JOHNS HOPKINS
MEDICINE

Achondroplasia in 2018

Paul D Sponseller MD

ICEOS

Mini-Symposium: CHALLENGES IN TREATING DYSPLASIA

November 15, 2018 1:40-1:49

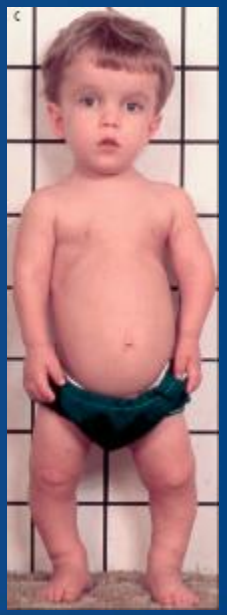
ORTHOPAEDIC SURGERY

Outline

- Pathogenesis and Treatment opportunities
- Spine Deformities

Achondroplasia

- Causative gene found (1995) by Bellus, Heffernon
  - Johns Hopkins
- Fibroblast growth factor receptor 3 *FGFR3*
  - *99% with same Gly380Arg substitution; <1% with Gly375Cys*
  - *Autosomal dominant*
  - *100% penetrant*
  - *80-90% spontaneous mutation*
  - *Advanced paternal age*
  - *Molecular prenatal diagnosis available*



GAIN OF FUNCTION: mutation associated with an increase in normal functions of protein

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NORMAL

FGFs bind to FGFR3

↓

Inhibits proliferation of cartilage cells

ACHONDROPLASIA

FGFR3 mutation

↓

Overactivity of normal growth inhibition

↓

Cartilage cells stop proliferating

↓

Short stature

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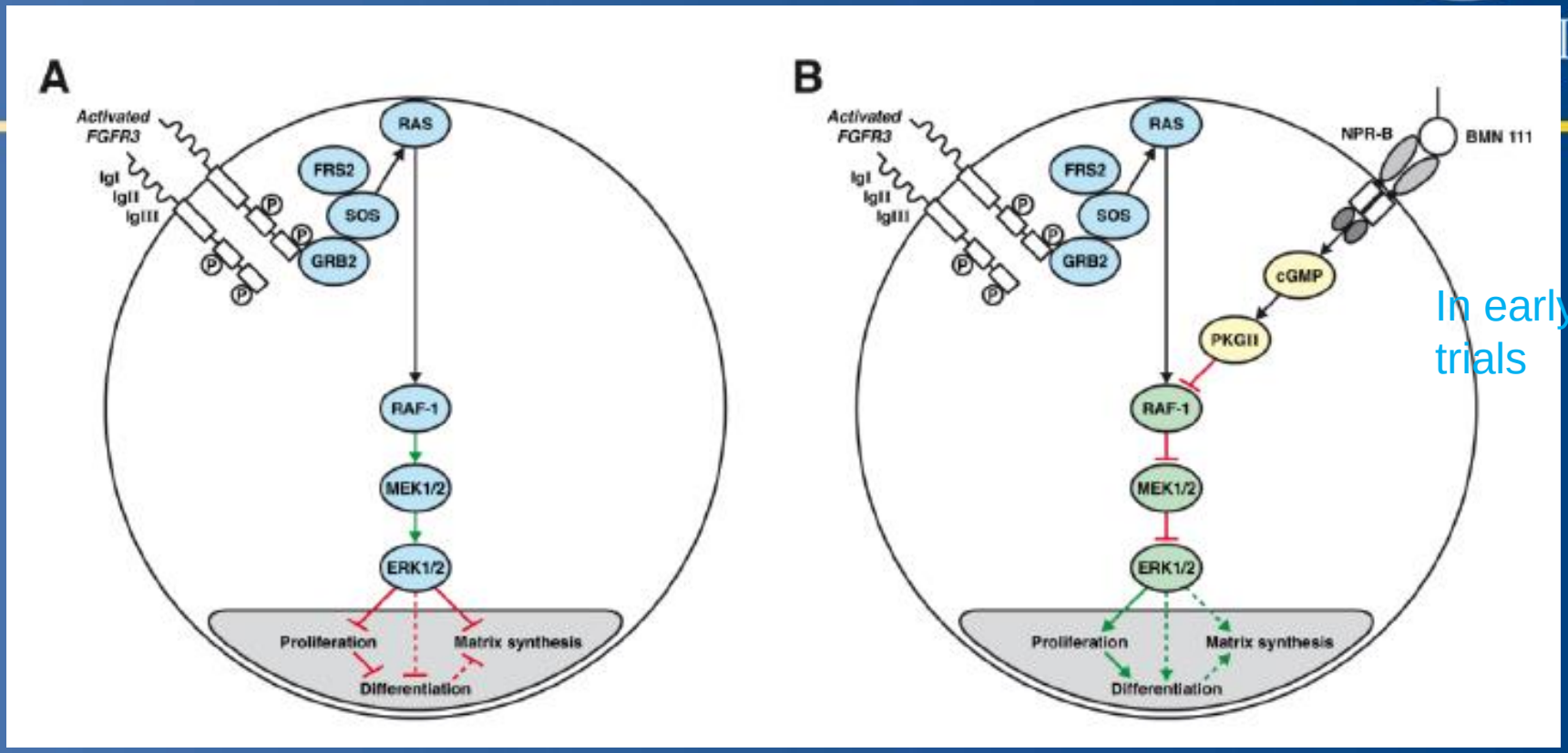
Vasoritide (C-natriuretic peptide analogue)



In early trials

A: Chondrocyte with mutated FGFR3 that down-regulates its development via the MAPK/ERK

B: Vosoritide (BMN 111) blocks this mechanism by binding to the atrial natriuretic peptide B, which subsequently inhibits the MAPK/ERK path

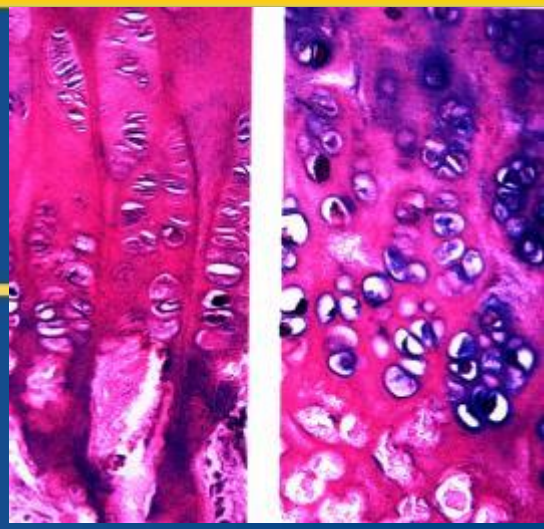
Medical complications in achondroplasia

- Obstructive sleep apnea
  - *Referral to pulmonology, ENT*
  - *Tonsillectomy / adenoidectomy*
  - *CPAP*
- Central sleep apnea
  - *Referral to neurosurgery*
  - *Foramen Magnum Decompression*

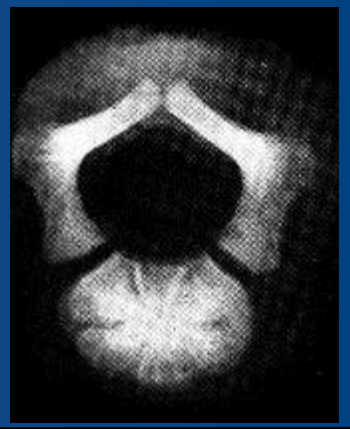
Skeletal Dysplasia Spine Summary

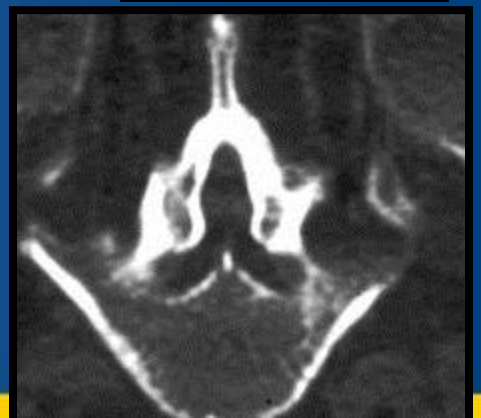
- ~~Upper cervical instability~~
- Kyphosis in Achon
- ~~Scoliosis~~
- **Stenosis**- Achon

Achondroplasia Spine



- Early-onset foramen magnum stenosis
  - *Some improve spontaneously*
  - *Suspect if sleep apnea, weakness*
  - *MRI, sleep study to evaluate*
  - *Foramen magnum decompression*





Achondroplasia Spine Issues

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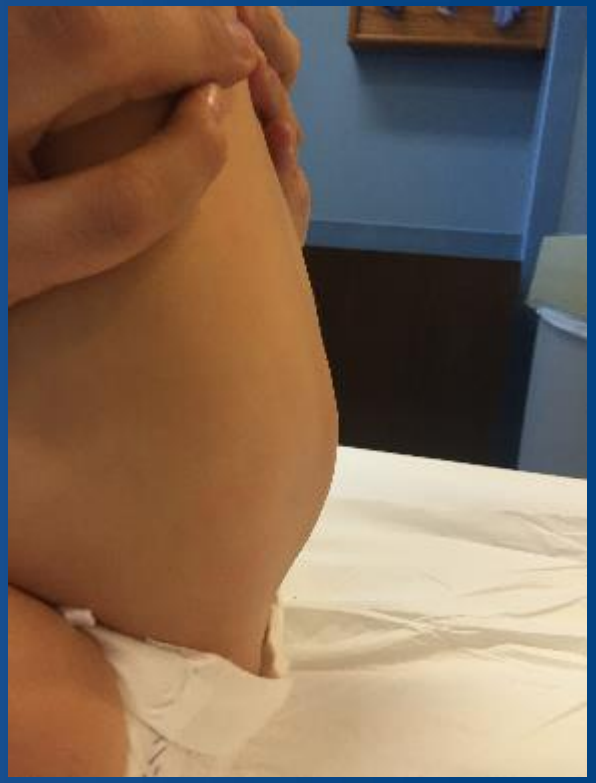
- How to manage kyphosis
- Does bracing work?
- Indications for spine fusion?
- When should you fuse to sacrum?

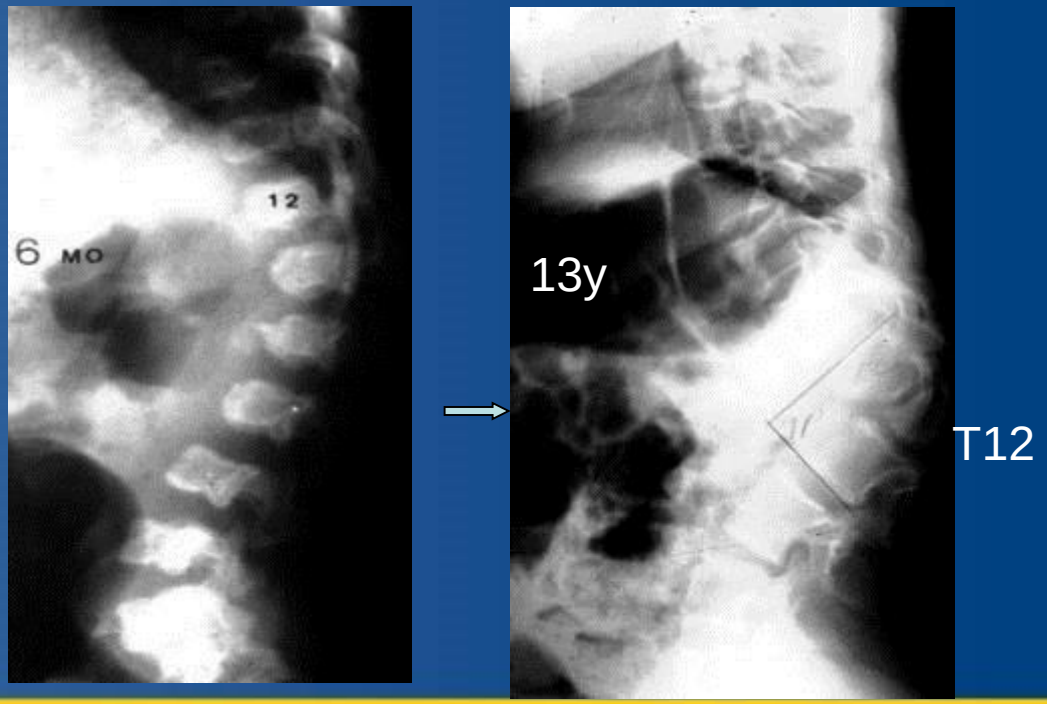
TL Kyphosis in Achondroplasia

- *Characteristic feature*
- *<1 year: 94% prevalence*
- *30% persistent*
- *Etiology: hypotonia*
- *T10-L4*
- *Corrects in prone position*



Achondroplasia
-Spinal problems

- Thoracolumbar kyphosis before walking
  - *usually resolves shortly after walking*
  - *If not, L1 may progressively wedge*



TLK Clinical Study

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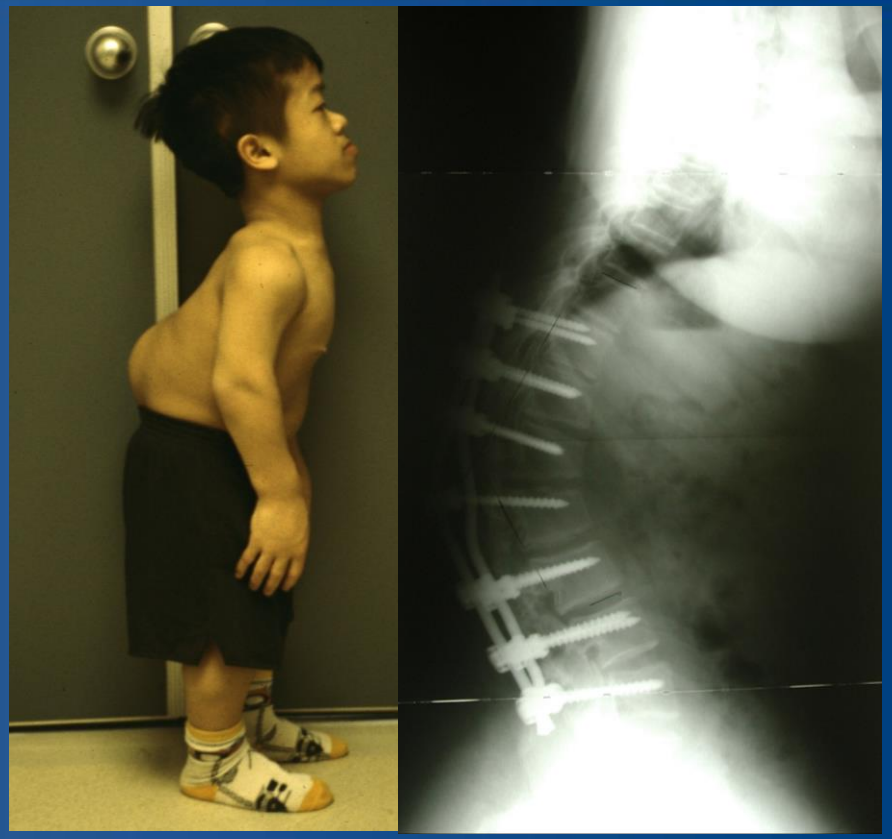
70% resolved

30% pts with persistent TLK at final FU

- 30% pts ≥40 ° of persistent TLK
  - (80% symptomatic - PSF)
- 70% pts 20-40° of persistent TLK
  - (15% symptomatic - PSF)



Radiographic Predictors of Persistent TLK

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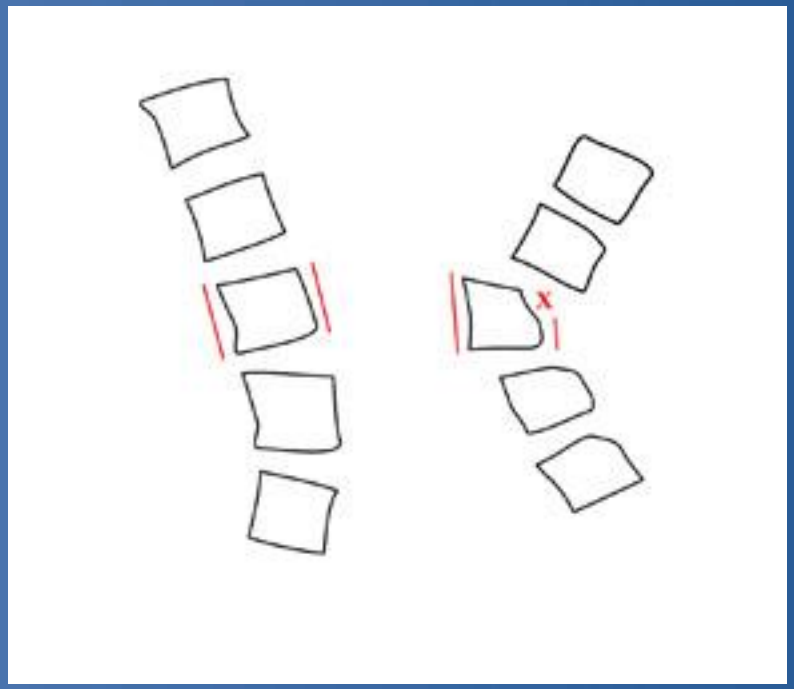
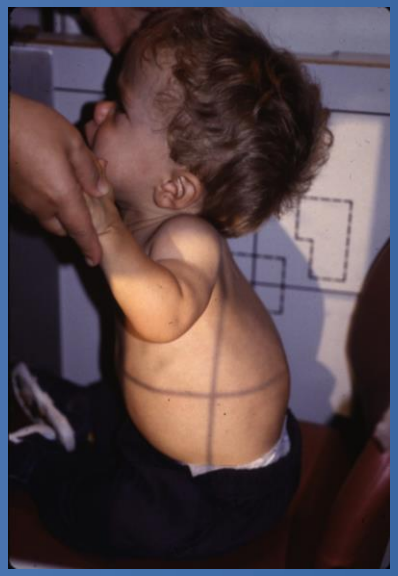
Resolved **Persistent**



- **Apical vertebral translation:**
  - **5% (*p*=0.001)**
- **Apical vertebral wedging for height:**
  - **6% (*p*=0.031)**

Clinical Parameters Predicting persistent TLK



Motor delay:
Inability to sit at 14 mos
or walk independently
At 30 months

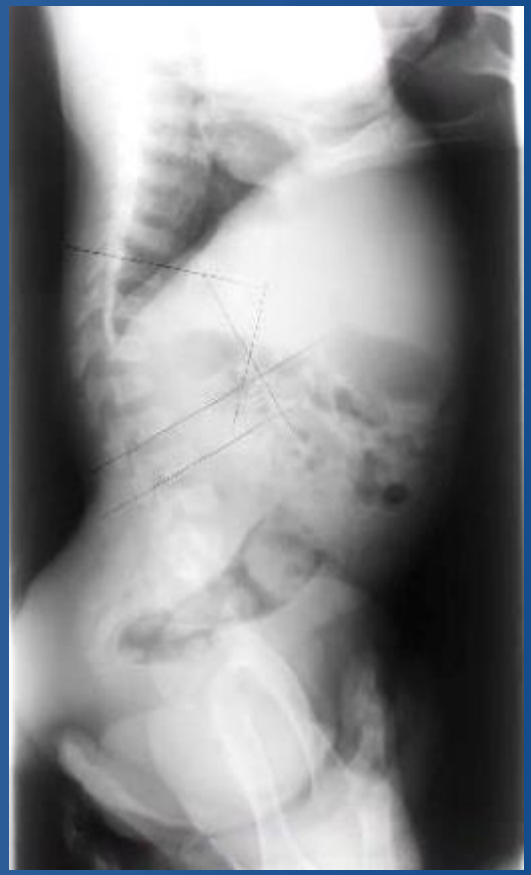
- Sitting:
  7 – 14 months
- Walking:
  15 – 30 months

Achondroplasia Spine Issues

- Does bracing work?
  - *No data on this point; try in late kyphosis*
- Indications for spine fusion:
  - *Any TL decompression for stenosis in immature patient*
    - Otherwise will progress
- For deformity alone:
  - *If painful, progressive*
  - *Most tolerate mild TL kyphosis*

Case example – interval improvement

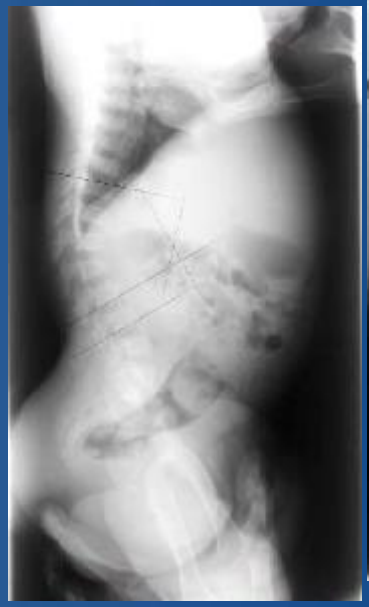
- Age: 14 months
- Sitting Age: 12 months
- Not yet walking



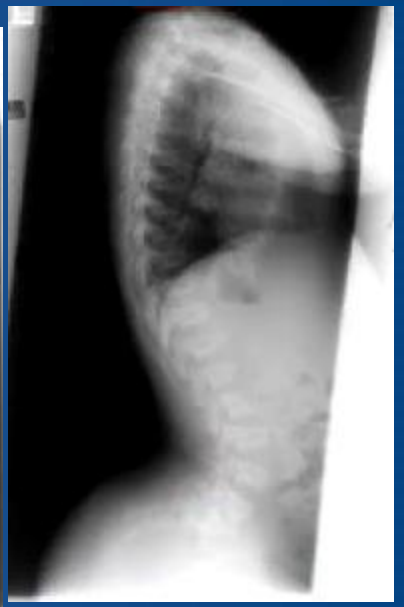
14 months
Kyphosis: 40 degrees

Case 1 – interval improvement

- Age: 14 months
- Walking age: 27 months
- No Brace; kyphosis improved
- Further follow up needed?



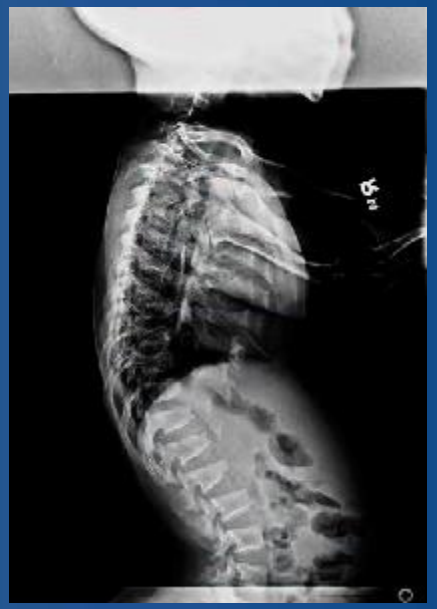
14 months
Kyphosis: 40°



4 years
Kyphosis: 40°

Case 1 – recurrence

- 14 yrs: claudication
- Squats after walking
- Temporary foot drop

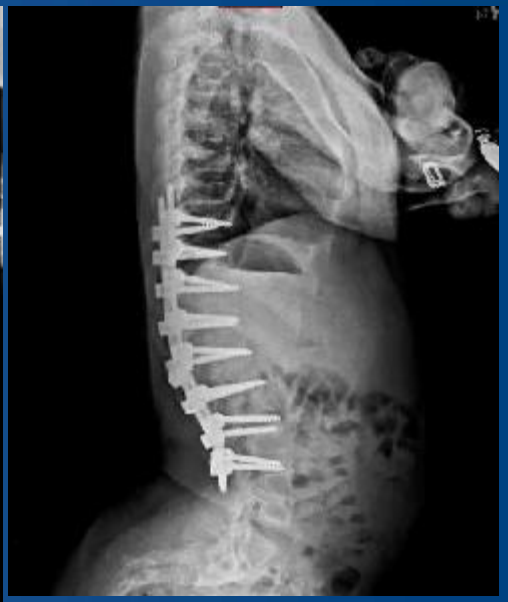


14 years
Kyphosis: 32^{o} degrees

Case 1 – recurrence

- MRI confirmed stenosis
- Decompression T12-L4
- Instrument kyphosis in immature pts
- Don’t overcorrect

14 years
Kyphosis: 52º



s/p PSF

Achondroplasia- Operative issues

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- High risk of IONM changes (~30%)
- Avoid Hooks, instruments in canal
- Pedicle & Screw diameter ok
  - *5-7 mm*
  - *Length decreased by ~1 cm*
- High risk of dural violation
  - *Nerve roots seem "pressurized"*

Achondroplasia: Operative Issues

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- Should you to fuse to sacrum ?
  - *Lower re-stenosis;*
  - *trend to difficulties with personal care*

Case 2
8 yr old with Achondroplasia

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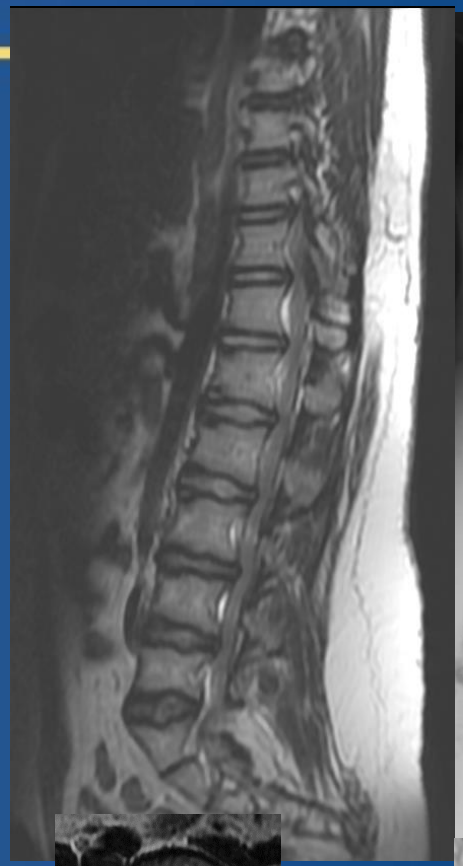
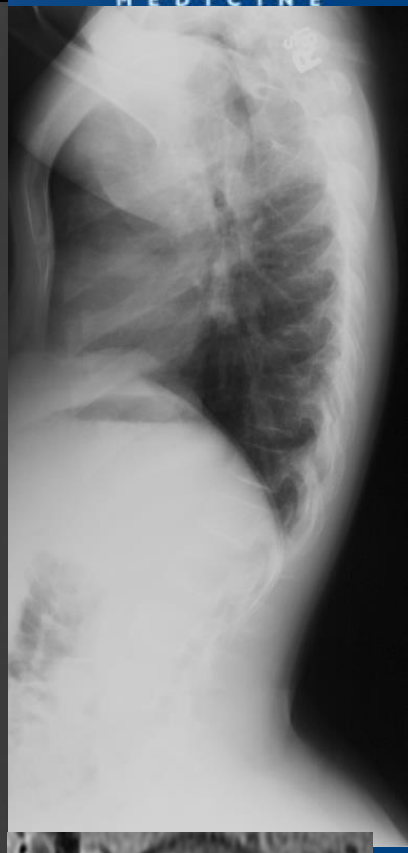
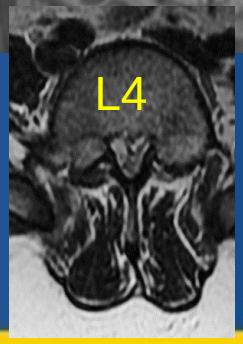
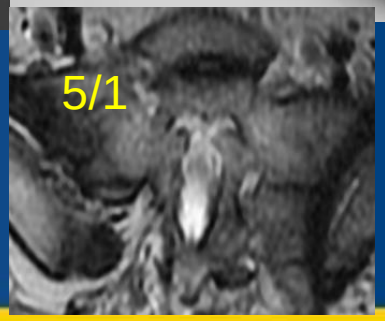
- S/P F. Magnum decomp x 2
- Neurogenic Claudication
- MR confirms stenosis
- Recommendation
  - *Decompress?*
  - *Fuse + metal?*
  - *Levels?*
  - *Or Wait?*









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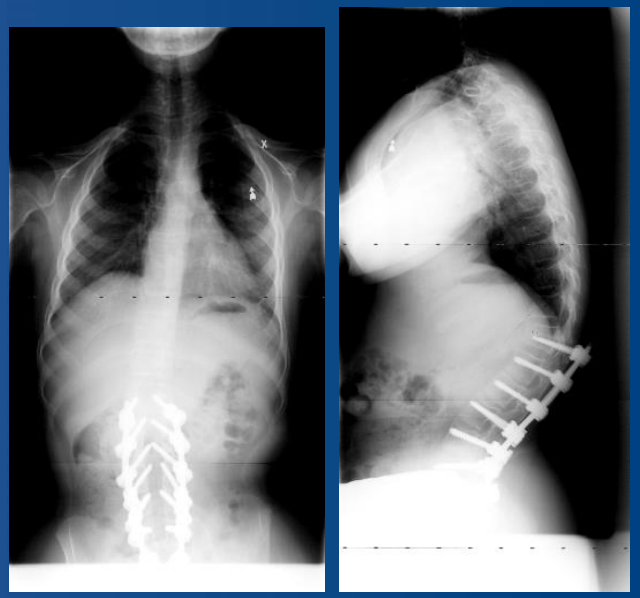
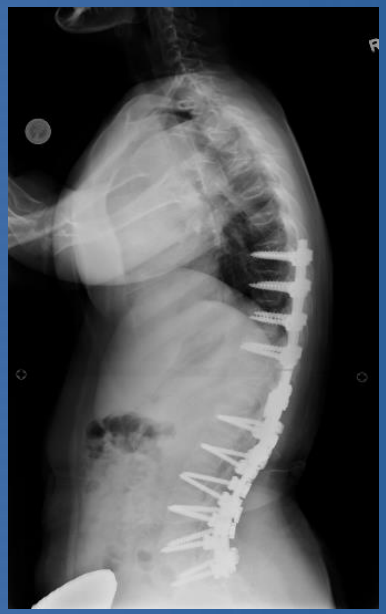
Case 2

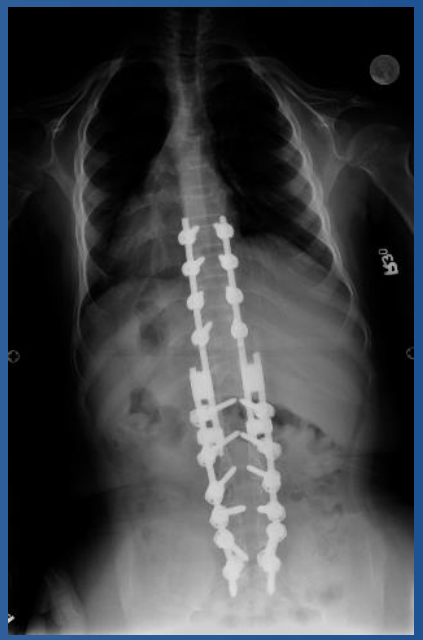
- Further surgery needed?
  - *What type*
    - And approach
  - *How far*
  - *What alignment?*



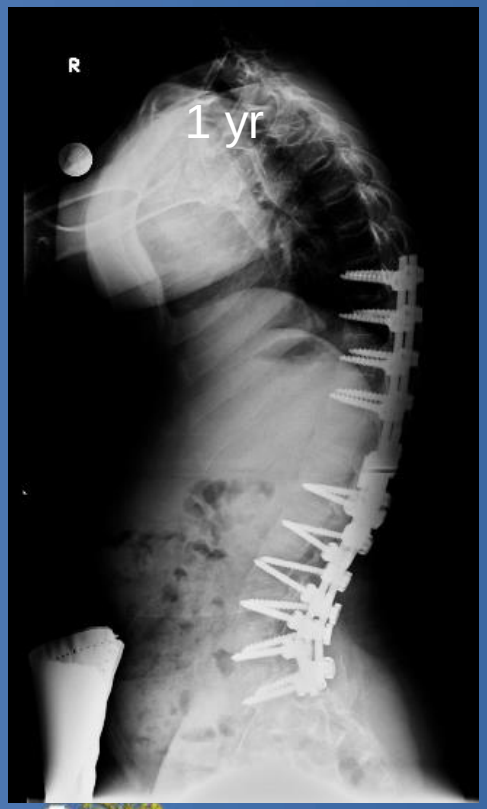
Case 2

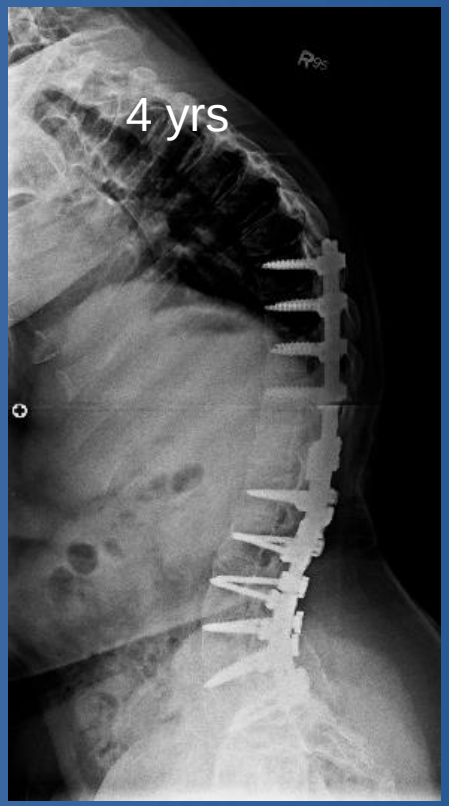
- Extension of Fusion to T8
  - *Looked good (then!)*

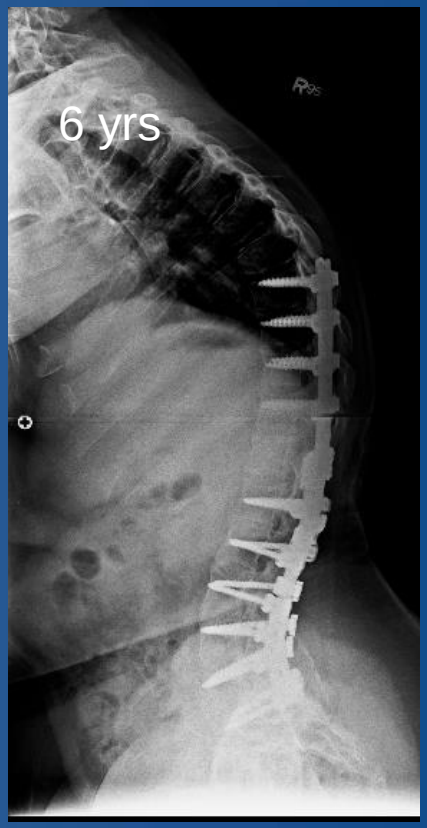




Next Steps?

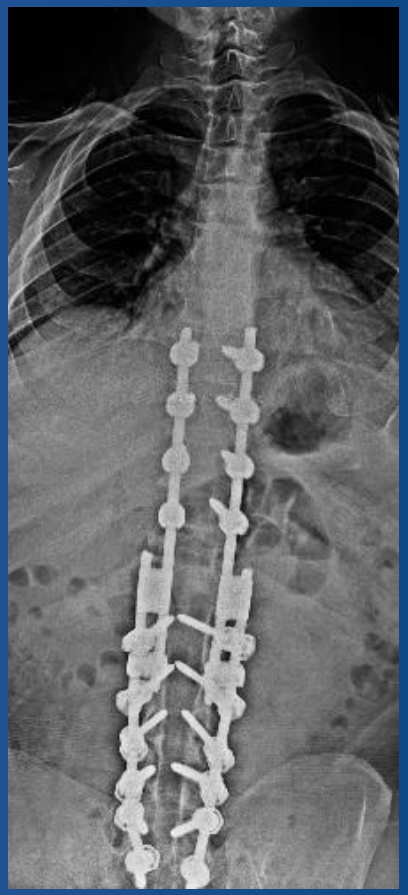


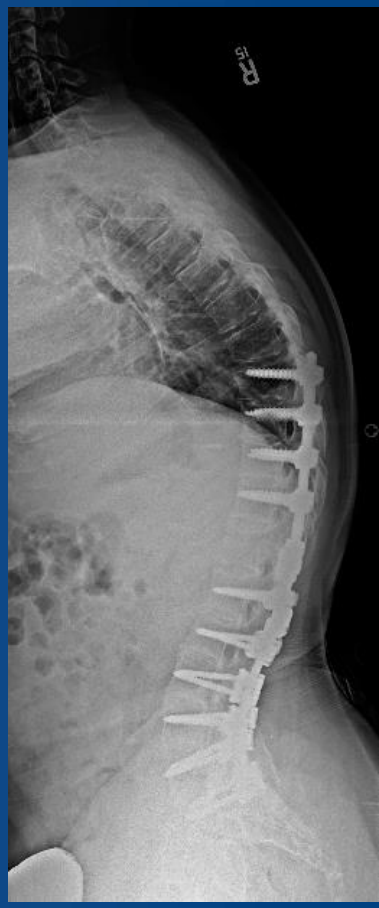




Case 2

- Stabilized, no further complaints
- Final AP and lat 4/18





Summary

- 70% of children “walk out of” kyphosis
- Bracing efficacy unknown
- Instrument all adolescent decompressions
- Correct only to prone kyphosis
- Judicious fusion to sacrum

- Geneticist invaluable in monitoring

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Thank you!

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Resources for Syndromes

- Online Mendelian Inheritance in Man (OMIM)
  - *Available through NLM/Pub Med*
  - *Allows search by findings*
- National Organization for Rare Disorders (NORD) (http://www.rarediseases.org/)
  - *Includes summaries of rare disorders*
- Medical Geneticist
  - *Some become "primary care" for syndromes*

Thank You

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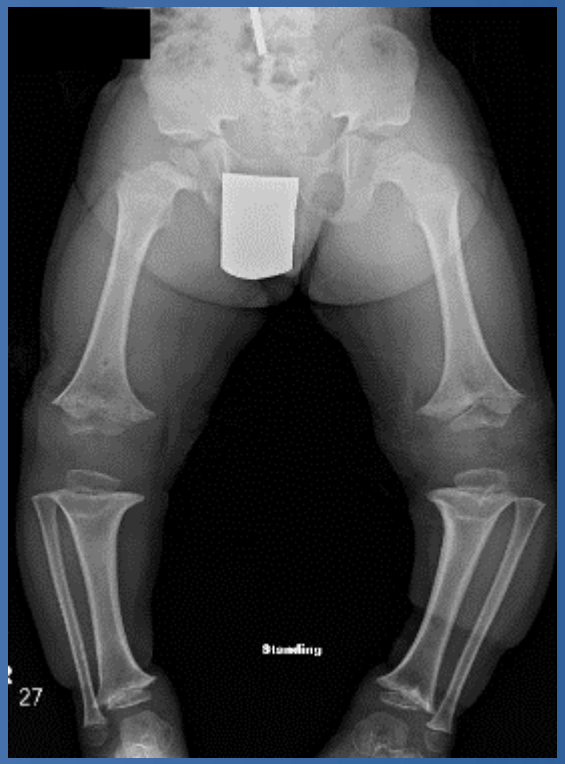
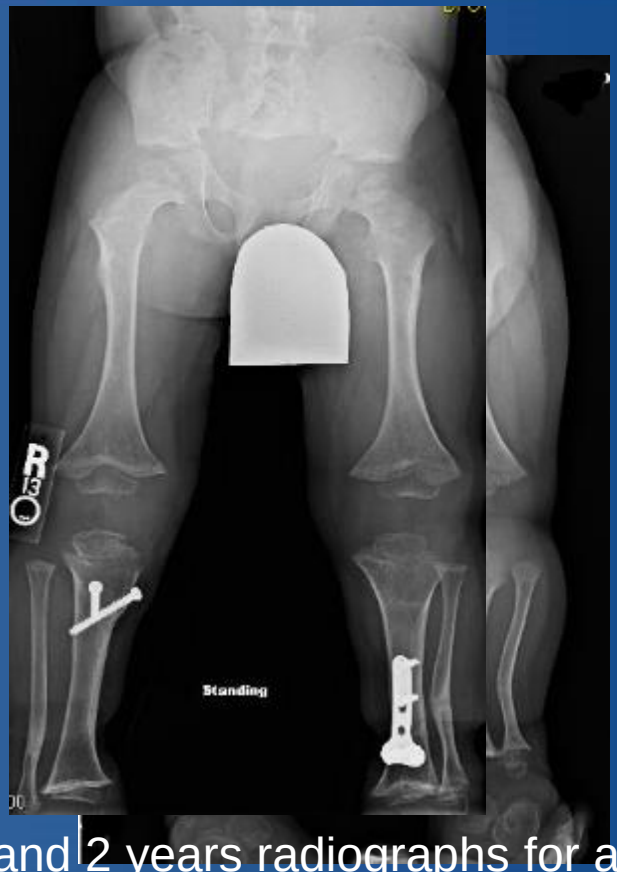
ORTHOPAEDIC SURGERY

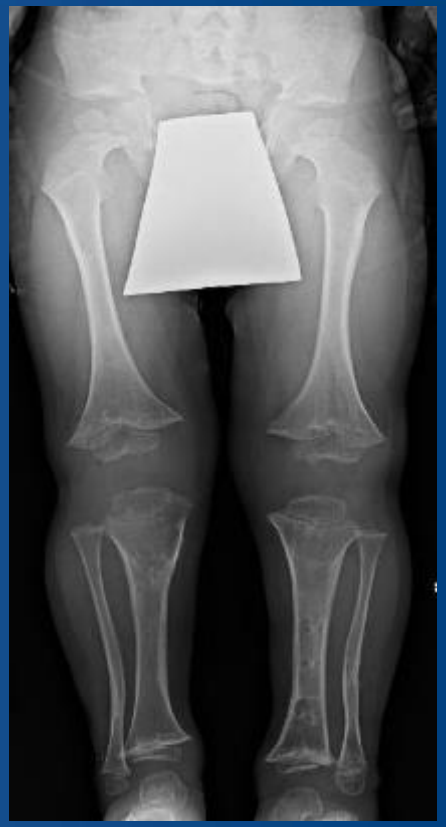
Thank You

ORTHOPAEDIC SURGERY

Genu Varum (Surgery)







- Preoperative, 1 year, and 2 years radiographs for a 2 year old boy with achondroplasia

Achondroplasia

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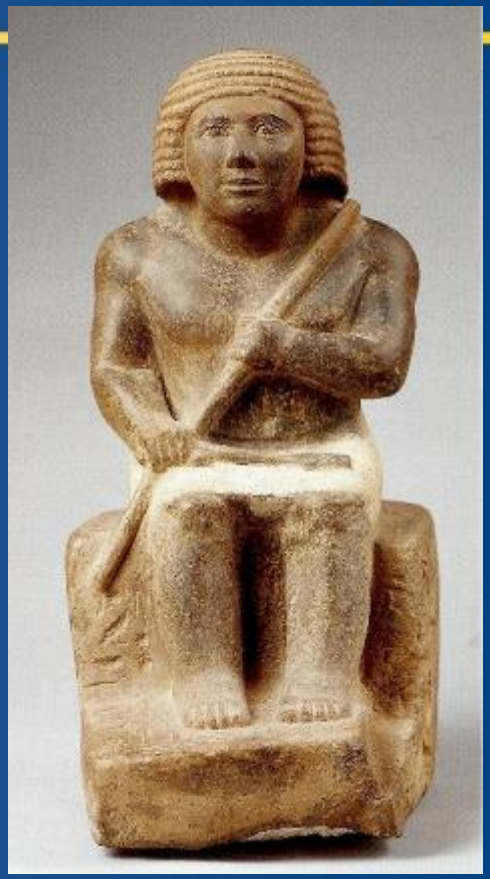
- Most common skeletal dysplasia
- 1:10,000-1:30,000
- Dwarfism in ancient Egypt, Greece, Rome, ~3,000 to ~30 BCE
- Revered by rulers, general population

Historical Review
Dwarfs in Ancient Egypt
Chahira Kozma*
Department of Pediatrics, Georgetown University Hospital, Washington, District of Columbia
Received 3 July 2005; Accepted 10 October 2005

Historical Review
Skeletal Dysplasia in Ancient Egypt
Chahira Kozma[1,*]

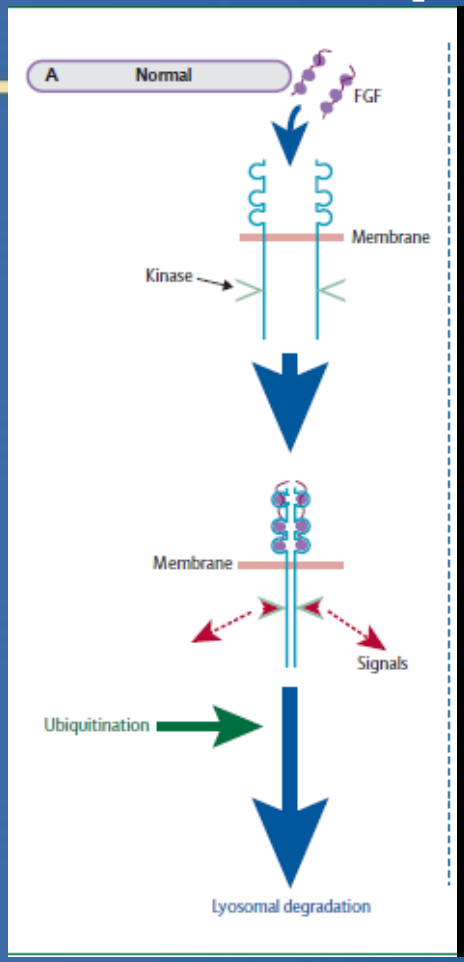
The Ancient Egyptian Dwarfs of the Pyramids: The High Official and the Female Worker
Chahira Kozma,[1]* Azza Mohamed Sarry El Din,[2] Rokia Abd El Shafy El Banna,[2] Wafaa Abd El Samie Kandeel,[2] and Ralph Lachman[3]

Per-ni-ankh



Discovered in limestone tomb in 1989
Western field of great pyramid Khufu

Binding FGF to FGFR3 dimerizes the receptors



Dimerization activates intrinsic tyrosine kinase activity

Activated FGFR3 ubiquitinated to direct to lysosomes to be degraded; signaling stops

With FGFR3 mutation, dimerization is *too* stable & too much signaling occurs

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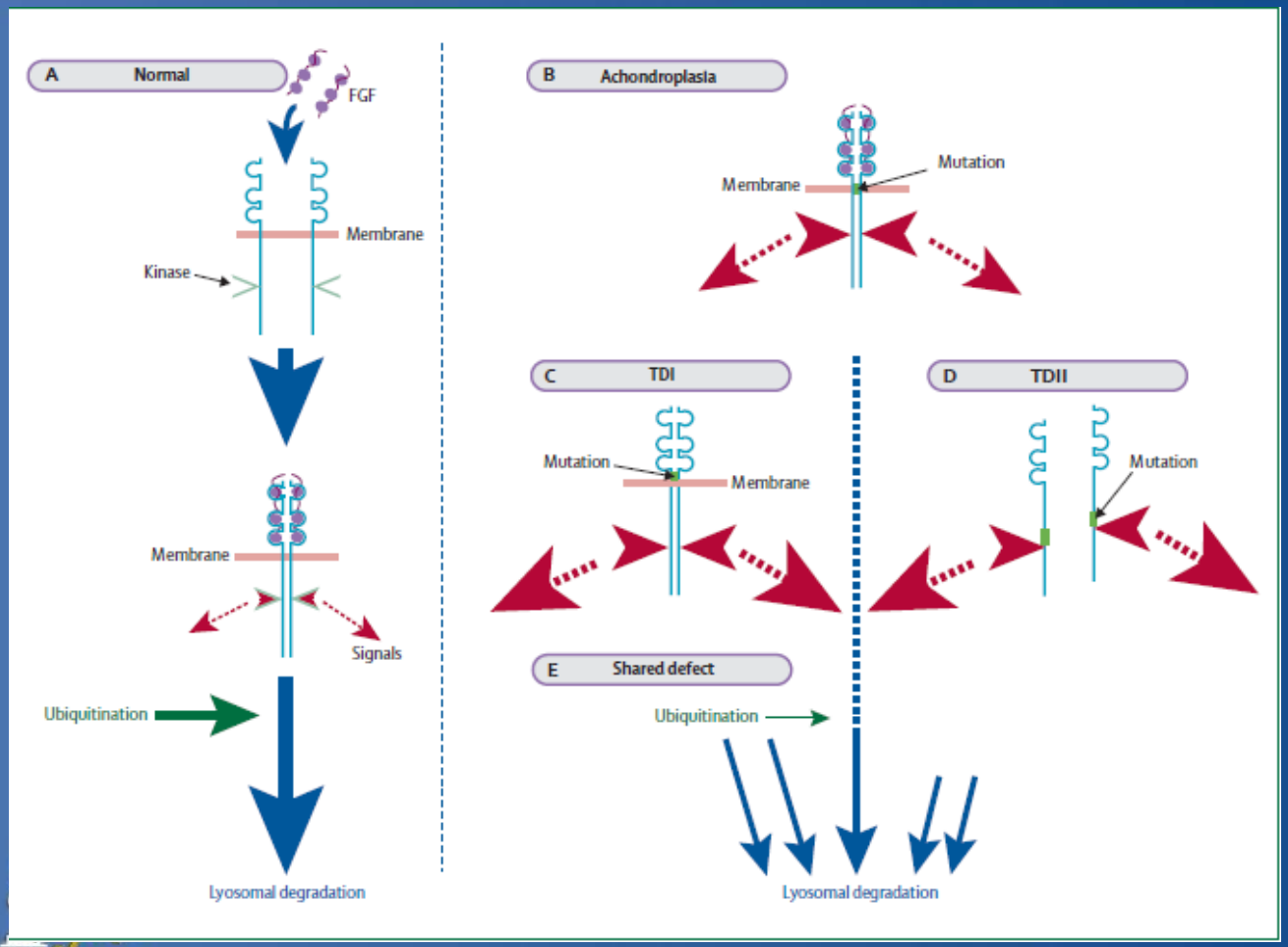


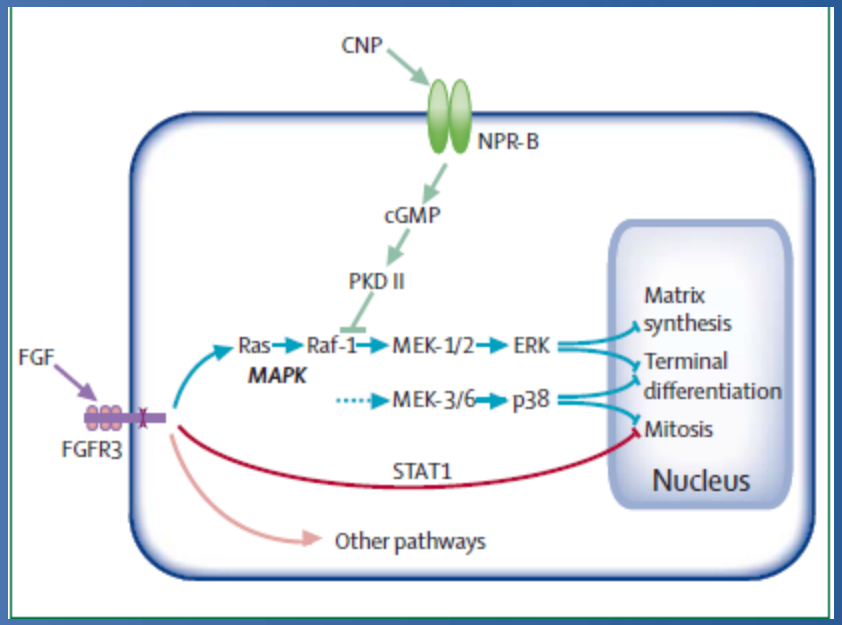
Achondroplasia: transmembrane domains stabilize dimers

TD1: disulfide bonds in extracellular domain stabilize dimers

TD2: kinases are activated

All mutations: kinases activated, hinders ubiquitination. Not degraded.

FGFR3 signaling pathways important in growth plate of chondrocytes



MAPK: Mitogen activated protein kinase. Negatively affects proliferation, terminal differentiation and matrix synthesis (via p38 and ERK)

STAT1: Signal transducer and activator of transcription. Inhibits chondrocyte proliferation.

FGFR3 signaling pathways important in growth plate of chondrocytes

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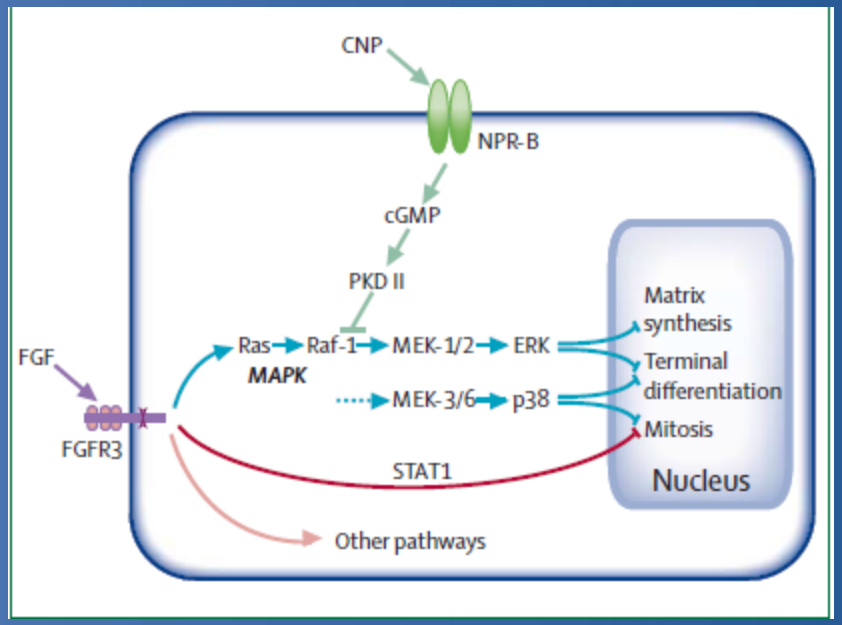
C-type natiuritic peptide can bind to natriuritic peptide receptor B.
Causes accumulation of intracellular cGMP.
CNP-NPR-B signals antagonize MAPK signaling.



THIS IS THE MECHANISM OF VOSORITIDE

ACHONDROPLASIA IS A **METAPHYSEAL** DYSPLASIA

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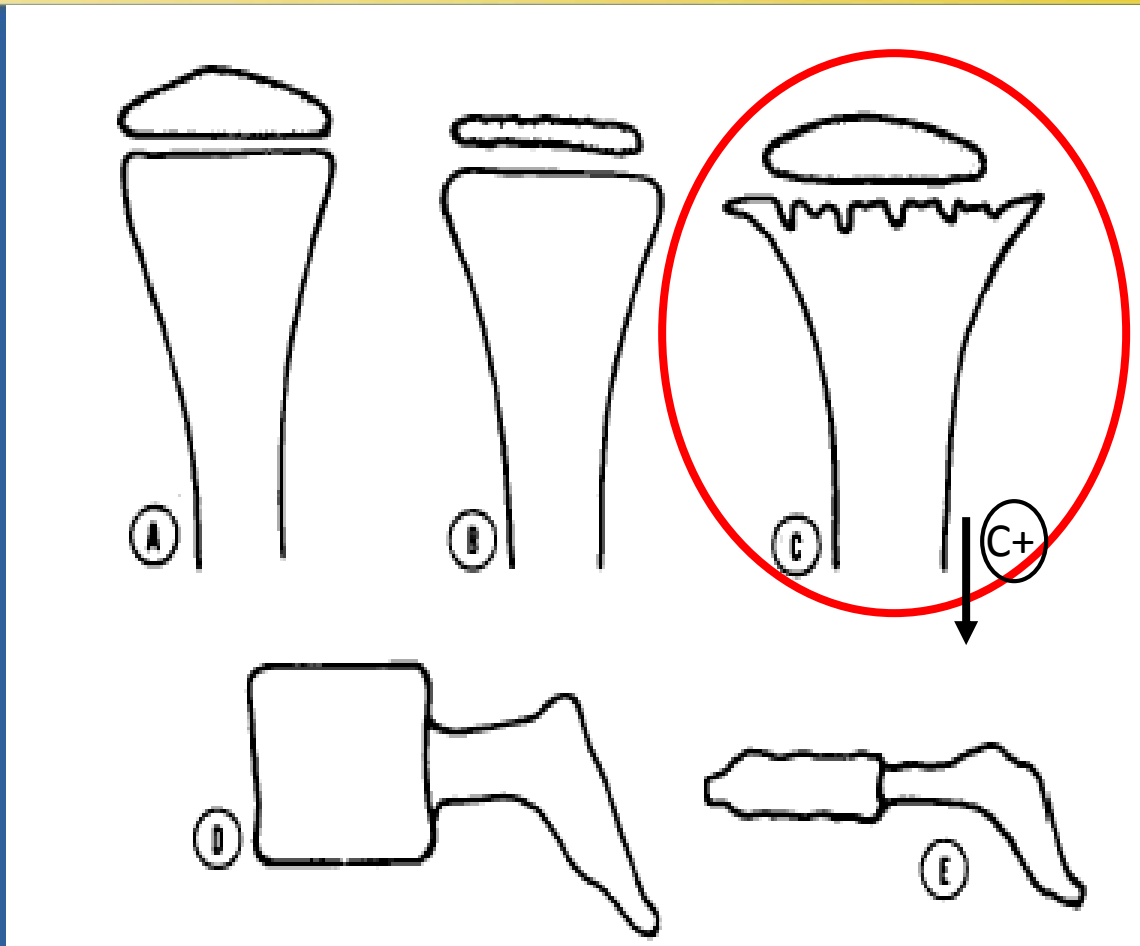
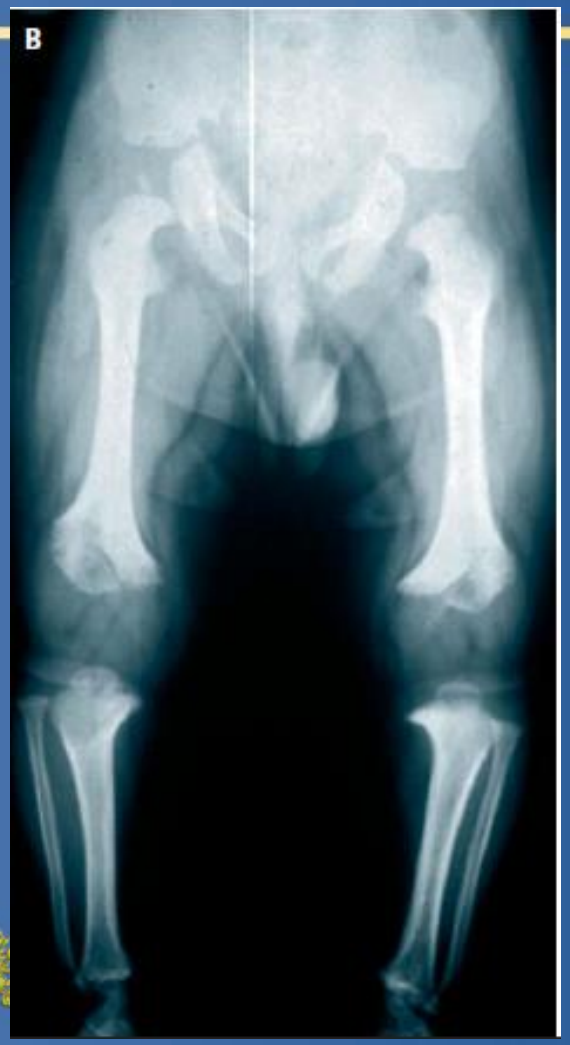
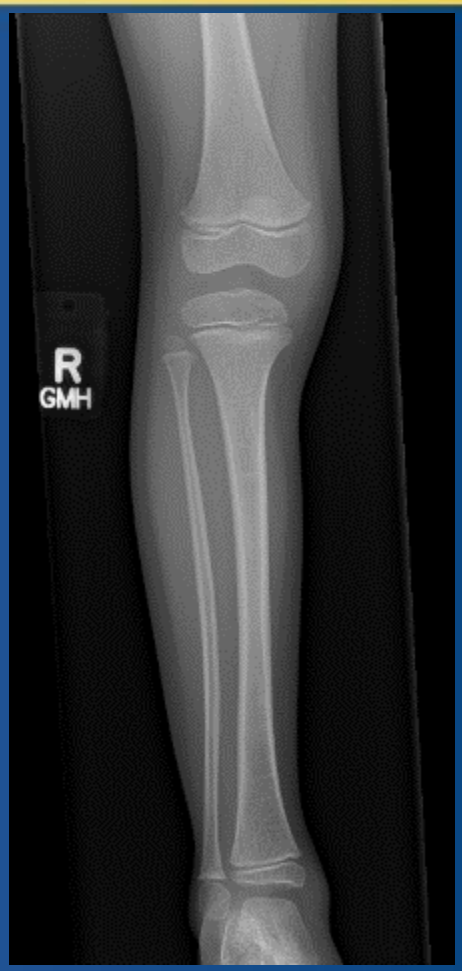
- Normal = A, D
- Epiphyseal = B
- **Metaphyseal = C**
- Diaphyseal = C
- Spondylo = E



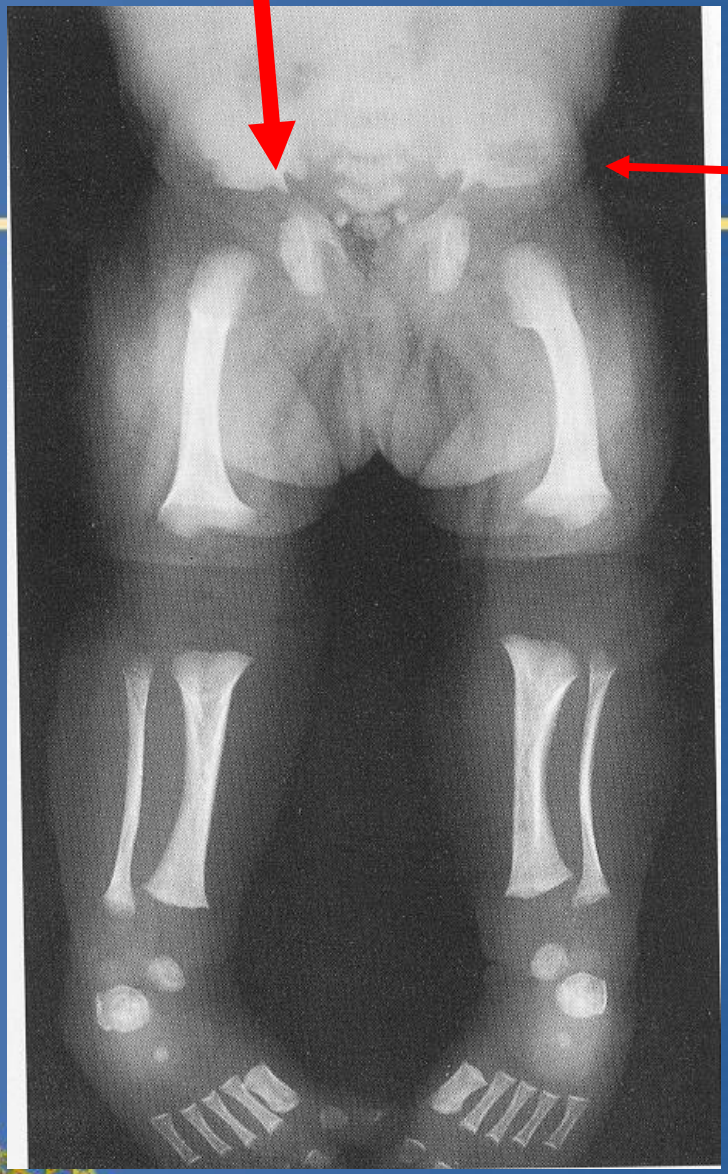
Achondroplasia

Average stature child





SMALL SACROSCIATIC NOTCHES



SQUARE, FLAT ILIAC BONES

Average stature child

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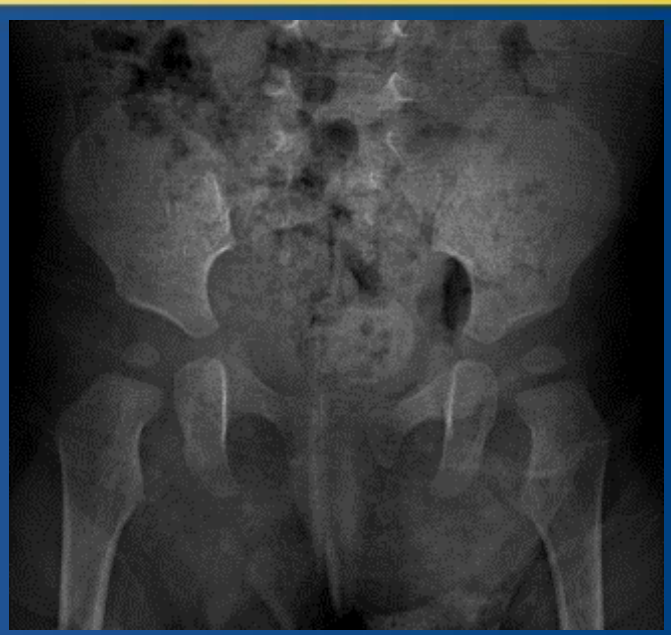
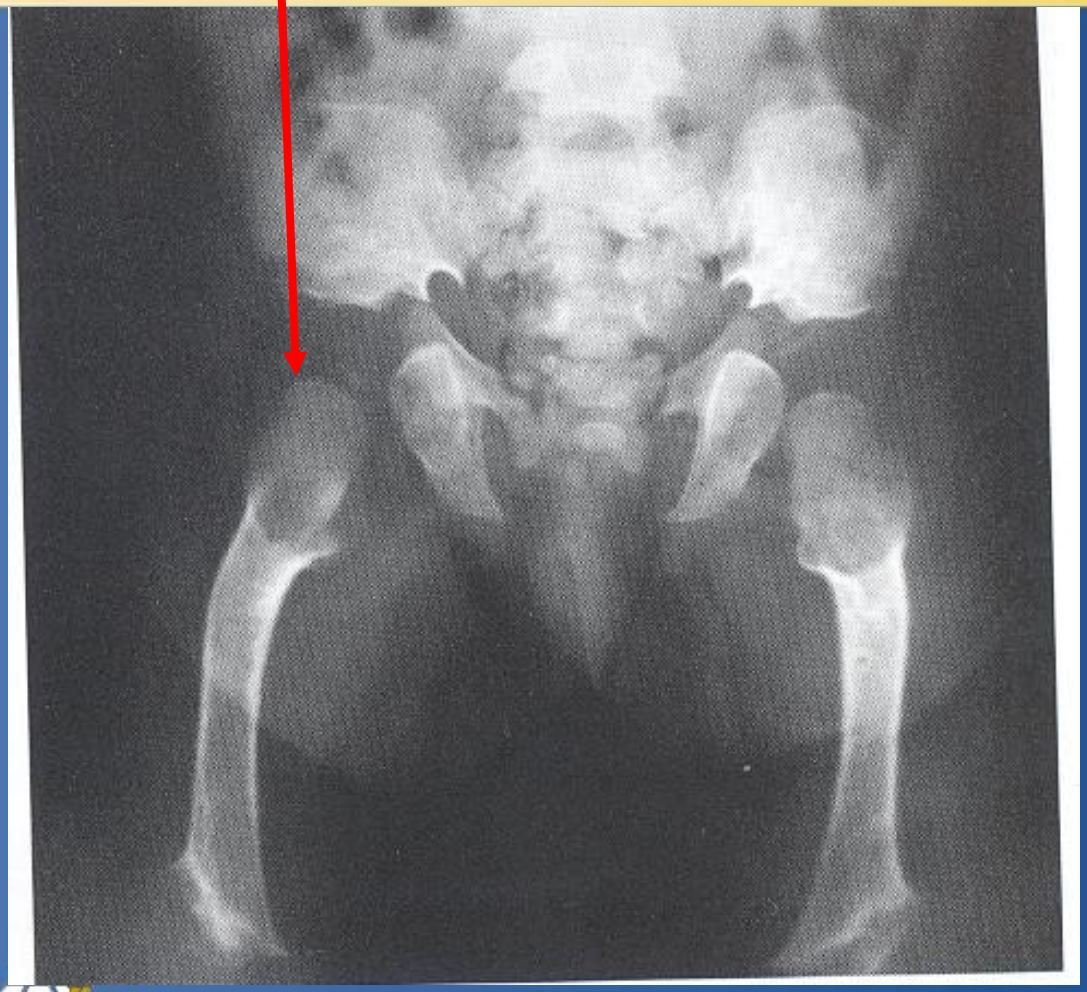


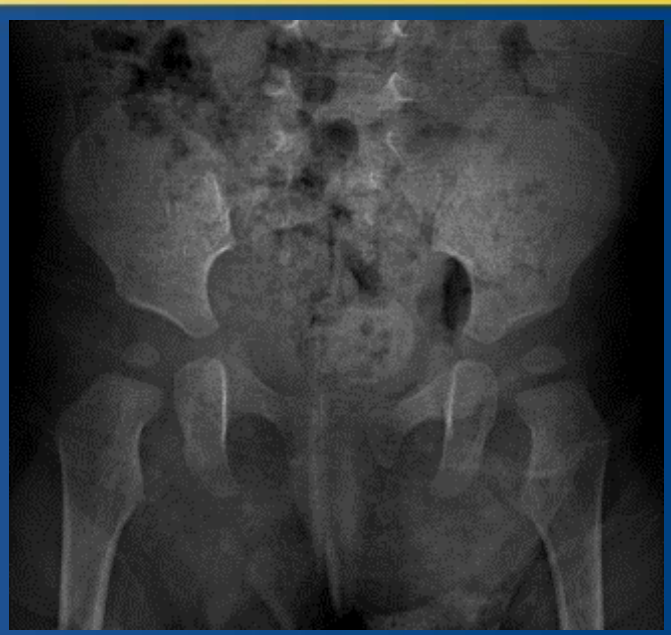
METAPHYSEAL FLARING

OVAL LUCENCY OF PROXIMAL FEMURS

'ice cream scoopers'



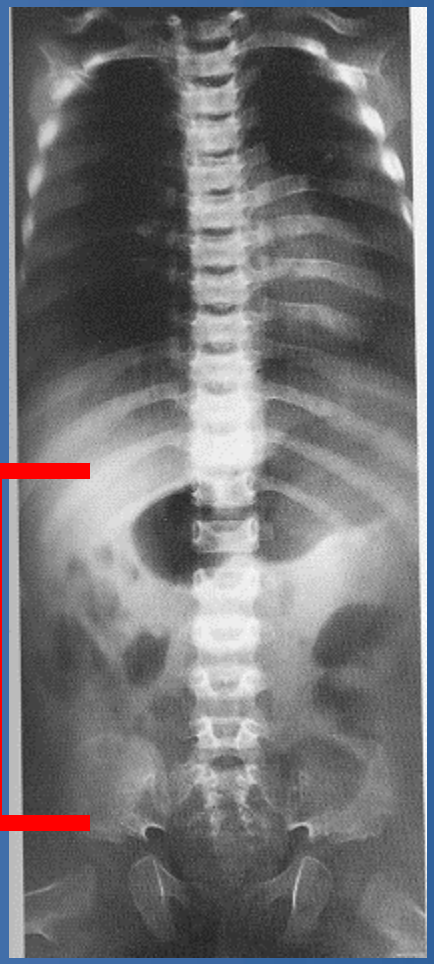
Average stature child

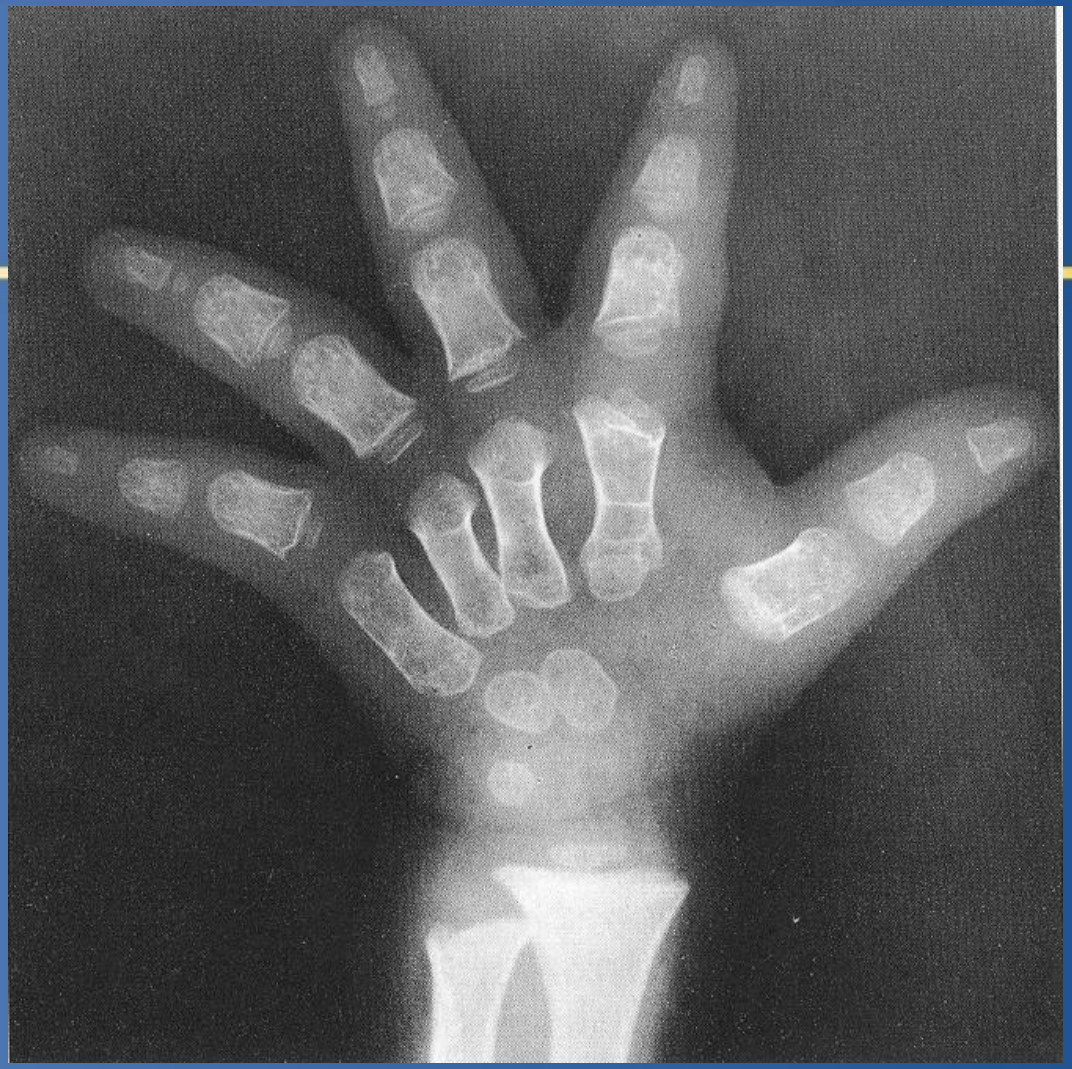


INTERPEDICULAR NARROWING

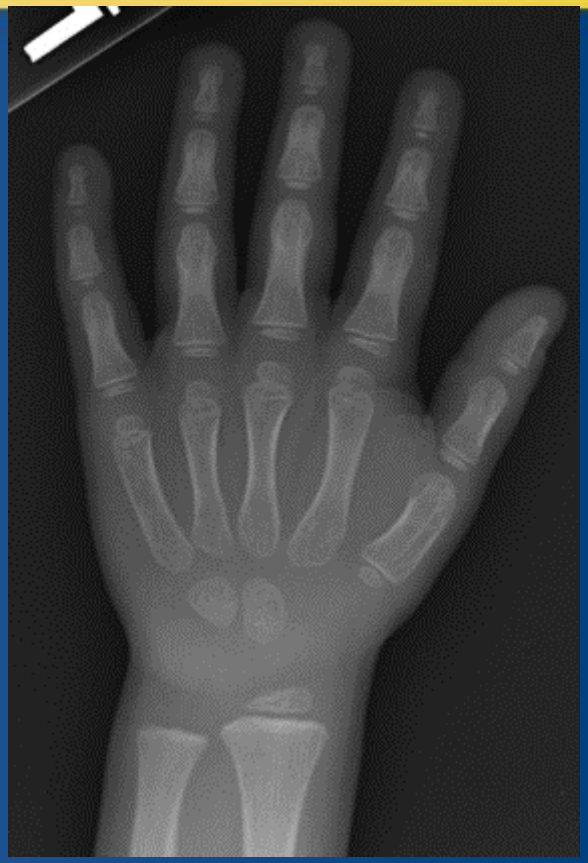
LUMBAR REGION

Average stature child





Average stature child

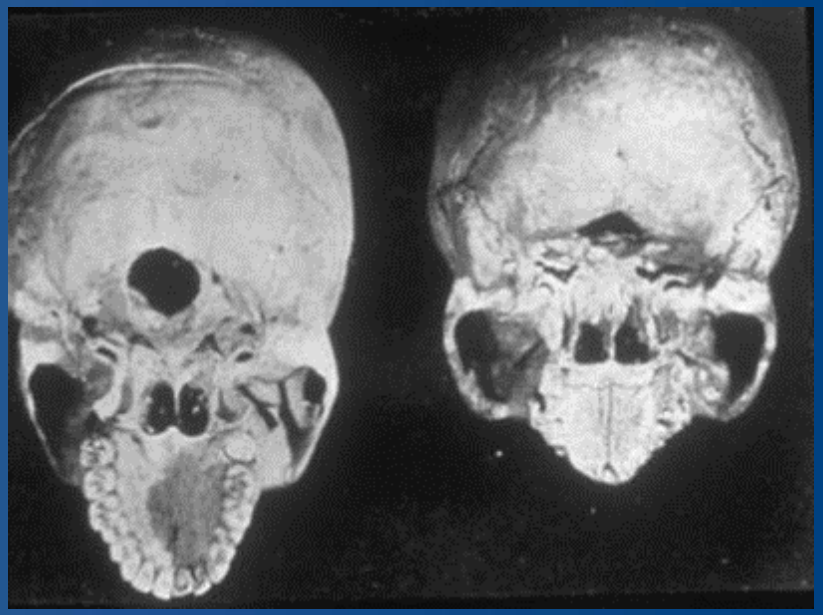


SHORT, BROAD CONE-SHAPED PROXIMAL AND MIDDLE PHALANGES

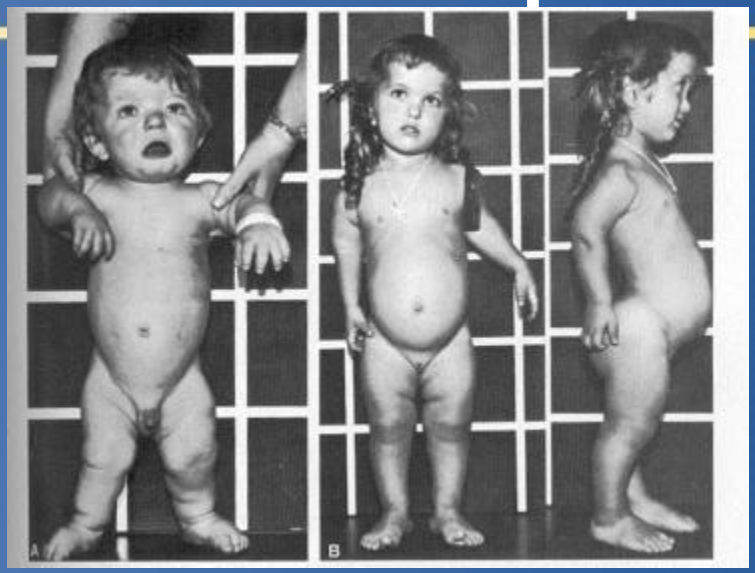
TRIDENT HAND DEFORMITY

Small foramen magnum in achondroplasia

- Cervicomedullary compression
- Central sleep apnea
- Hydrocephalus
- Long track signs (hyperreflexia, clonus, paresis)
  - *Monthly OFC on achondroplasia-specific curves, regular complete neurologic exam/developmental assessment*
  - *MRI, sleep study*



Other phenotypic features of achondroplasia



INCOMPLETE
ELBOW
EXTENSION

RHIZOMELIA

MID-FACE HYPOPLASIA

LUMBAR LORDOSIS

RELATIVE MACROCEPHALY

HYPOTONIA
JOINT LAXITY

ORTHOPAEDIC SURGERY

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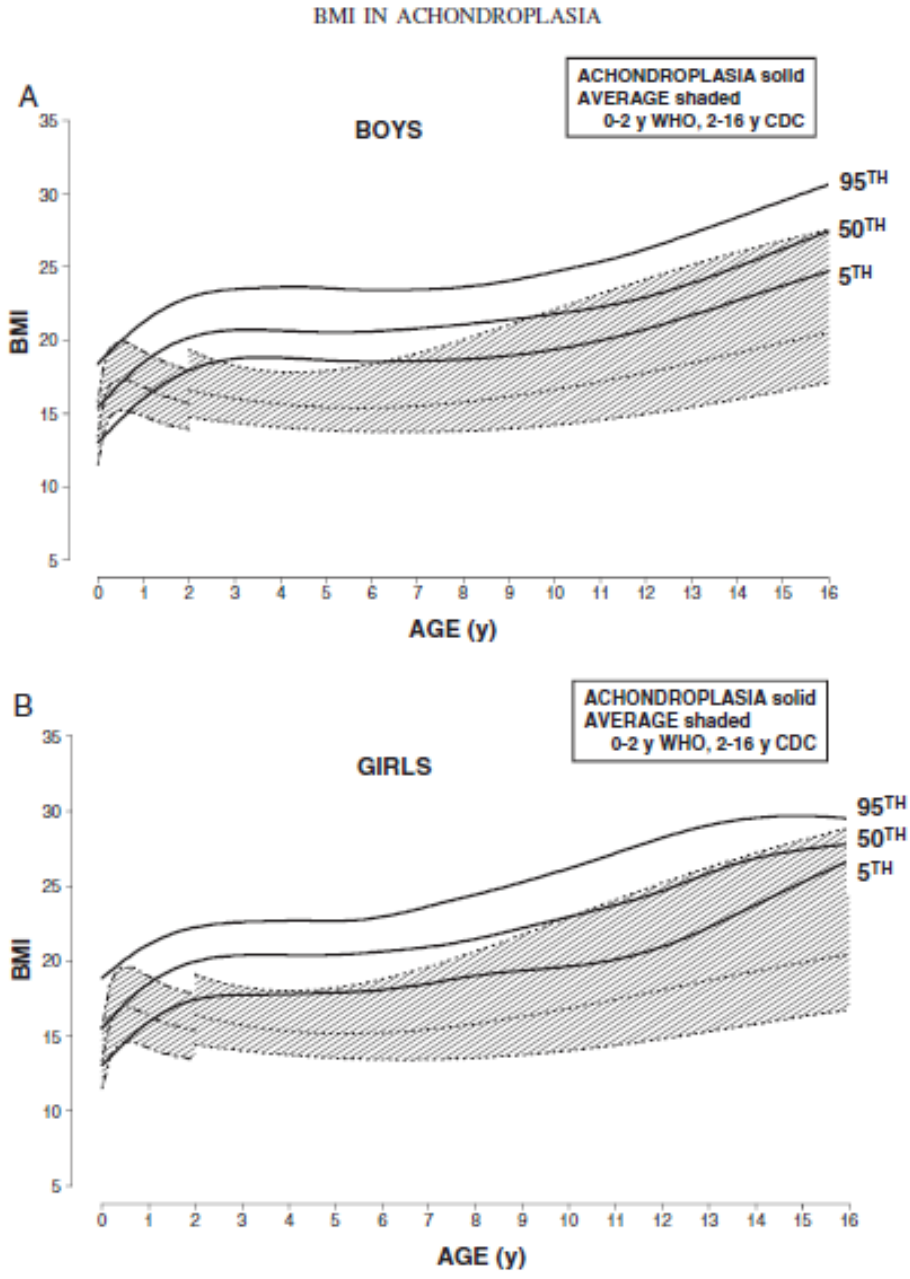
UNIQUE GROWTH FEATURES OF ACHONDROPLASIA

ORTHOPAEDIC SURGERY



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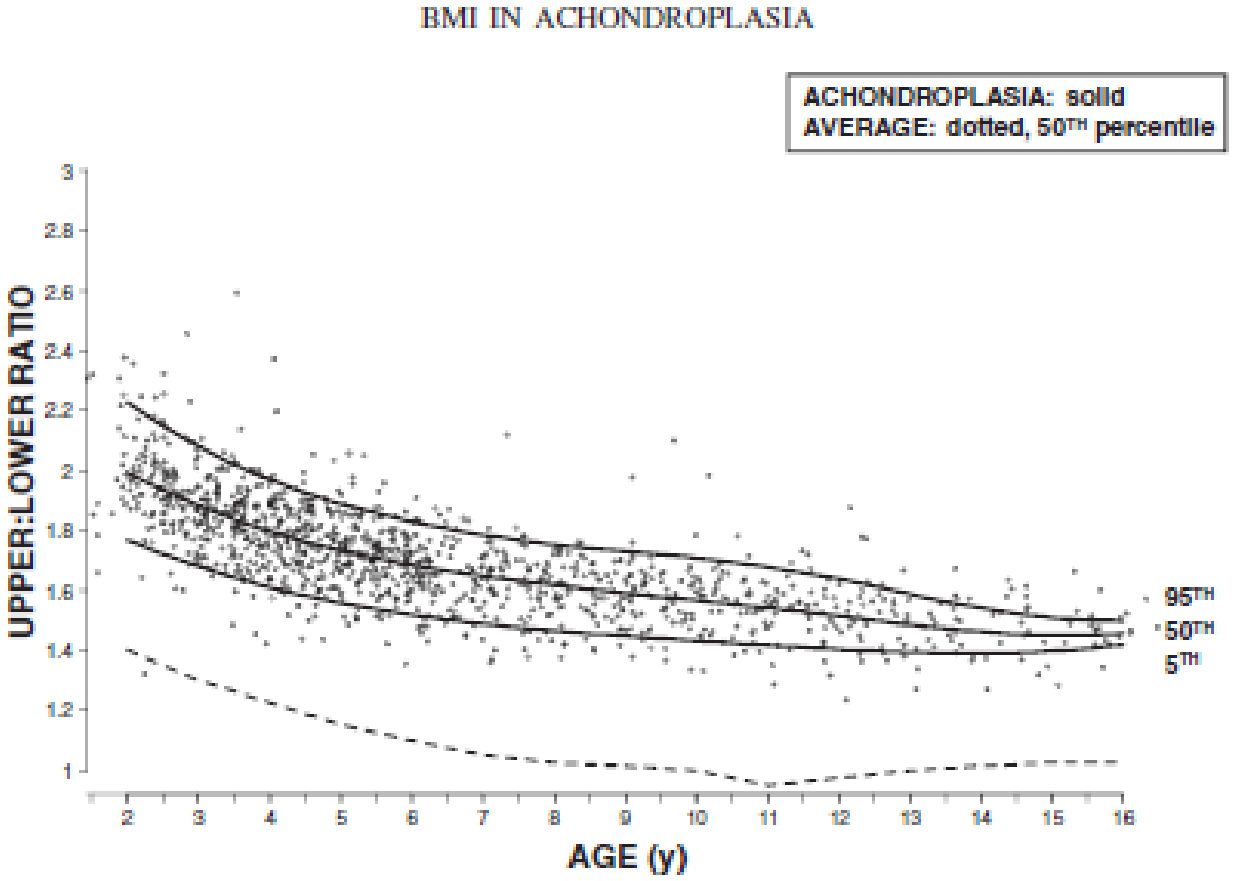
BMI FORMULA

USA $\text{BMI} = 703 \times \frac{\text{weight (lb)}}{\text{height}^2\ (\text{in}^2)}$

METRIC $\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2\ (\text{m}^2)}$

BMI is inaccurate surrogate for body fat without more research to define its correlation with body composition



Dramatic disproportion in upper segment: lower segment at all ages as compared to average stature

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Medical Complications, Treatment

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Achondroplasia- techniques

- Correct kyphosis only to “best bend”

Medical complications in achondroplasia

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- Recurrent otitis, chronic middle ear fluid
  - *Speech delay, hearing deficit*
  - *Screen with annual audiology*
  - *Refer to ENT*
  - *Placement of tubes*
  - ***Jugular bulb dehiscence = absence of roof over jugular bulb*

Medical complications in achondroplasia

- Narrow spinal canal, lordosis
  - *Nerve compression*
  - *Pain*
  - *Decreased endurance*
  - *Bowel/bladder incontinence*
  - *Inactivity cycles with overweight/obesity*
  - *Squatting, weight reduction, decompression*

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410-614-0977
Colleen Gioffreda, Program administrator
Julie Hoover-Fong, MD, PhD, Director

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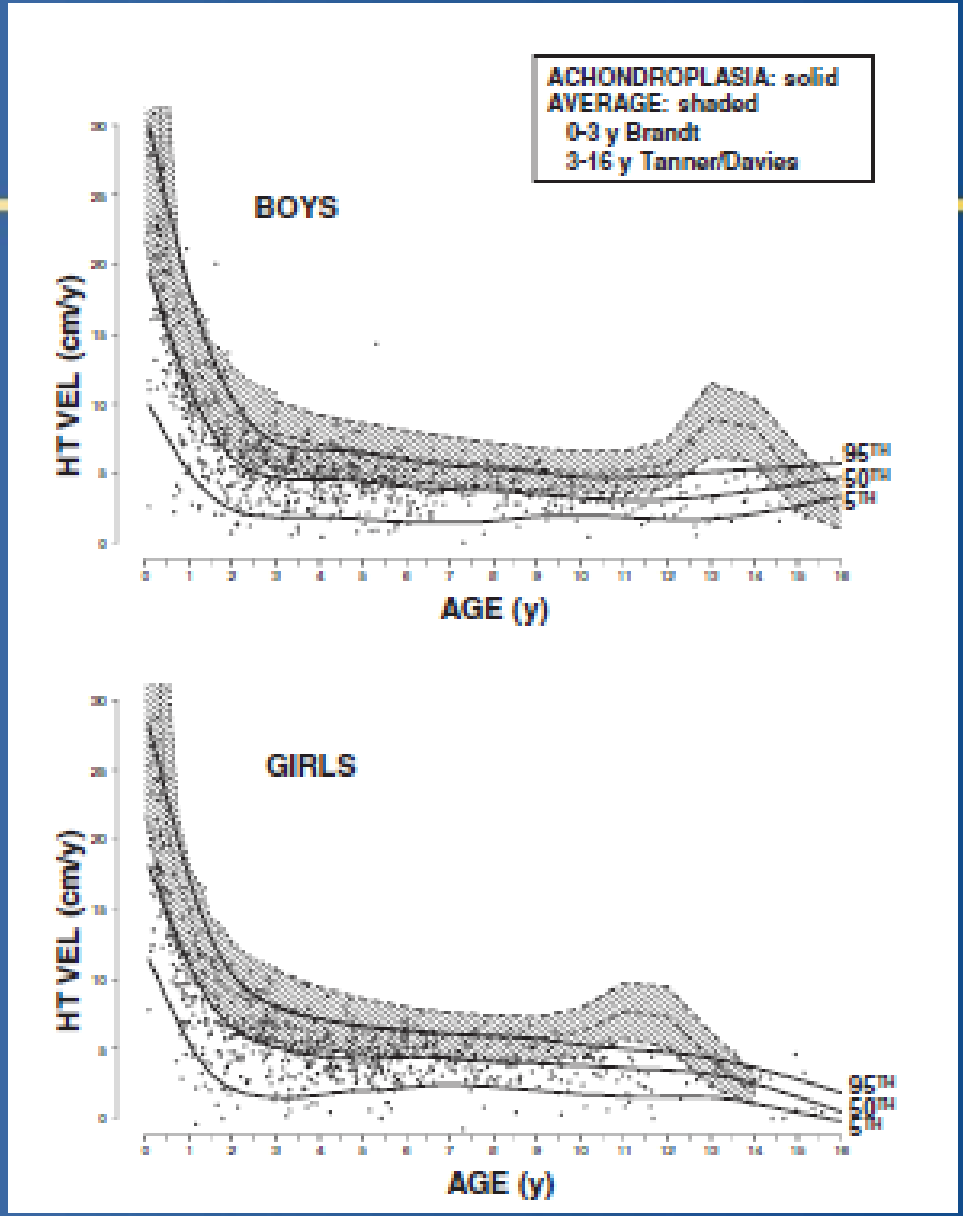
Skeletal Dysplasia Spine Summary

- Upper cervical instability in SED, Kneist, MPS
- Kyphosis in Achon, Larsen, Diastrophic (resolving?)
- Scoliosis in SED, Metatropic
- Stenosis: Achon, r.chondrodysplasia punctata



No pubertal growth spurt in achondroplasia

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Achondroplasia Spine Cases

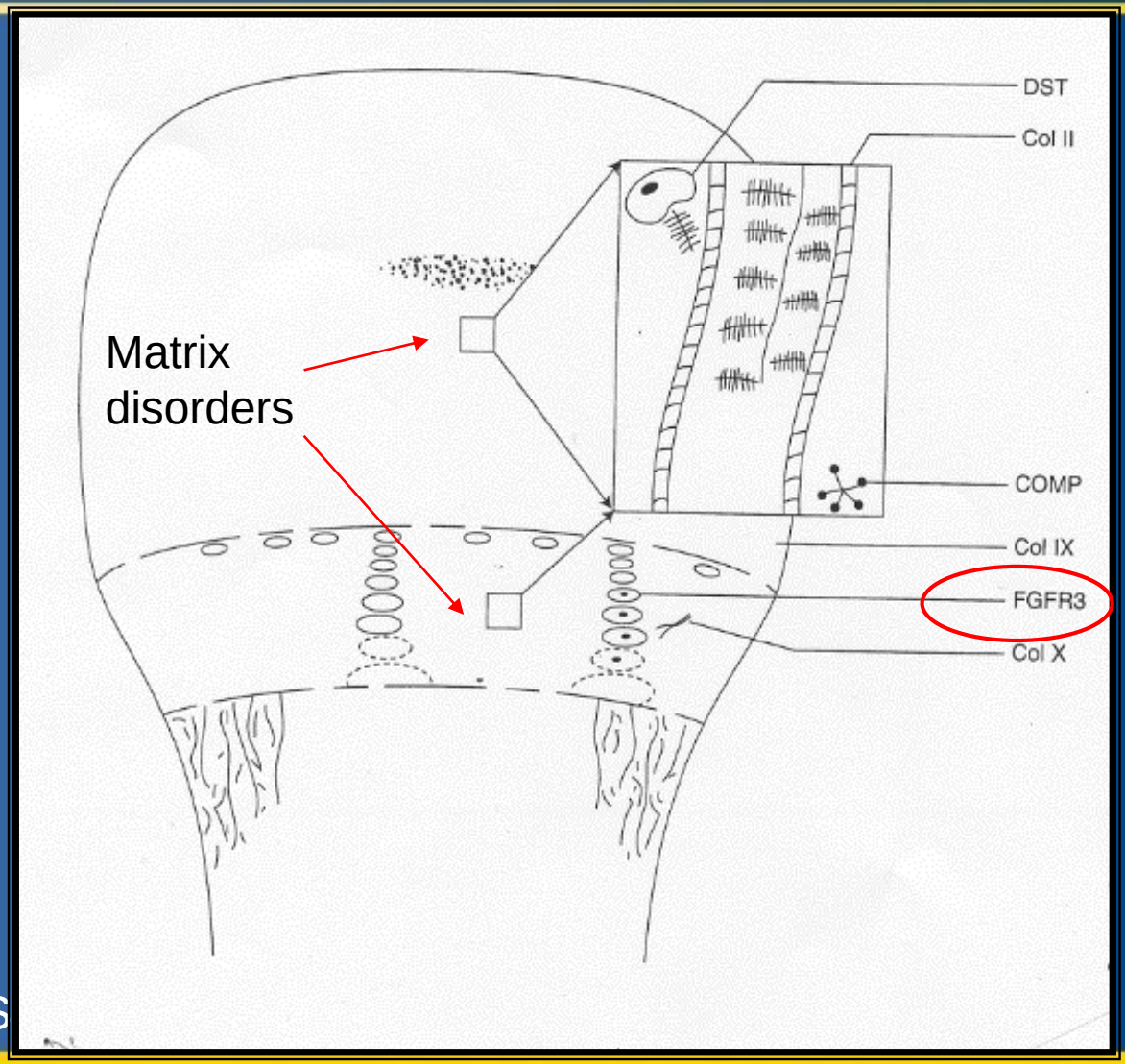
John E. Herzenberg
IPOS

BAD TO THE BONE: CHALLENGES IN TREATING DYSPLASIA AND GENETIC SYNDROMES

November 30, 2017 4:05

ORTHOPAEDIC SURGERY

Known Cartilage Defects



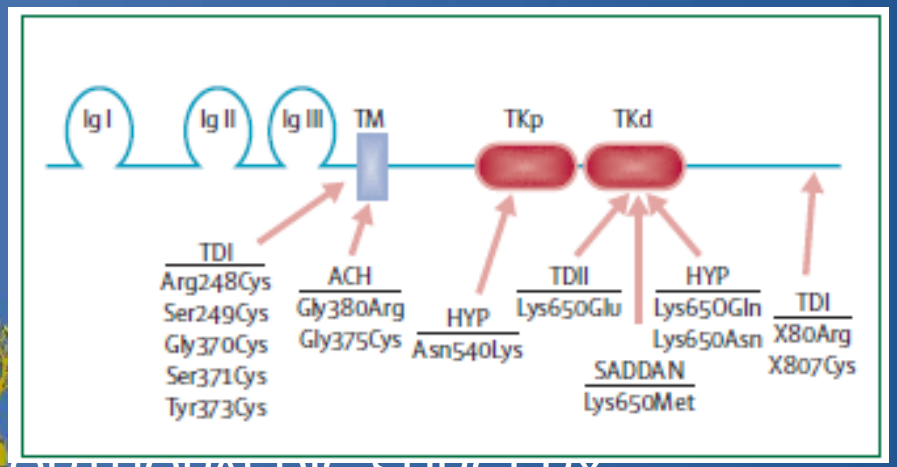
No significant effect on matrix

Additional comments about achondroplasia

- Average adult height: male = 51”, female = 48”
- Growth hormone- no significant improvement
- Limb lengthening
- Obesity
- Hypertension

Achondroplasia

- *FGFR3* encodes 1 of 4 FGF receptors
- All FGF receptors have:
  - *Extracellular ligand-binding domain*
  - *Transmembrane domain*
  - *Intracellular domains*

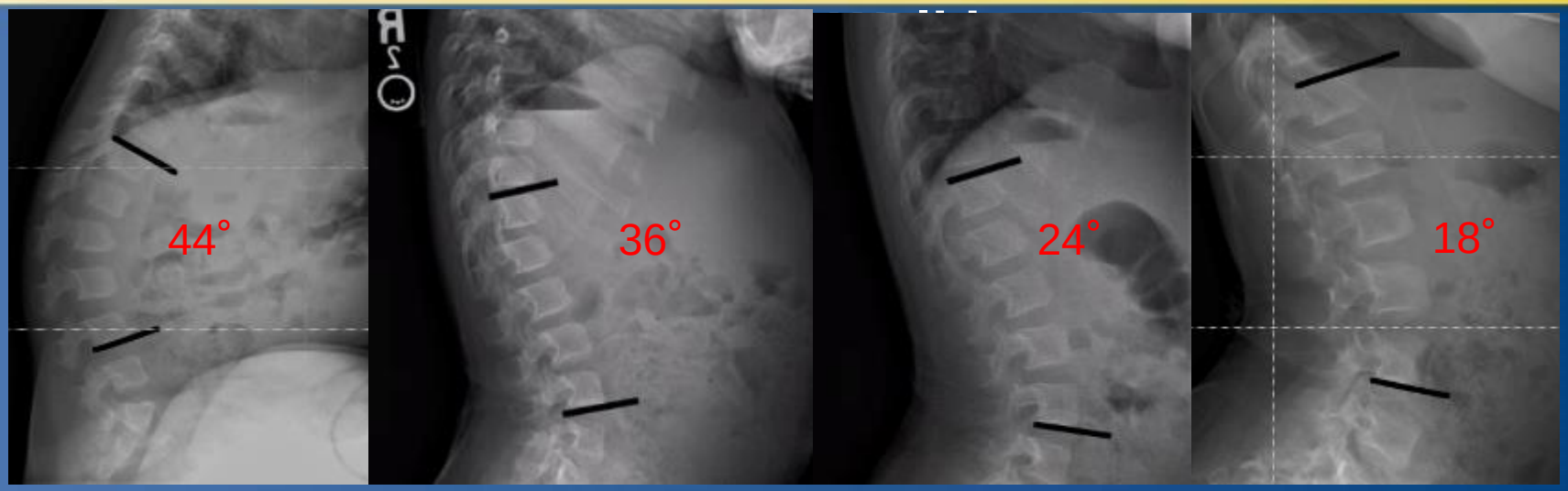


TDI = thanatophoric dysplasia type 1
ACH = achondroplasia
HYP = hypochondroplasia
TDII = thanatophoric dysplasia type 2
SADDAN = severe achondroplasia
developmental delay acanthosis nigricans

Skeletal Findings in Achondroplasia

- Rhizomelia
  - *Hindered reach*
  - *Adaptive equipment*
- Thoracolumbar kyphosis
  - *Often resolves spontaneously*
  - *Monitor*
- Genu varus, tibial bowing
  - *Pain*
  - *Monitor closely early, osteotomies*

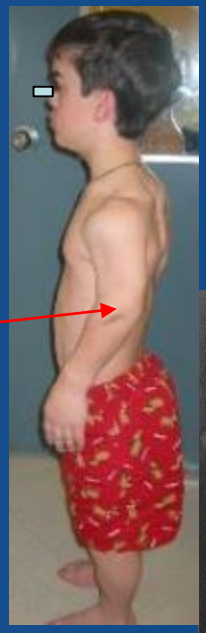
1. TLK in relation to walking age

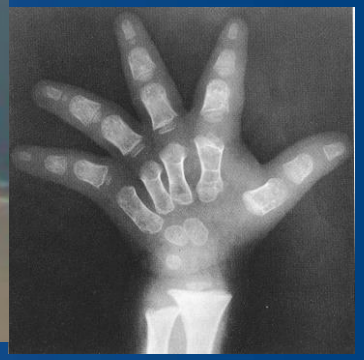


Presentation	Walking age	1 yr after walking age	Final FU
Mean: 11 mo.	Mean: 21 mo.	Mean: 33 mo.	Mean: 7 y/o
• 100% TLK	• 15% resolved	• 58% resolved	• 70% resolved

Other Clinical Features of Ach

- Midface hypoplasia / relative macrocephaly
- Rhizomelia
- Hypotonia, joint laxity
- Elbow flexion contractures
  - *No significant effect on function*
- Trident hand
- Increased lumbar lordosis- worsens stenosis





Associated Clinical Parameters

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Odds of Clinical Factors Predicting Thoracolumbar Kyphosis in 60 Patients With Achondroplasia

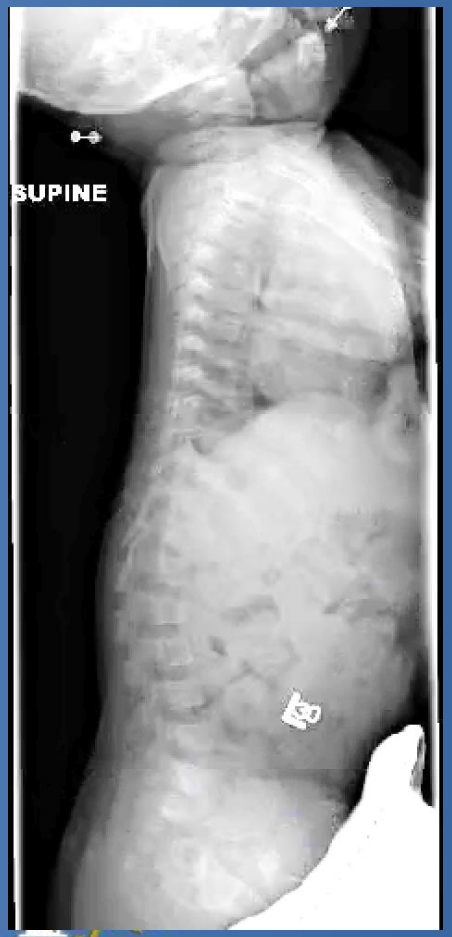
	Multivariate Model		
Variables	OR	95% CI	P
Developmental motor delay			
	4	**1.05-15.11**	**0.043**
Foramen magnum decompression			
	1.64	0.42-6.45	0.476
Hydrocephalus			
	2.45	0.39-15.15	0.337
Female			
	1.59	0.43-5.85	0.485
Ventriculoperitoneal Shunt			
	0.63	0.04-9.58	0.739

CONCLUSION

- Most pts with TLK ≥ 20° improve after 1 year of walking age (58%)
- TLK 20-40° → non-surgical management
- TLK ≥40 ° or symptomatic → decompression and PSF

- Apical vertebral wedging for height and apical translation is associated with persistent TLK
- Developmental motor delay is associated with persistent TLK

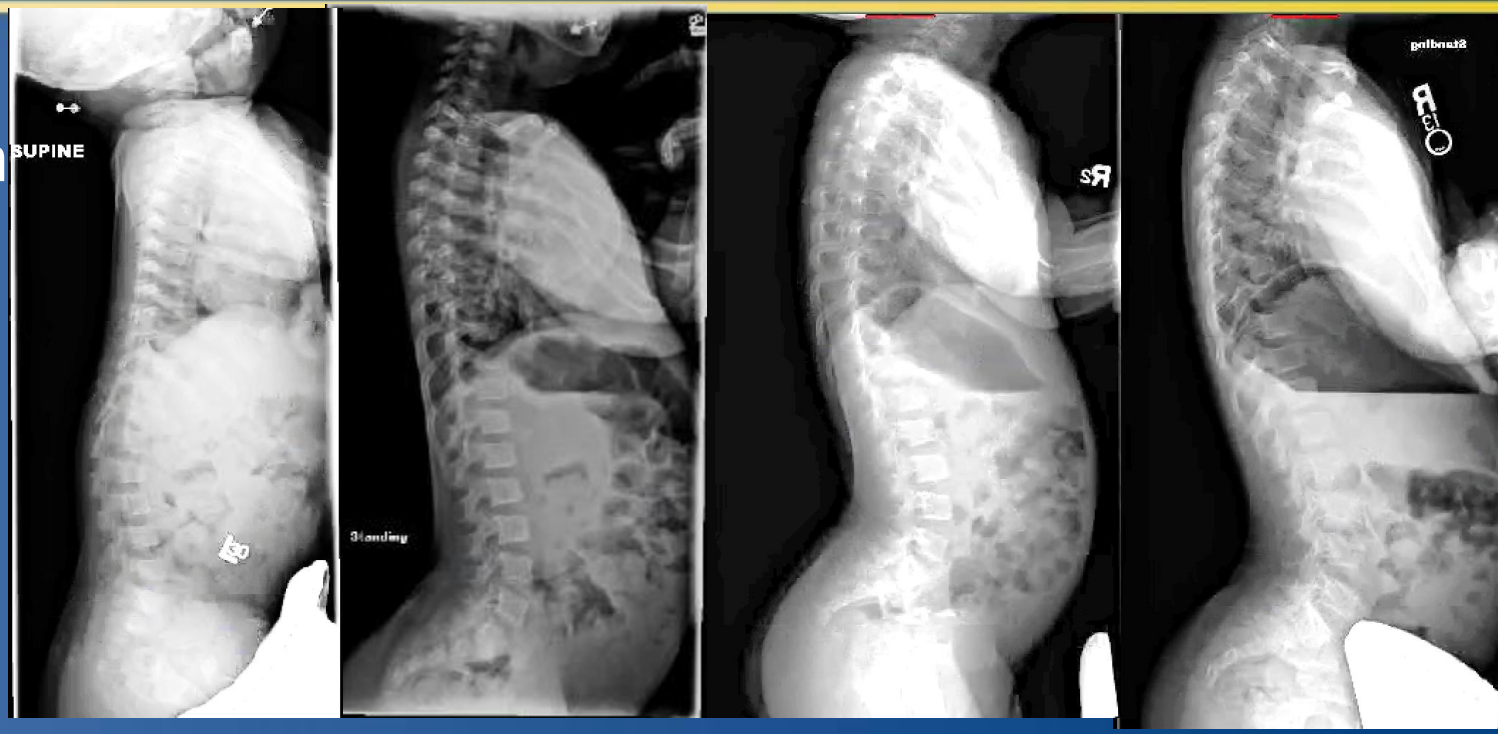
Case 1 – improvement



- 14 month old
- Sat 9 months
- Not yet walking
- Kyphosis 33 degrees supine
- Discussion:
  - *Is this a hemivertebra?*
  - *What workup for non-ambulation?*
  - *Rx for Kyphosis:*
    - restrict sitting, brace, cast?

Case 1 –Follow up

- Walked 15m
- No brace
- Neuro Nl.



14 months | 2 years | 3 years | 6 years

Case 2 Summary

- 2001, decompression/laminectomy from L1 to L5 to relieve a lumbosacral stenosis
- fused T12 through S1 with rods and hardware fixation.
- 11/27/01, there was skin breakdown over the hardware with a dark eschar
  - *covered by a rhomboid flap*
- 11/29/06 revision and fusion of T-12 to T-8.