Campomelic Dysplasia:

Medical Treatment, Musculoskeletal Management, and Mistakes Not to Make

12th International Congress on

Early Onset Scoliosis

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Washington, DC

Children's National

DISCLOSURES

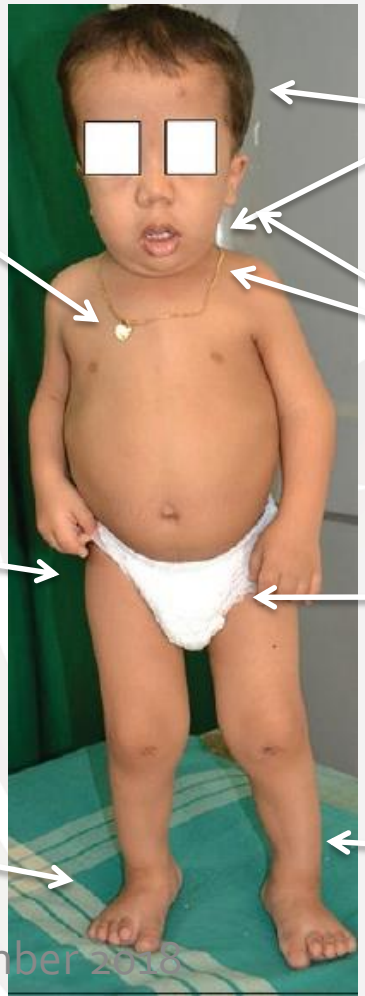
- No financial disclosures
- No conflicts of interest related to this talk

WHAT DOES IT MEAN – "CAMPOMELIC"

- Campto
  - Greek
  - Kamptos – flexible, base of "kamp-" meaning to bend of curve
- Melia
  - Greek
  - Denotes a condition of the limb
- Campomelic
  - "Bent limb"

CLINICAL DIAGNOSIS

- Based on clinical features
  - No single clinical finding is obligatory
  - Short, bowed limbs are classic (LE>UE)



Respiratory Distress

Large Head
Pierre Robin Sequence

Flat Face
Laryngotracheomalaica

Dislocatable hips

Unambiguous genitalia

Clubfeet

Bowed limbs

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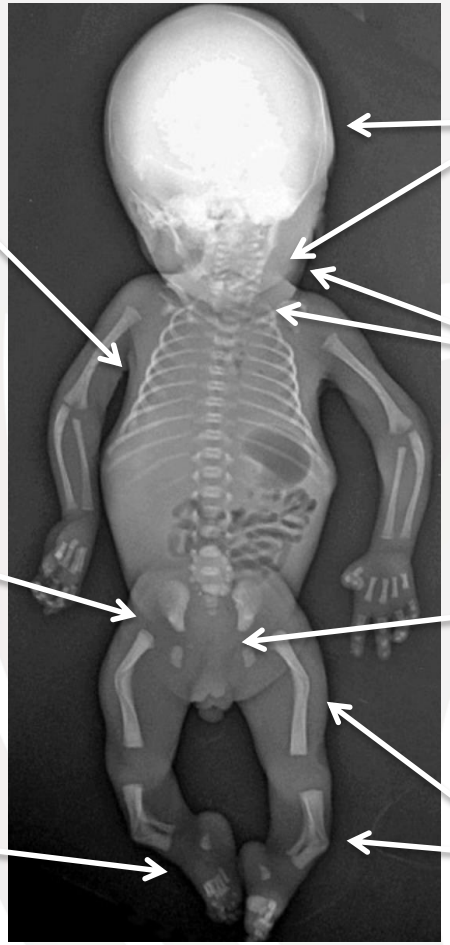

Respiratory Distress

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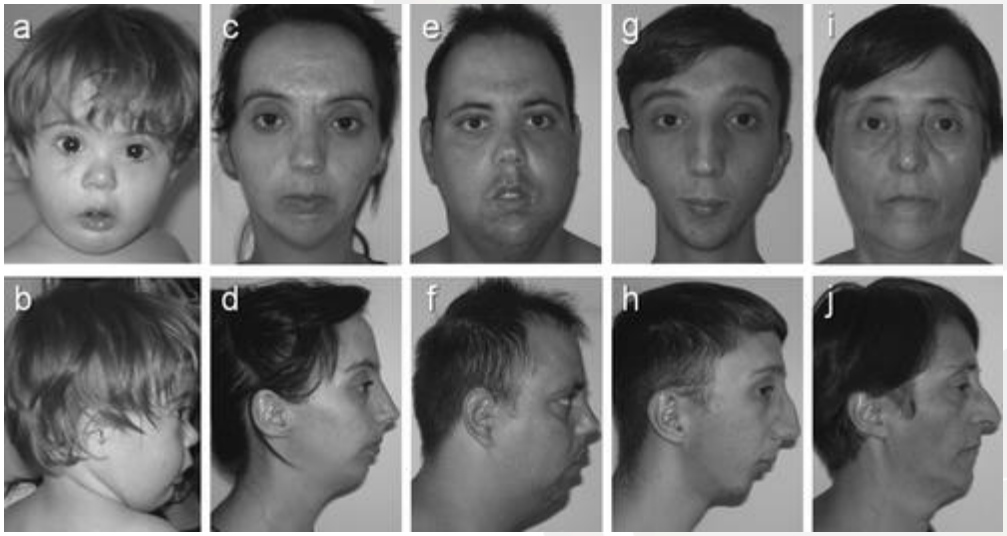
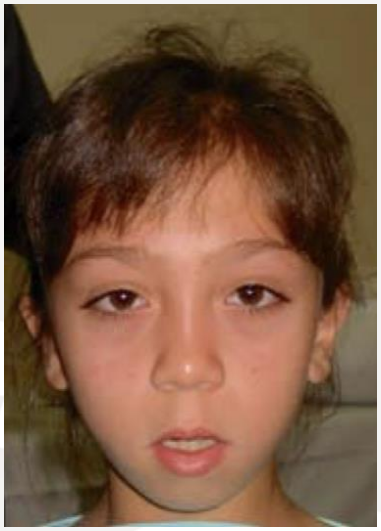
Clubfeet

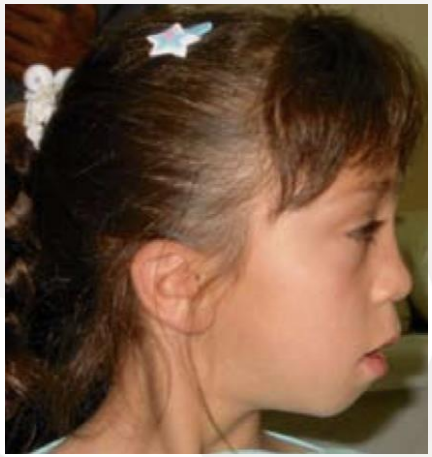
Bowed limbs

FACIAL DYSMORPHOLOGY

- Triangular long face, prominent nose, microstomia, and retrognathia

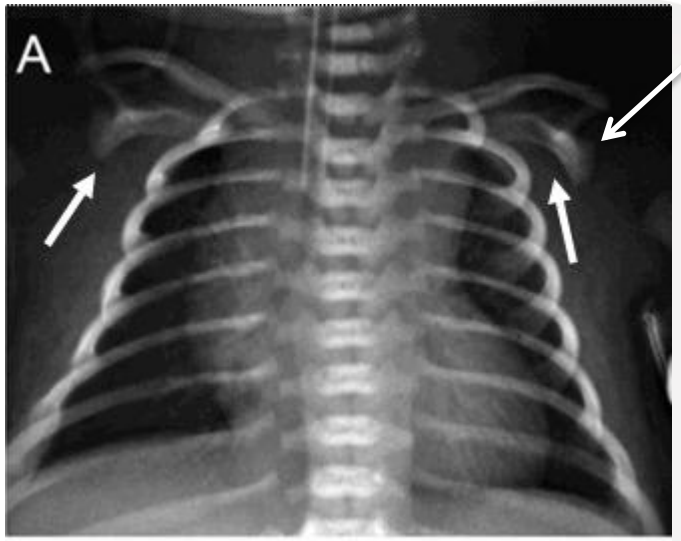




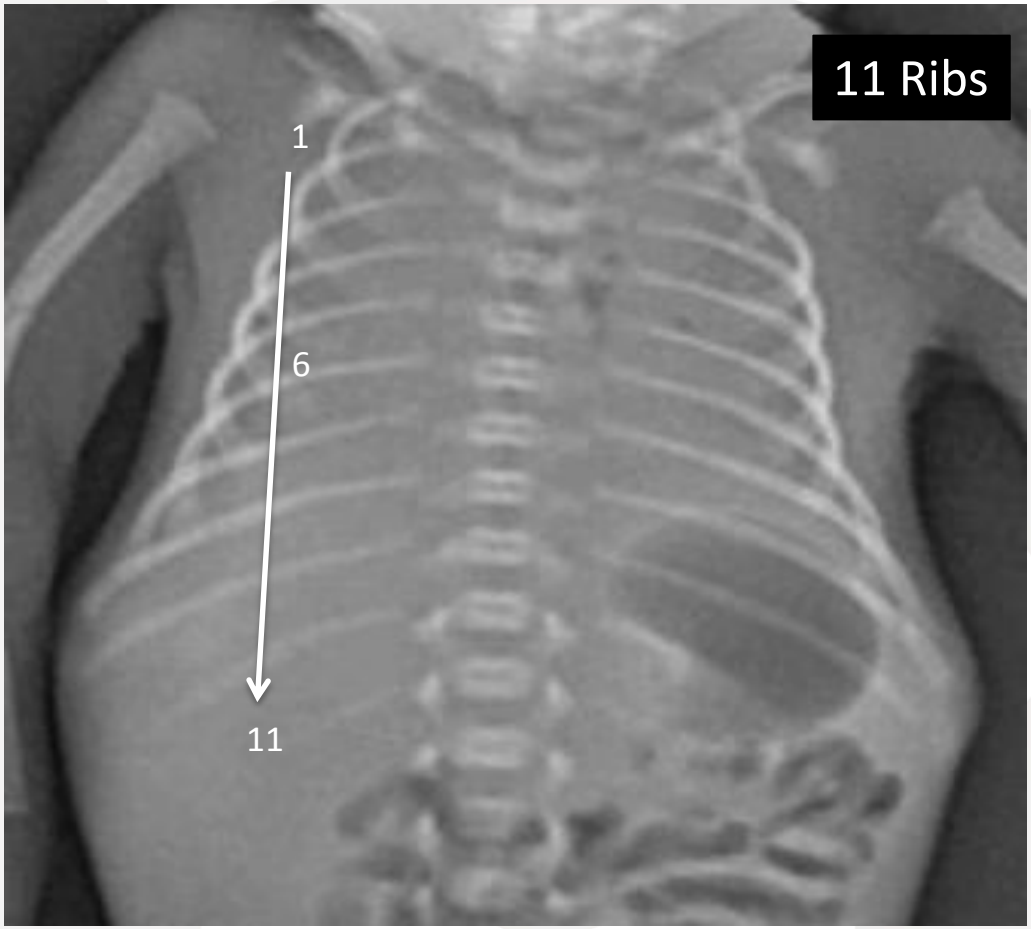


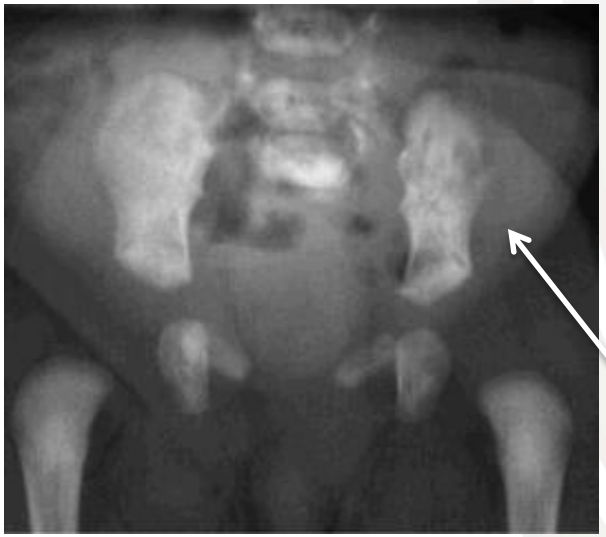
Castori M, et al. Variability in a three-generation family with Pierre Robin sequence, acampomelic campomelic dysplasia, and intellectual disability due to a novel ~1 Mb deletion upstream of SOX9, and including KCNJ2 and KCNJ16. Birth Defects Res A Clin Mol Teratol. 2016 Jan;106(1):61-8.

RADIOGRAPHIC FINDINGS



Scapular Hypoplasia





Vertically oriented Iliac wings

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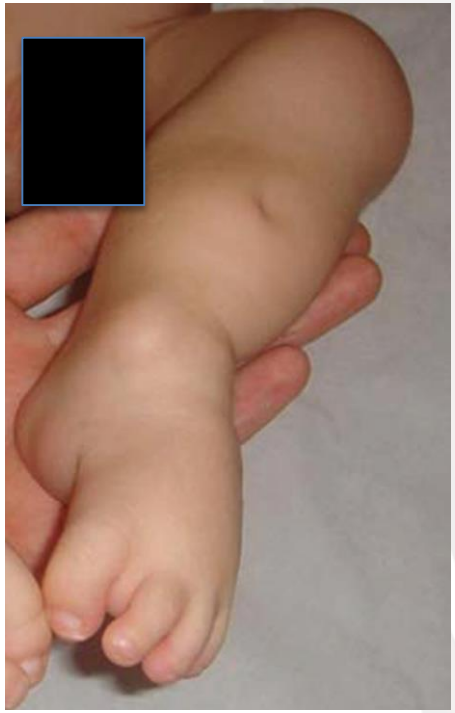
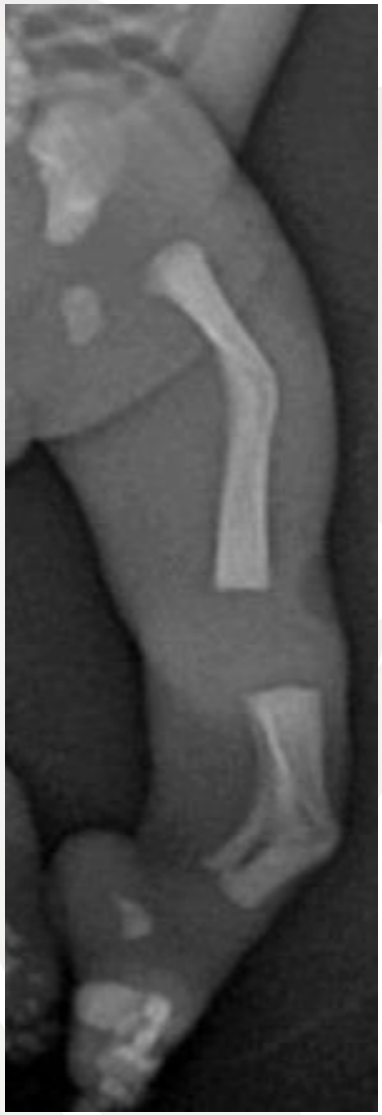
RADIOGRAPHIC FINDINGS

Limbs

- Bent - Not Always!
- Pre-tibial dimpling



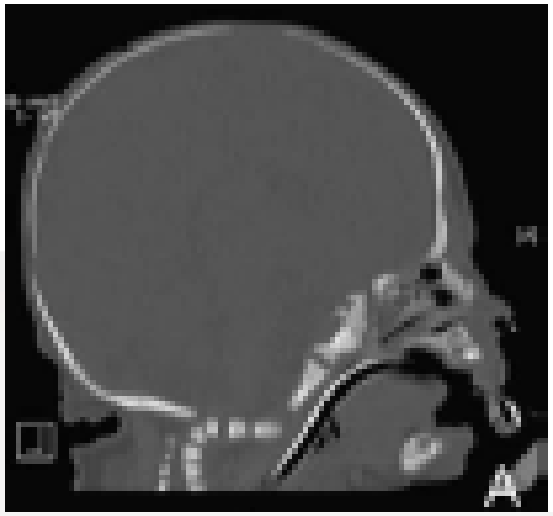


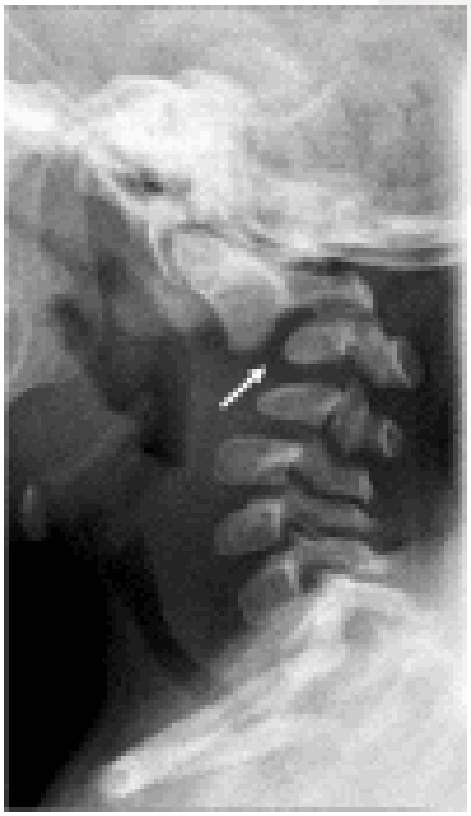
Acampomelic
Campomelic Dysplasia

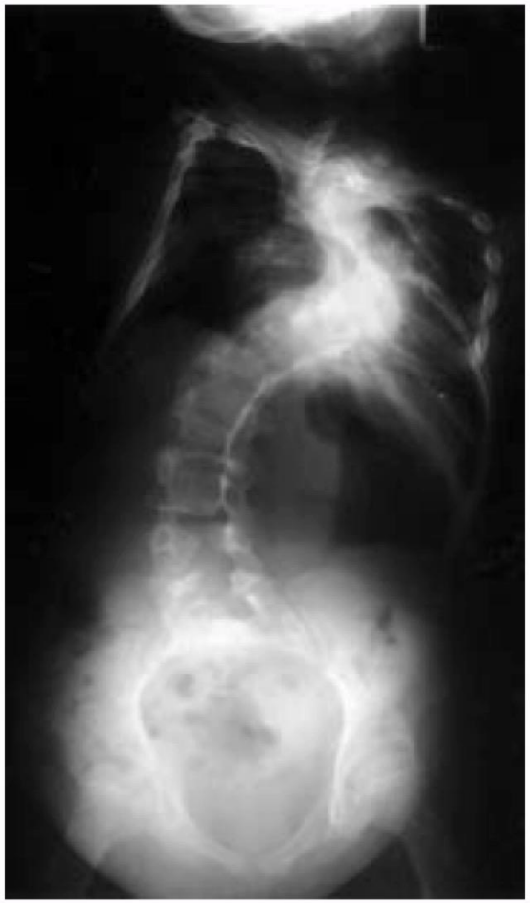
RADIOGRAPHIC FINDINGS

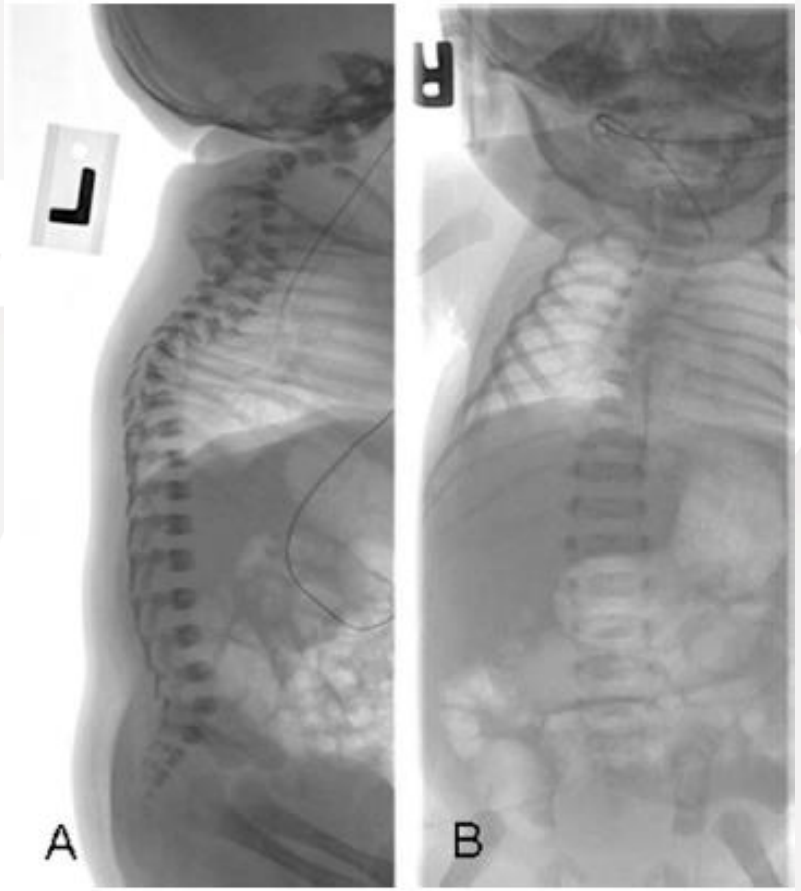
Spine

- Cervical spine deformity
- Kyphoscoliosis

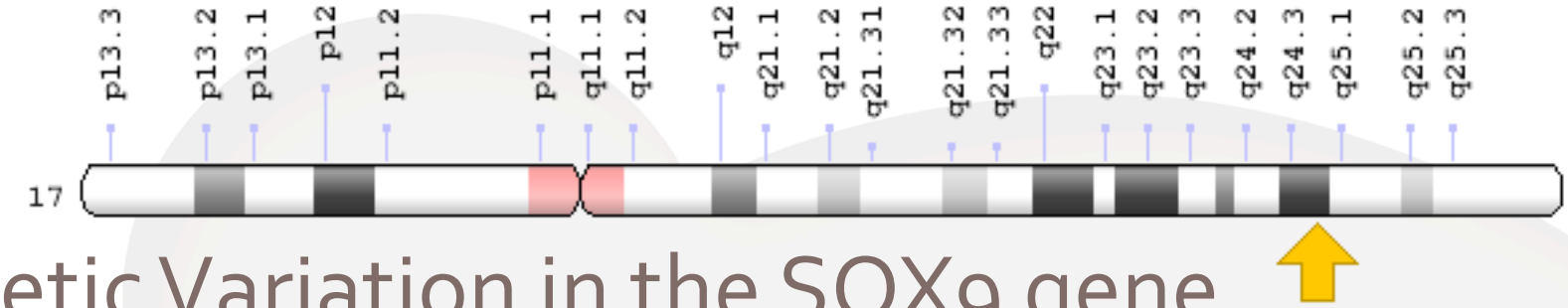








GENETIC PATHOLOGY



- Genetic Variation in the SOX9 gene
  - Found on Chromosome 17, q arm
- Encodes for SOX9 protein
  - Binds to DNA and regulates skeletal development and sex determination
- Genetic Variations
  - ~ 90% sequence variations (missence, splice variations)
  - ~5% chromosomal translocations
  - ~2% whole/partial gene deletion

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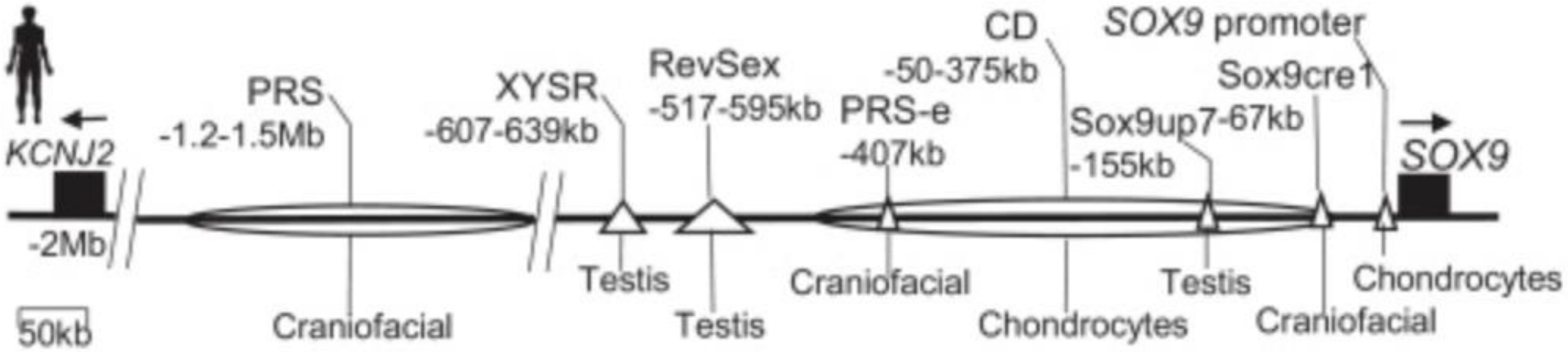
GENETIC PATHOLOGY



- Location of mutation leads to phenotype
  - Coding vs regulatory regions

GENETIC PATHOLOGY

- Prevalence
  - 1:40,000-80,000
  - ~15 case reports of living patients in the literature
- Penetrance
  - 100%
- Inheritance
  - Autosomal dominant
  - Most cases are *de novo* genetic variants
  - Some cases of mosaicism – can affect inheritance

DIFFERENTIAL DIAGNOSIS

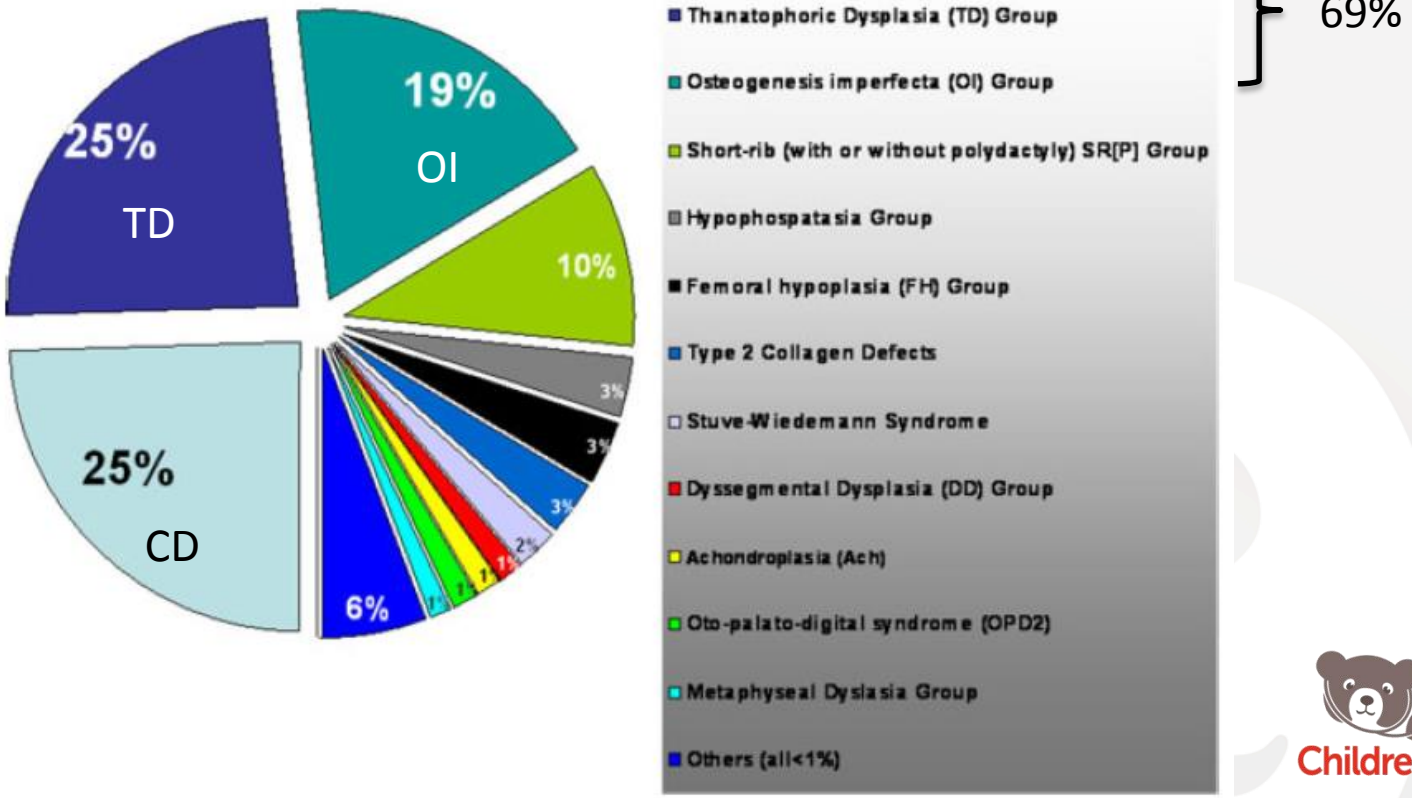
- Severe OI – type 2,3
- Hypophosphatasia
- Cartilage Hair Hypoplasia
- Thanatophoric Dysplasia
- SED, congenita
- Stickler's Syndrome (similar facial features)

DIFFERENTIAL DIAGNOSIS – PRENATAL BENT FEMURS

Angulated Femurs and the Skeletal Dysplasias:
Experience of the International Skeletal Dysplasia Registry (1988–2006)

American Journal of Medical Genetics Part A 143A:1159–1168 (2007)

- > 40 disorders can be associated with bent femurs
- 459 cases reviewed



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GENETIC COUNSELING

- AD - 50% chance of inheritance
- *De novo* case
  - *Test parents for mosaicism*
- Many newborns die in neonate period
  - Respiratory compromise
- Variably affected intelligence
- Short stature
- Hearing loss, aggressive scoliosis

TREATMENT

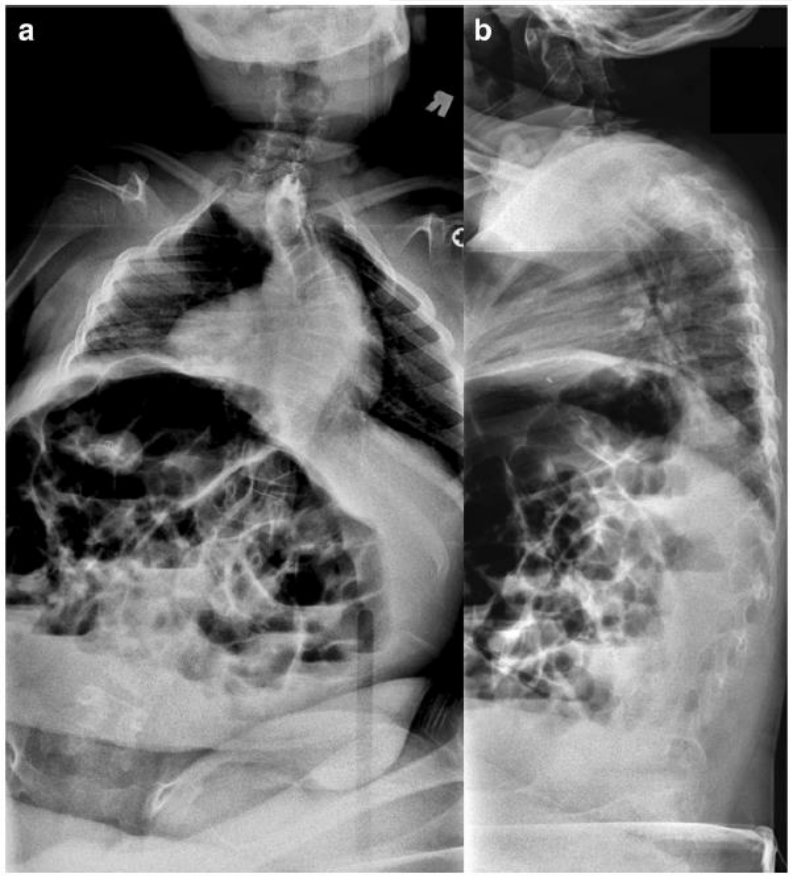
- Airway Considerations
  1. Cleft Palate
  2. Laryngotracheomalacia / Pierre Robin Sequence
- Genitourinary
  1. Can have XY karyotype and female genitalia
  2. Recommend gonadectomy due to risk of gonadoblastoma
- General Orthopaedics
  1. Clubfoot casting
  2. Hip dysplasia per routine

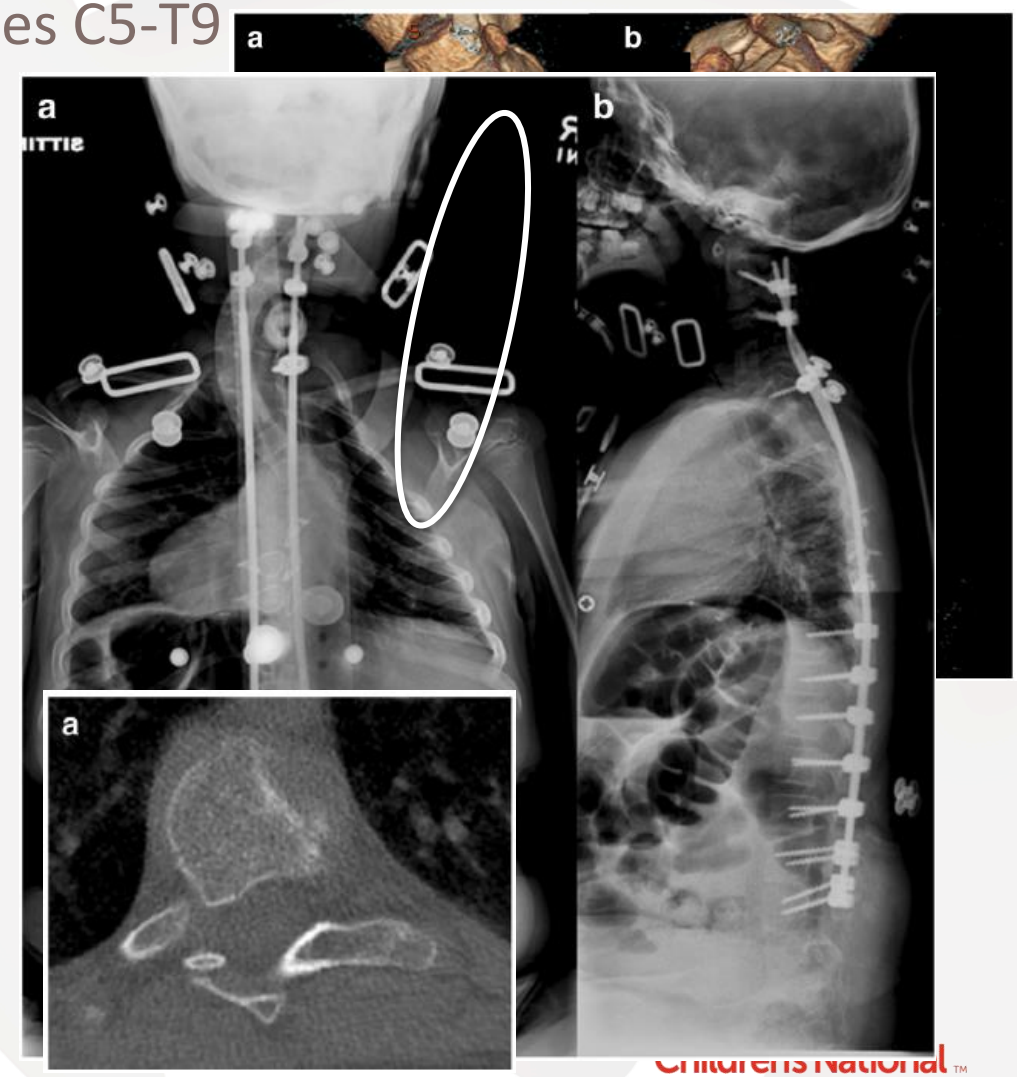
TREATMENT

- Cervical Spine
  1. Early assessment necessary
  2. Bracing/early fusion may be needed
- Spinal deformity
  1. Progressive kyphoscoliosis – cervico-thoracic apex
  2. Bracing difficult
  3. Variable congenital abnormalities
- Respiratory Compromise
  1. Chest typically ok
  2. Airway instability
  3. Neurologic – c-spine instability/deformity

WHAT NOT TO MISS – CONGENITAL SPINAL DEFORMITIES

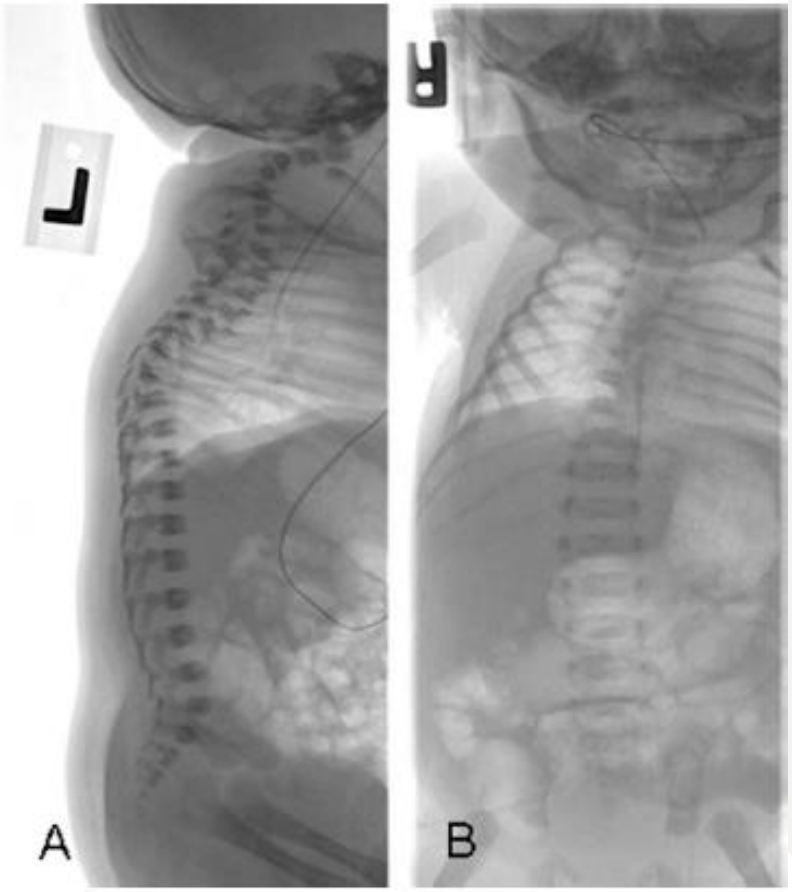
- 10 yo girl with CD and severe progressive scoliosis
- Congenital absence of pedicles C5-T9

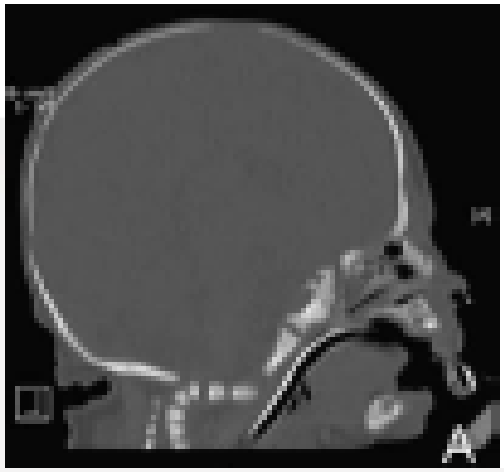


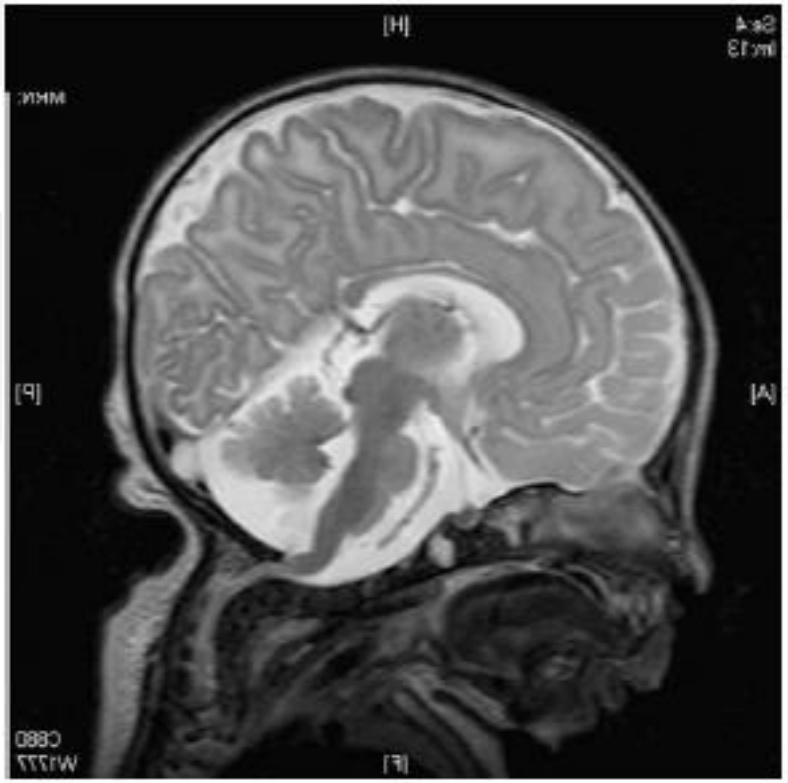


WHAT NOT TO MISS – SEVERE CERVICAL ABNORMALITY

- Intubated after birth for apnea
- CTO brace attempted, but support withdrawn

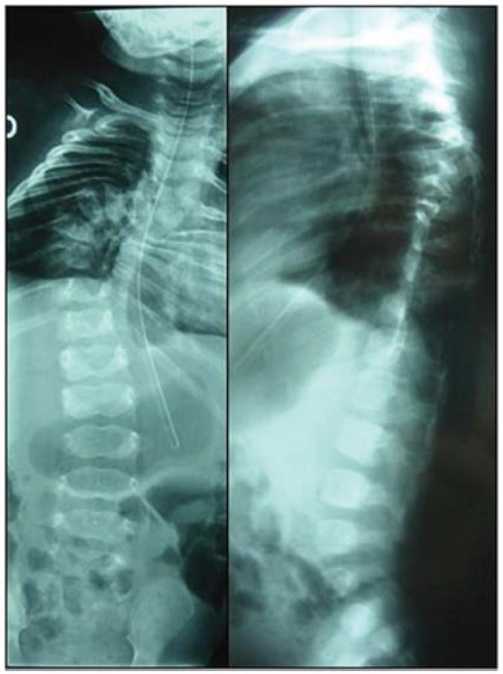


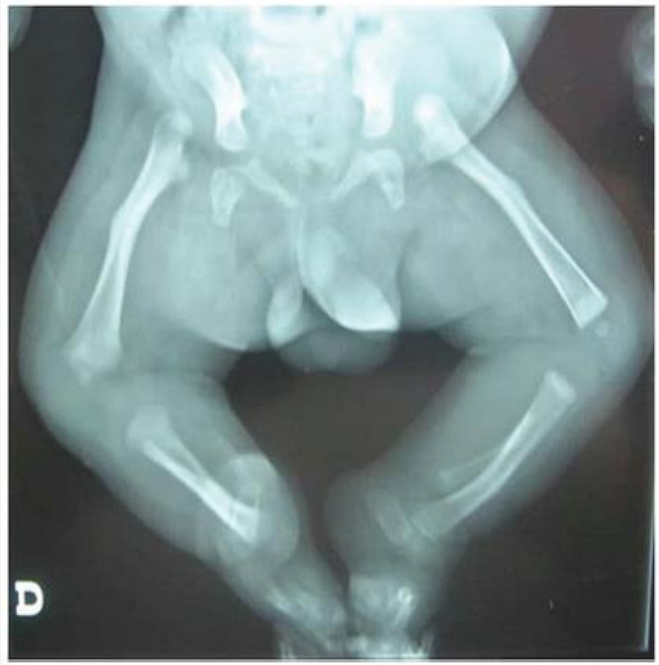




WHAT NOT TO MISS – MALIGNANT HYPERTHERMIA

- 16 month old boy with CD and significant medical issues
  - CHD, lung hypoplasia, skeletal pattern c/w CD
- Presented with severe respiratory compromise c/w malignant hyperthermia (prolonged fever, hypercarbia, elevated CK)
- Delayed diagnosis → cardiopulmonary arrest

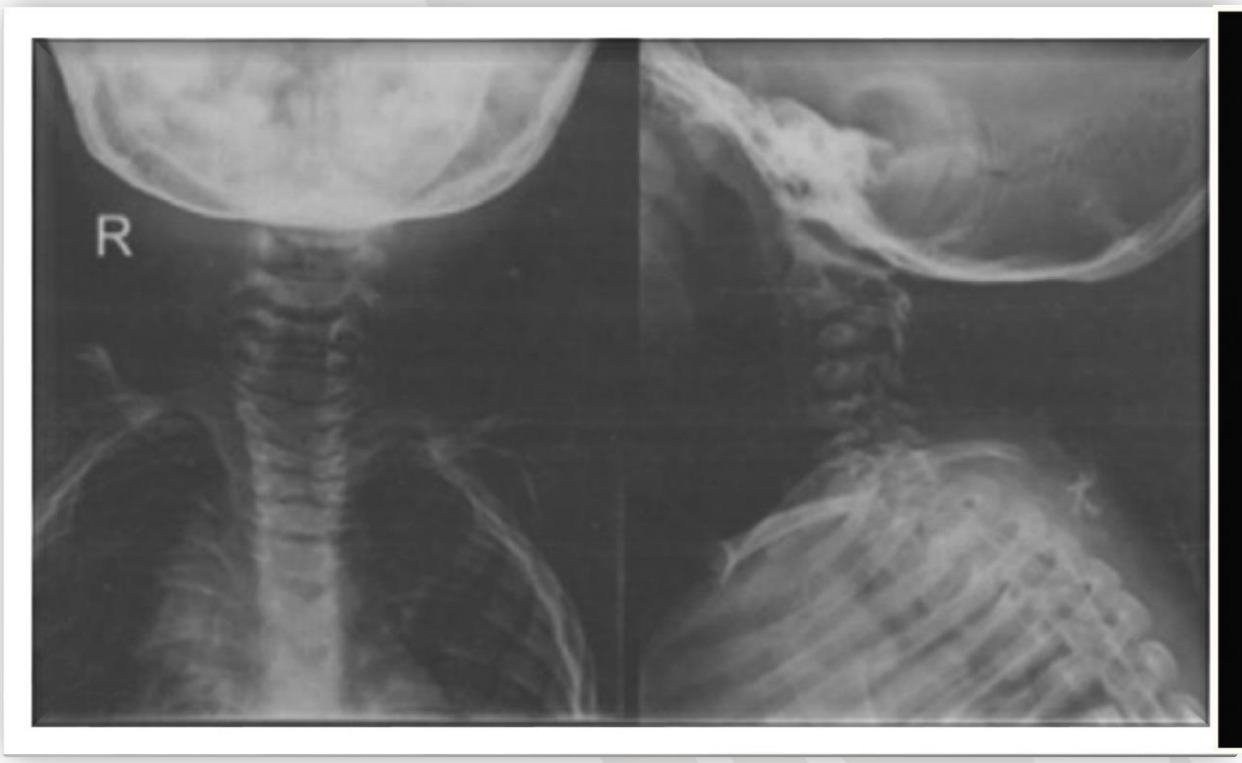


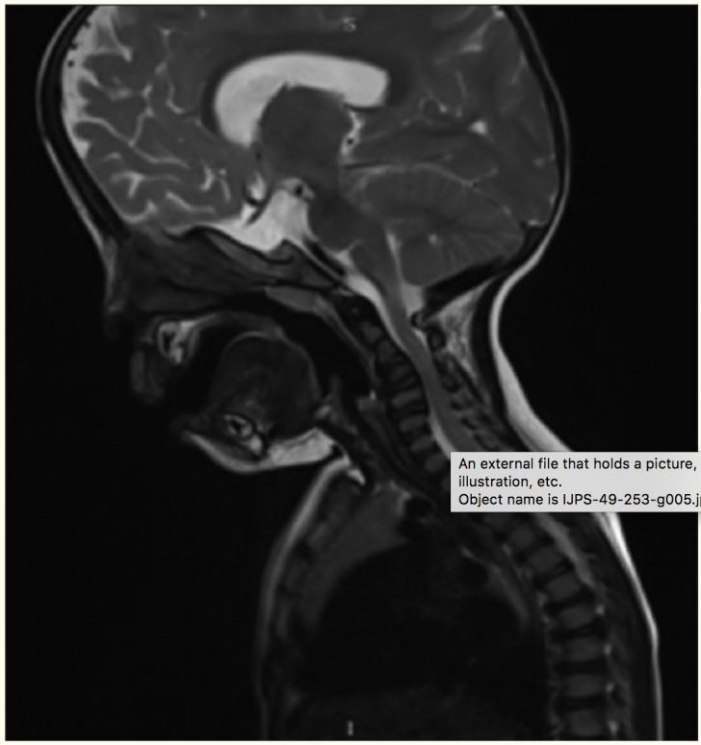


CLEFT PALATE REPAIR – C SPINE ABNL

- 18 mn old – evaluated for cleft palate repair
- Xray and MRI showed dysplastic upper c spine and stenosis
- Intubated with little neck flexion, head stabilized during surgery

neck extension avoided





The phenotype of survivors of campomelic dysplasia

S Mansour, A C Offiah, S McDowall, P Sim, J Tolmie, C Hall

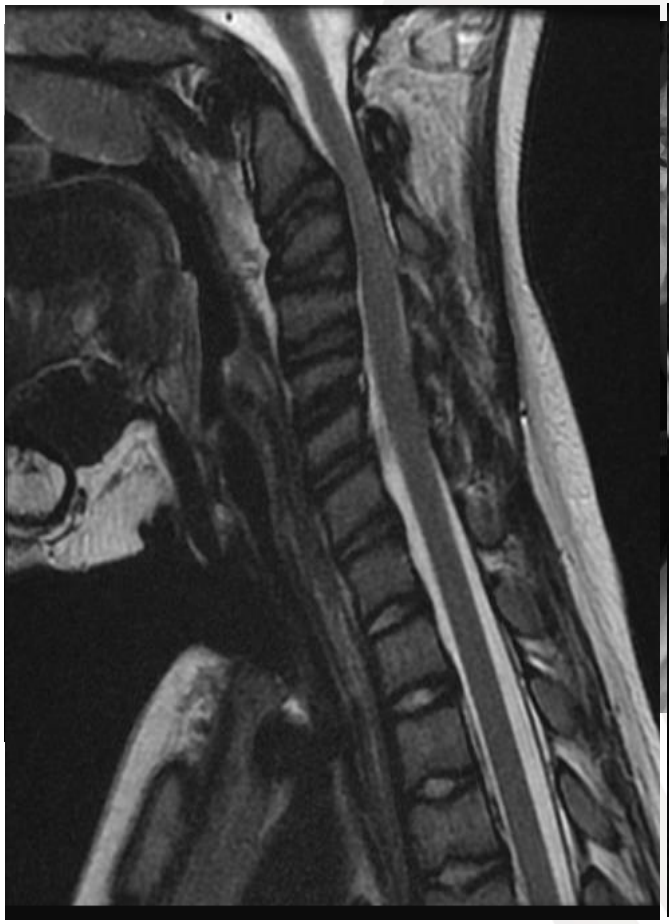
J Med Genet 2002;**39**:597–602

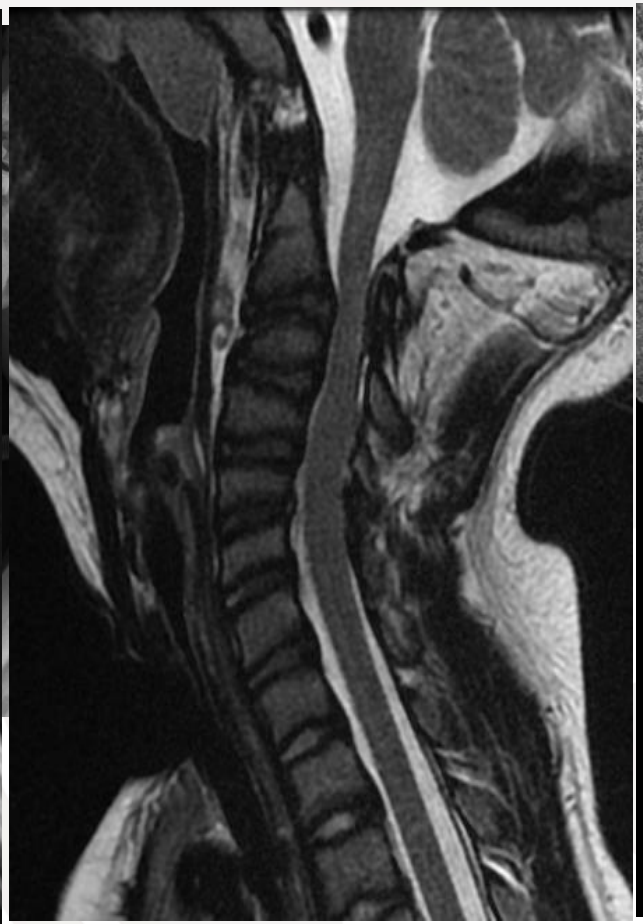
Table 1 A comparison of the clinical facial features and complications in the five patients presented

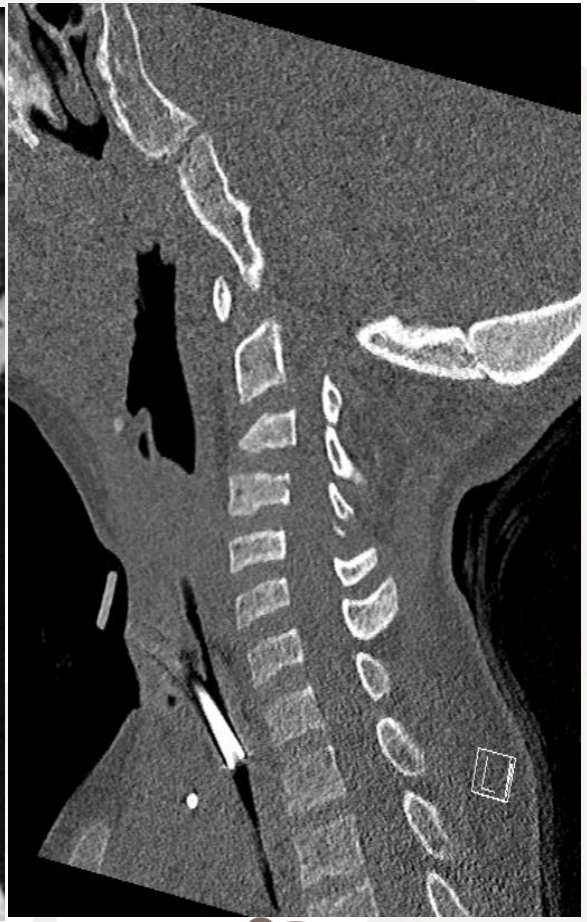
Facial features						
Flat face	5/5					
Hypertelorism	5/5					
Long philtrum	5/5					
Depressed nasal bridge	5/5					
Micrognathia	5/5					
Relative macrocephaly	5/5					
Complications						
Kyphoscoliosis	Mild thoracic scoliosis	Yes, moderate, progressive	Yes, severe and progressive	Yes, severe and progressive	Yes, severe and progressive	4/5
Developmental delay	No	Moderate	Gross motor delay only	Mild to moderate, global	Mild to moderate, global	4/5
Short stature	<3rd centile	<3rd centile	<3rd centile	<3rd centile	<3rd centile	
Recurrent apnoea and respiratory problems	No	Yes, required tracheostomy	Yes	Mild	Yes	4/5
Conductive hearing loss	Yes (left side)	Yes	Yes	?	Yes	3/5
Dislocation of hips	No	Yes	No	Yes	No	

+ = feature present, ? = not known.

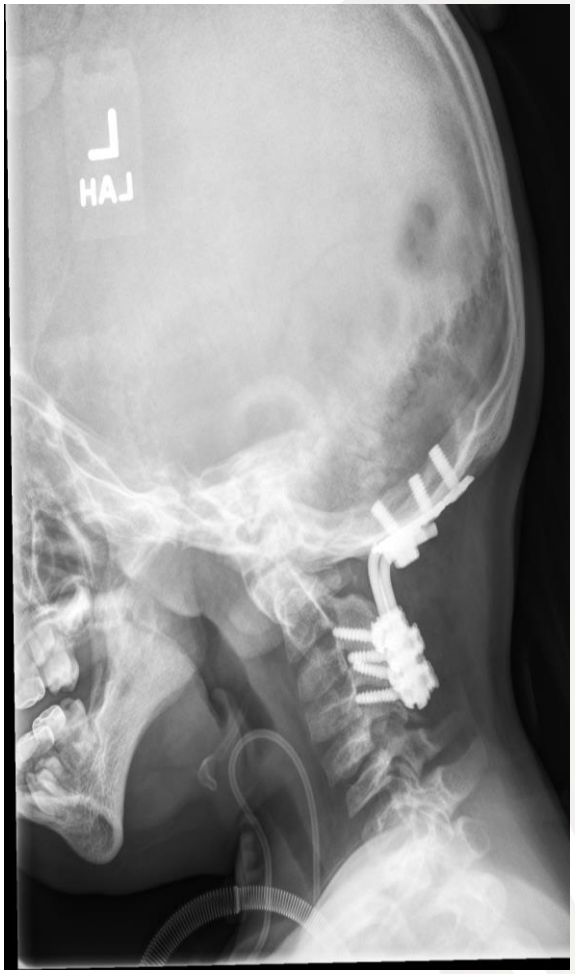
CASE - 7 YEAR OLD FEMALE WITH C2/3 KYPHOSIS AND STENOSIS AT C2/3 WITH CORD COMPRESSION

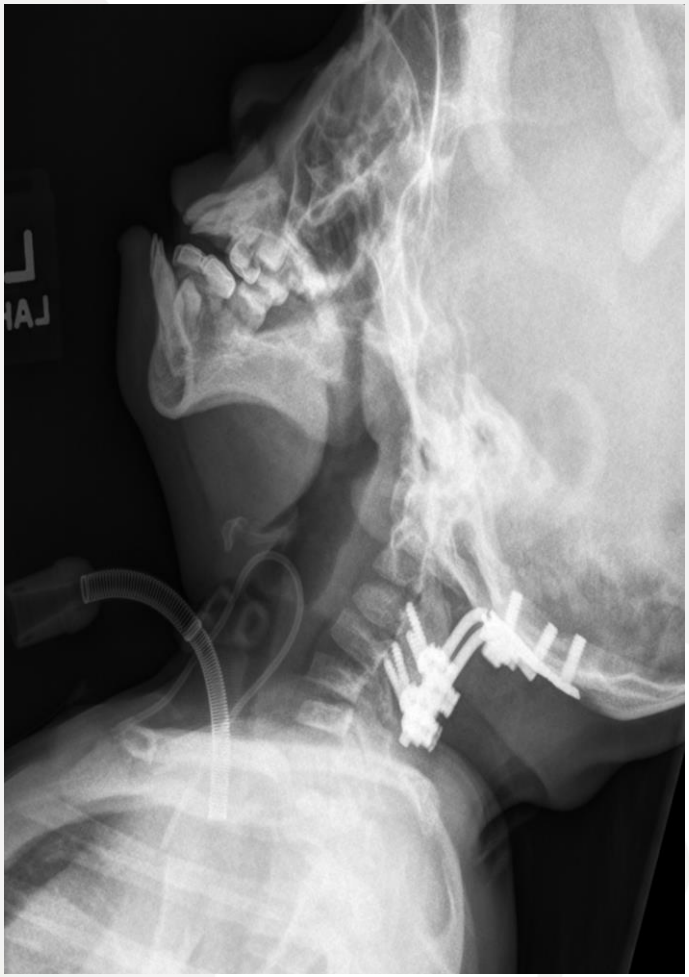






CASE – O-C4 PSF





Courtesy of W. Mackenzie

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CONCLUSIONS

1. Rare disease – but can test for genetic abnl in SOX9 gene
2. Clinical diagnosis
   - Bent limbs, 11 ribs, scapular hypoplasia, facial dysmorphism
   - No single feature is necessary for diagnosis
3. Genetic counseling → bent limb finding
4. Know what "not to miss"

- C spine deformity
- Airway issues
- Progressive scoliosis with congenital issues
- Malignant hyperthermia risk

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