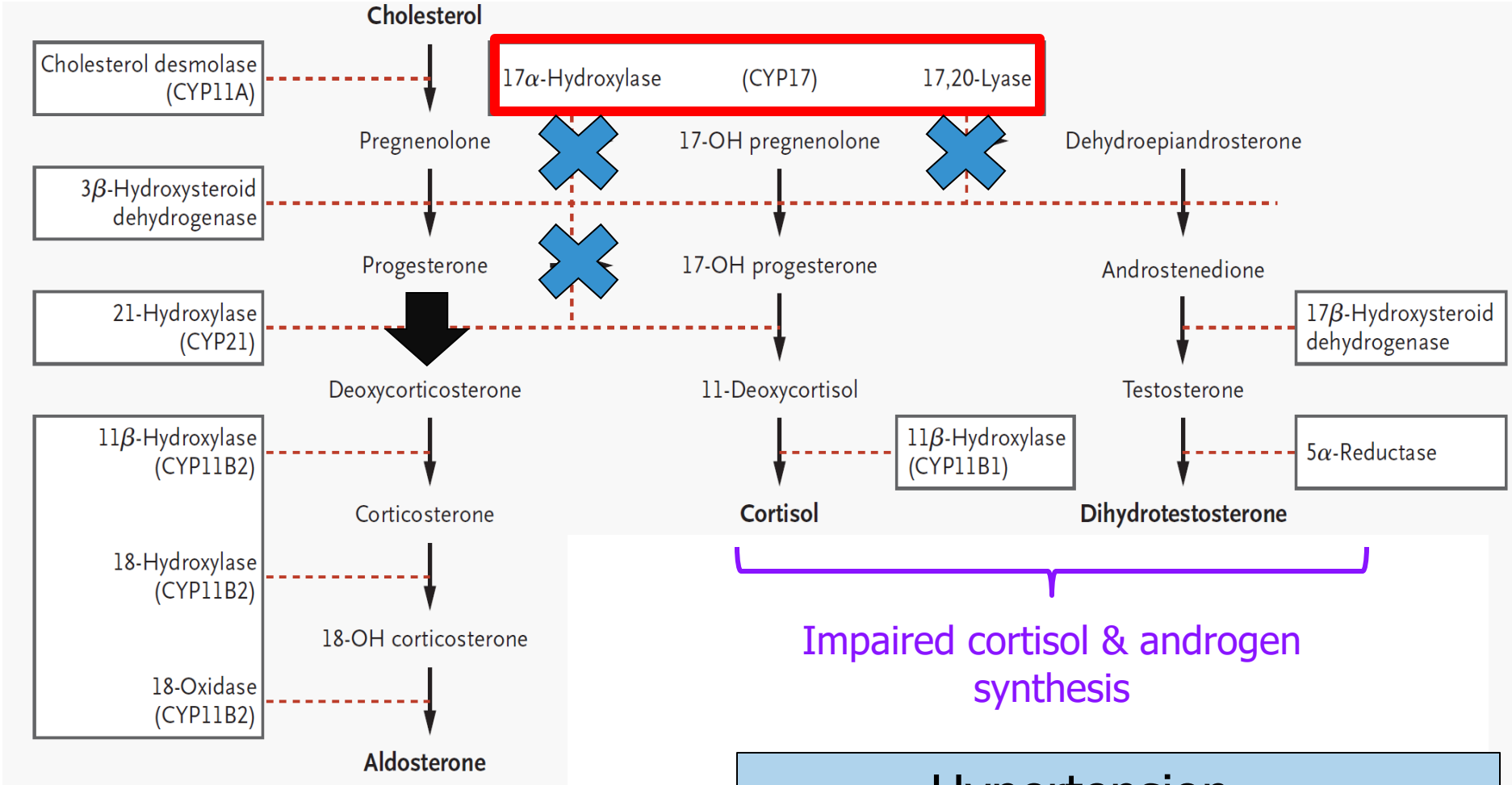


Increased androgen production

No hypertension
Virilization : Female

Impaired cortisol & aldosterone synthesis

17 OH deficiency

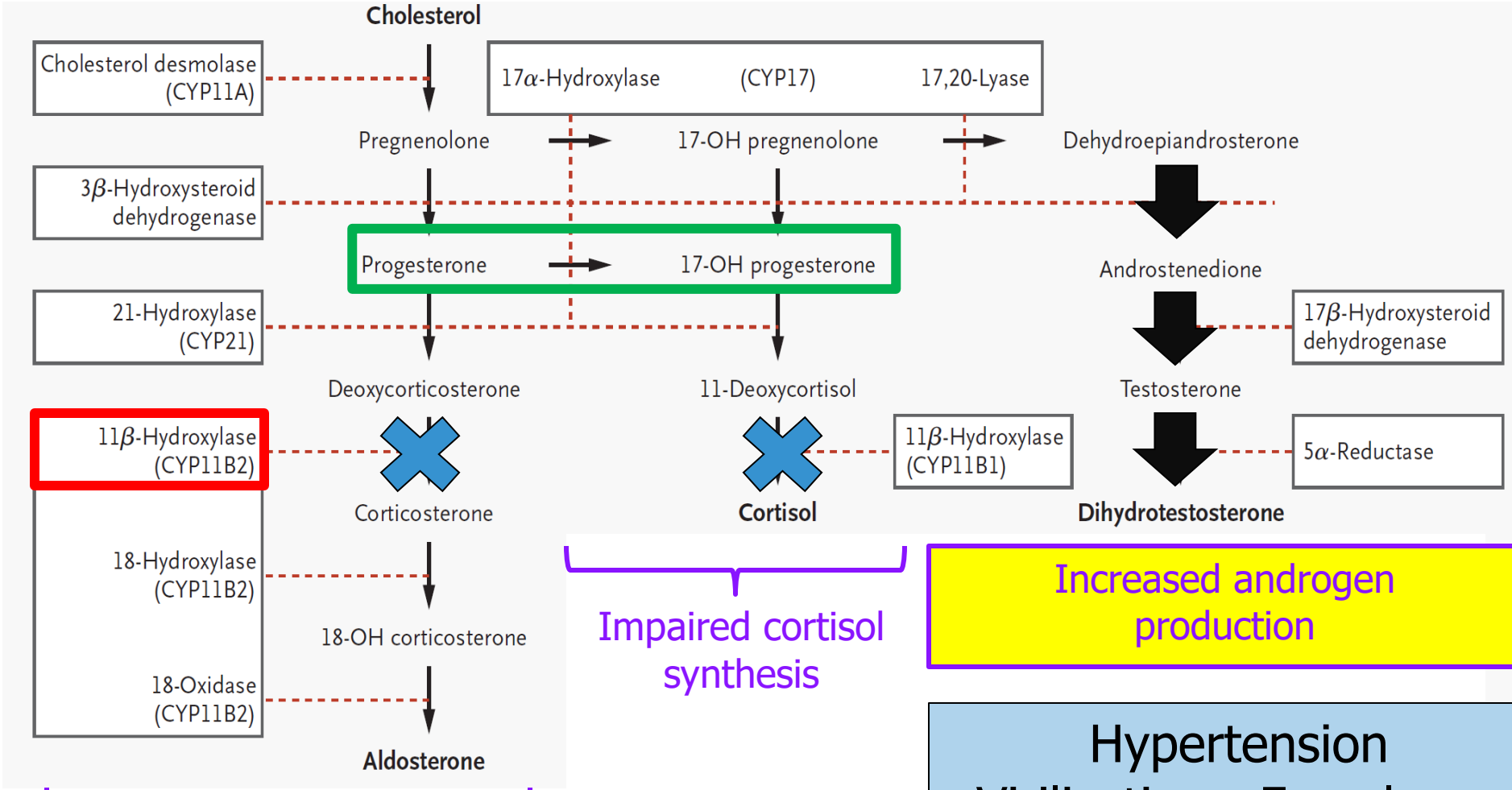


Impaired cortisol & androgen synthesis

Hypertension from mineralocorticoid excess

Hypertension
XY Male pseudohermaphrodite

11 OH deficiency



Impaired cortisol synthesis

Increased androgen production

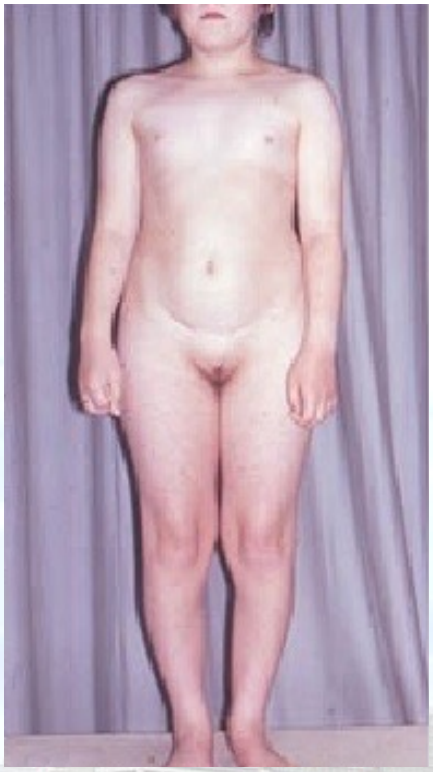
Hypertension
Virilization : Female

HT from deoxycorticosterone excess

Case

17 year-old female presented with

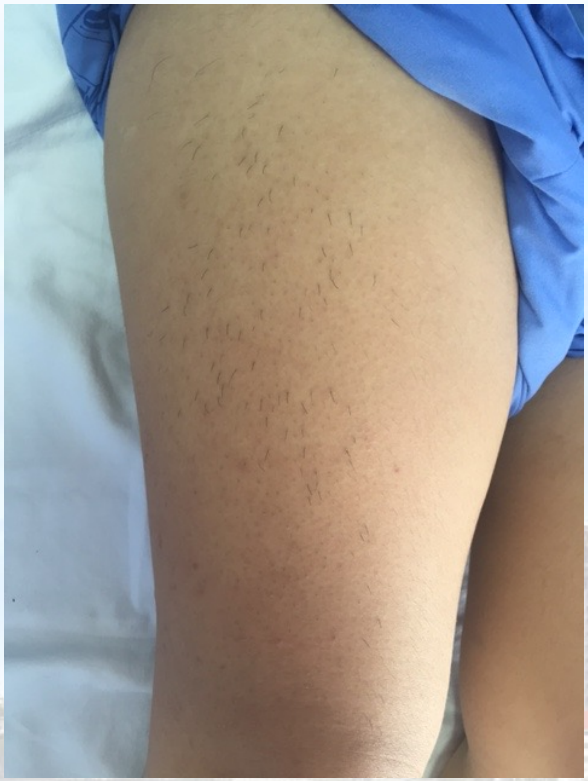
- ✓ Primary amenorrhea
- ✓ Hypertension BP 160/90
  K 3.0, HCO_3 29
- ✓ No secondary sex characteristics
- ✓ Height 170 cm

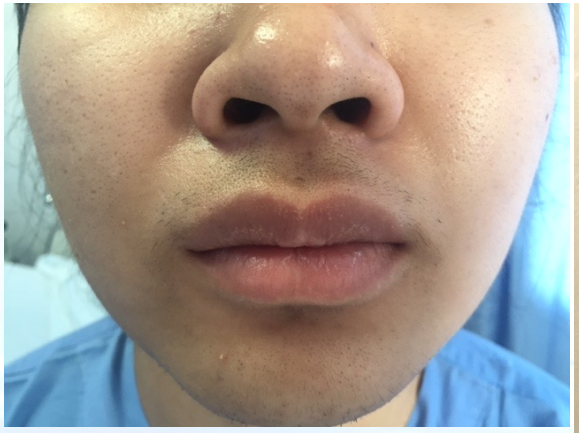


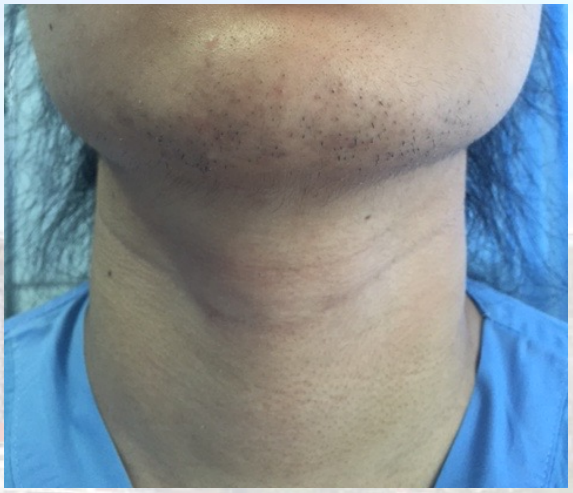
Chromosome 46 XY

17-OH deficiency

A 15 year-old female presented with hirsutism for 1 year

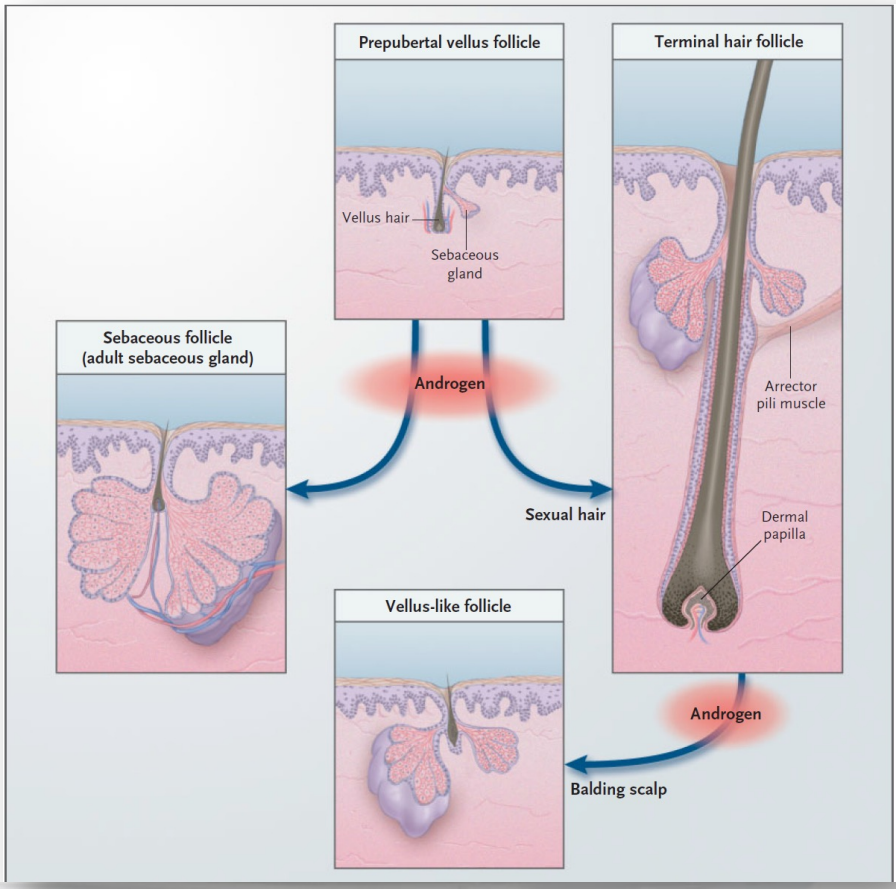






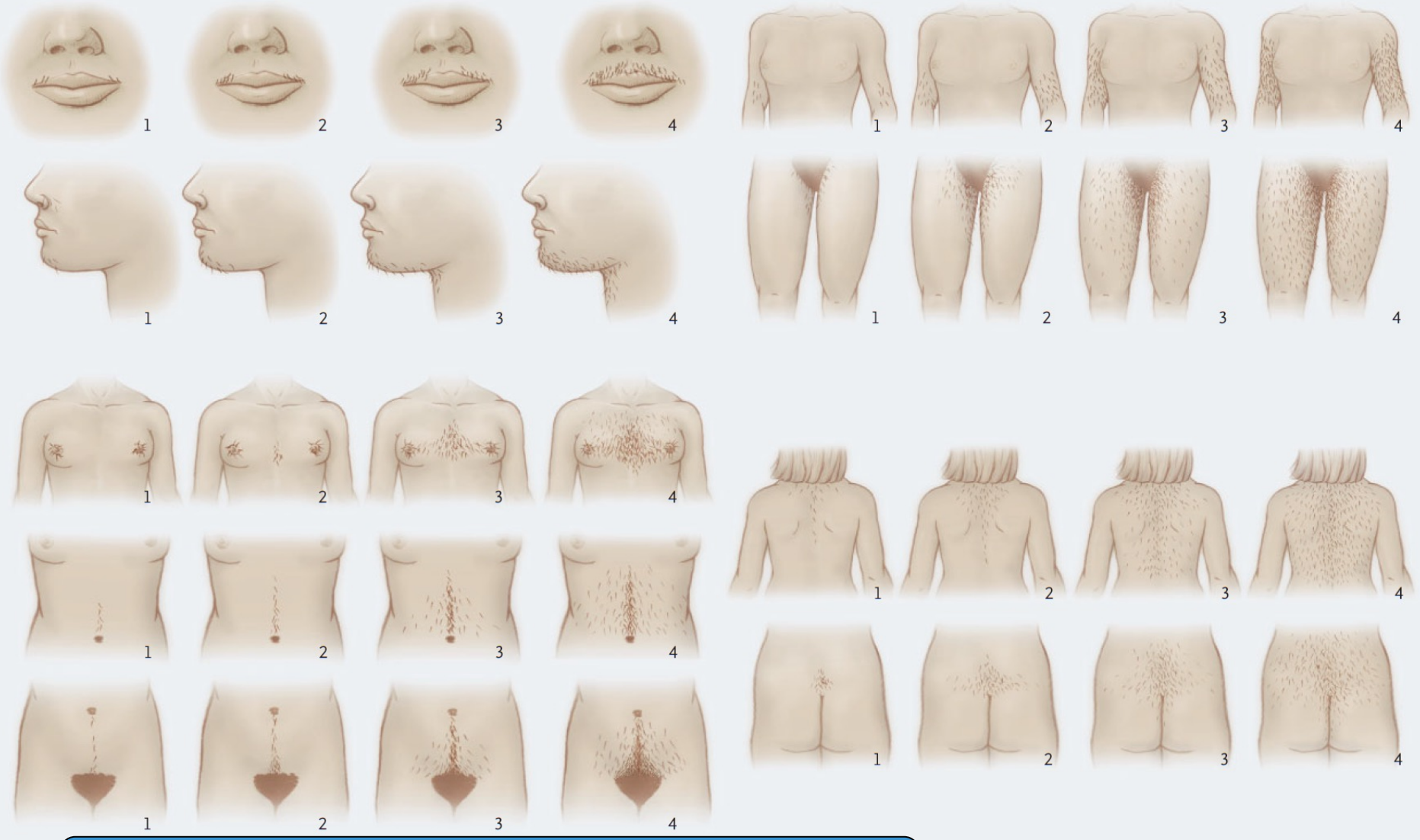
Hirsutism

- **Hirsutism** is defined as excessive **terminal hair** that appears in a male pattern in women
- Indicated by a score of 8 or more on the Ferriman-Gallwey scale
- Hirsutism results from an interaction between the **androgen level** and the sensitivity of the hair follicle to androgen



N Engl J Med 2005;353:2578-88.

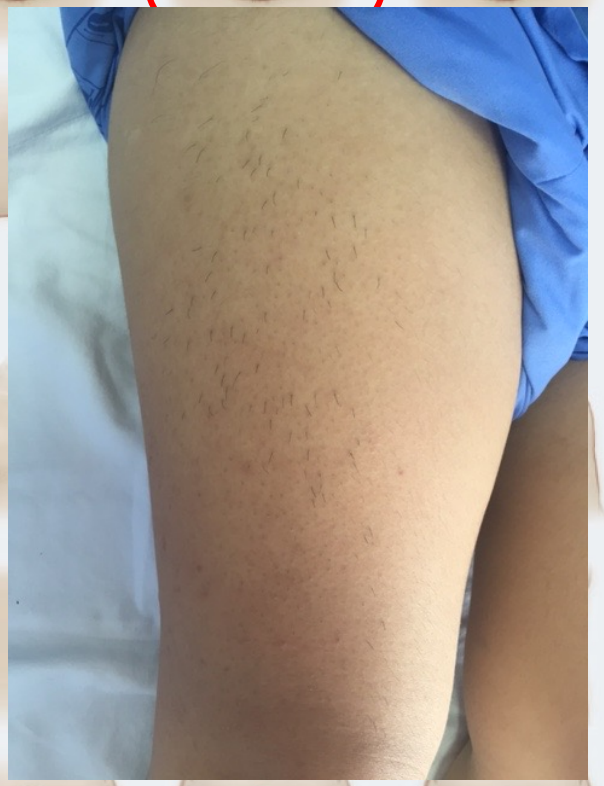
Ferriman–Gallwey scale

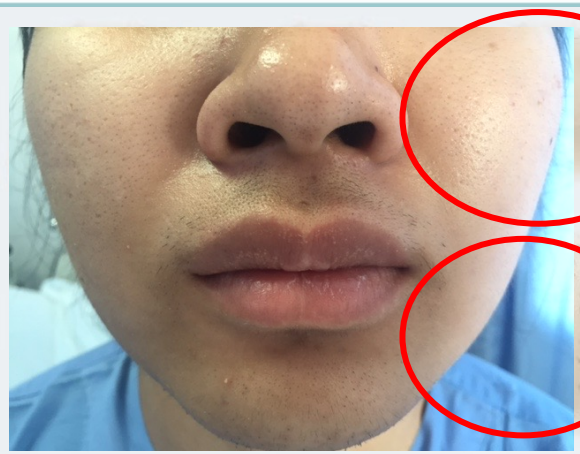


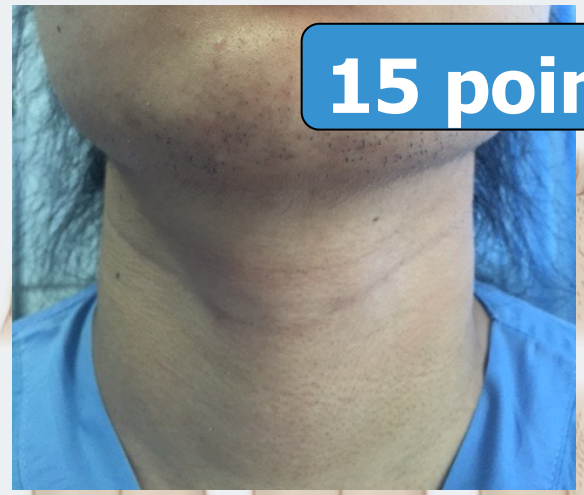
A score of 8 or more = Hirsutism

N Engl J Med 2005;353:2578-88.

Ferriman–Gallwey scale : our pt







15 points

A score of 8 or more = Hirsutism

N Engl J Med 2005;353:2578-88.

Androgen excess vs Virilization

Androgen excess

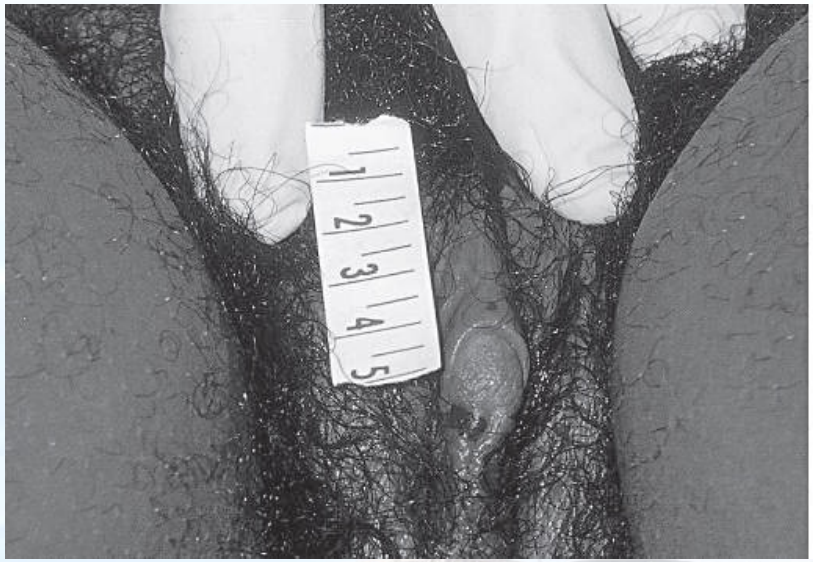
- Hirsutism
- Acne
- Amenorrhea
- Virilization

Virilization

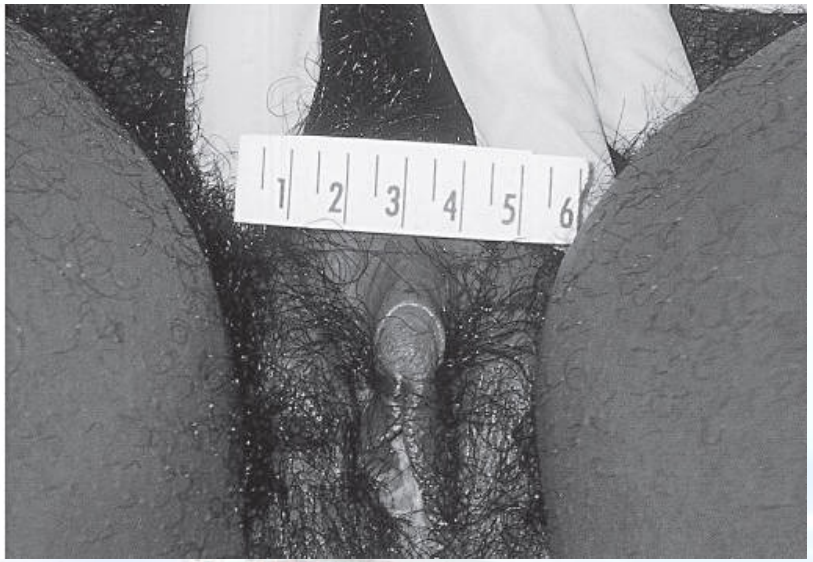
Virilization

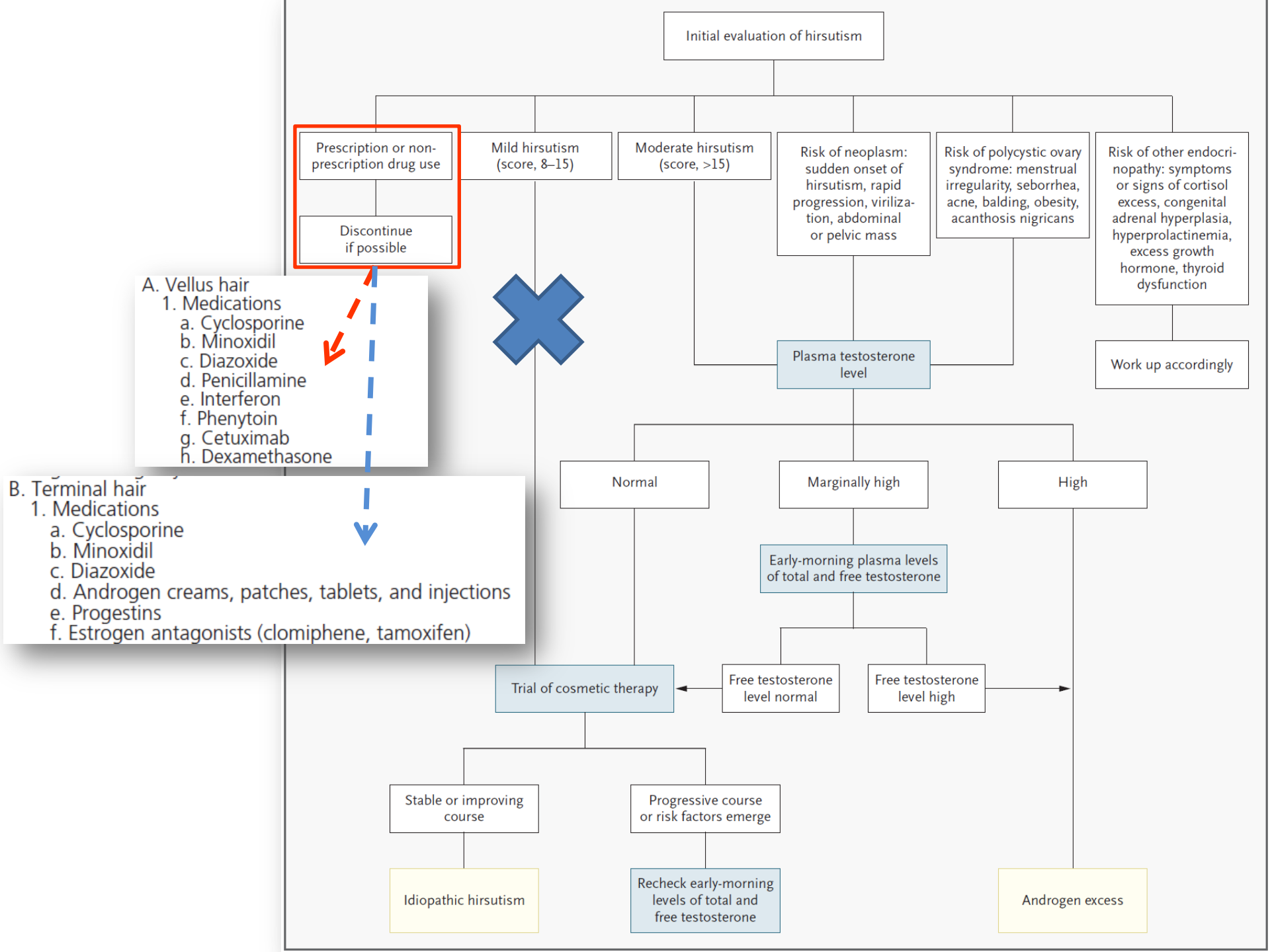
- **Clitoromegaly**

Length < 10 mm



Width < 7 mm




Initial evaluation of hirsutism
Prescription or non-prescription drug use
Discontinue if possible
Mild hirsutism (score, 8–15)
Moderate hirsutism (score, >15)
Risk of neoplasm: sudden onset of hirsutism, rapid progression, virilization, abdominal or pelvic mass
Risk of polycystic ovary syndrome: menstrual irregularity, seborrhea, acne, balding, obesity, acanthosis nigricans
Risk of other endocrinopathy: symptoms or signs of cortisol excess, congenital adrenal hyperplasia, hyperprolactinemia, excess growth hormone, thyroid dysfunction
Work up accordingly
Plasma testosterone level
Normal
Marginally high
High
Early-morning plasma levels of total and free testosterone
Free testosterone level normal
Free testosterone level high
Trial of cosmetic therapy
Stable or improving course
Progressive course or risk factors emerge
Idiopathic hirsutism
Recheck early-morning levels of total and free testosterone
Androgen excess
A. Vellus hair
1. Medications
a. Cyclosporine
b. Minoxidil
c. Diazoxide
d. Penicillamine
e. Interferon
f. Phenytoin
g. Cetuximab
h. Dexamethasone
B. Terminal hair
1. Medications
a. Cyclosporine
b. Minoxidil
c. Diazoxide
d. Androgen creams, patches, tablets, and injections
e. Progestins
f. Estrogen antagonists (clomiphene, tamoxifen)

Initial evaluation of hirsutism

✓Moderate hirsutism (>15)
✓Risk of neoplasm
*** rapid virilization, sudden onset
✓Abnormal menstruation

Risk of other endocrinopathy: symptoms or signs of cortisol excess, congenital adrenal hyperplasia, hyperprolactinemia, excess growth hormone, thyroid dysfunction

Work up accordingly

Testosterone

Normal

Marginally high

High

Early-morning plasma levels of total and free testosterone

Trial of cosmetic therapy

Free testosterone level normal

Free testosterone level high

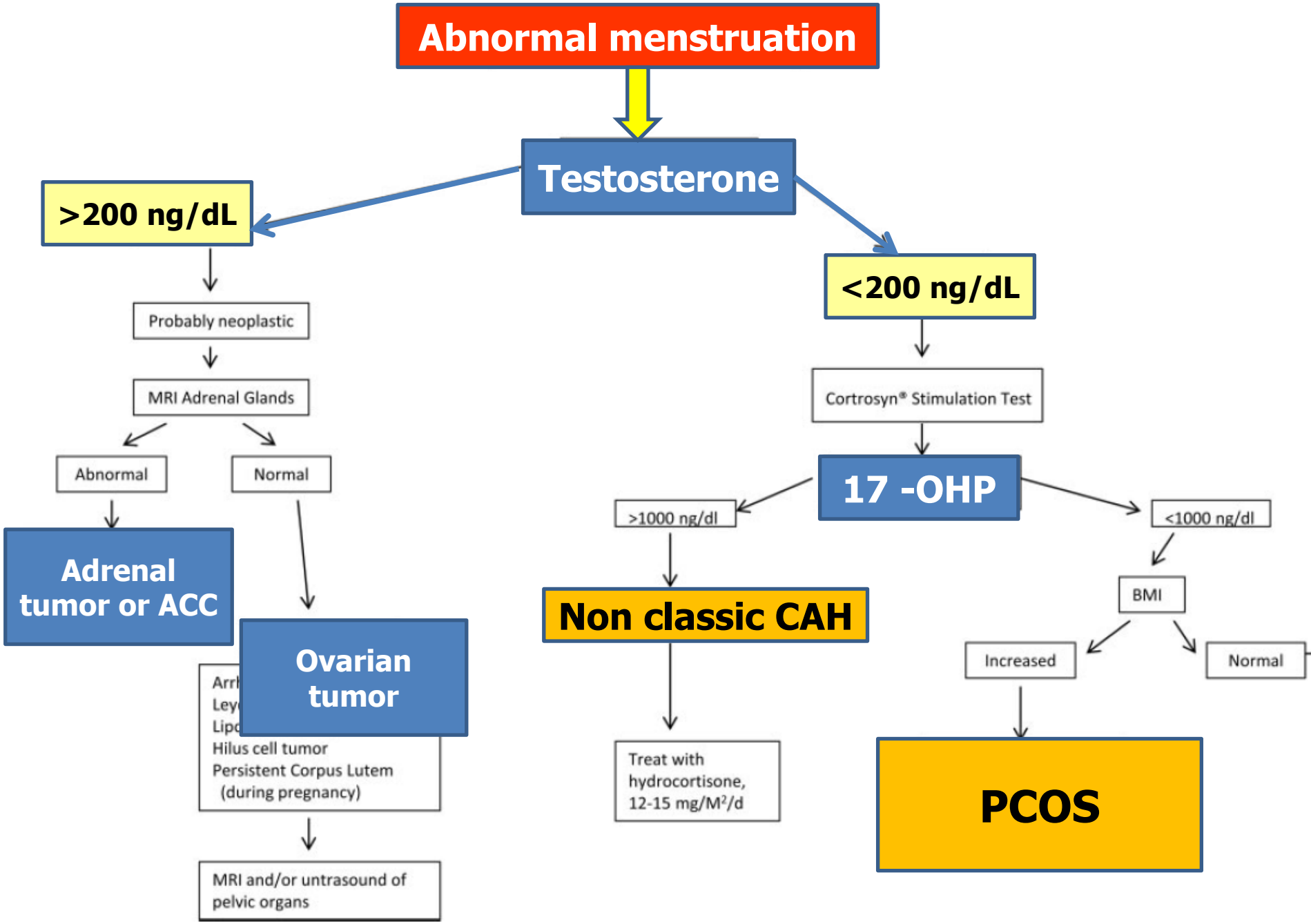
Stable or improving course

Progressive course or risk factors emerge

Idiopathic hirsutism

Recheck early-morning levels of total and free testosterone

Androgen excess



J Clin Endocrinol Metab, September 2012, 97(9):2957–2968

Causes of hirsutism

Am Fam Physician. 2019; 100(3):168-175

Causes of Hirsutism and Their Diagnostic Clues

Diagnosis	Percentage of cases	Historical and clinical clues
Polycystic ovary syndrome	71	Acanthosis nigricans Acne Central obesity Infertility Insulin resistance Menstrual dysfunction Normal or slightly elevated androgen levels Polycystic ovary morphology on ultrasonography
Idiopathic hyperandrogenism	15	Elevated androgen levels No other secondary cause Normal menses Normal ovarian morphology on ultrasonography
Idiopathic hirsutism	10	No other secondary causes Normal androgen levels Normal menses Normal ovarian morphology on ultrasonography
Nonclassic congenital adrenal hyperplasia	3	Elevated 17-hydroxyprogesterone level before and after corticotropin stimulation test Family history of adrenal hyperplasia High-risk ethnic group (e.g., Ashkenazi Jews, Hispanics, Slavic people) Infertility Menstrual dysfunction (including primary amenorrhea)
Androgen-secreting tumors	0.3	Elevated testosterone or dehydroepiandrosterone sulfate level Palpable abdominal or pelvic mass Progression of hirsutism despite treatment Rapid onset of hirsutism Small masses may have indolent presentation Virilization (e.g., clitoromegaly, increased muscularity, deepened voice)

2/3 of

1) **Chronic anovulation**
2) **Hyperandrogenism**
3) **PCO feature**

Ovulatory PCOS?

Causes of hirsutism

Am Fam Physician. 2019; 100(3):168-175

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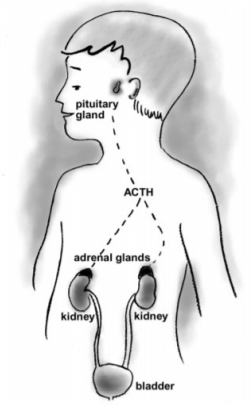
2/3 of
1) Chronic anovulation
2) Hyperandrogenism
3) PCO feature

Ovulatory PCOS?

21-OH def CAH

- Overproduction of pituitary corticotropin, stimulates the accumulation of cortisol precursors and increases adrenal androgen
- The classic form is the most common cause of atypical genitalia in 46,XX newborns and of primary adrenal insufficiency during childhood

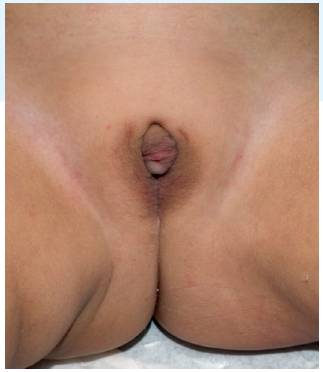


- **Classic CAH** occurs in 1 in 10,000 to 1 in 20,000 live births, **Non-classic CAH** occurs in 1in 200 t0 1 in 1000

21-hydroxylase deficiency CAH

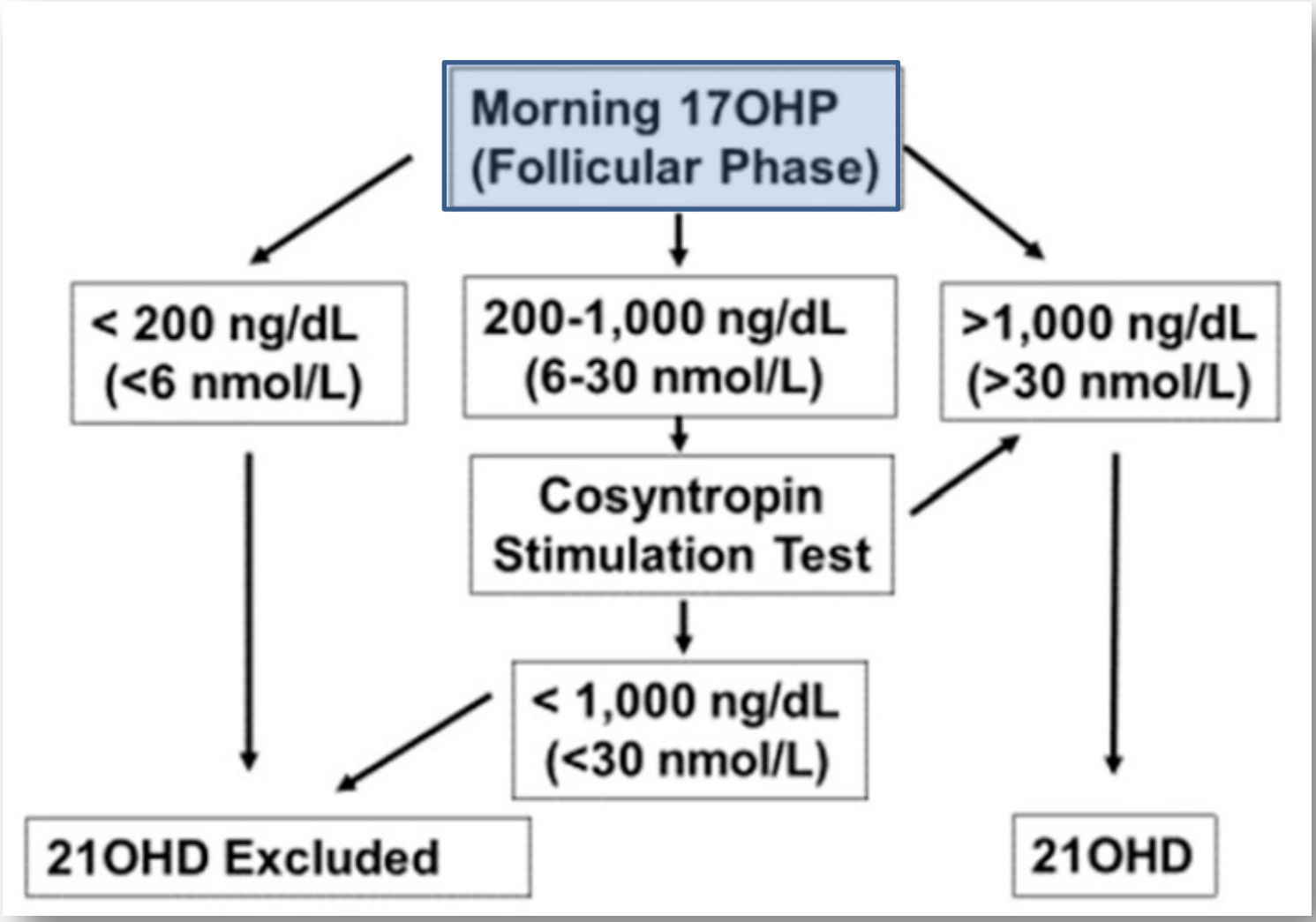
Forms of 21-Hydroxylase Deficiency

Phenotype	Classic Salt Wasting	Simple Virilizing	Nonclassic
Age at diagnosis	Newborn to 6 mo	*Female:* Newborn to 2 yr *Male:* 2-4 yr	Child to adult
Genitalia	*Female:* Ambiguous *Male:* Normal	*Female:* Ambiguous *Male:* Normal	*Female:* Virilized *Male:* Normal
Incidence	1:20,000	1:60,000	1:1000
Hormones			
Aldosterone	Reduced	Normal	Normal
Renin	Increased	Normal or increased	Normal
Cortisol	Reduced	Reduced	Normal
17-OHP	>5000 ng/dL	2500-5000 ng/dL	500-2500 ng/dL (ACTH stimulation)
Testosterone	Increased	Increased	Variable, increased
Growth	–2 to –3 SD	–1 to –2 SD	Probably normal
21-Hydroxylase activity (% of wild type)	0	1-5	20-50
Typical *CYP21A2* mutations	Deletions, conversions, nt656g G110Δ8nt, R356W I236N, V237E, M239K, Q318X	I172N Intron 2 splice site (nt656g)	V281L P30L



William textbook of Endocrinology, 13th edition

Diagnosis of 21-OHD



J Clin Endocrinol Metab, November 2018, 103(11):1–46

Causes of hirsutism

Am Fam Physician. 2019; 100(3):168-175

Causes of Hirsutism and Their Diagnostic Clues

Diagnosis	Percentage of cases	Historical and clinical clues
Polycystic ovary syndrome	71	Acanthosis nigricans Acne Central obesity Infertility Insulin resistance Menstrual dysfunction Normal or slightly elevated androgen levels Polycystic ovary morphology on ultrasonography
Idiopathic hyperandrogenism	15	Elevated androgen levels No other secondary cause Normal menses Normal ovarian morphology on ultrasonography
Idiopathic hirsutism	10	No other secondary causes Normal androgen levels Normal menses Normal ovarian morphology on ultrasonography
Nonclassic congenital adrenal hyperplasia	3	Elevated 17-hydroxyprogesterone level before and after corticotropin stimulation test Family history of adrenal hyperplasia High-risk ethnic group (e.g., Ashkenazi Jews, Hispanics, Slavic people) Infertility Menstrual dysfunction (including primary amenorrhea)
Androgen-secreting tumors	0.3	Elevated testosterone or dehydroepiandrosterone sulfate level Palpable abdominal or pelvic mass Progression of hirsutism despite treatment Rapid onset of hirsutism Small masses may have indolent presentation Virilization (e.g., clitoromegaly, increased muscularity, deepened voice)

2/3 of
1) Chronic anovulation
2) Hyperandrogenism
3) PCO feature

Ovulatory PCOS?

Back to this patient

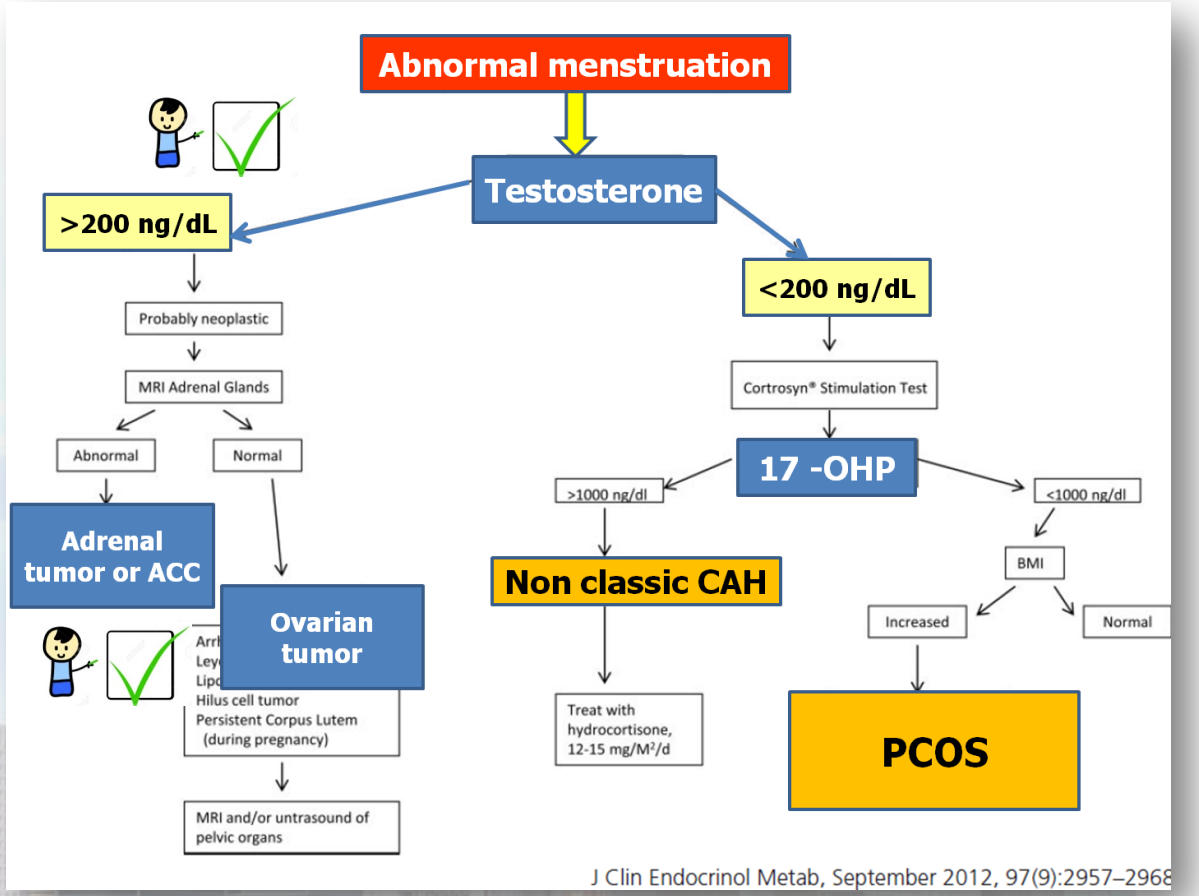
A 15 year-old F presented with hirsutism for 1 year

Ferriman-Gallwey scale = 15
Primary amenorrhea
Virilization : Clitoromegaly, Temporal baldness

Testosterone level 426 ng/dL

Back to this patient

A 15 year-old F presented with hirsutism for 1 year



DHEAS = 1410 mcg/dL

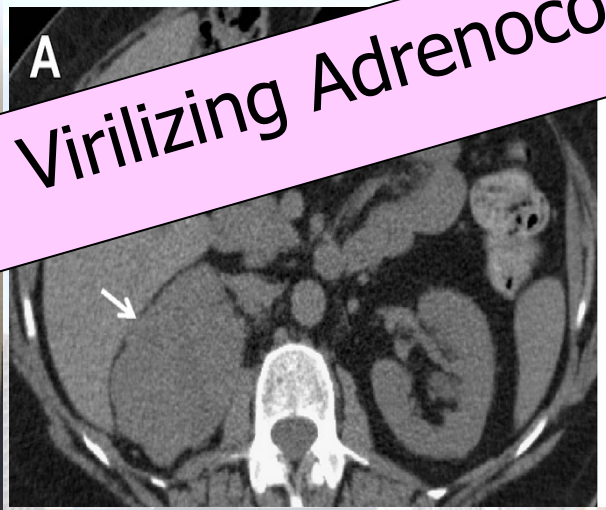
Back to this patient

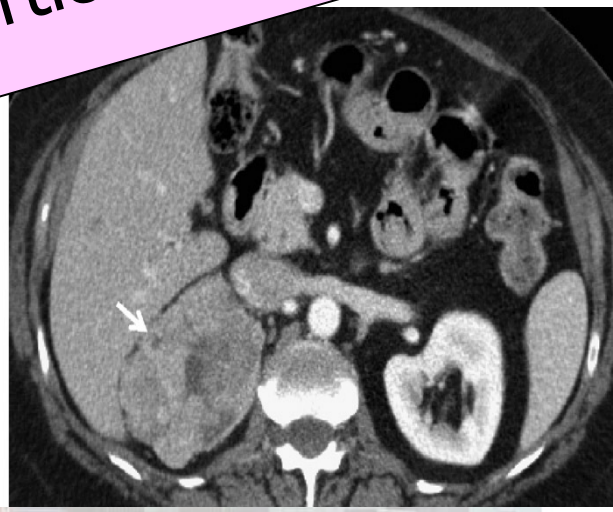
A 15 year-old F presented with hirsutism for 1 year

Ferriman-Gallwey scale = 15
Primary amenorrhea
Virilization : Clitoromegaly, Temporal baldness

Testosterone level

Final Diagnosis : Virilizing Adrenocortical carcinoma

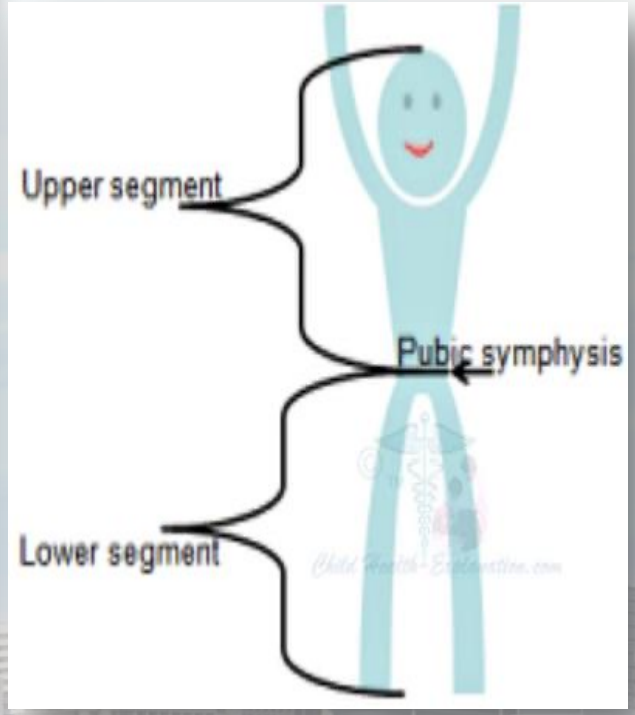


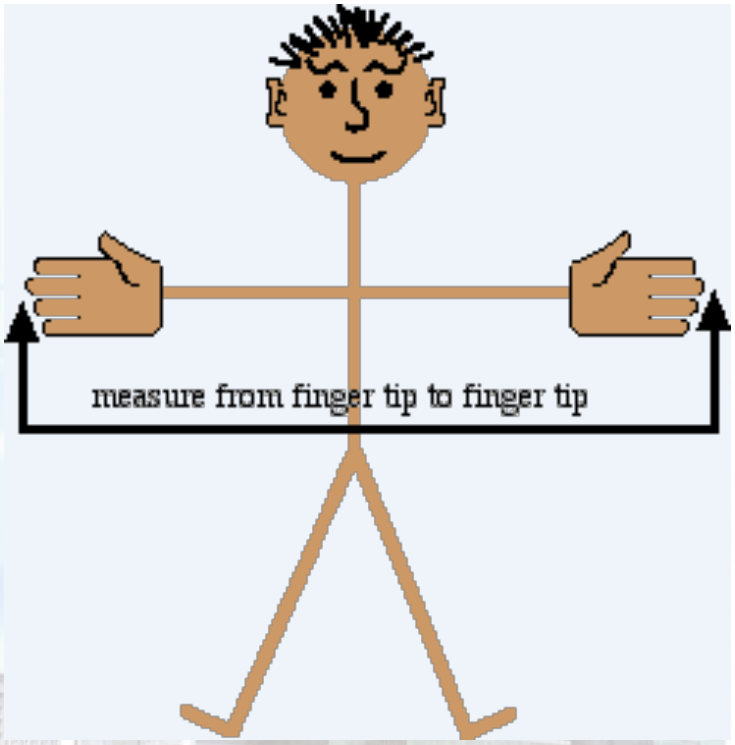


DHEAS = 1410 mcg/dL

Conclusion

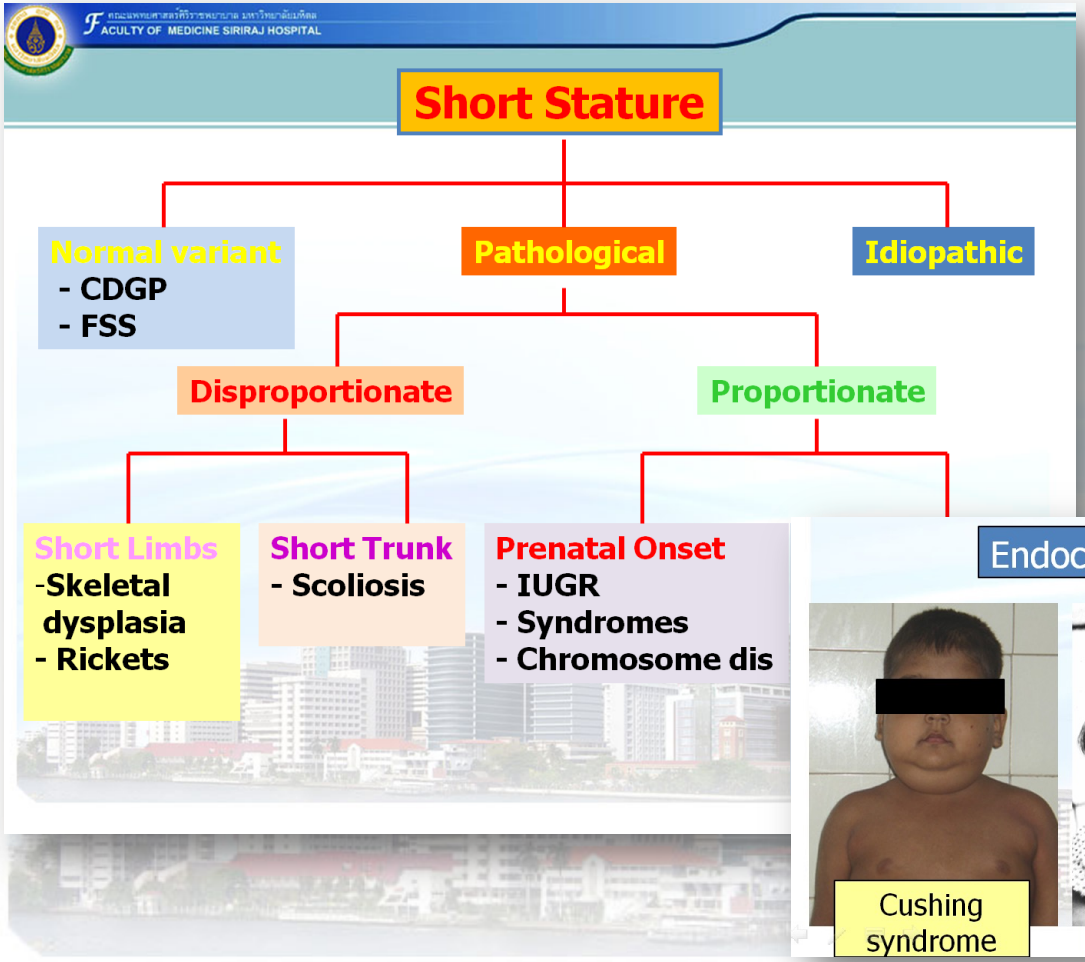
Short stature : Tools

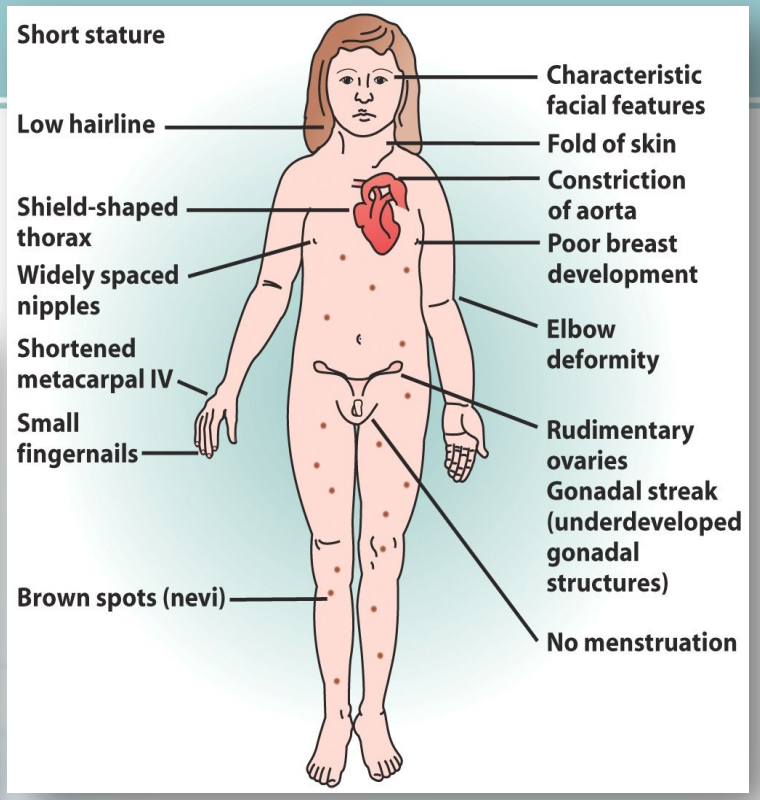


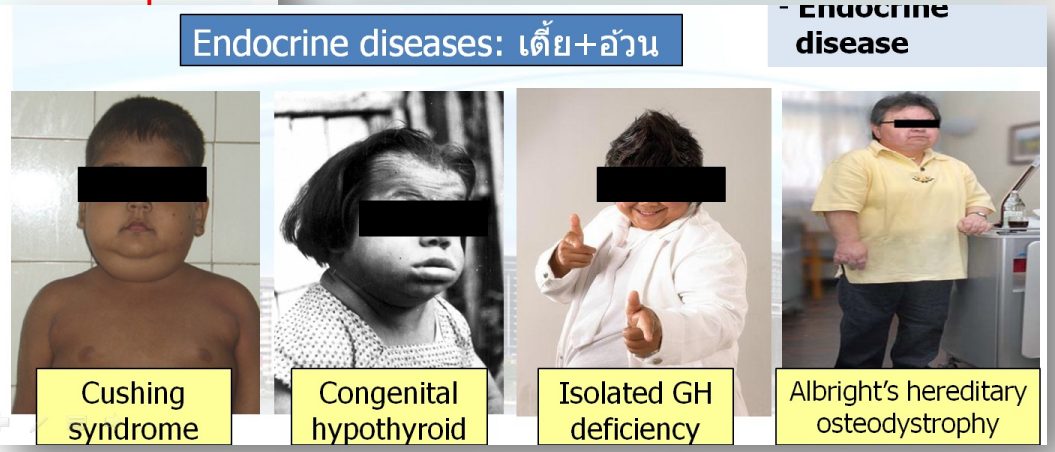


Conclusion

Short stature : Algorithm

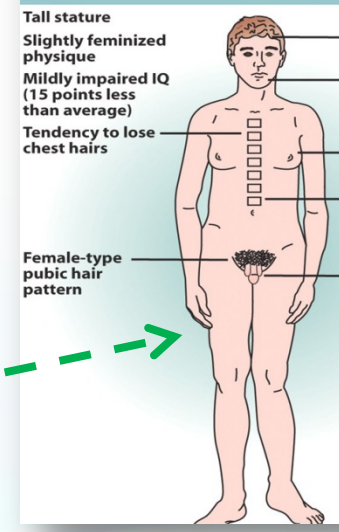






Conclusion : Male hypogonadism

Klinefelter's syndrome



Abnormal finding	%
Infertility	**99 – 100**
Small testis	**99 – 100**
Gynecomastia	50 -75
Less pubic hair	30 – 60
Less facial hair	60 – 80
Low testosterone level	65 – 85
High Gn level	90 – 100
Small penis	10 – 25

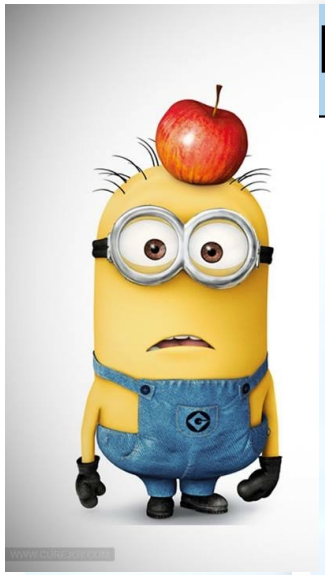
↓T ↑FSH/LH
Primary hypogonadism

↓T ↓FSH/LH
Secondary hypogonadism

Secondary hypogonadism

Prepubertal onset	Postpubertal onset
•**Kallmann's syndrome**	•Acquired idiopathic hypogonadotropic hypogonadism
•Idiopathic hypogonadotropic hypogonadism	•**Pituitary macroadenoma**
•Pituitary tumor (Craniopharyngioma)	•Uremia
•Uremia	•Severe systemic illness
•Severe systemic illness	•Cranial radiation
•Cranial radiation	•Hyperprolactinemia
•Hyperprolactinemia	•Hemochromatosis
	•Cushing's syndrome
	•Cirrhosis
	•Morbid obesity

Conclusion: Gynaecomastia



Exclude common disease

Cirrhosis, Renal failure
Hyperthyroid
Hypogonadism ★ testicular vol

Hormone testing (total and bioavailable T, E_2, prolactin, LH, hCG assays)

- ↓T + ↑LH → Primary hypogonadism
- ↓T + ↓LH → Secondary hypogonadism
- ↑hCG → Testicular US
  - Testicular germ cell tumor
  - Normal findings → Evaluate for: Extragonadal germ cell tumors (bronchogenic, hepatic, renal) Nontrophoblastic hCG-secreting tumors
- ↑Prl with or without ↓T and normal or low LH → MRI of the head → Pituitary adenoma, empty sella, or mass panhypopituitarism
- ↑E_2 and normal to low LH → Testicular US
  - Mass (Leydig or Sertoli cell tumor)
  - Normal findings → CT of the abdomen
    - Adrenal neoplasm
    - Normal findings → Increased aromatase activity (obesity, adrenal or liver disease, thyrotoxicosis) Exogenous estrogens (eg, sex reassignment, phytoestrogens)
- Negative work-up → Idiopathic gynecomastia

Imbalance of estrogen and androgen

↓ Free androgen

↑ Free estrogen

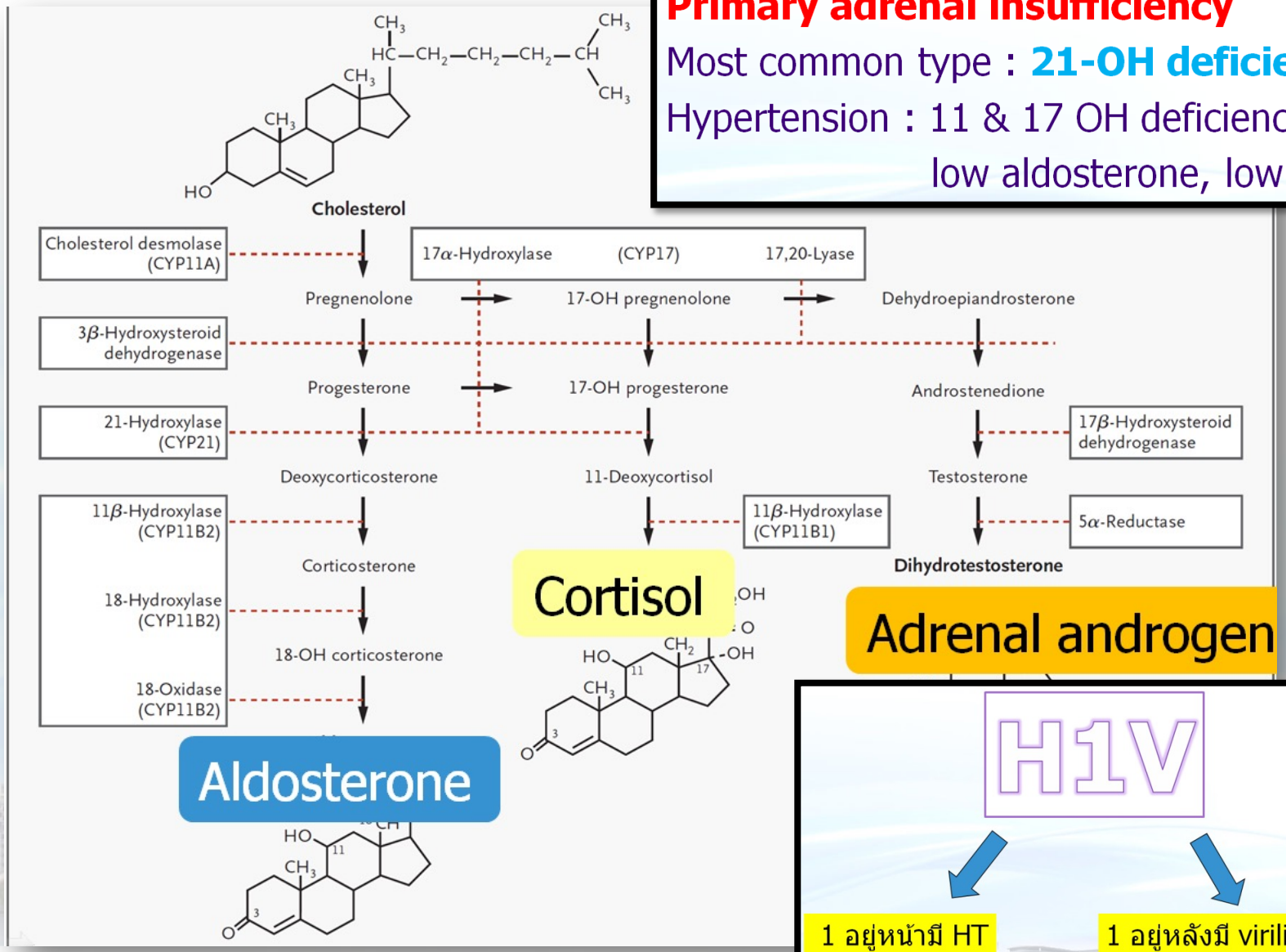
Conclusion: CAH

Primary adrenal insufficiency

Most common type : **21-OH deficiency**

Hypertension : 11 & 17 OH deficiency

low aldosterone, low renin



H1V

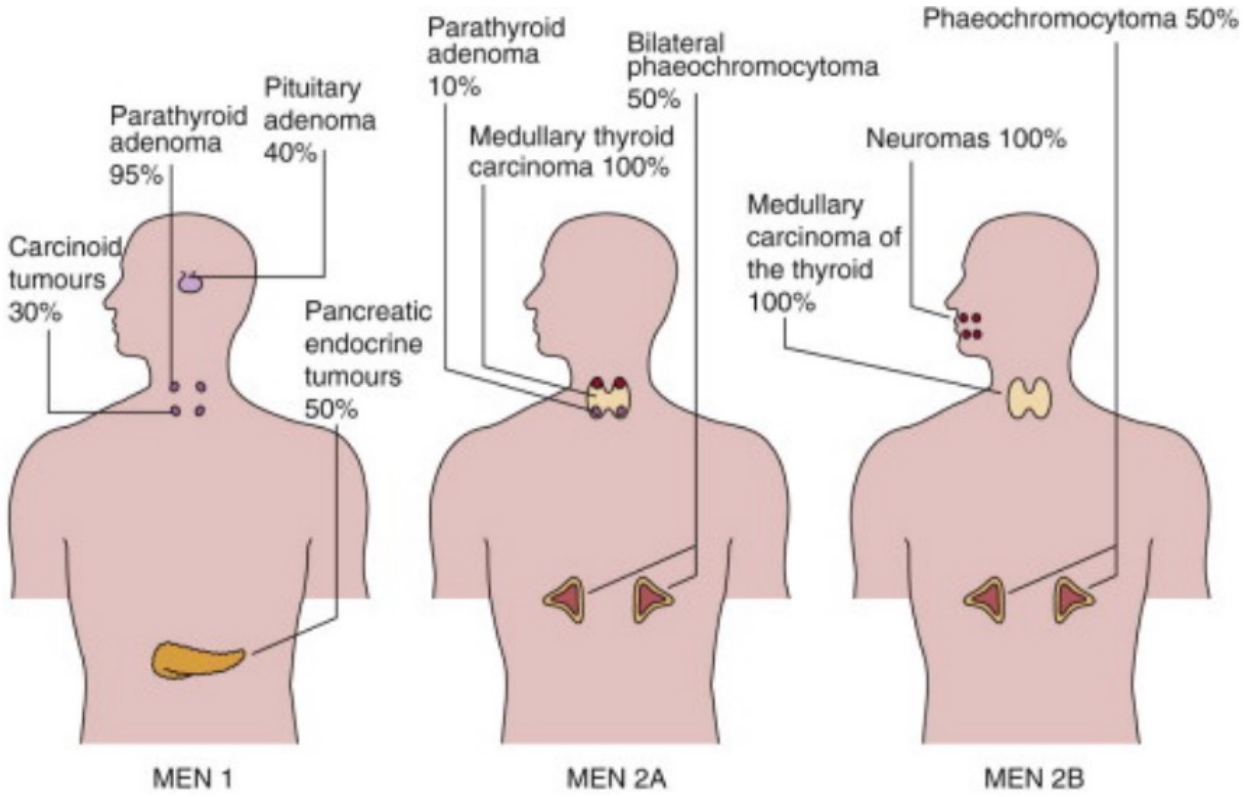
1 อยู่หน้ามี HT

1 อยู่หลังมี virilization

SIENDO

Faculty of Medicine Siriraj Hospital

MEN



Pa: hyperPTH
Pan: PNET
Pit: pitu tumor

MEN1
MENIN

Med: MTC
Pa: hyperPTH
Phe: pheo

MEN2A
RET

Med: MTC
Phe: pheo
Mu: mucosal neuroma
Mar: marfanoid habitus

MEN2B
RET