Short Stature

Sabitha Sasidharan Pillai, MD
Pronouns: She/her

Center for Endocrinology, Diabetes and Metabolism,
Children's Hospital Los Angeles; Department of Pediatrics,
Keck School of Medicine, University of Southern California.
Los Angeles, California, United States

I have no disclosures

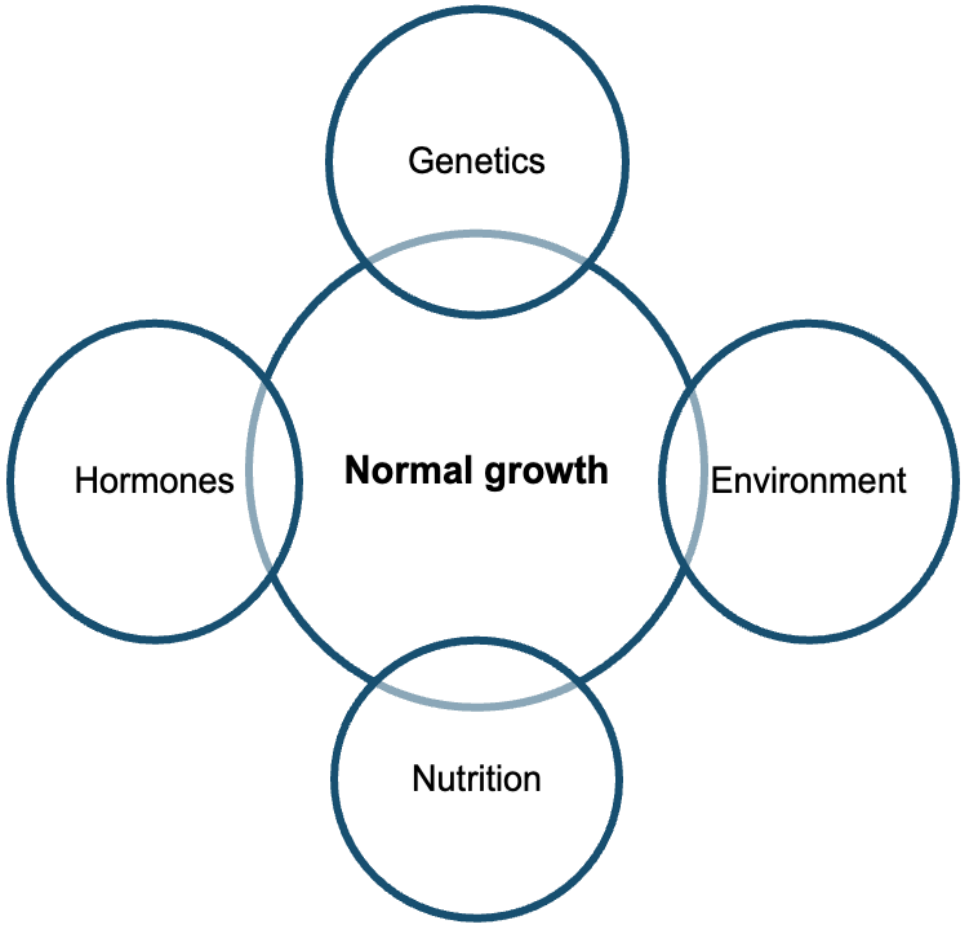
Learning objectives:

1. Review normal growth in children

2. Distinguish normal variant short stature from pathological causes of short stature

3. Discuss diagnosis and management of normal variant and pathological causes of short stature

Determinants of normal growth



Size at birth

- Maternal nutrition
- Uterine factors
- Placental factors
- Correlation coefficient between
  birth length and adult height- 0.25.

Phases of Post natal growth

- Infantile
  - Rapid linear growth initially with gradual deceleration
  - Channeling up and channeling down
- Childhood
  - Linear growth at a relatively constant velocity
  - Variation within 2 large bands on the growth chart
- Pubertal
  - Growth spurt of 8-14 cm/year

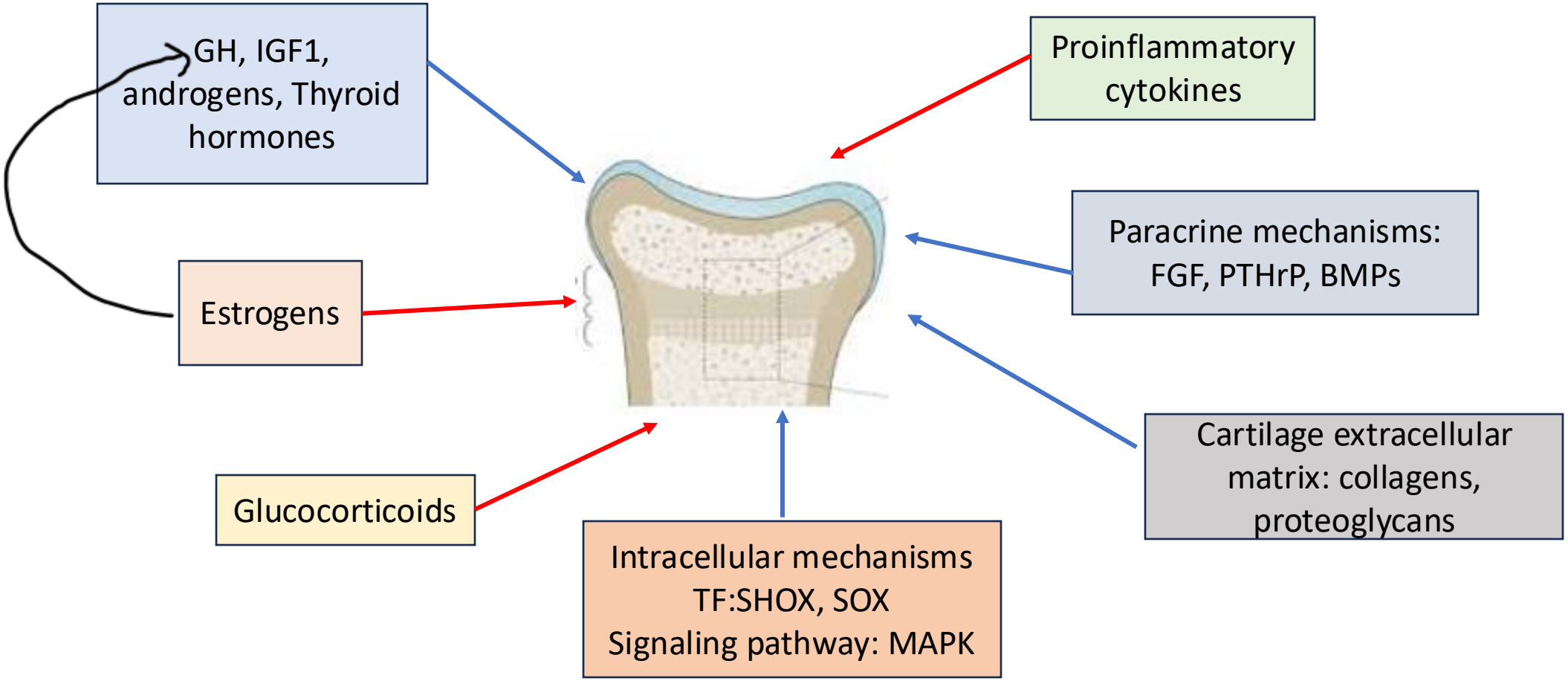
What influences normal growth?

- Prenatal: Insulin, maternal nutrition, IGF1, IGF2
- Infancy: Predominantly growth hormone and thyroid hormone
- Childhood: Nutrition, growth hormone, and thyroid hormone
- Adolescence: Nutrition, growth hormone, thyroid hormone, sex steroids

Expected growth rates/year: Rule of 5

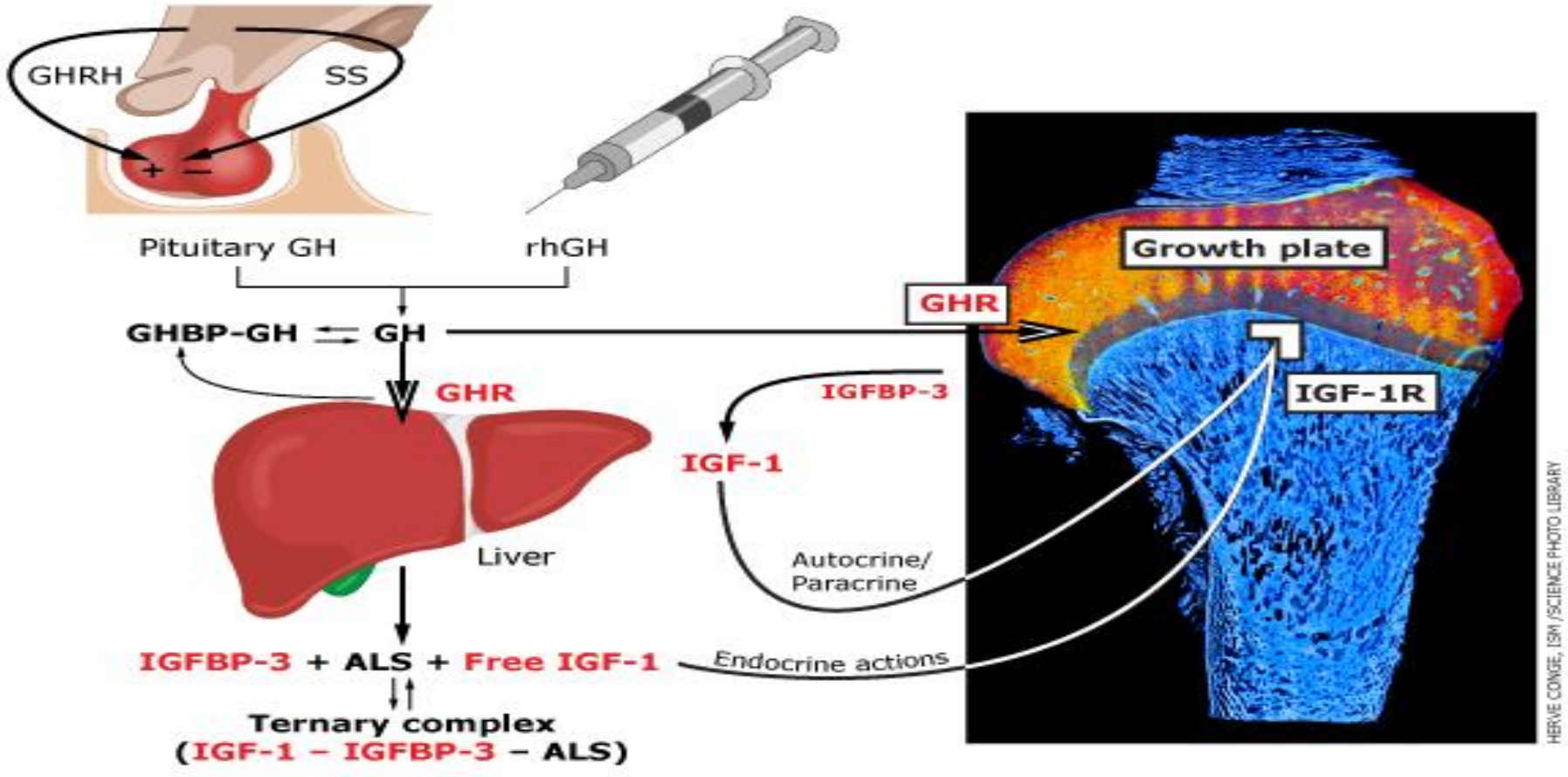
Age	Inches/year	Cms/year
Birth to 12 mo	10	25
12 to 24 mo	4	10 -12
24 to 36 mo	4	10
3 yrs to puberty	2	5

Factors that determine linear growth



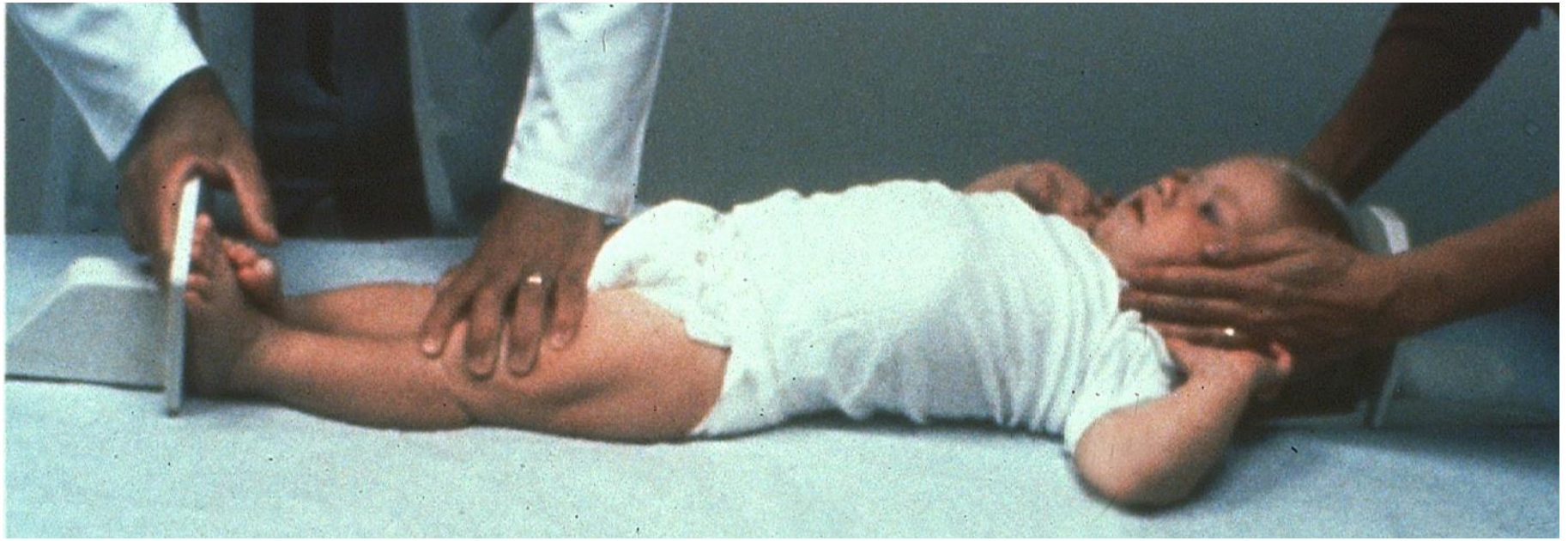
BMP-bone morphogenic protein; FGF-fibroblast growth factor; MAPK-mitogen activated protein kinase; PTHrP-PTH related protein; SHOX- short stature homeobox; SOX –SRY related HMG box; TF- transcription factor

Hypothalamic-Pituitary-GH-IGF1 axis

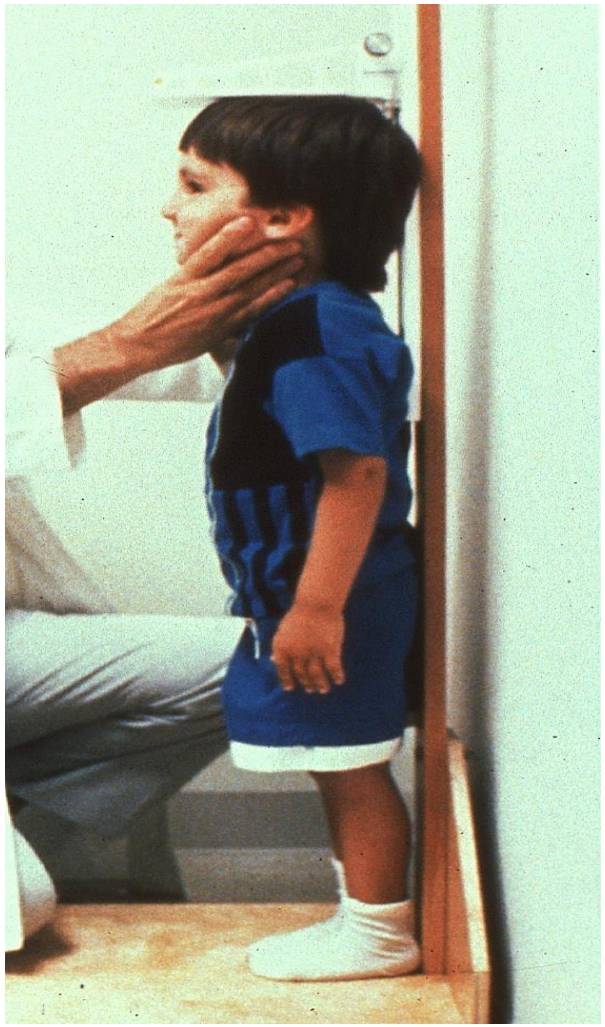


ALS-acid labile subunit; GHRH-growth hormone releasing hormone; GHR-GH receptor, IGF1-insulin like growth factor 1; IGF-1R; IGF1 receptor; IGFBP3- IGF binding protein 3; SS-somatostatin

Length measurement: 0-24 months

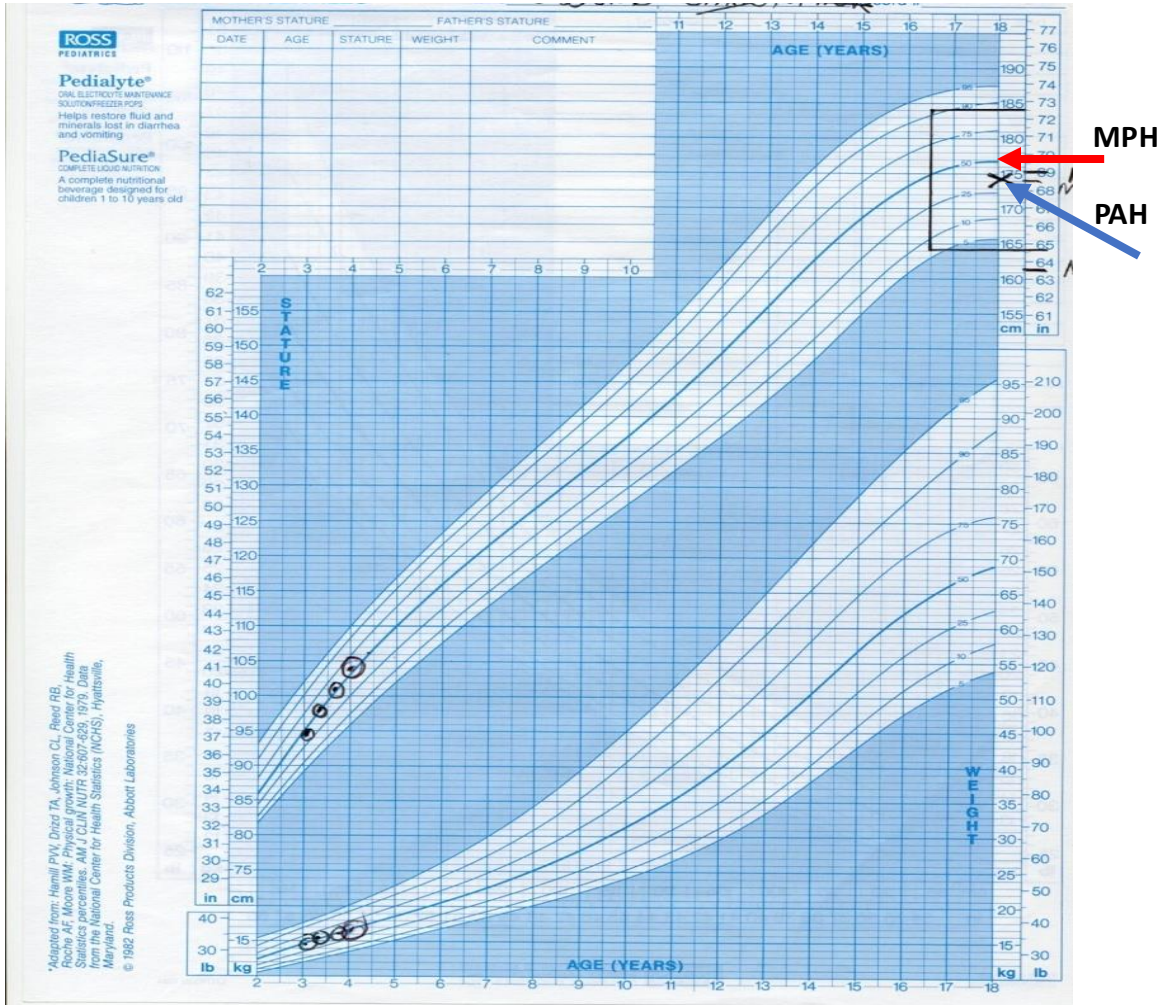


Height measurement ≥ 2 years



- Harpenden stadiometer
- Measure three times
- No > 0.3 cm variation
- Mean recorded

Projected adult height (PAH)& Mid-Parental Target Height (MPH)



MPH calculation

- **Girls**

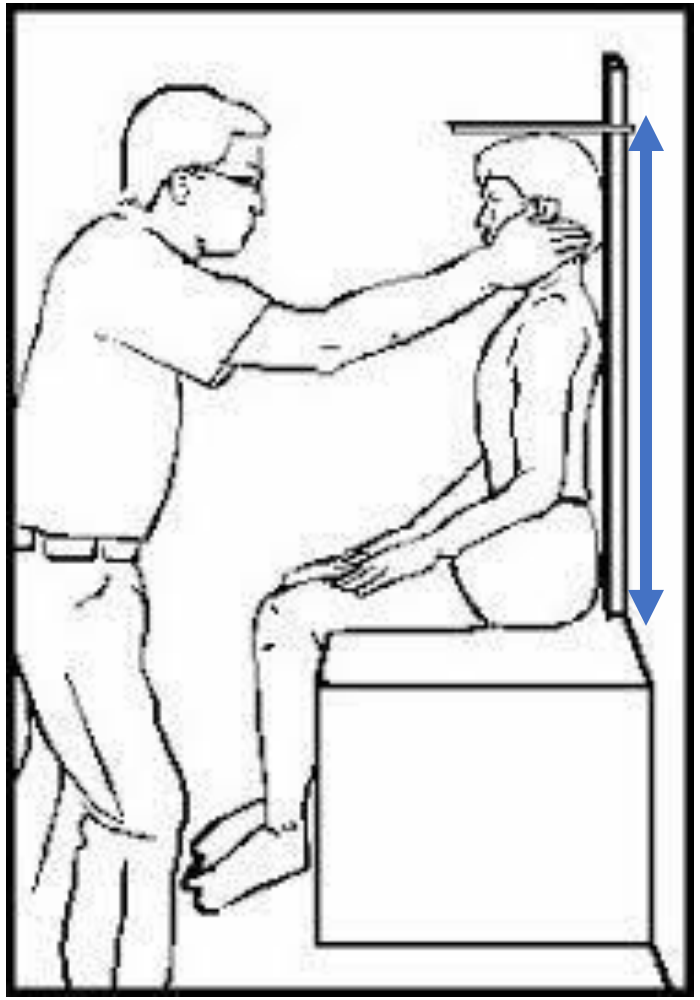
$$\frac{(\text{Ht of F} + \text{Ht of M}) - 13\ \text{cm}}{2}$$

- **Boys**

$$\frac{(\text{Ht of F} + \text{Ht of M}) + 13\ \text{cm}}{2}$$

- Target height
  - MPH ± 2 SD
  - 1 SD ~ 5cm or 2 inches

Upper segment (US) & Lower segment (LS)



Sitting height = US

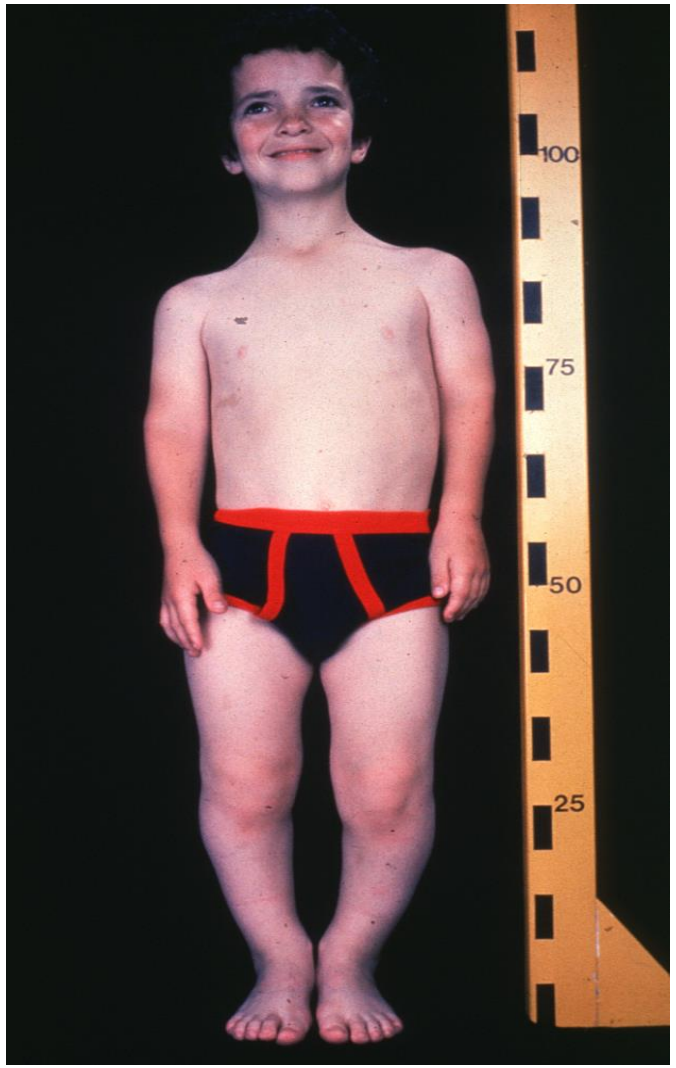
Height – Sitting height = LS

Upper Segment : Lower segment ratio

- US:LS – 1:7 at birth
  - 0.9 – 1 by 10 years of age

- Increased US:LS
  - Achondroplasia, hypochondroplasia
  - Rickets

- Decreased US:LS
  - Spondyloepiphyseal dysplasia
  - Marfan syndrome, Klinefelter syndrome
  - Homocystinuria



Arm span

- Younger children: Arm span< height
- Arm span= Height by 10-12y
- Arm span < Height

  Achondroplasia, hypochondroplasia

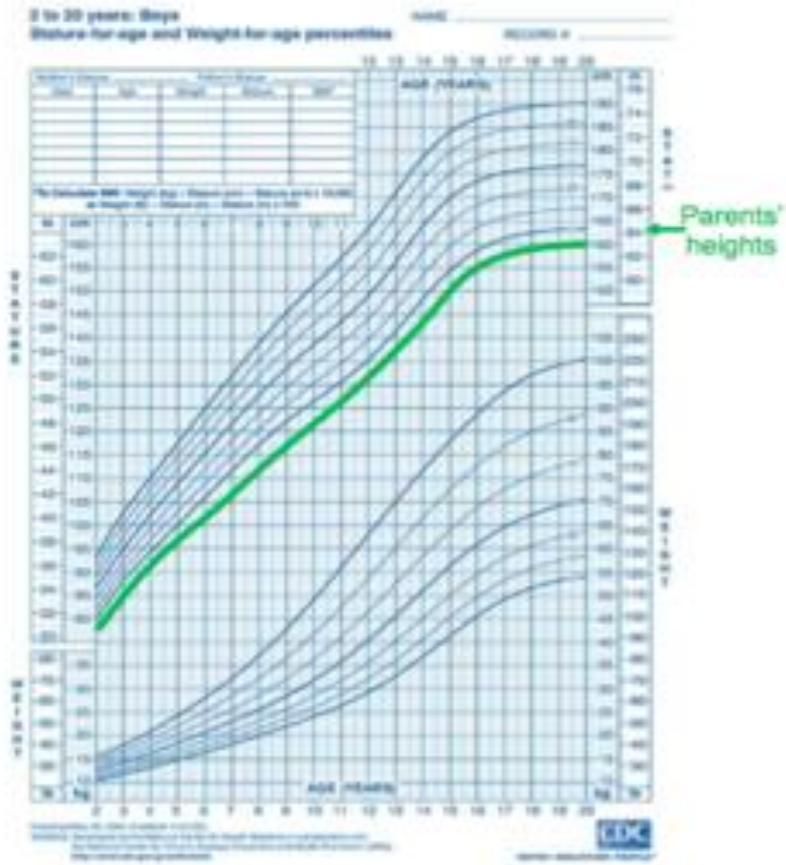
Short stature

- Height > 2 SD below the mean height
- Most common cause is constitutional delay in growth and puberty (CDGP) & Familial short stature (FSS)
- Children may have both CDGP+FSS

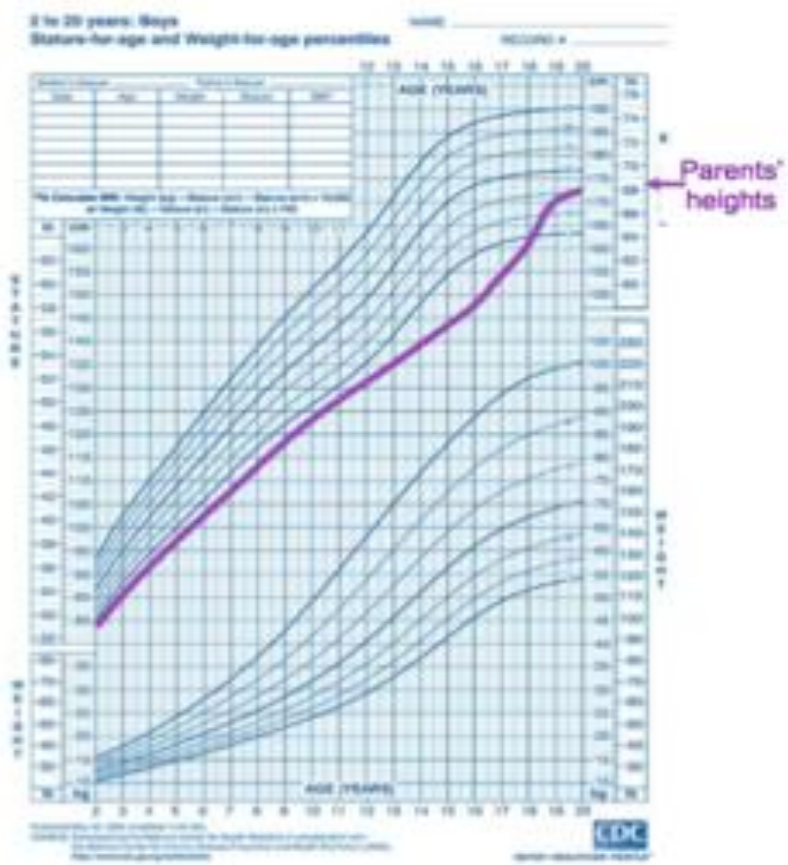
Normal variants of short stature

	Familial short stature	Constitutional delay of growth
Height	<-2SD	<-2SD
Growth rate	Normal	Normal
Bone age	Bone age = chronological age	Bone age < chronological age
Puberty	Normal	Delayed
Adult height	Short	Normal
Parents	Short	Normal
Family history	Short stature	Delayed puberty

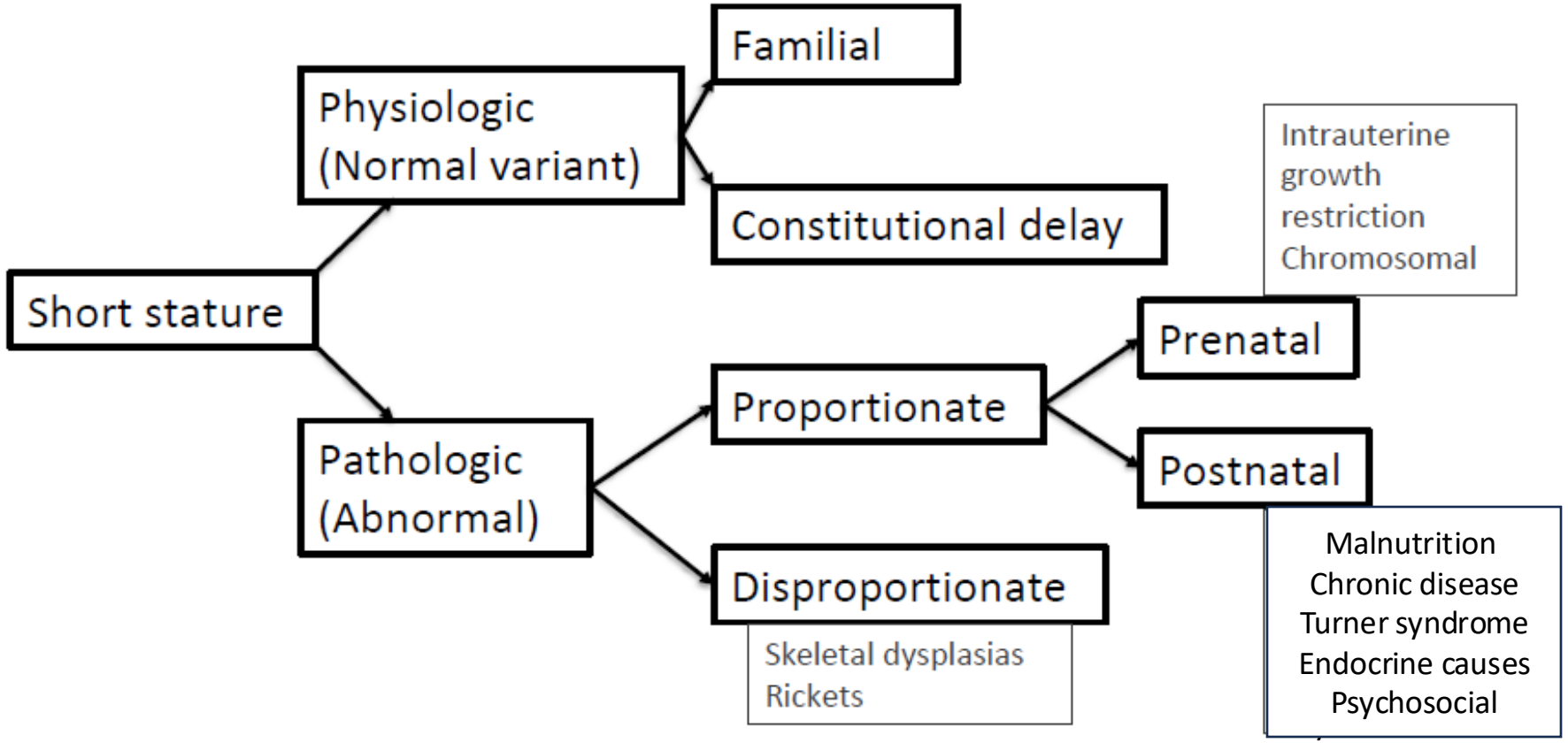
Familial Short Stature



Constitutional Delay



Short stature



Etiology of Short stature

- Primary (Intrinsic)

-Familial short stature (FSS)

-Constitutional delay in growth and puberty (CDGP)

-Genetic

-IUGR/SGA

-Skeletal dysplasia

-Idiopathic Short stature (ISS)

- Secondary

-Malnutrition

-Drugs (Steroids, stimulants)

- Cranial irradiation,

- Chronic Diseases

-Psychosocial short stature

-Endocrinopathies

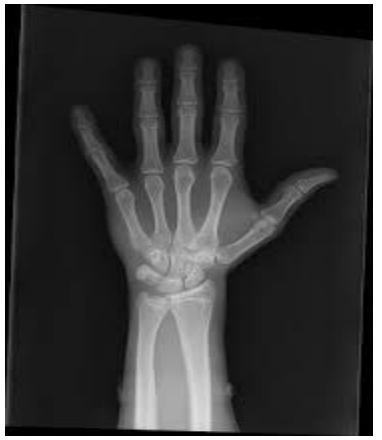
GH deficiency, hypothyroidism

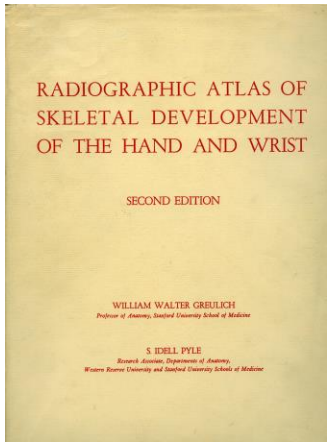
Pseudohypoparathyroidism

Cushing syndrome

Evaluation of short stature

- Detailed history
- Thorough physical examination
- Careful evaluation of growth parameters
- Bone age study





Key elements in history

- Sluggishness, lethargy, cold intolerance, constipation: hypothyroidism.

- Gastrointestinal symptoms(poor appetite, abdominal pain, diarrhea, and rectal bleeding): inflammatory bowel disease (Crohn disease, ulcerative colitis) or celiac disease.

- Pulmonary symptoms (wheezing, chronic productive cough): severe asthma, cystic fibrosis

Key elements in history

- Recurrent infections: immunodeficiency

- Recurrent otitis media with the need for myringotomy tubes: Turner syndrome

- Headache, vomiting, visual disturbances: craniopharyngioma

- Arthralgia or arthritis: inflammatory bowel disease, rheumatic diseases (eg, juvenile idiopathic arthritis), or celiac disease

Key elements in the history

- Birth history:
  - Appropriate for gestational age vs. Small for gestational age
  - neonatal hypoglycemia, prolonged jaundice, microphallus, CNS infection

- Past Medical History:
  - Chronic illness
  - Cranial irradiation
  - Head trauma/traumatic brain injury - risk for hypopituitarism
  - CNS infections - meningitis

Key elements in the history

- Surgical History
  - Orchiopexy for cryptorchidism: Noonan syndrome
  - Penoscrotal hypospadias/chordee in a short boy - 45 X/46XY mosaicism

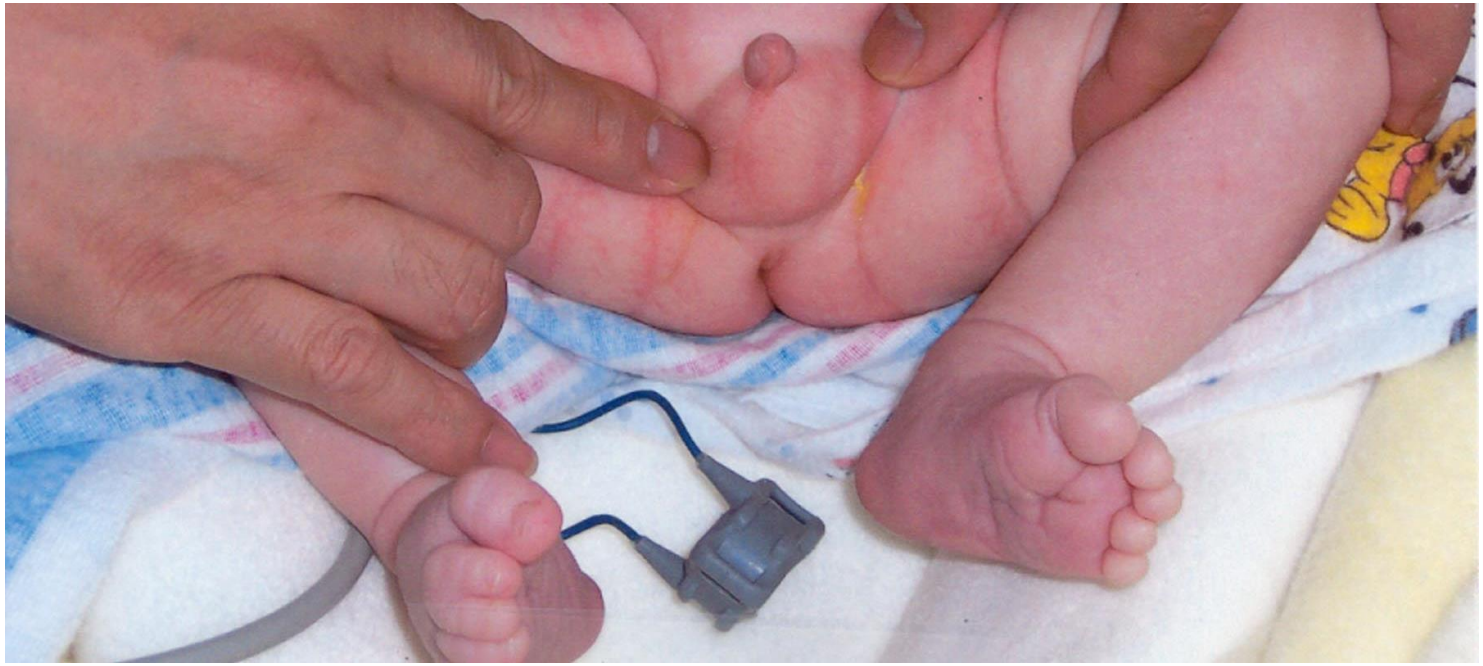
- Medications
  - steroids
  - stimulants (Concerta, Adderall)
  - chemotherapy

Key elements in the history

- Developmental History- delays, learning disabilities
  - Noonan syndrome, Turner syndrome, Prader-Willi syndrome, Russel-Silver syndrome, Pseudohypoparathyroidism (AHO)
- Diet History
- Family History
  - Heights of parents
  - Pubertal timing of parents
  - 3 generation pedigree

Key findings that may suggest pathological causes of short stature

Neonate with hypoglycemia



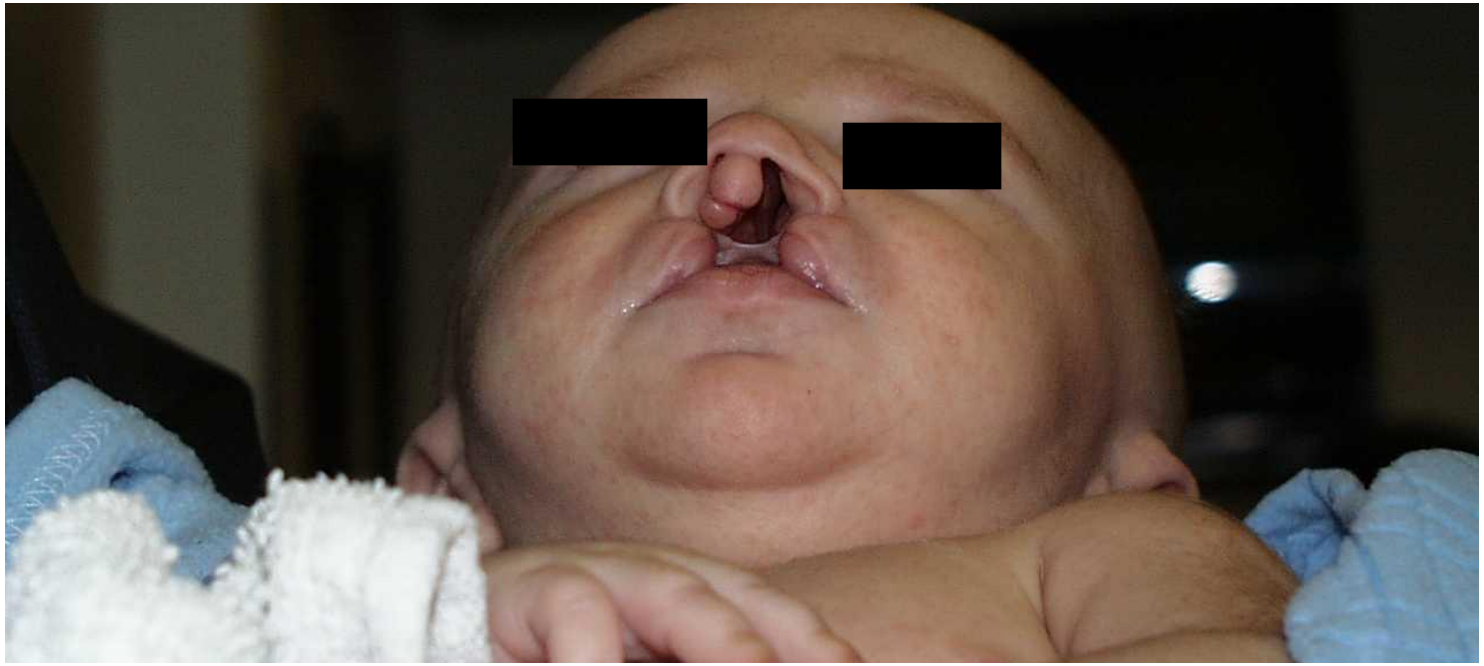
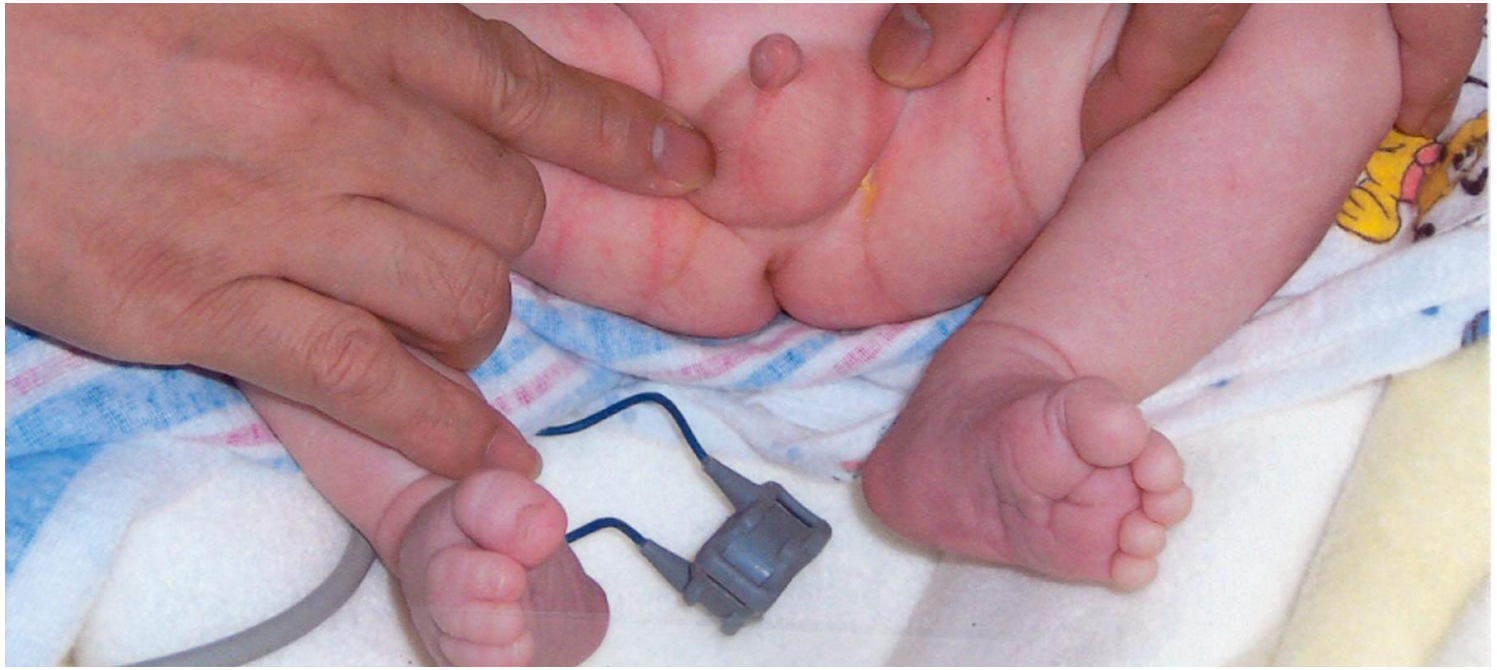
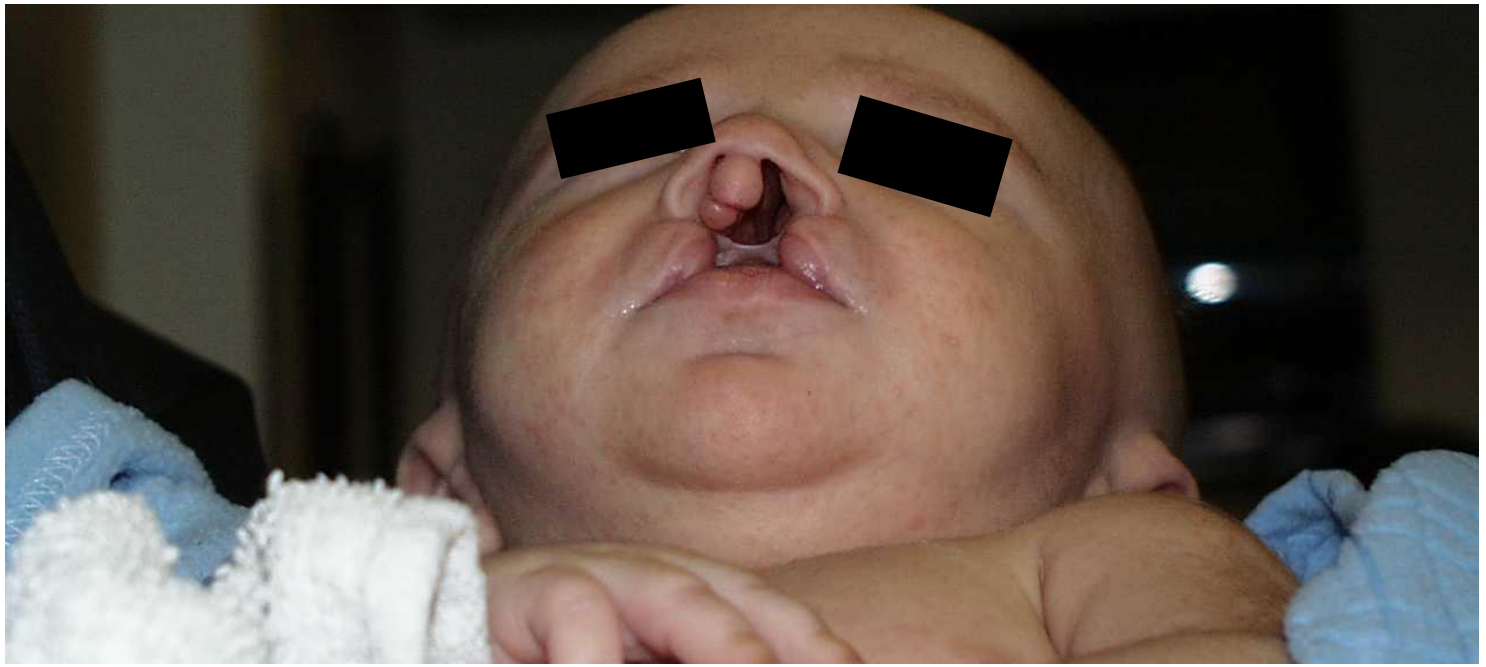


Image with parent consent

Hypopituitarism

- Midline defect
- Micropenis- due to LH and testosterone deficiency
- Hypoglycemia- due to ACTH and GH deficiency
- Cortisol <0.5 mcg/dl
- Growth hormone 1 ng/mL





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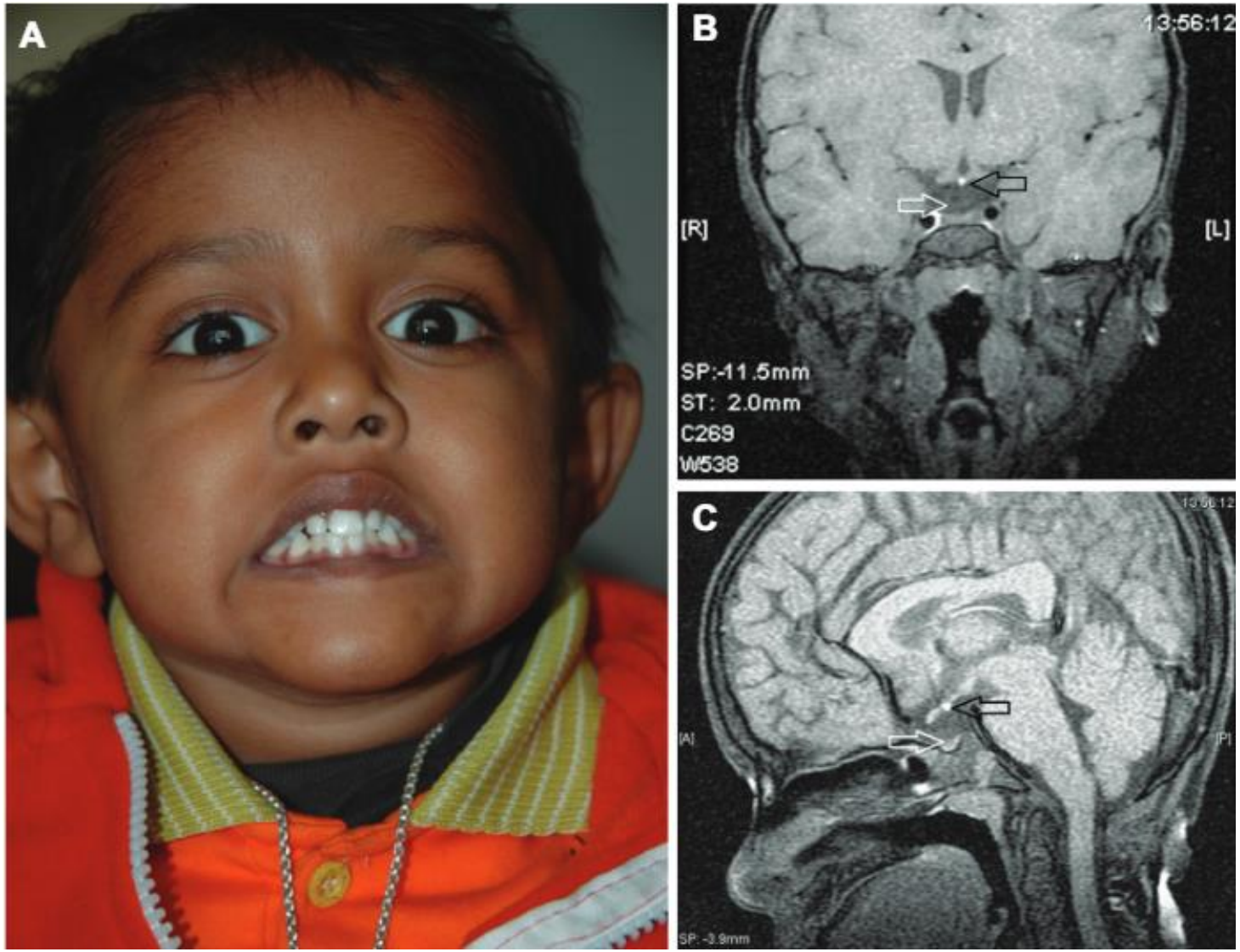


Dutta, D, et al, JPEM,2013;26(9-10);809-810

Noonan syndrome

Image with parent consent

- Facial dysmorphism
- Pectus carinatum/excavatum
- First degree relative with NS
- Pulmonary valve stenosis
- Hypertrophic obstructive cardiomyopathy
- Cryptorchidism (77% of patients)

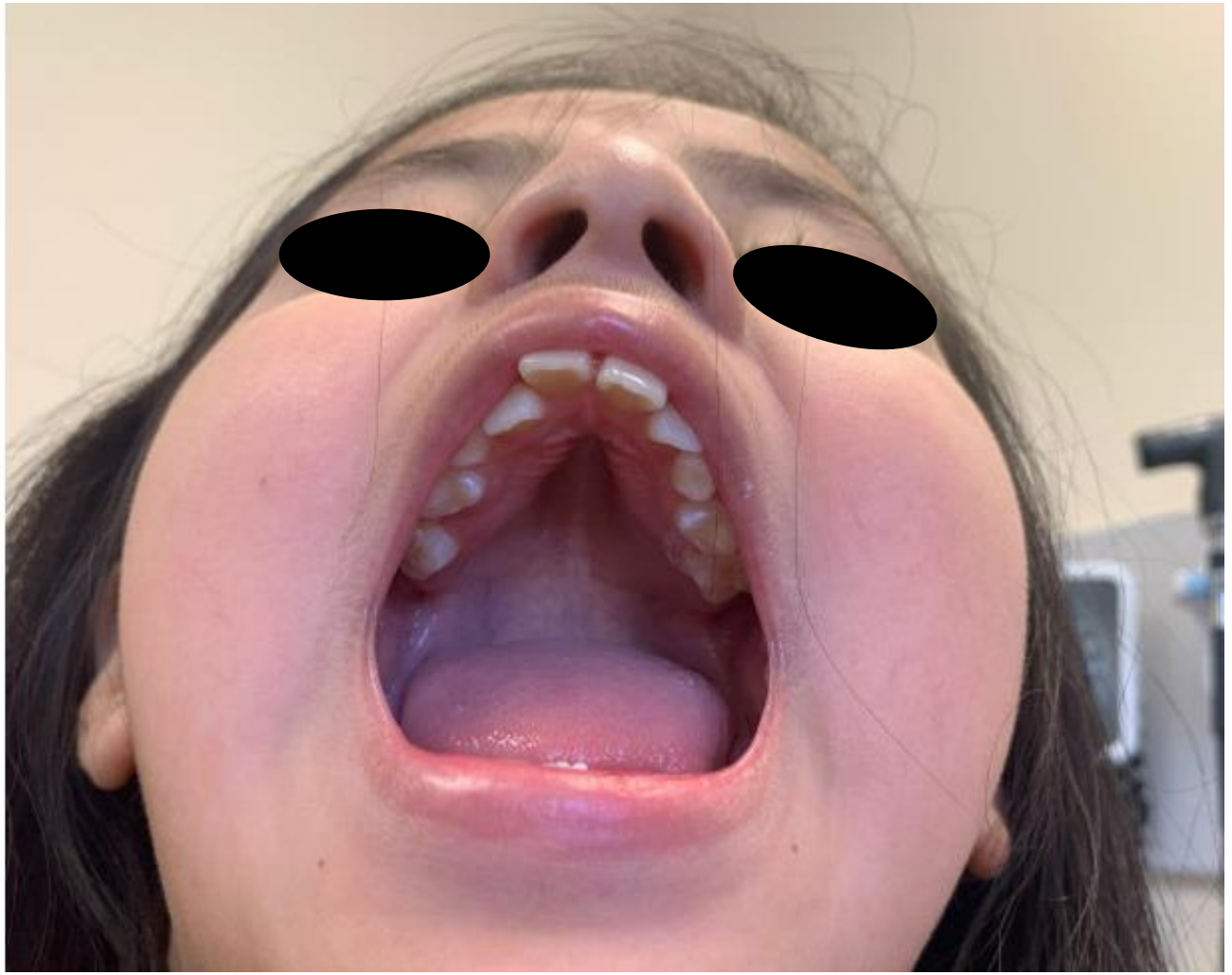
Van der Burgt, 2007, Orphanet Journal of Rare Diseases,2:4 1-6

Russel Silver Syndrome

- Gestational growth restriction followed by post natal growth failure
- Prominent forehead/frontal bossing
- Relative macrocephaly at birth
- Limb-length discrepancy

MED GEN, PRICE SM, 1999;36;837-842

Turner syndrome



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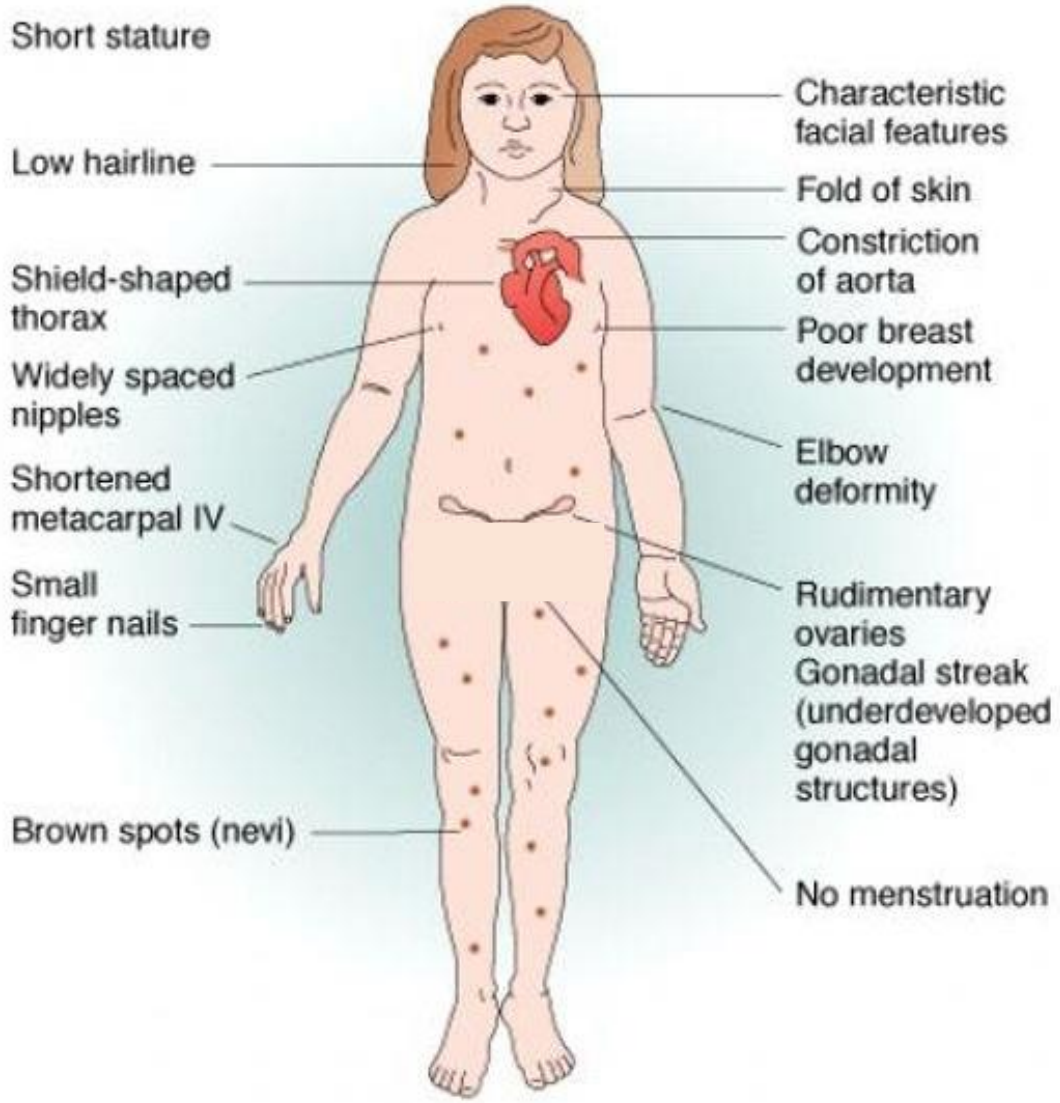
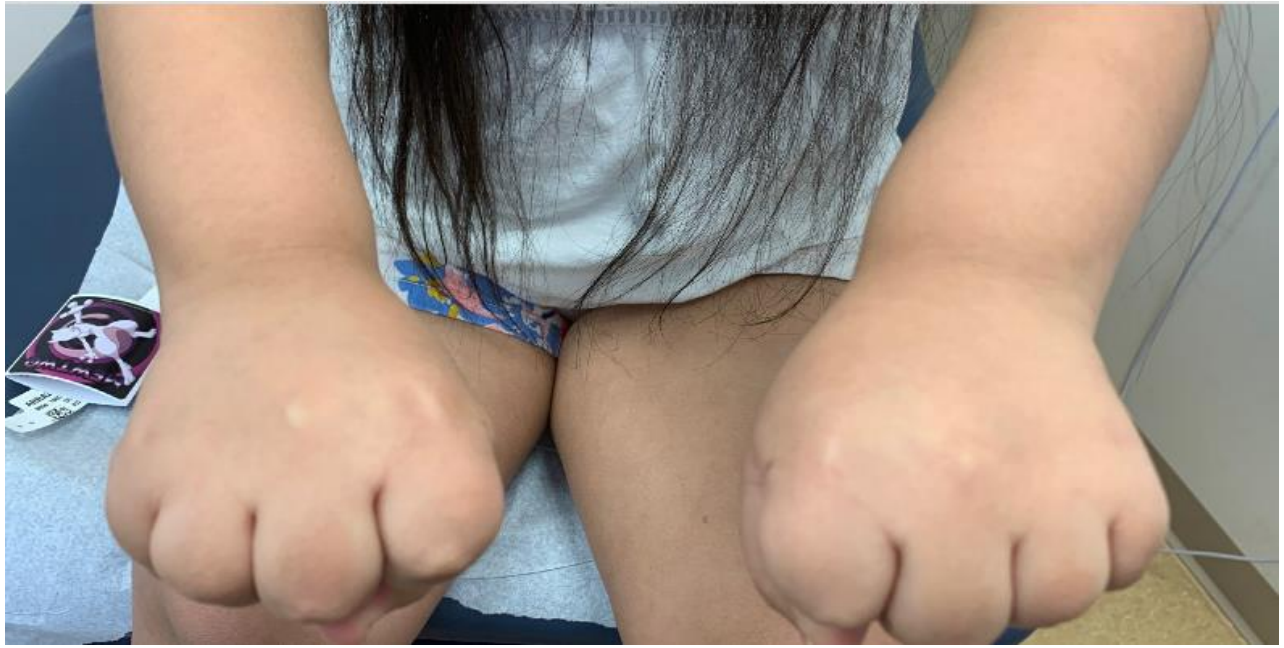
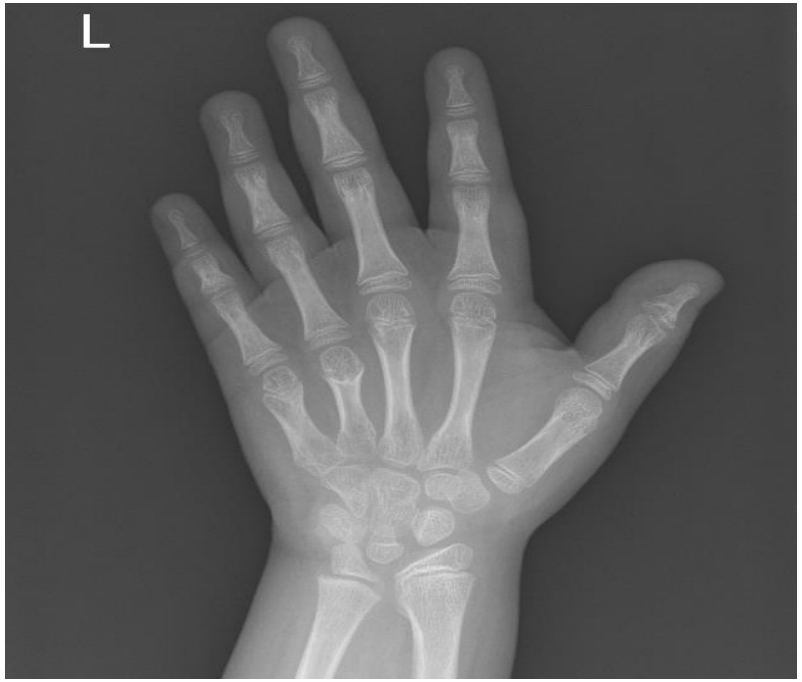
Turner syndrome



Short 4th metacarpal





Images with parent consent

Albright hereditary osteodystrophy

- Pseudohypoparathyroidism type 1a

- Short stature, obesity, round face, brachydactyly, and subcutaneous ossifications

Germain-Lee, E, Curr Opin Pediat,2019,31(4),537-549

Growth parameters

- Weight loss, poor weight gain, underweight for height: systemic diseases, psychosocial deprivation, or food restriction.

- Increased weight for height:

  Obesity: Cushing syndrome (with central fat distribution).

  Increased weight for height: also consistent with hypothyroidism, growth hormone deficiency, or pseudohypoparathyroidism.

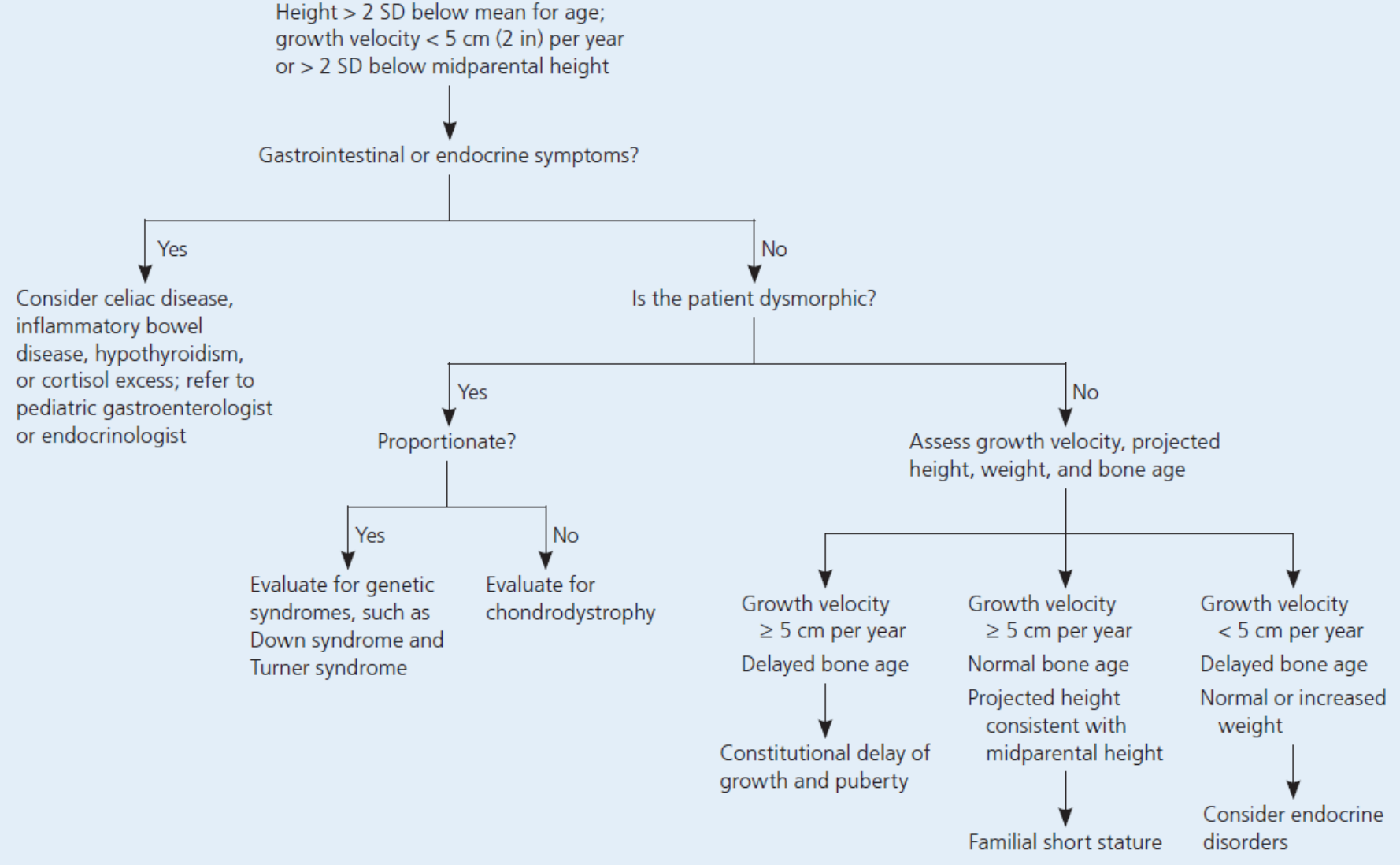
Bone age (skeletal age)

- Measure of skeletal maturity
- Assess the appearance and shape of the growth plates and bones of the left hand and wrist from a radiograph
- Most commonly used method – Greulich and Pyle Atlas

Bone Age in Short Stature

Delayed	Normal	Advanced
Constitutional delay of puberty	Familial short stature	Aggrecan Mutation
Undernutrition	SGA without catch up	Pseudohypoparathyroidism
Chronic disease	Turner syndrome	
GH deficiency	Noonan	
Hypothyroidism	SHOX deficiency	
Cushing syndrome	Skeletal dysplasia	

Evaluation of short stature



Barstow C, et al. Evaluation of Short and Tall Stature in Children. *Am Fam Physician*. 2015;92(1):43-50.

Workup for short stature

Test	Indication
Complete blood count	Anemia
Comprehensive metabolic panel	Hepatic and renal diseases
ESR, CRP	Inflammatory bowel disease
IgA, TTG IgA	Celiac disease
Karyotype	Turner syndrome
TSH, FT4	Hypothyroidism
IGF1, IGFBP3	GH deficiency

CRP-c reactive protein; ESR-erythrocyte sedimentation rate; IgA-immunoglobulin A; FT4-free thyroxine; TSH-thyroid stimulating hormone; TTG IgA- Tissue transglutaminase IgA

CASES

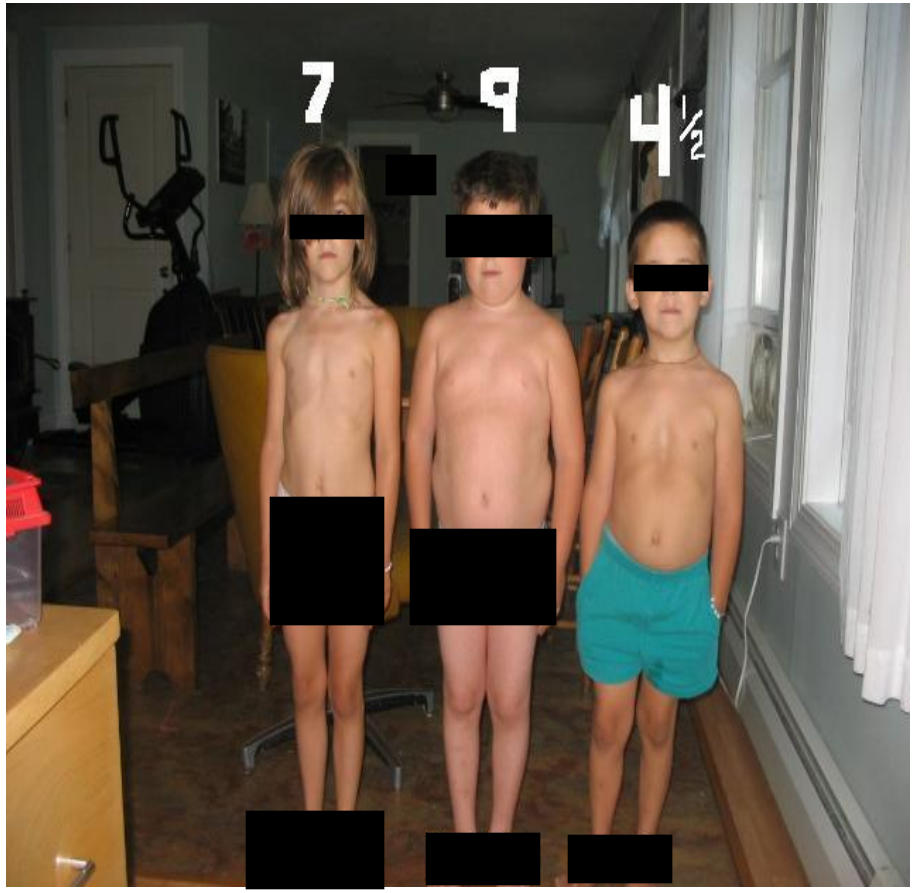
9 y old boy referred for short stature

HPI: Linear growth declining over last 3 years

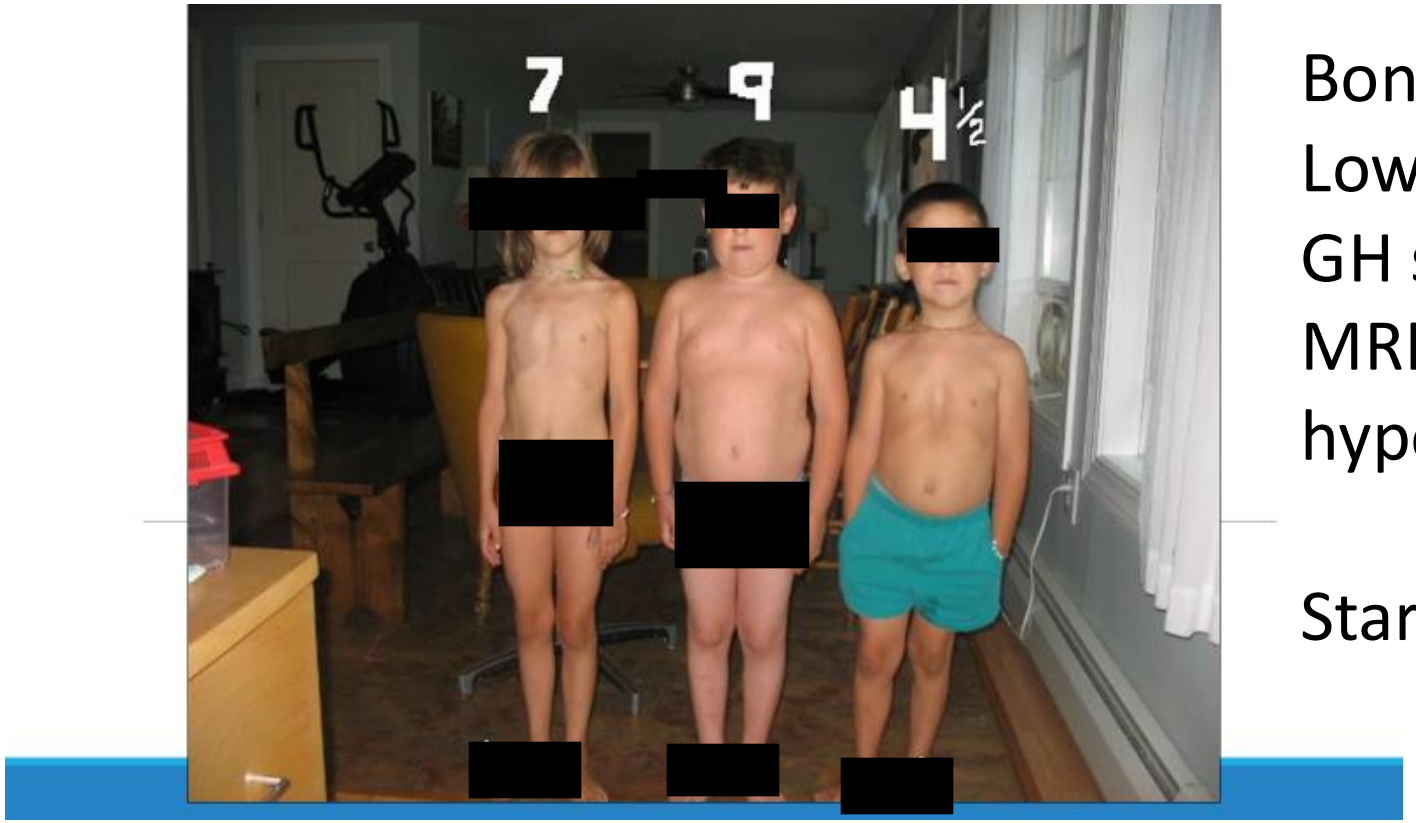
PMH: Born FT, 3.2 Kg; normal perinatal hx, normal development

FH: Mom 62 inches, menarche 12 yrs;
Dad 70 inches with normal puberty
Mid-parental target height-68.5 inches

PE: Tanner 1; height - 118 cm (<3rd%ile)
weight -28 kg (50th%ile)



Growth hormone deficiency

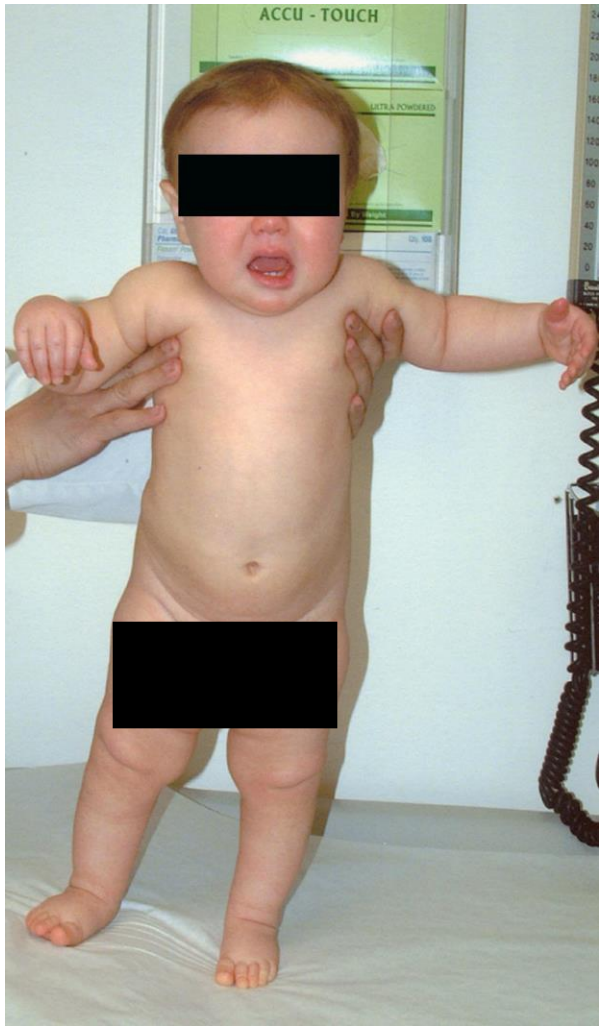


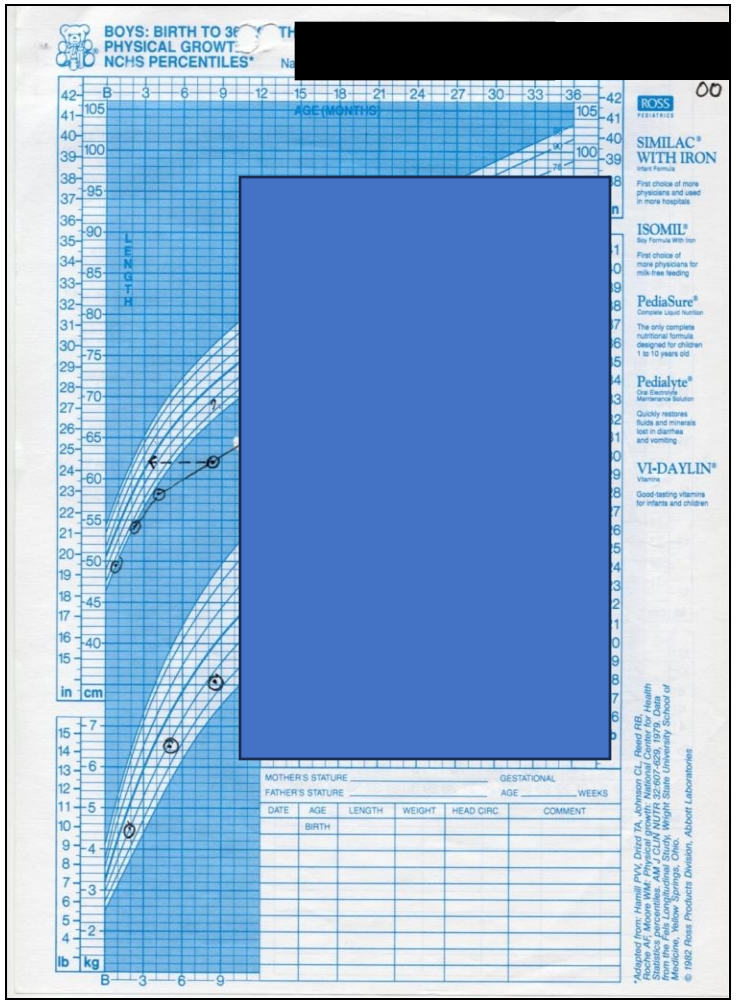
Bone age 5y
Low IGF1 and IGF BP3
GH stim test - < 1ng/mL
MRI brain: anterior pituitary hypoplasia

Started on GH therapy

Image with parent consent

Infant referred for short stature





- Height of
  Father- 69 inches
  Mother 64 inches

- Mid-parental target height : 69 +/-4 inches

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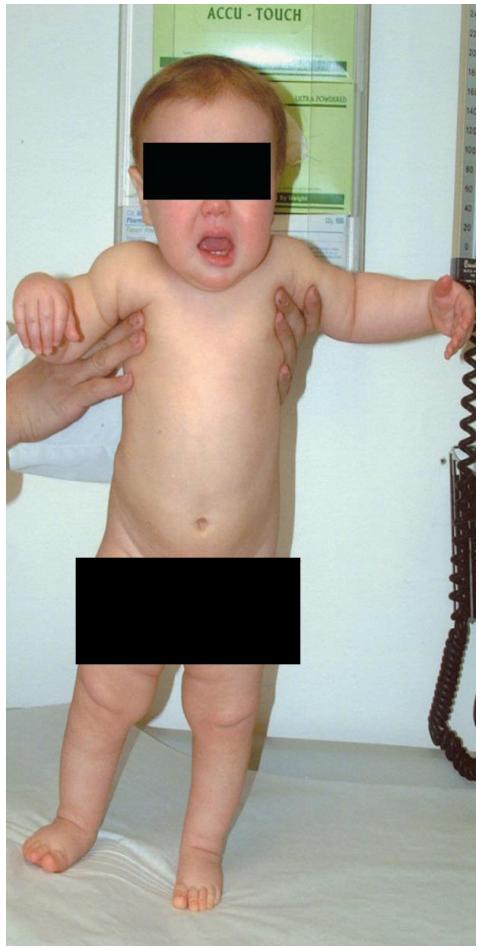
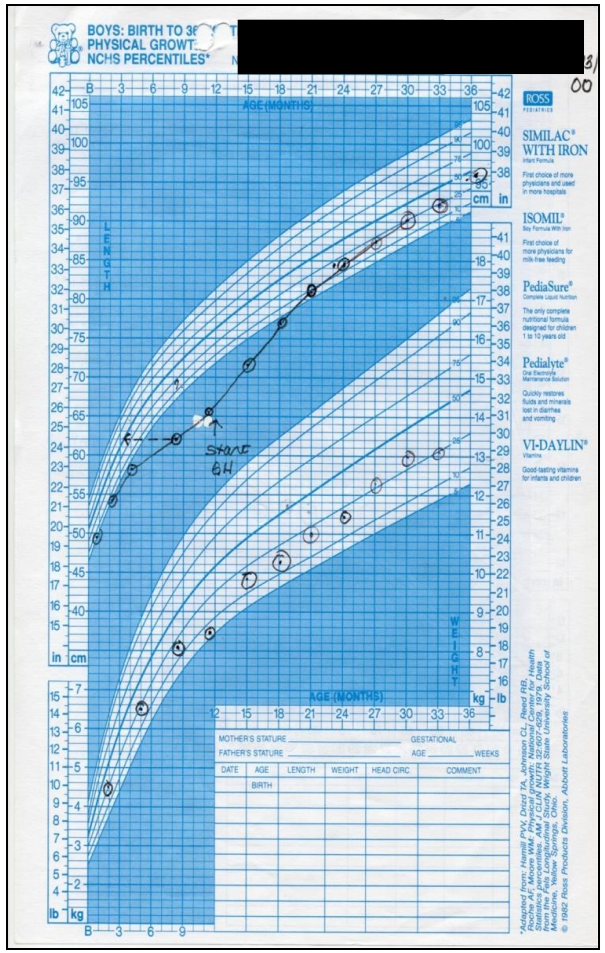
Congenital GHD





- Low IGF1 and IGFBP3
- Failed GH simulation test – peak GH level < 1 ng/ml
- MRI: small anterior pituitary gland and stalk
- Started GH at 9 months of age

Image with parent consent

Growth hormone deficiency

Phenotype of GH deficiency

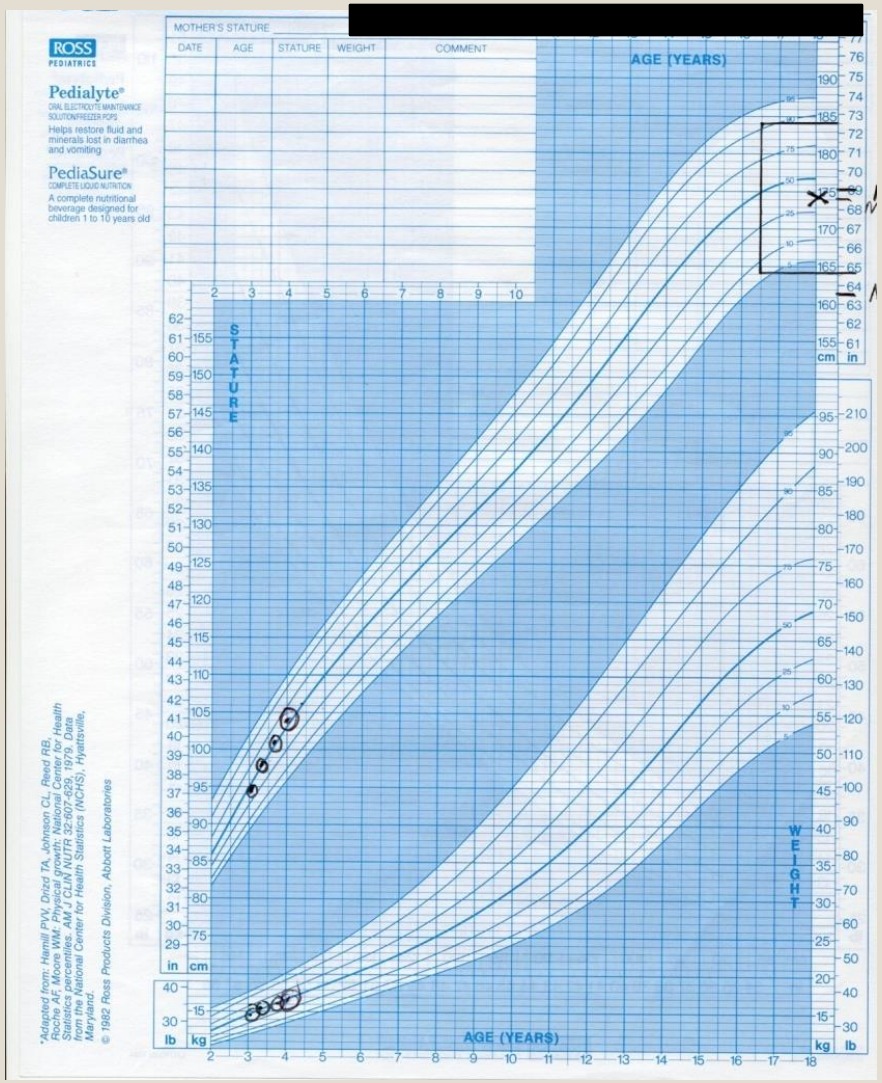
Low IGF1,IGFBP3 Low GH levels (post GH stim test)

Pituitary abnormality or genetic defect

Treatment:

Growth hormone

After 3 years on growth hormone treatment



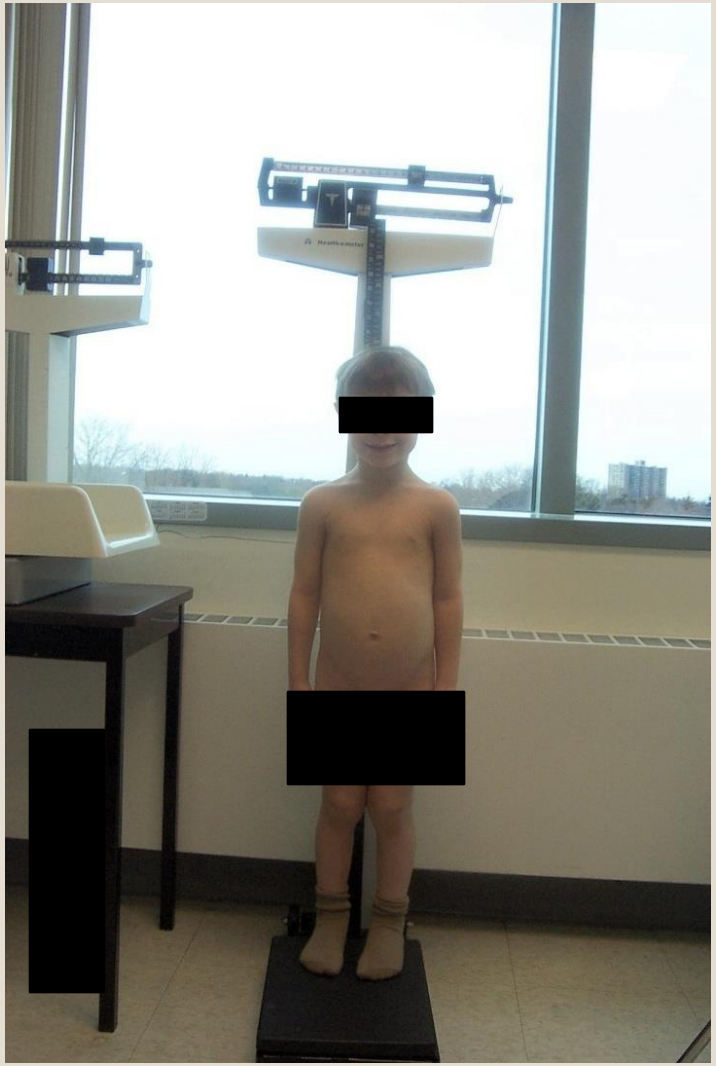
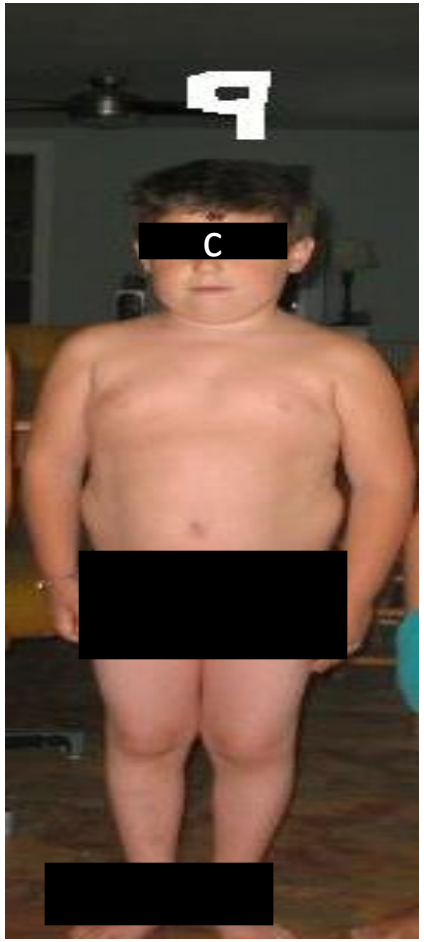


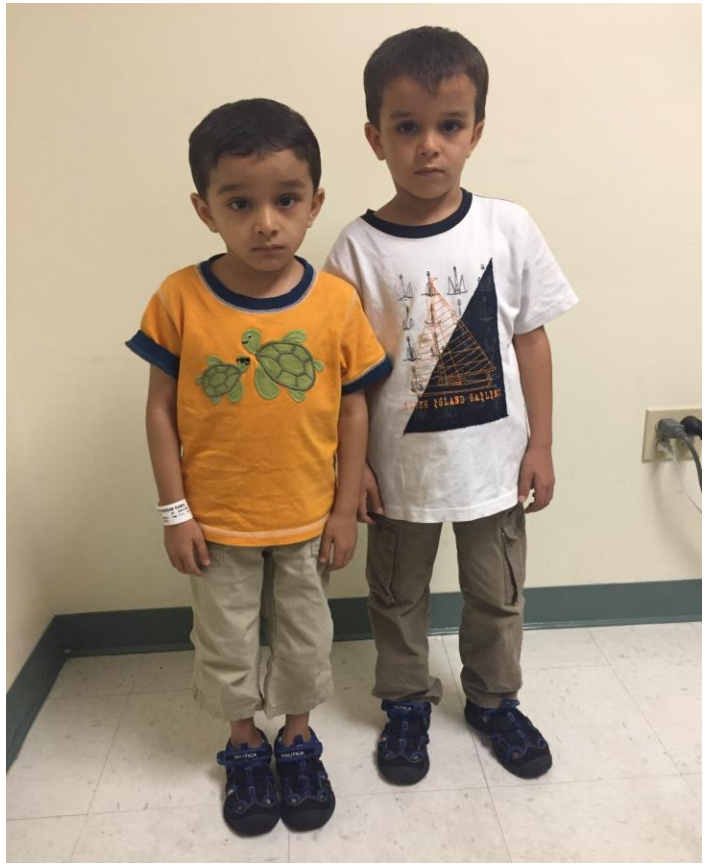
Image with parent consent

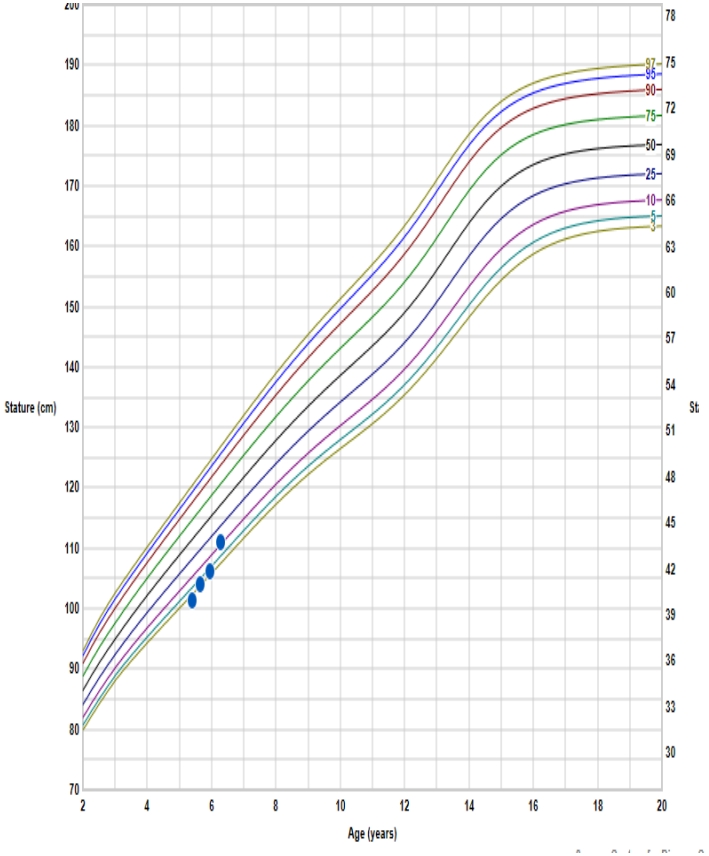
GH treatment: What to tell patients and family?

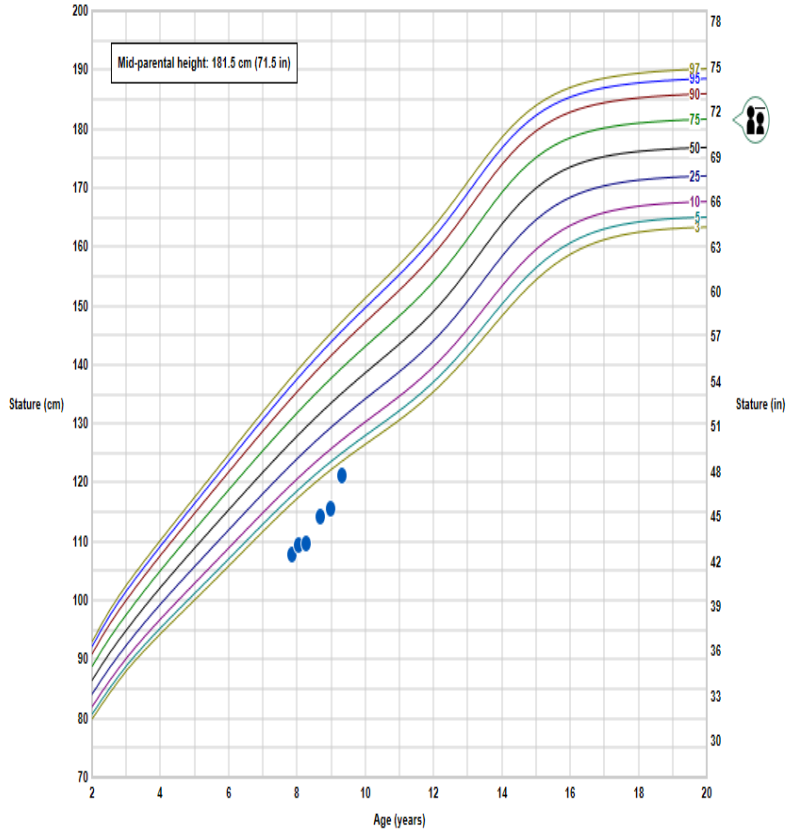


- Dose: 0.16-0.3 mg/kg/week
- Goal: achieve an adult height within the mid-parental target height
- Side effects: Pseudotumor cerebri, SCFE, swelling of hands and feet, glucose intolerance, pancreatitis
- Good prognostic factors: taller parents, duration of treatment, early diagnosis

Siblings with very low IGF1 (<10 ng/ml) and very high GH levels (peak GH >20 ng/ml)







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Growth hormone insensitivity syndrome
Laron Dwarfism

Phenotype of GH deficiency

Low IGF1, IGFBP3

Elevated GH levels

Defective GH receptor,

Autosomal recessive

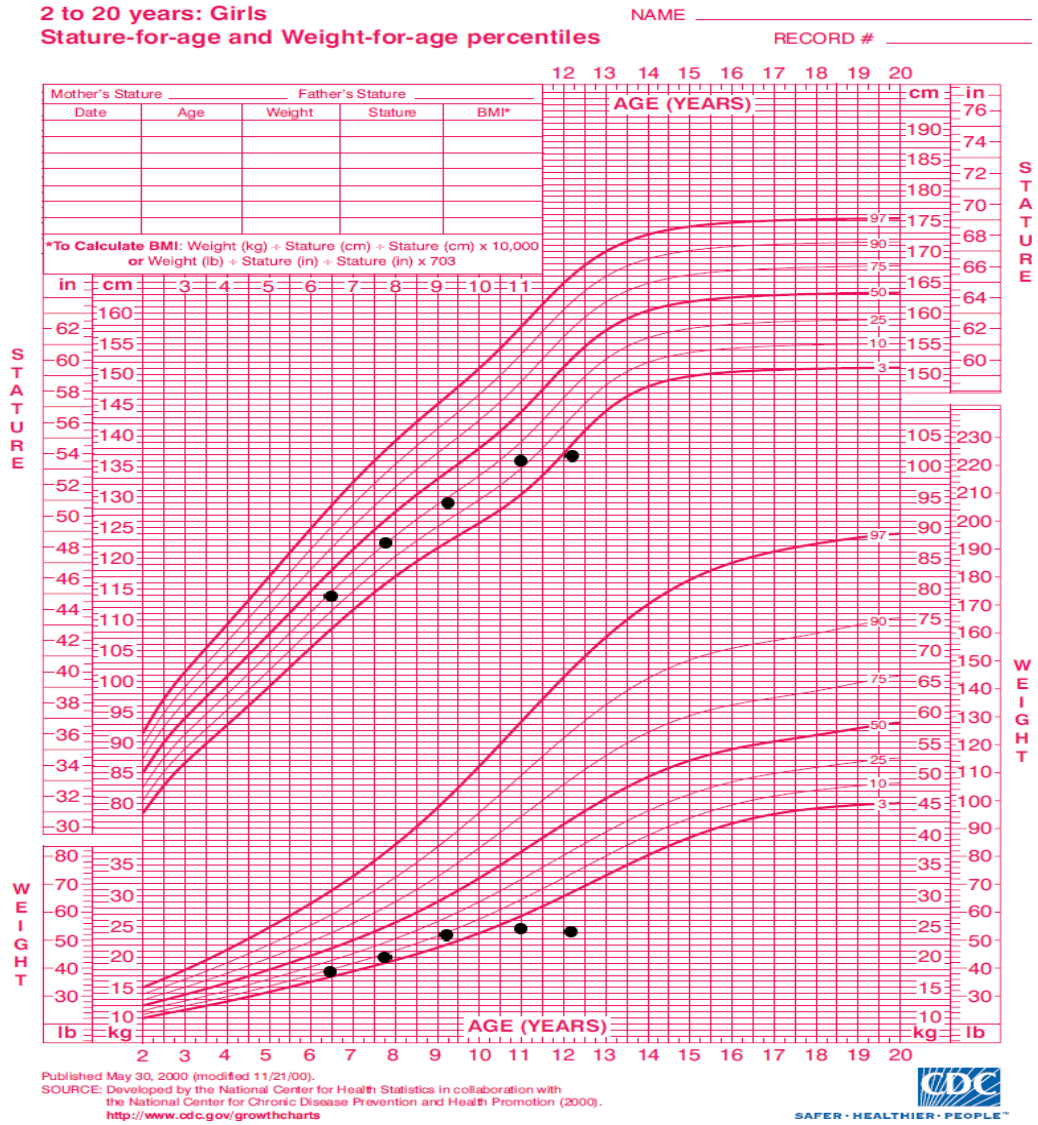
Treatment:

Recombinant IGF1 therapy

Hwa, V et al, Rev Endocr Metab Disord , 2021,; 22(1) 43-58.

12-year-old girl referred for poor growth

- **Hgb: 8.7 g/dl (11.5-15.3)**
- Hct: 30% (34-46)
- MCV: 70 fl (78-98)
- RDW: 15.7% (11-15)
- **ESR: 42 mm/hour**
- **Total iron: < 10 mcg/dl (27-164)**
- TTG IgA Ab: <1 U/ml
- TSH normal
- Low normal IGF 1 and IGF BP3



When to suspect IBD?

Crohn's Disease

- Poor growth maybe the presenting symptom
- Anemia, elevated ESR, CRP, abnormal albumin
- Growth failure: due to nutritional deficiencies, inflammation, glucocorticoid treatment, low IGF1

Mack, DR, et al, Pediatrics, 2007;119-1113-1119

Idiopathic Short Stature

- Height < -2.25 SD below the mean
- Normal physical examination
- Normal screening labs
- Normal IGF1, IGFBP3 and growth hormone stimulation test
- Minimal or no bone age delay
- Predicted adult height is < 4’11 in girls or <5’3 in boys
- Normal chromosome (R/O Turner syndrome)

Indications for referral to pediatric endocrinologists

- Children born SGA wo do not have catch up growth by 2 years of age
- Height > 2 standard deviations below the mean for age
- Growth velocity < 5 cm (2 inches) per year
- Projected height > 2 standard deviations (10 cm [4 inches]) below the midparental height
- Bone age > 2 standard deviations below the chronologic age
- Diagnosis of conditions approved for recombinant GH therapy

Indications for GH therapy in children

- Growth hormone deficiency: 1985
- Chronic renal insufficiency: 1993
- Turner syndrome: 1996
- Prader-Willi syndrome: 2000
- Small for gestational age/IUGR without catch up growth: 2001
- Idiopathic Short Stature: (>-2.25 SD): 2003
- SHOX haploinsufficiency: 2006
- Noonan syndrome: 2007

Key points

- Short stature: Height > 2 SD < the mean height for individuals of same sex and chronologic age

- Common causes of short stature beyond the first 2 years of life: familial short stature and constitutional short stature

- Initial evaluation of short stature includes detailed history, through physical examination, careful assessment of growth parameters and bone age study

You are now a growth expert!

Thank you for your attention!

CME Questions

Q1. In which of the following conditions is the bone age consistent with chronologic age ?

- A. Acquired hypothyroidism.
- B. Constitutional delay of growth and adolescence
- C. Familial short stature
- D. Glucocorticoid excess
- E. Psychosocial dwarfism

Q2. You are evaluating a 6-year-old girl for short stature. Her growth chart reveals a birth length at the 60th percentile and a current height at the 5th percentile. Her growth velocity over the last 2 years has been 3 cm/y. Her weight is at the 50th percentile. Findings on her physical examination otherwise are within normal limits, and her intelligence appears normal. There are no midline defects or dysmorphic features. Her bone age is 4 years. Of the following, the most likely diagnosis is:

- A. Congenital hypothyroidism
- B. Crohn disease
- C. Growth hormone deficiency
- D. Spondylodysplasia
- E. Turner syndrome

Q3. Which of the following is NOT an FDA approved indication of GH therapy?

- **A.** Down syndrome
- **B.** Noonan syndrome
- **C.** Prader Willi syndrome
- **D.** Turner syndrome

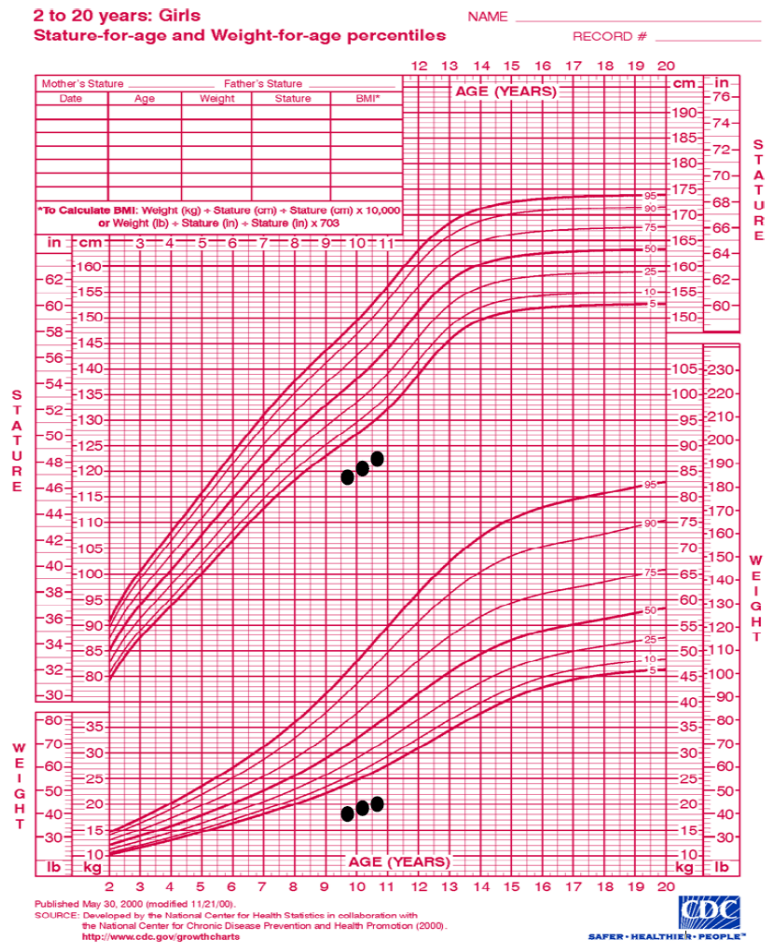
- **Q4.** A 12-year-old boy presents to the clinic for evaluation of short stature. He has lived in and out of foster care since 5 years of age. He has a history of hoarding food and hiding in his room. His height is 124 cm (−3.5 SDS), weight is 25 kg (−3 SDS), and BMI is16.3 kg/m^2 (−0.78 SDS). He has Tanner stage II pubic hair and prepubertal testes. His laboratory test results are normal except for a low IGF-1 level, and his bone age is 10years. What is the most likely diagnosis?

- A. Constitutional delay in growth and puberty
- B. Growth hormone deficiency
- C. Inflammatory bowel disease
- D. Psychosocial dwarfism

- **Q5.** A 10-year-old girl presents for evaluation of short stature. She has been an otherwise healthy child. Her parents are healthy: mother is 152 cm (59.8 inches) tall and had menarche at age 15 years; father is 170 cm(66.9 inches) tall and grew until age 20 years. Physical examination is noncontributory. Using the standards of Greulich and Pyle, her bone age is 7 years and 10 months.

What is the most likely diagnosis?

- **A.** Constitutional short stature
- **B.** Familial short stature
- **C.** Growth hormone deficiency
- **D.** Inflammatory bowel disease



- **Q6.** A 15-year-old boy is brought to your clinic by his mother. He is concerned that he is the shortest boy in his class at school. His mother's height is 155 cm (61 inches), and his father's height is 178 cm (69 inches). His height is 158 cm (62 inches), which is between the 5th and 10th percentiles. You think that he likely has either constitutional delay of growth and adolescence or familial short stature. In addition to an evaluation of his pubertal development, the assessment that is most likely to give you the information you need to distinguish between these two conditions is

- A. Bone age
- B. Calculation of his target height
- C. Calculation of his upper-to-lower body segment ratio.
- D. Growth hormone assay
- E. Growth velocity measurement

True or False?

- **Q7.**The most common causes of short stature beyond the first 2 years of life are familial short stature and constitutional delay in growth and puberty.

A. True

B. False.

- **Q8.** Bone age is delayed in cases of Turner syndrome**.**

A. True

B. False

- **Q9.** Congenital heart disease occurs in 50%-80% of individuals with Noonan syndrome. Hypertrophic cardiomyopathy, often with dysplasia, is the most common heart defect and is found in 20-50% of these patients.

A. True

B. False

- **Q10.** Most common endocrinopathy seen in children with craniopharyngioma is growth hormone deficiency.

A. True

B. False

Answers to CME questions

Q1. In which of the following conditions is the bone age consistent with chronologic age (ie, not delayed)?

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- E. Psychosocial dwarfism

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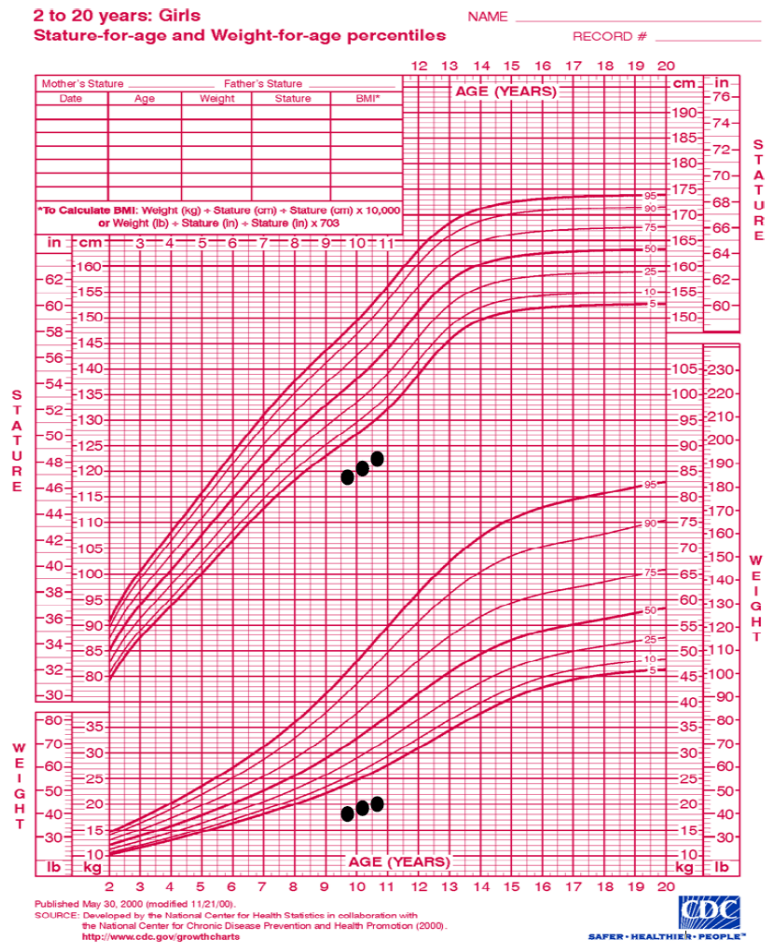

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A. True

B. False

Pulmonary valve stenosis, often with dysplasia, is the most common heart defect seen in Noonan syndrome and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood

- **Q10.** Most common endocrinopathy seen in children with craniopharyngioma is growth hormone deficiency.

A. True

B. False


Thank You...