Prenatal Diagnosis of Skeletal Dysplasias

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Disclosures

Luis F. Goncalves, M.D

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Honoraria from Philips Health Care – Philips Doppler course

Learning Objectives

After completing this presentation, the learner will be able to:

1. List the most common phenotypic features of skeletal dysplasias that can be diagnosed prenatally
2. Develop an approach to the differential diagnosis of the most common skeletal dysplasias
3. Understand the capabilities and limitations of ultrasound to determine if a skeletal dysplasia is lethal

Introduction

Skeletal Dysplasias

- Heterogenous group of rare disorders
- Affect bone and cartilage
- Abnormal bone size, mineralization and shape
- Incidence:
  - General population: 1/10,000 births
  - Prenatal series: 7.5/10,000 births
  - Consanguineous unions: 9.5/10,000 births

Lecture Outline

- Findings that raise suspiction for a skeletal dysplasia
- The fetus with a short femur
- Is the skeletal dysplasia lethal?
- Most frequent skeletal dysplasias
- Differential diagnosis

Prenatal Dx - Clinical Scenarios

Previously affected child or family member → Phenotype known
↓
Targeted US
↓
Genetic testing

Incidental finding during ultrasonographic study → Phenotype unknown
↓
Comprehensive US
↓
3DUS and/or 3DCT
↓
Ddx ± genetic testing

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Findings that Raise Suspicion for Skeletal Dysplasias

- Long bone shortening
- Bowing
- Poor mineralization and fractures
- Rib shortening and thoracic hypoplasia
- Malformations of the spine and pelvic bones
- Premature / delayed closure of sutures & fontanelles

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3DUS / 3DCT

- Better characterization of :
  - Enlargement of sutures and fontanelles
  - Craniosynostosis
  - Spine and ribs abnormalities
  - Pelvic abnormalities
  - Metaphyseal changes
  - Abnormalities of hands and toes

Ruano et al. UOG;2004;24:134-140
Victoria et al. AJR 2013;200:989-1000

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Fetal MRI

- Role not firmly established in skeletal dysplasias
- May change with 3T:
  - Better delineation of bones vs.1.5T
  - Cartilaginous epiphyses well seen

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Multidisciplinary Team

- Imaging specialist
- Geneticist
- Pediatrician
- Orthopedic surgeon
- Psychologist
- Pathologist
- Other specialists as needed (neurologist, neurosurgeon, cardiologist)

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Postnatal Examination

- <u>ESSENTIAL</u>
- Postnatal radiographs
- Autopsy, including bone histology
- Karyotype
- Molecular diagnosis
  - Confirm the phenotypic diagnosis
  - DNA extracted and preserved if diagnosis not currently possible

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The Fetus with a Short Femur

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Definitions

- Most investigators define a short femur length as < 5th percentile for GA
- High risk of significant skeletal dysplasia:
  - > 4 SD below mean for GA
  - 5 mm below -2 SD for the mean for GA

Kurtz et al. Radiology 1990;177:197-200
Papageorghiou et al. UOG 2008;31:507-11

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Short femur length

Detailed ultrasonographic examination

Additional anomalies 34% (22% - 47%)

- Chromosomal anomalies 24% - 40%
- Skeletal dysplasias 24% - 35%
- Multiple anomalies no unifying dx 24% - 35%
- Single gene disorders 4-9%

Papageorghiou et al. UOG 2008;31:507-11
Vermeer et al. Prenat Diagn 2013;33:365-370
Todd's et al. BJOG 2004;111:83-85

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Short femur length

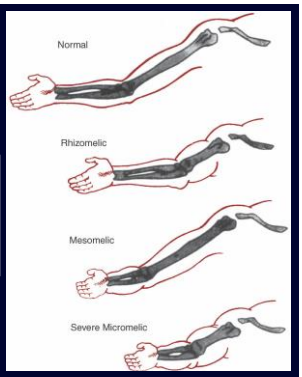
Detailed ultrasonographic examination

Isolated shortening 66% (53% - 78%)

- No identifiable cause 38% - 61%
- False + diagnosis 13% - 20%
- IUGR 39% - 43%
  - Abnormal Uterine a. Doppler 90%

Papageorghiou et al. UOG 2008;31:507-11
Vermeer et al. Prenat Diagn 2013;33:365-370
Todd's et al. BJOG 2004;111:83-85

Types of limb shortening



Romero et al. Prenatal Diagnosis of Congenital anomalies, 1988

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Lethality

- Best predictor: accurate diagnosis!
- Common pathway = small chest ➤ lung hypoplasia
  - Chest biometry:
    - chest circumference, chest circumference/abdominal circumference, thoracic length, right lung diameter, lung volumetry (3DUS or MRI)
  - FL/AC ratio

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No Single Parameter is 100% Sensitive and 100% Specific

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Prediction of lung hypoplasia FL / AC < 0.16

Author/Year	N	Lethal	Sensitivity	Specificity	PPV	NPV
Rahemtullah et al./1997	18	9	100%	100%	100%	100%
Ramus et al./1998	30	12	100%	94.4%	92.3%	100%
Goncalves et al./2006	41	14	85.7%	85.2%	75.0%	92.0%
Nelson et al/2014*	38	11	90.9%	88.9%	76.9%	96.0%
Waver et al./2014	23	12	83.3%	63.6%	71.4%	77.8%

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Prediction of lung hypoplasia CC / AC < 0.60

Author/Year	N	Lethal	Sensitivity	Specificity	PPV	NPV
Goncalves et al./2006	41	14	85.7%	85.2%	75.0%	92.0%
Barros et al./2016	24	18	66.0%	75.0%	92.0%	33.0%

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Prediction of lung hypoplasia (Right) lung diameter

Author/Year	N	Lethal	Sensitivity	Specificity	PPV	NPV
Merz et al./1999	7	7	100%	100%	100%	100%
Goncalves et al./2006	41	14	85.7%	85.2%	75.0%	92.0%

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Prediction of lung hypoplasia Lung volumes by 3DUS

Author/Year	N	Lethal	Sensitivity	Specificity	PPV	NPV
Goncalves et al./2006	41	14	85.7%	85.2%	75.0%	92.0%
Barros et al./2016	24	18	66.0%	75.0%	92.0%	33.0%

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Skeletal Dysplasias

Skeletal Dysplasias

- Group of complex and heterogeneous disorders that affect bone development and growth, resulting in alterations of bone size, shape, density and/or integrity
- Prevalence: 1.1 to 2.4/10,000 births

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RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Nosology and Classification of Genetic Skeletal Disorders: 2015 Revision

Luisa Bonafe,[1] Valerie Cormier-Daire,[2] Christine Hall,[3] Ralph Lachman,[4] Geert Mortier,[5] Stefan Mundlos,[6,7,8] Gen Nishimura,[9] Luca Sangiorgi,[10] Ravi Savarirayan,[11] David Sillence,[12] Jürgen Spranger,[13] Andrea Superti-Furga,[14] Matthew Warman,[15] and Sheila Unger[16]*

372 to 436 conditions since 2006

37 to 42 groups

Molecular defect known for 364 (previously 215)

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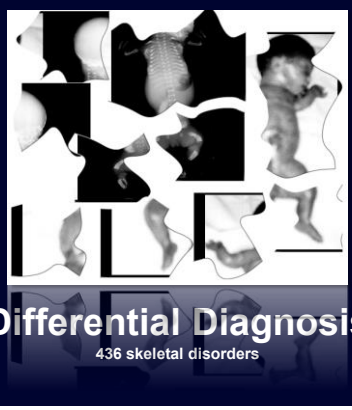
Bonafe et al. Am J Med Genet A 2015;167:2869-2892



Differential Diagnosis

436 skeletal disorders

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Most Frequent Skeletal Dysplasias Diagnosed Prenatally

- Thanatophoric dysplasia
- Osteogenesis imperfecta type 2
- Achondrogenesis type 2 40 - 60% of the cases
- Campomelic dysplasia
- Short-rib dysplasias (with or without polydactyly)

Camera & Mastroiacovo. Prog Clin Biol Res 1982
Connor et al. Am J Med Genet 1985
Schramm et al. Ultrasound Obstet Gynecol 2009
Krakow et al. Am J Med Genet A 2008

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Less Frequent but Still Among the 10 Most Common

- Achondroplasia
- Chondroenctodermal dysplasia (Ellis-van-Creveld)
- Asphyxiating thoracic dysplasia
- Chondrodysplasia punctata
- Diastrophic dysplasia

Camera & Mastroiacovo. Prog Clin Biol Res 1982
Connor et al. Am J Med Genet 1985
Schramm et al. Ultrasound Obstet Gynecol 2009
Krakow et al. Am J Med Genet A 2008

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FGFR3 Group

- Thanatophoric dysplasia
- SADDAN
- Achondroplasia
- Hypochondroplasia
- Camptodactyly, tall stature and hearing loss syndrome
- Hypochondroplasia-like dysplasias

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Thanatophoric Dysplasia

- Most common lethal skeletal dysplasia
- Only a few cases of survival and only for a few months
- Autosomal dominant
- DNA mutation:
  - fibroblast growth factor receptor 3 (FGFR3)
- Types 1 and 2

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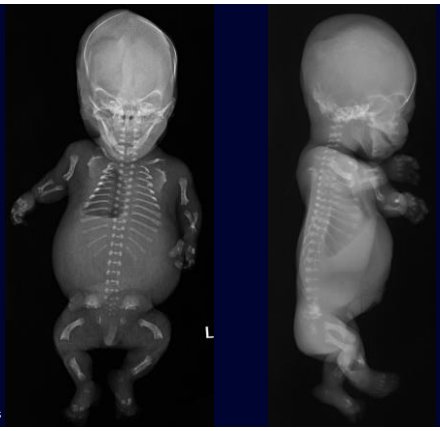

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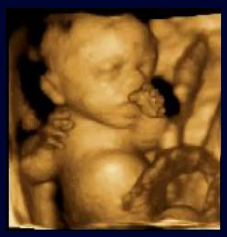

Torso and Face 3D

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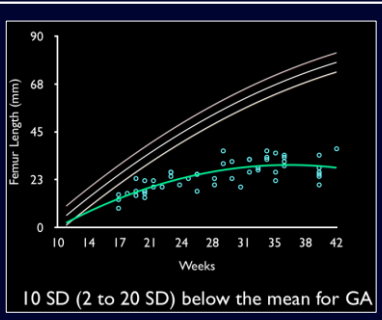
Perinatology Research Branch, NICHD, NIH/DHHS

Thanatophoric Dysplasia



10 SD (2 to 20 SD) below the mean for GA

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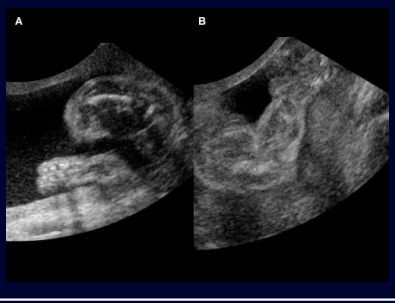
Gonçalves & Jeanty JUM 1994;13:977-85



Lower Extremities

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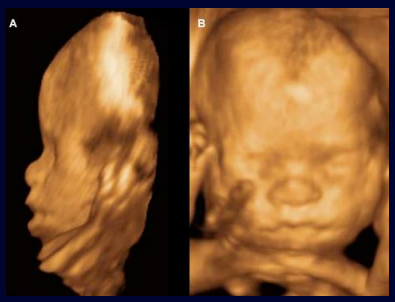
Clinica Materno-Fetal, Florianopolis, Brasil



Face

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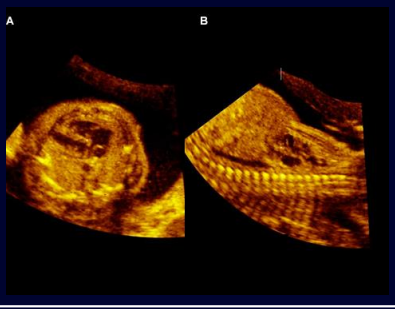
Clinica Materno-Fetal, Florianopolis, Brasil



Chest / Abdomen

Clinica Materno-Fetal, Florianopolis, Brasil

Thanatophoric Dysplasia Phenotypic Features

- Severe micromelic limb shortening
- Relatively large cranium
- Depressed nasal bridge
- Hypoplastic thorax
- Platyspondyly
- Polyhydramnios
- Short and stubby fingers

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Thanatophoric Dysplasia Type 1

- Most common
- Short bowed femora - "telephone receiver"
- Macrocephaly but NOT cloverleaf skull
- Common FGFR3 mutations (60 to 80%)
  - S248C
  - Y373C

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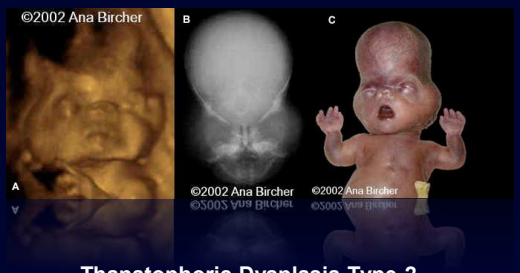

Thanatophoric Dysplasia Type 2

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Thanatophoric Dysplasia Type 2

- Cloverleaf skull
  - craniosynostosis involving multiple sutures
- Short and straight long bones
- FGFR3 mutation: K650E
  - Almost exclusively in thanatophoric dysplasia type 2

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Temporal Lobe Dysplasia

- Highly specific for thanatophoric dysplasia
- Also seen in hypochondroplasia
- One report in achondroplasia

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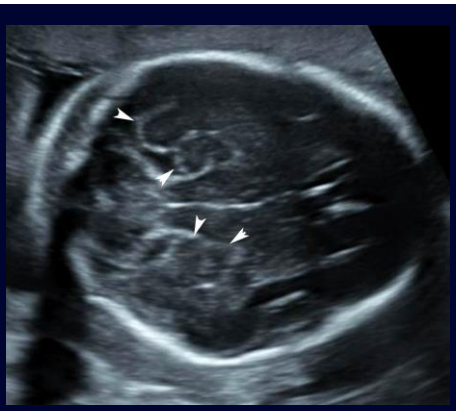

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Thanatophoric Dysplasia Differential Diagnosis

- Homozygous achondroplasia
- Skeletal dysplasia SADDAN type
- Platyspondylic dysplasia Torrance type
- Other skeletal dysplasias with severe bone shortening:
  - Osteogenesis imperfecta
  - Fibrochondrogenesis
  - Atelosteogenesis
  - Ciliopathies with major skeletal involvement

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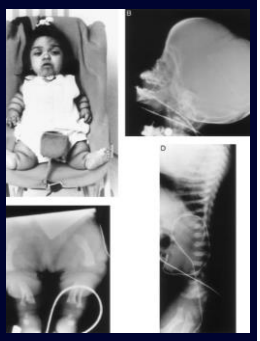
A Novel Skeletal Dysplasia with Developmental Delay and Acanthosis Nigricans Is Caused by a Lys650Met Mutation in the Fibroblast Growth Factor Receptor 3 Gene

Patricia L. Tavormina,[1,*] Gary A. Bellus,[2,*,†] Melanie K. Webster,[1] Michael J. Bamshad,[3] Alexander E. Fraley,[4] Iain McIntosh,[5] Jinny Szabo,[1] Wen Jiang,[6] Ethylin W. Jabs,[7,8] William R. Wilcox,[1,9] John J. Wasmuth,[1,3] Daniel J. Donoghue,[1] Leslie M. Thompson,[1] and Clair A. Francomano[2,9]



- Phenotype similar to TD type I
- Tibia and fibula have characteristic (reverse) bowing
- Acanthosis nigricans
- Severe neurological delay
- Survival beyond infancy without life support
- FGFR3 mutation K650M

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Lethal Platyspondylic Skeletal Dysplasia, Torrance Type

Similar to Thanatophoric Dysplasia
Severe micromelia
Hypoplastic thorax / protuberant abdomen
Relative macrocephaly
Severe platyspondyly
Depressed nasal bridge

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Lethal Platyspondylic Skeletal Dysplasia, Torrance Type

Similar to Thanatophoric Dysplasia	Different from Thanatophoric Dysplasia
Severe micromelia	Short ribs w/ cupped anterior ends
Hypoplastic thorax / protuberant abdomen	No “telephone receiver” femora
Relative macrocephaly	Irregular and cupped metaphases of long bones
Severe platyspondyly	Radial bowing
Depressed nasal bridge	No temporal lobe dysplasia

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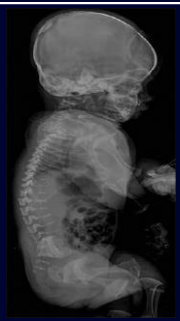
Fibrochondrogenesis

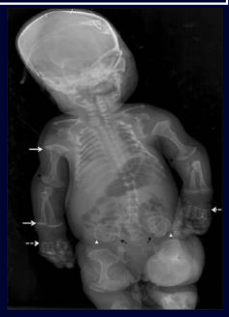
- Flat vertebral bodies (platyspondyly)
- Pear shaped vertebral bodies (rounded anteriorly and narrow posteriorly)



Kundaragi et al. J Clin Imaging Sci 2012;2:5

Fibrochondrogenesis

- Rhizomelic micromelia
- Dumbbell-shaped metaphyses
- Peripheral spurs
- Long and thin clavicles
- Short, distally cupped ribs
- Iliac bones are small rounded and broad



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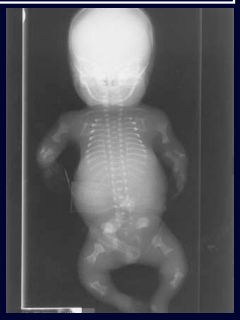
Kundaragi et al. J Clin Imaging Sci 2012;2:5

Fibrochondrogenesis

- Sagittal midline vertebral clefts
- Less ossified vertebral bodies in the cervical spine



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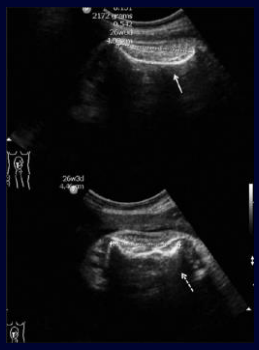
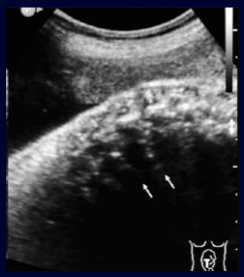
Leeners et al. Am J Med Genet 2004;127A;318-20





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Kundaragi et al. J Clin Imaging Sci 2012;2:5

Fibrochondrogenesis

- Very rare
- Caused by COL11A1 and COL11A2 mutations
- Autosomal recessive
- Diagnosis: radiographic features and histopathology
- Perinatally lethal
  - Few survivors reported with orthopedic handicaps, bilateral hearing loss and global developmental delay

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Atelosteogenesis Types 1 and 3

- Autosomal dominant
- Sporadic
- Caused by mutations in the filamin beta gene
- Severe limb shortening, bowing
- Thoracic hypoplasia
- Hypertelorism, flat nasal bridge, micrognathia
- Dislocated hips, knees, elbows, clubfeet

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Atelosteogenesis Type 1 and 3

- Type 1 is lethal, more severe than type 3
- Absent of various long bones are common, specially fibula
- Hypoplastic humeri that tapers distally
- Hypoplastic femora
- Platyspondyly with coronal clefts
- Incomplete ossification of thoracic vertebrae
- Brachydactyly

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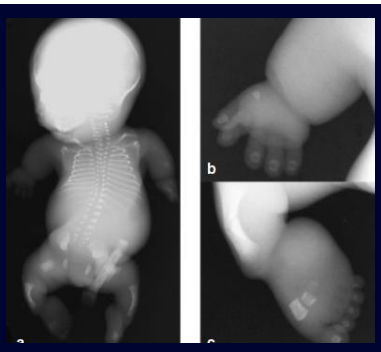

Atelosteogenesis type I

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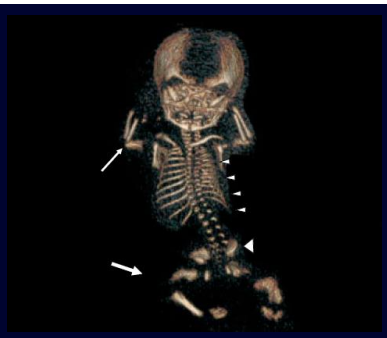
Ueno et al. Prenatal Diagn 2002;22;1071-5



Atelosteogenesis type 3

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Cordier et al. Prenat Diagn 2008; 28: 975–977

Atelosteogenesis Type 2

- Caused by mutations in the DTST gene
  - Same gene that causes diastrophic dysplasia and achondrogenesis type IB
  - Hitchhiker thumbs
- Autosomal recessive

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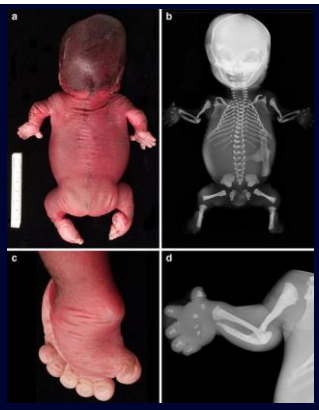

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Miller et al. Ped Rad 2008;38:1345-49

Ciliopathies with Major Skeletal Involvement

- New nomenclature for short-rib dysplasias (with or without polydactyly group)
- Includes:
  - Chondroectodermal dysplasia (Ellis van-Creveld)
  - Asphyxiating thoracic dysplasia
  - Short-rib polydactyly syndromes:
    - Types I/3 (Saldino-Noonan/Verma-Naumoff)
    - Type 2
    - Type4
    - Type 5
  - Orofaciodigital syndrome
  - Cranioectodermal dysplasia

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Absence of Polydactyly Does Not Exclude the Diagnosis

- Constant:
  - SRPS type 2
- Common:
  - SRPS types 1/3
- Rare:
  - SRPS type 4

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Considerable Phenotypic Overlap

	SPRS 1/3	SPRS 2	SPRS 4	SPRS 5
Limb shortening	1: marked micromelia, "flipper-like", pointed metaphyses 3: moderate micromelia, spurred metaphyses	Marked mesomelic micromelia Ovoid tibiae shorter than fibulae Premature ossification of proximal epiphyses	Marked micromelia Tibiae longer than fibula Bowed ulnae and radii	Marked mesomelic micromelia Forearm and lower limb bowing Absent ossification of radii ulnae tibiae and fibulae
Scapulae	Small		Small	Small
Spine	Coronal clefts			
Clavicle	Sup. located			
Acetabula	Trident			

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SRPS - Molecular Basis

- Types 1 and 3: DYNC2H1, IF80, WDR60
- Type 2: DYNC2H1, NEK1
- Type 4: not yet elucidated
- Type 5: WDR35

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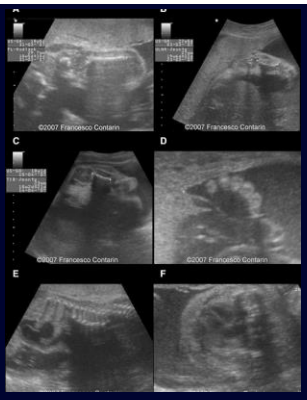
Yeo et al. In Fleischer Sonography in Obstetrics and Gynecology, 2008



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Asphyxiating Thoracic Dysplasia (Jeune Syndrome)

- Autosomal recessive
- Genetically heterogeneous (several mutations)
- Three main phenotypic characteristics:
  - Narrow, bell-shaped thorax
    - Short, broad, horizontal ribs
- Short bones
  - Mesomelic, mild bowing, metaphyseal spurs
- "Trident" acetabular roof

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Additional Phenotypic Features

- Proximal femoral epiphyseal center may be ossified at birth (2/3 of the cases)
- Clavicles: lateral clavicular hook, a.k.a. "bycicle handle-bar"
- Brachydactyly
- Postaxial polydactyly in 10% of the cases (as opposed to 100% in chondroectodermal dysplasia)

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Additional Phenotypic Features

- Directly related to prognosis:
  - Dysplastic kidneys
    - renal failure in childhood
    - may require transplant
  - Joubert syndrome

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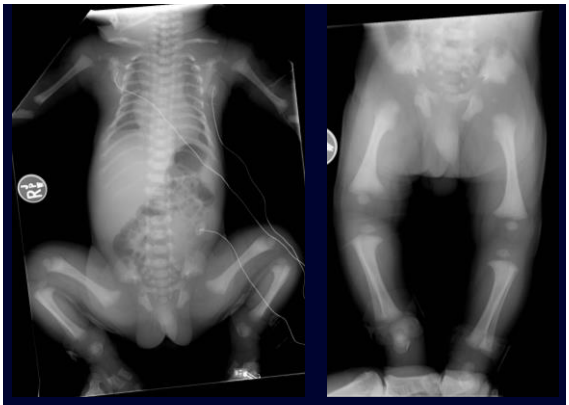

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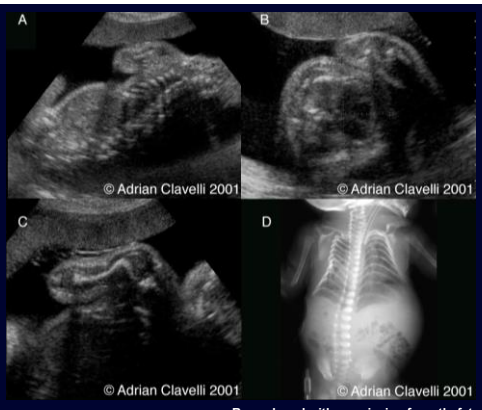

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Prognosis

- Severe thoracic narrowing:
  - Lung hypoplasia, respiratory failure, early death
- Mild thoracic narrowing:
  - Long term survival possible
    - Severity of renal and hepatobiliary involvement
    - Presence of CNS anomalies (Joubert)

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Chondroectodermal Dysplasia (Ellis van-Creveld Syndrome)

- Autosomal recessive, ECV1 and ECV2 genes
- 1/60,000 births
- Except Amish of Lancaster County, Pennsylvania
- Classic tetrad:
- Chondrodysplasia
- Ectodermal dysplasia
- Postaxial polydactyly
- Congenital heart disease

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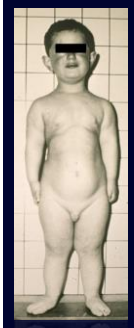
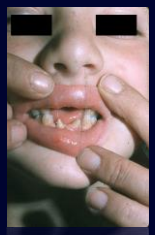
Chondroectodermal Dysplasia

- Mesomelic or acromesomelic limb shortening
- Polydactyly (usually w/ formed metacarpal and phalanges):
- Hands 100% / Feet 10%
- CHD (60%)
- AV canal 88%, high frequency of single atrium
- Trident acetabulum
- Normal skull and spine
- Narrow thorax with short horizontal ribs

Goncalves


Ellis van-Creveld Syndrome

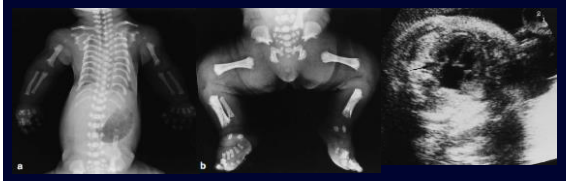
Goncalves

Baujat and Le Merrer. Orphanet J Rare Dis 2007;2:27

Pediatr Radiol (1997) 27: 942–944
© Springer-Verlag 1997

Hitoshi Horigome
Hiromi Hamada
Satoshi Sohda
Yuji Oyake
Yoshihisa Kurosaki

Prenatal ultrasonic diagnosis of a case of Ellis–van Creveld syndrome with a single atrium



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Prognosis

- Can range from death in the neonatal period due to cardiopulmonary disease to long-term survival
- Average adult height is 110 - 160 cm
- Normal cognitive development

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Most Frequent Skeletal Dysplasias Diagnosed Prenatally

- Thanatophoric dysplasia
- Osteogenesis imperfecta type 2
- Achondrogenesis type 2
- Campomelic dysplasia
- Short-rib dysplasias (with or without polydactyly)

Camera & Mastroiacovo. Prog Clin Biol Res 1982
Connor et al. Am J Med Genet 1985
Schramm et al. Ultrasound Obstet Gynecol 2009
Krakow et al. Am J Med Genet A 2008

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Osteogenesis Imperfecta

- Group of heterogeneous disorders usually caused by mutations in type 1 pro collagen
- 5 types
  - Overall prevalence: 6-7/100,000
- OI type 2 is the perinatal lethal form
  - Prevalence: 2/100,000
  - Autosomal recessive and dominant forms

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Bonafe et al. Am J Med Genet A 2015;167:2869-2892

Osteogenesis Imperfecta Type 2 Phenotype

- Almost no ossification of the skull
- Micromelic dwarfism
- Multiple fractures, including ribs (beaded)
- Short thorax, not necessarily narrow
- Neonatal death due to pulmonary hypoplasia
- Spine is not demineralized

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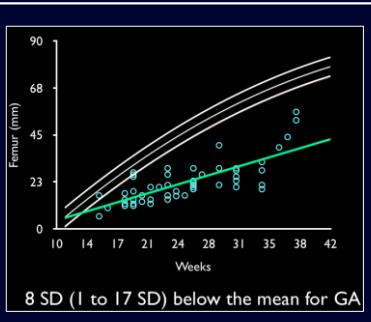
Osteogenesis Imperfecta Type 2



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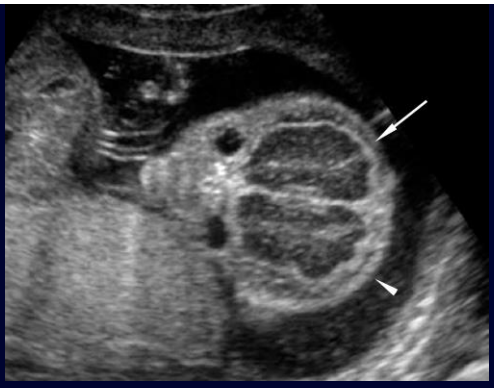
Gonçalves & Jeanty JUM 1994;13:977-85



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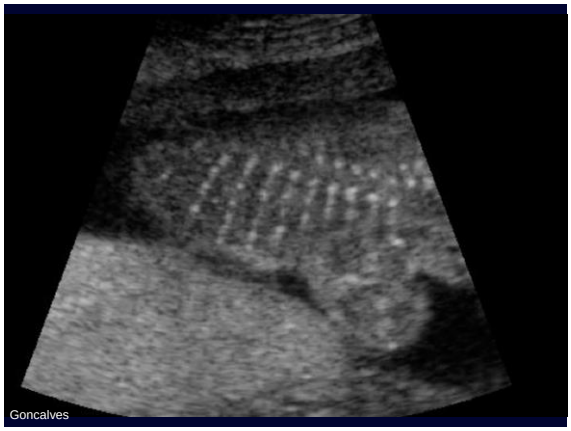

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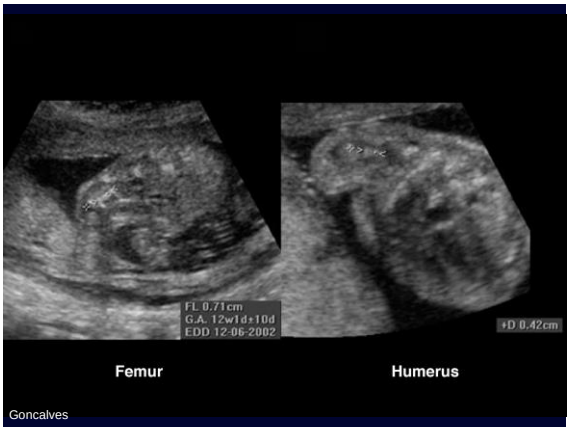

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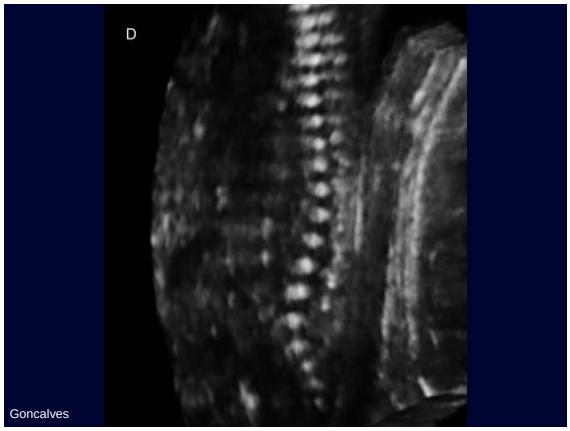

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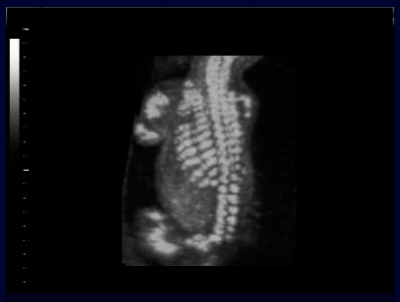

Osteogenesis Imperfecta Type 2

Perinatology Research Branch, NICHD, NIH/DHHS

Other Forms of OI

- Type 1
  - Autosomal dominant
  - No prenatal deformities
  - After birth:
    - Bone fragility (fractures), blue sclera
    - Hearing loss (50%)
    - Normal or near normal final stature

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Other Forms of OI

- Type 3
- Autosomal dominant and recessive forms
- Rare, nonlethal
- High morbidity and long term mortality
- Multiple fractures that can be detected at birth
- Unossified skull, wormian bones, blue sclera
- Mildly shortened bones / marked angulations
- May overlap with less severe cases of type 2

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Osteogenesis Imperfecta Type 3

- Second most important for prenatal diagnosis
- Less severe than type II
- May manifest at birth
  - Bowed long bones, almost normal length
  - Neonatal fractures with trivial handling of the newborn
  - Rib fractures may lead to death in the first weeks or months
- High morbidity and long term mortality
- Majority of affected individuals require ambulation assistance and/or wheelchair

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Other Forms of OI

- Type 4
  - Autosomal dominant and recessive forms
  - Mildest form
  - Normal long bones and sclera
  - Mild to moderate osseous fragility
  - Femoral bowing may be present at birth
  - 25% of the newborns may present with fractures

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Other Forms of OI

- Type 5
  - Autosomal dominant and recessive forms
  - Moderate to severe bone fragility
  - Calcified interosseous membrane of the forearm
  - Predisposition to develop hyperplastic calluses

Differential Diagnosis (OI)

- Skeletal dysplasias with micromelic limb shortening or bowing or demineralization
  - Thanatophoric dwarfism
  - Hypophosphatasia
  - Cleidocranial dysplasia
  - Achondrogenesis
  - Campomelic dysplasia

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Ddx Case 1

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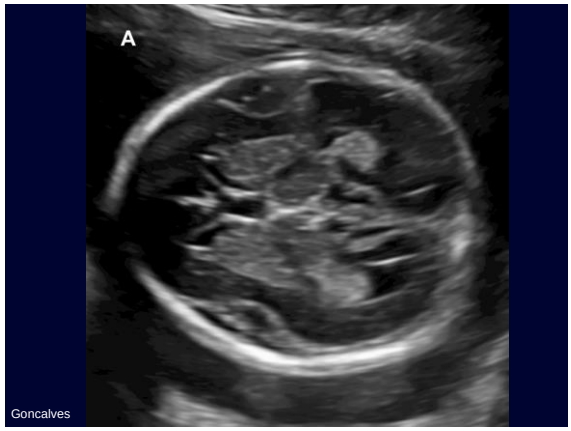

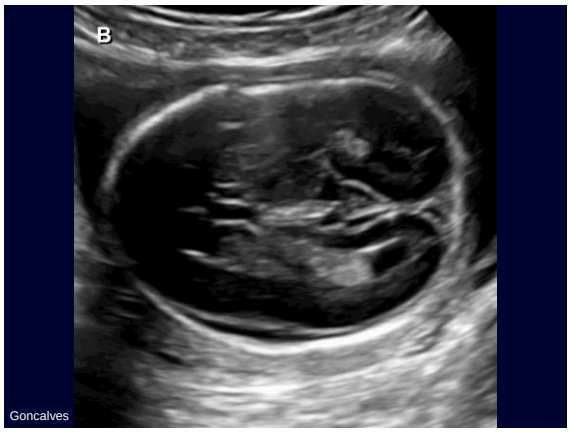

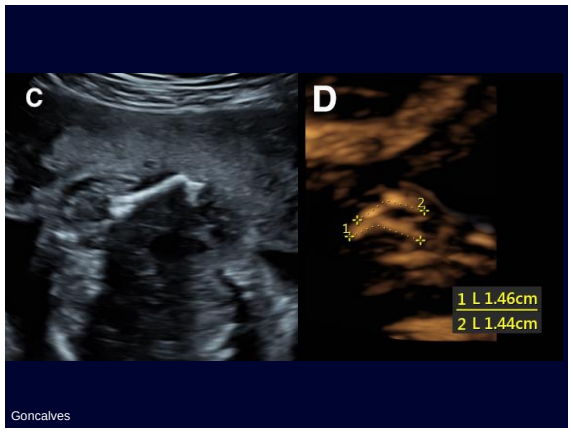

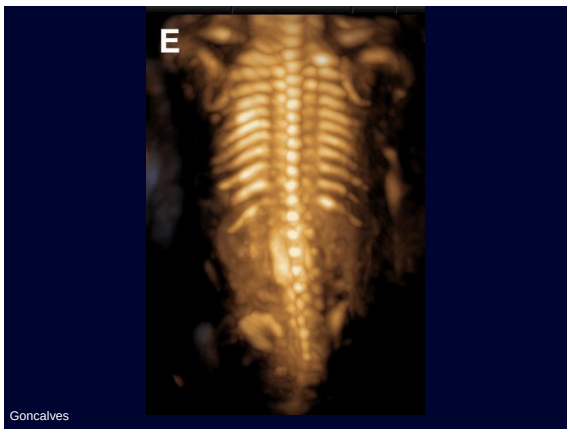

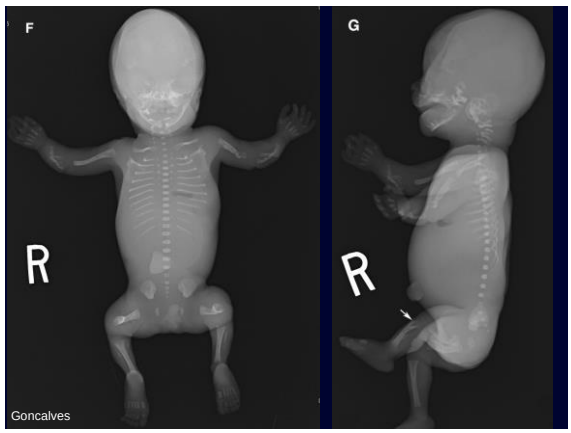

Hypophosphatasia

- Rare, autosomal recessive
- Low alkaline phosphatase in tissues
  - Bone demineralization
- 6 subtypes: perinatal (lethal), prenatal benign, infantile, childhood, adult, and odontophosphatasia

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Perinatal Lethal Hypophosphatasia

- Markedly demineralized skull (caput membranaceum)
  - Ddx: OI type 2 and achondrogenesis type 1A
- Spine:
  - Absent ossification vertebral bodies:
    - Thoracic, sharp demarcation w/ ossified vertebrae
  - Posterior elements may be more unossified
- Ribs:
  - Short, thin, unossified ends

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Perinatal Lethal Hypophosphatasia

- Cupped metaphyses (as in rickets)
- Prominent central lucency from metaphysis to diaphysis
- Skin covered osteochondral spurs forearms or legs (characteristic)

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Perinatal Lethal Hypophosphatasia

- Thoracic spine demineralization
- Sharp demarcation between ossified vs. unossified vertebral bodies
- Thin ribs
- Patchy demineralization spine and ribs ("gum eraser" effect)
- Caput membranaceum
- Central y-shaped metaphysical lucency

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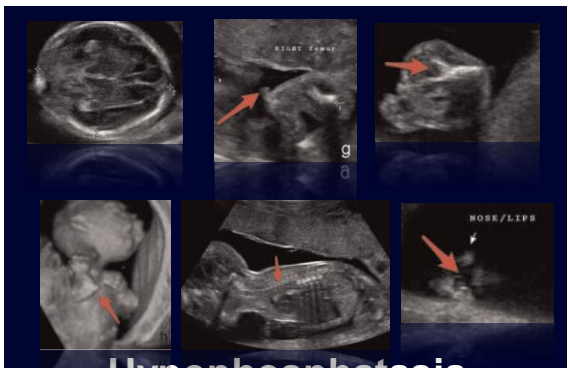
Zankl et al.. Am J Med Genet 2008;146:1200-4



Hypophosphatasia

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Zankl et al.. Am J Med Genet 2008;146:1200-4

Ddx Case 2

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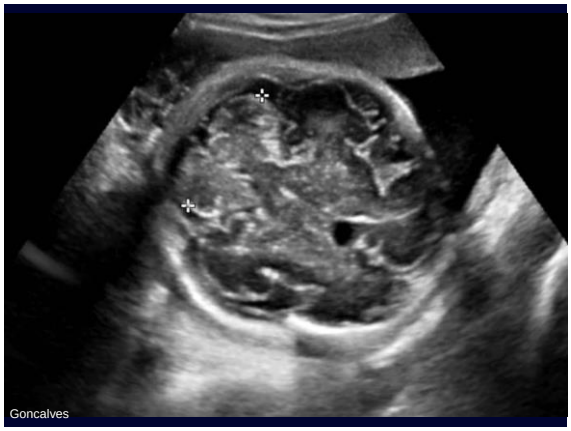
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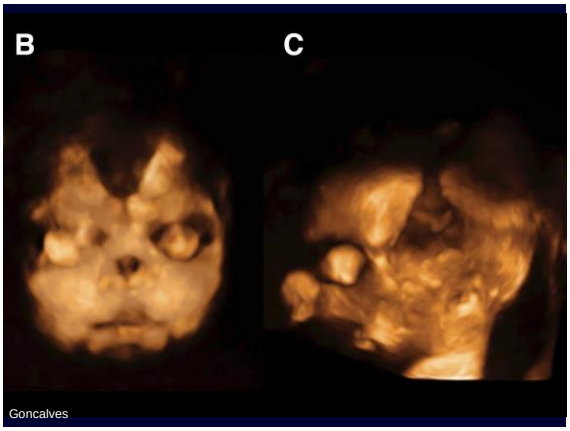

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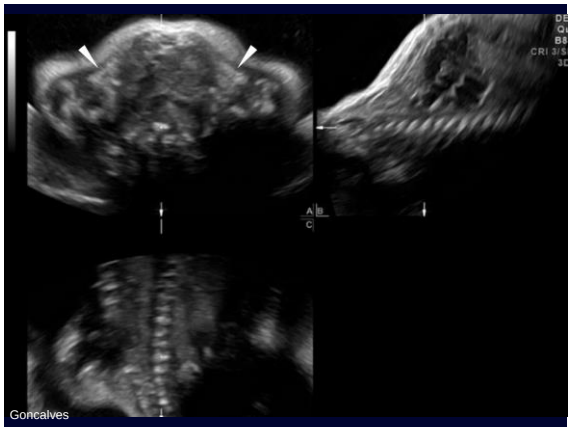
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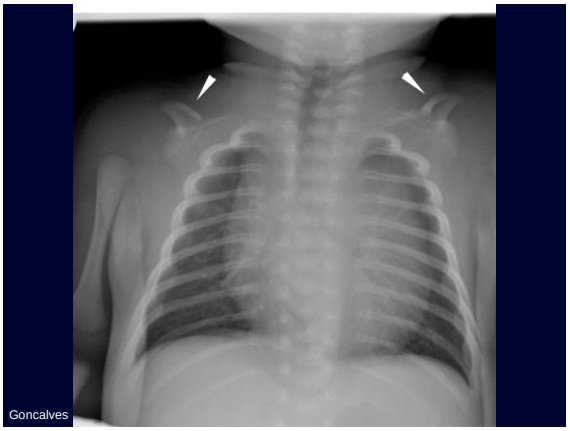
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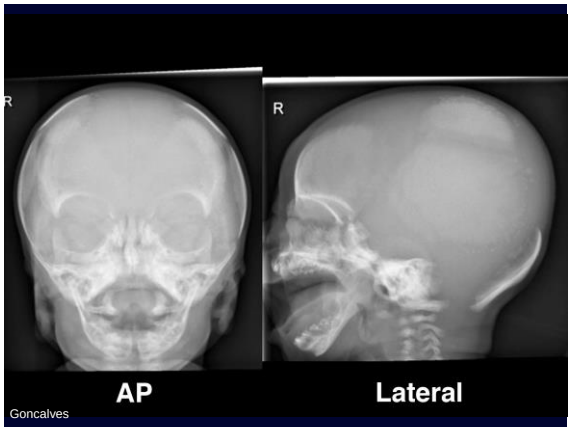

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Cleidocranial Dysplasia

- 1/200,000 births
- Autosomal dominant, mutations in RUNX2
- Absent, hypoplastic, pseudoarthrosis of clavicles
- Wide sutures and fontanels
- Wormian bones
- Lack of ossification of pubic rami
- Not lethal / survivors with normal intellect

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Most Frequent Skeletal Dysplasias Diagnosed Prenatally

- Thanatophoric dysplasia
- Osteogenesis imperfecta type 2
- Achondrogenesis type 2
- Campomelic dysplasia
- Short-rib dysplasias (with or without polydactyly)

Camera & Mastroiacovo. Prog Clin Biol Res 1982
Connor et al. Am J Med Genet 1985
Schramm et al. Ultrasound Obstet Gynecol 2009
Krakow et al. Am J Med Genet A 2008

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Achondrogenesis

- Most severe limb shortening
- Uniformly lethal
- When to suspect:
  - Severe micromelia
  - Macrocephaly with varying degrees of skull mineralization
  - Demineralization of the spine

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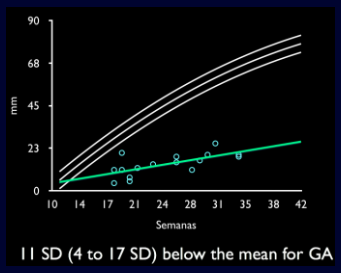
Achondrogenesis



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Gonçalves & Jeanty JUM 1994;13:977

Achondrogenesis Types

- Type 1A - Houston-Harris
  - Severe spondylodysplastic dysplasias group
  - Autosomal recessive
  - TRIP11 mutation
- Type 1B - Fraccaro
  - Autosomal recessive
  - SLC26A2 mutation (diastrophic dysplasia sulfate transporter gene)
- Type 2 and hypochondrogenesis - Langer-Saudino
  - Autosomal dominant
  - COL21 mutation

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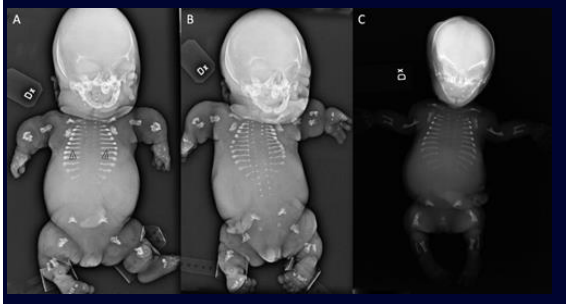
Achondrogenesis 1A

- Unossified calvarium (caput membranaceum)
- Severe micromelia, feet may be externally rotated
- Unossified vertebral bodies and sacrum
  - Cervical and thoracic pedicles may be ossified
- Small ilia, crescentic and concave inferiorly
- Poorly ossified pubis and ischia
- Short ribs with fractures and beaded appearance, cupped ends
- Flat nasal bridge, micrognathia, cystic hygroma

The phenotype range of achondrogenesis 1A



Grigelioniene et al. American Journal of Medical Genetics Part A Volume 161, Issue 10, pages 2554-2558, 16 AUG 2013

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Achondrogenesis 1B

- Sulphation disorders group
  - Other disorders in this group include:
    - diastrophic dysplasia
    - atelosteogenesis type 2
- Autosomal recessive
- Caused by mutations in the DTDST gene
- Also known as Parenti-Fraccaro
- Remember hitchhiker thumbs

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Achondrogenesis 1B

- Ossified skull
- Extremely short bones (shorter than type 1A) / clubfeet
- Unossified vertebral bodies and sacrum
- Widened interpedicular distances cervical and lumbar ("cobra head" appearance)
- Small ilia, crescentic and concave inferiorly
- Unossified pubis and ischia
- Hitchhiker thumb
- Cystic hygroma

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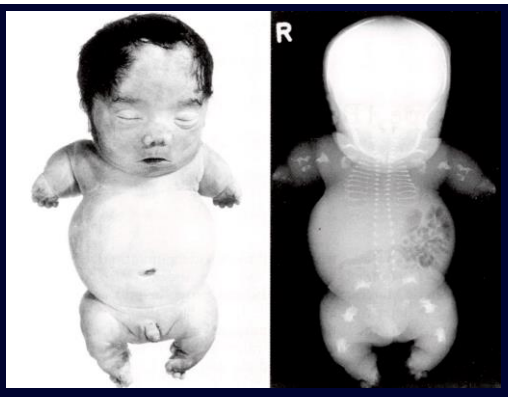

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Superti-Furga. Achondrogenesis type 1B. J Med Genet 1996;33:957:61

Achondrogenesis Type 2 / Hypochondrogenesis

- Both are lethal autosomal dominant disorders
- Mutations in COL2A1 gene
- Regarded as a continuum within same spectrum

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Achondrogenesis Type 2

- Severe micromelia
- Lack of mineralization of vertebral bodies, sacrum and ischium
- Short, horizontal ribs with no fractures
- Cranium
  - larger than expected for gestational age
  - Relatively normal mineralization
- Other findings:
  - Cystic hygroma, cleft palate, fetal hydrops, polyhydramnios

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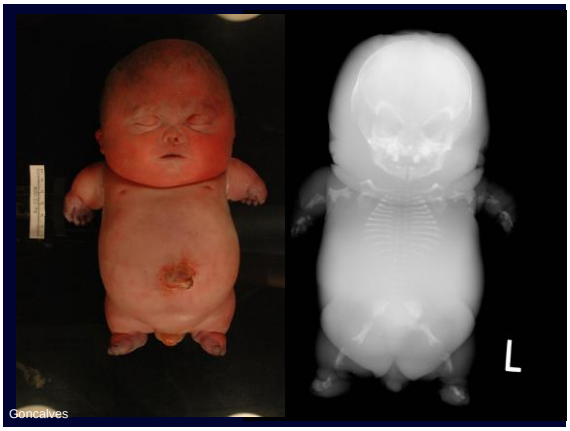

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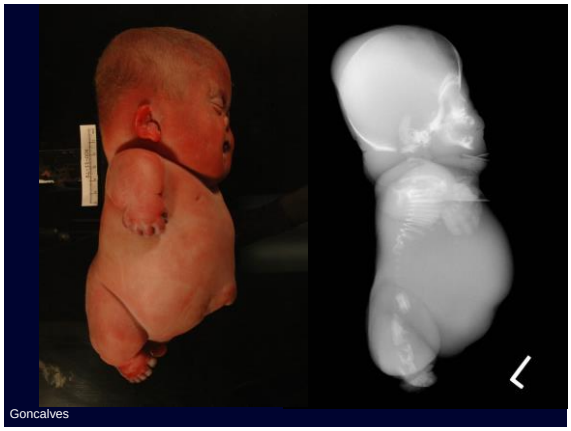

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Prenatal Ultrasound
20 3/7 weeks

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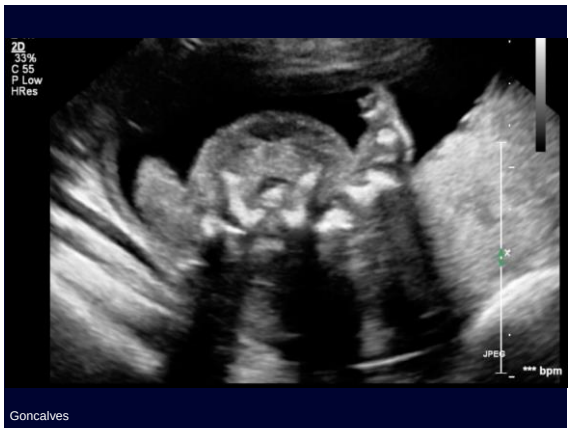

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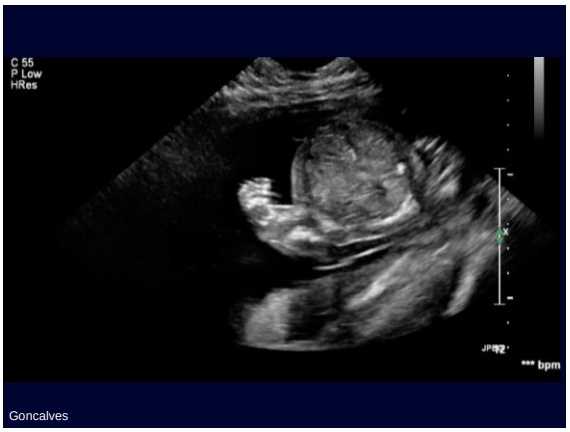

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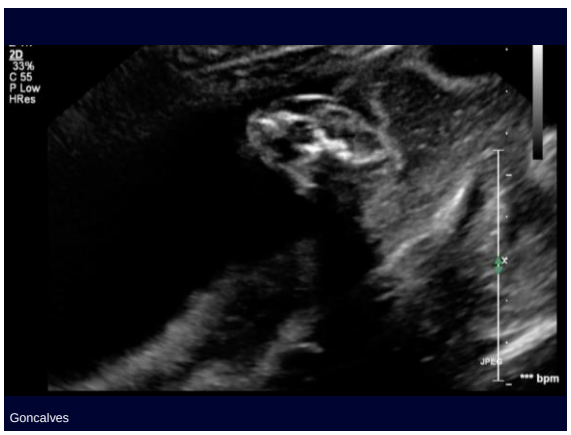

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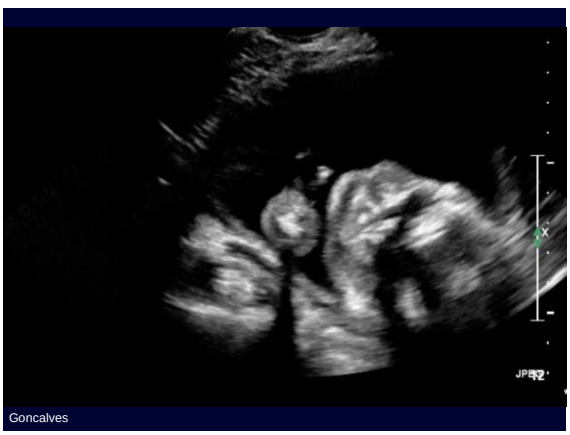

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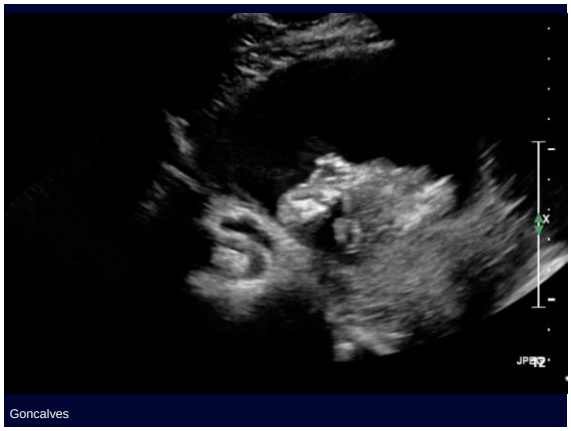
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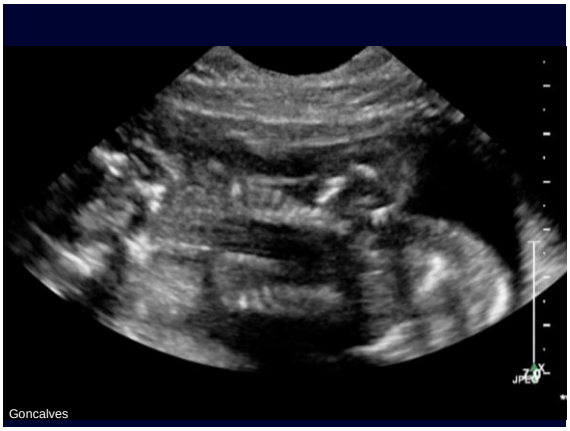
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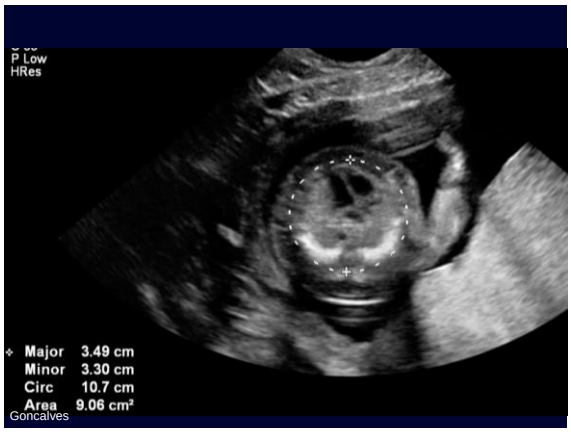

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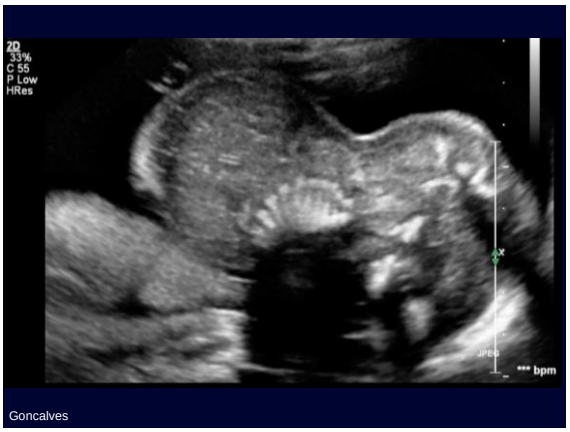

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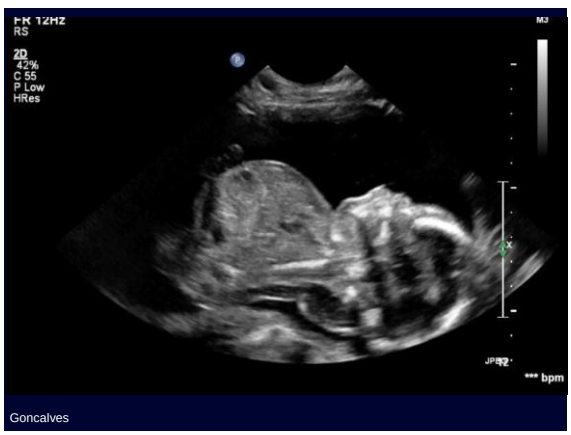

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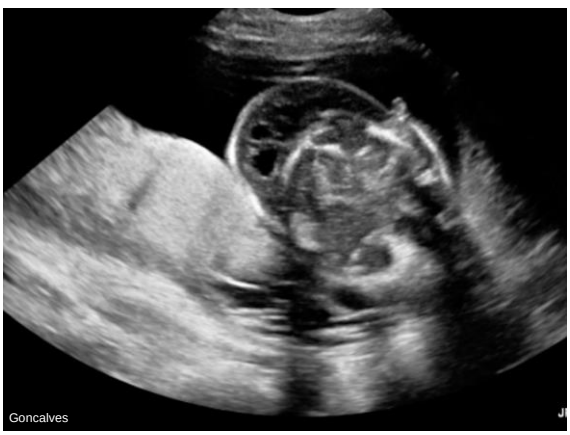
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Achondrogenesis Differential Diagnosis

- Disorders with severe limb shortening and bone demineralization:
  - Osteogenesis imperfecta type II
  - Hypophosphatasia
  - Schneckenbecken dysplasia
  - Grebe syndrome
- If hitchhiker thumb present
  - Diastrophic dysplasia
  - Atelosteogenesis type 2

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Most Frequent Skeletal Dysplasias Diagnosed Prenatally

- Thanatophoric dysplasia
- Osteogenesis imperfecta type 2
- Achondrogenesis type 2
- Campomelic dysplasia
- Short-rib dysplasias (with or without polydactyly)

Camera & Mastroiacovo. Prog Clin Biol Res 1982
Connor et al. Am J Med Genet 1985
Schramm et al. Ultrasound Obstet Gynecol 2009
Krakow et al. Am J Med Genet A 2008

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Campomelic Dysplasia

- Rare
- Autosomal dominant
- Almost always lethal
- Caused by SRY-box 9 or SOX-9 gene mutation
  - this gene also controls testicular differentiation in vertebrates

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Campomelic Dysplasia
Sex Reversal Syndrome

- 75% of the fetuses with a male karyotype
- Female or ambiguous genitalia
- Due to SOX-9 gene mutation
  - fundamental for testicular differentiation in vertebrates

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Campomelic Dysplasia Limbs

- Femur
  - Symmetric shortening and bowing
  - Approximately 5.5 SD below mean for GA
  - Mild anterolateral angulation proximal third
- Tibia:
  - Anterolateral angulation distal third
  - Hypoplastic fibula
- Clubfeet
- Normal vs. mild shortening of upper extremity bones
  - No bowing

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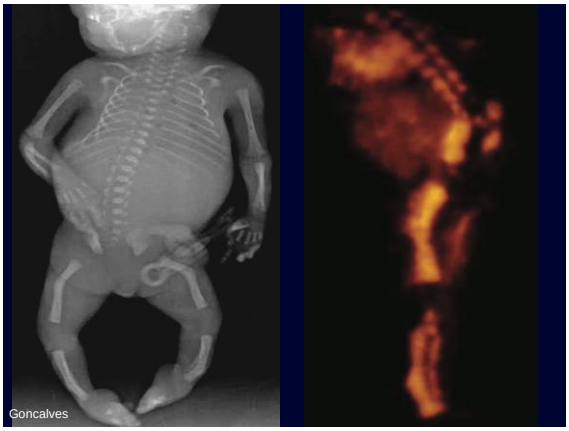

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Campomelic Dysplasia
Thorax

- Hypoplastic scapulae
- Narrow, "bell-shaped"
- 11 rib pairs (frequent)
- Majority (but not all) affected fetuses die in the neonatal period from pulmonary hypoplasia

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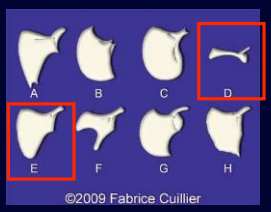
Scapula in the Differential Diagnosis of Skeletal Dysplasias



- A - Luton type of PLSD
- B - San Diego type of PLSD
- C - Torrance type of PLSD
- D - Campomelic dysplasia
- E - Kyphomelic dysplasia
- F - Antley-Bixler syndrome
- G - SRP type II (Majewski)
- H - SRP type III (Verma-Naumoff)

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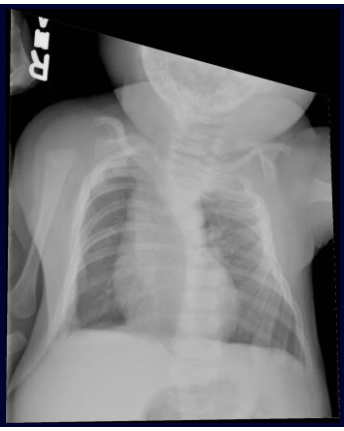
Adapted from: Mortier et al. Pediatr Radiol 1997;27:447-51.



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Campomelic Dysplasia
Spine and Pelvis

- Cervical:
  - Hypoplastic, poorly mineralized cervical vertebrae
- Thoracic:
  - Demineralized pedicles
- Pelvis:
  - Hip dysplasia

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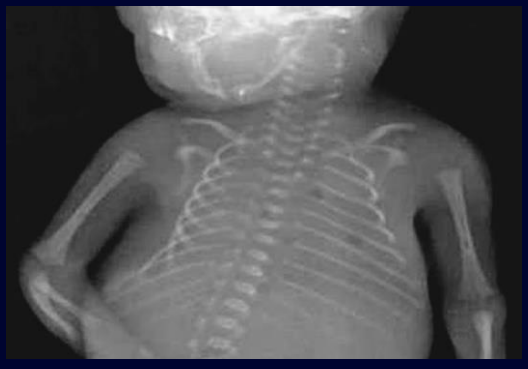

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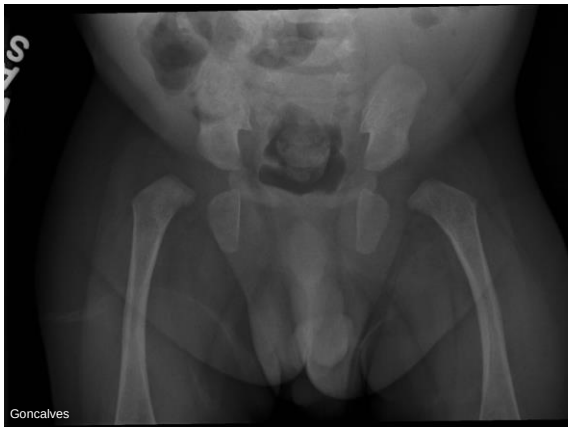

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Campomelic Dysplasia
Other Phenotypic Findings

- Macrocephaly / hydrocephaly
- Hypertelorism
- Hypoplastic face / cleft palate / micrognathia
- Hydronephrosis
- Cardiac anomalies

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Bowed Femur
Differential Diagnosis

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ISDR Radiology Database (1988-2006)	Fetus	Neonate	Total (%)
Campomelic disorders			
Campomelic dysplasia	21	36	112 (24%)
Kyphomelic dysplasia	21	34	
Thanatophoric dysplasias	82	28	110 (23.9%)
Osteogenesis imperfecta	55	28	83 (18.1%)
Short-rib polydactyly syndromes	26	21	47 (10.2%)
Hypophosphatasia	11	5	16 (3.5%)
Disorders with hypoplastic femora	9	7	16 (3.5%)
Collagen type 2 skeletal dysplasia	11	3	14 (3.1%)
Other 20 skeletal dysplasias	28	33	61 (13.2%)
Total	264	195	459

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Less Frequent but Still Among the 10 Most Common

- Achondroplasia
- Chondroenctodermal dysplasia (Ellis-van-Creveld)
- Asphyxiating thoracic dysplasia
- Chondrodysplasia punctata
- Diastrophic dysplasia

Camera & Mastroiacovo. Prog Clin Biol Res 1982
Connor et al. Am J Med Genet 1985
Schramm et al. Ultrasound Obstet Gynecol 2009
Krakow et al. Am J Med Genet A 2008

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Achondroplasia

- Most common non-lethal skeletal dysplasia
- Mild rhizomelic limb shortening
- Prenatal diagnosis is difficult
- Length of the long bones is relatively normal until the end of the second trimester

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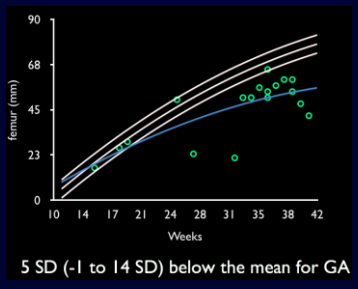
Achondroplasia



5 SD (-1 to 14 SD) below the mean for GA

Gonçalves & Jeanty, JUM 1994;13:977-85

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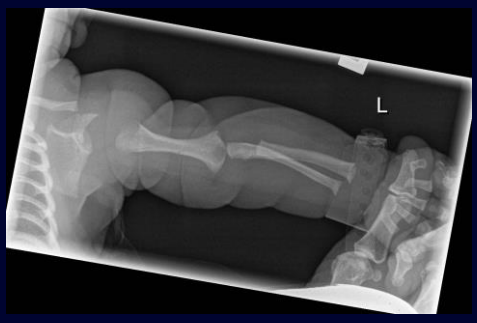

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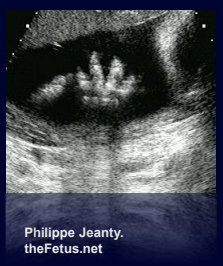

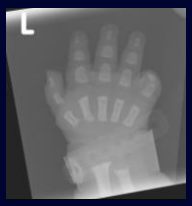

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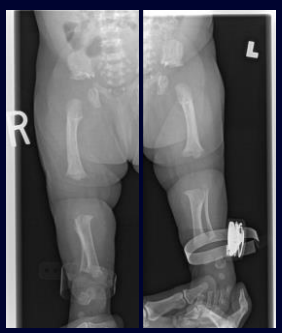

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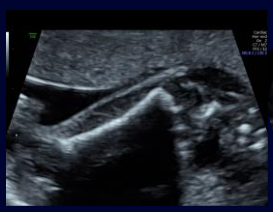
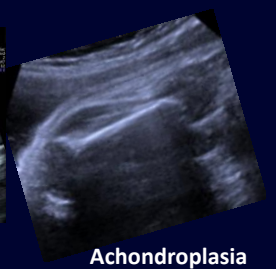


Normal



Achondroplasia

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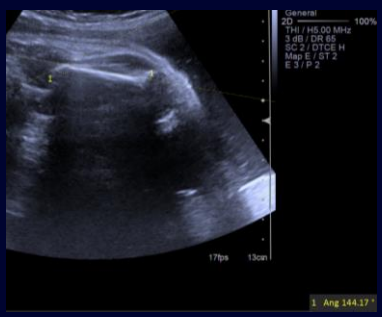

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Proximal Femoral Metaphysical-Diaphyseal Angle

- **Normal fetuses:**
  - **22 weeks: 98.5º ± 6.8º**
  - **32 weeks: 105.6º ± 7.3º**
    - **Boulet et al. Prenat Diagn 2009;29:697-702**
- **Achondroplasia**
  - **> 130º (5 of 6 fetuses)**
    - **Khalil et al. UOG 2014;44:69-75**

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Achondroplasia
Characteristic Findings

- Decreased interpedicular distance in the lumbar spine
- Trident Acetabulum
- "Champagne glass" configuration of the pelvis

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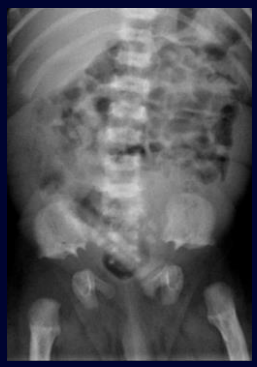

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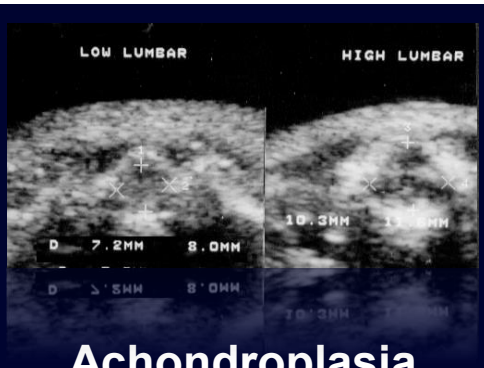

Achondroplasia

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Achondroplasia
Other Findings

- Large cranium
- Frontal bossing
- Depressed nasal bridge
- Facial hypoplasia
- Trident hand

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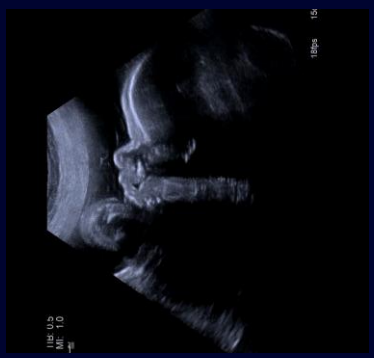

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Achondroplasia
Heterozygous Form

- Normal mental and sexual development
- Life expectancy similar to normal adult
- Long term morbidity:
  - Narrow craniocervical junction
  - Brain stem compression
  - Lumbar spine stenosis
  - Obesity

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Achondroplasia Homozygous Form

- Uniformly lethal
- Phenotype similar to thanatophoric dysplasia
- Both parents with achondroplasia
  - 25% chance of normal child
  - 50% chance of heterozygous achondroplasia
  - 25% chance of homozygous achondroplasia

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Hypochondroplasia

- Similar but milder radiographic findings than achondroplasia
- Differentiation based on clinical and radiologic criteria
- Autosomal dominant, but not always caused by FGFR3 mutation
- Narrow interpedicular distance of the lumbar spine
- However, trident hand is typical of achondroplasia

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Less Frequent but Still Among the 10 Most Common

- Achondroplasia
- Chondroenctodermal dysplasia (Ellis-van-Creveld)
- Asphyxiating thoracic dysplasia
- Chondrodysplasia punctata
- Diastrophic dysplasia

Camera & Mastroiacovo. Prog Clin Biol Res 1982
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Krakow et al. Am J Med Genet A 2008

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Chondrodysplasia Punctata

- Defining finding = stippling
  - aberrant calcium deposition in cartilage during endochondral bone formation
- Genetically heterogeneous disorders with additional common features:
  - maxillofacial hypoplasia - flat mid face and nose
  - limb shortening (various degrees and patterns)

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CDP Group

Condition	Inheritance	Gene
CDPX2 (Conradi-Hünermann)	X-linked dominant	EBP
CDPX1 (Brachytelephalangic type)	X-linked recessive	ARSE
CHILD	X-linked dominant	NSDHL
Keutel syndrome	Autosomal recessive	MGP
Greenberg dysplasia	Autosomal recessive	LBR
Rhizomelic CDP type 1	Autosomal recessive	PEX7
Rhizomelic CDP type 2	Autosomal recessive	DHPAT
Rhizomelic CDP type 3	Autosomal recessive	AGPS
CDP tibial-metacarpal type	Autosomal dominant	Unknown
Astley-Kendall dysplasia	Autosomal recessive ?	Unknown

CHILD: Congenital Hemidysplasia, Ichthyosis, Limb Defects

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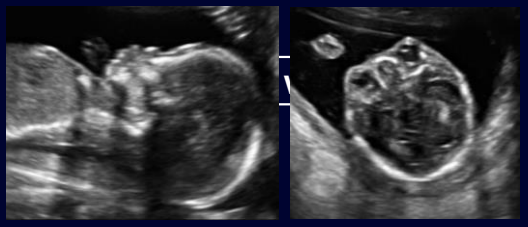

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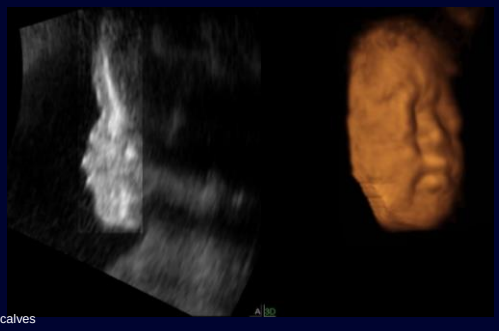

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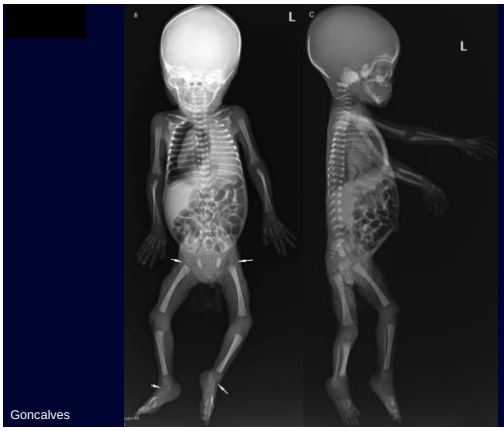

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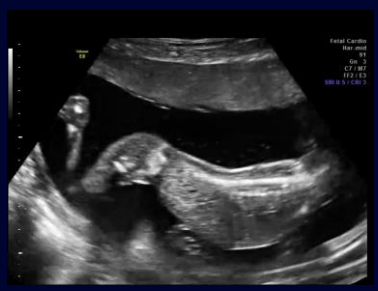
US at 20 Weeks



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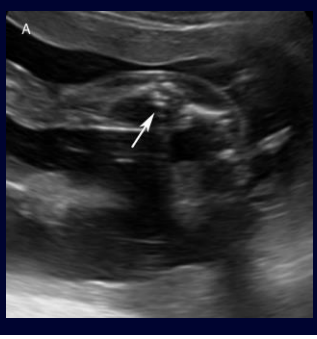
Stippling



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Rhizomelic CDPs (1, 2, 3)

- Autosomal recessive
- Rhizomelic shortening
  - Humerus more affected than femur
- Stippling
  - Proximal humerus more than distal
  - Great femoral trochanters
  - Patellae
  - Ischium, pubis, sacral allae
  - Tarsus, carpus
  - Sternum and laryngeal cartilages
- Metaphyseal splaying and irregularities (attention knee)
- Brachymetacarpalia, 4th more frequently involved
- Hypoplastic distal phalanges
- Spine: coronal vertebral body clefts
- Other: microcephaly / Cataracts

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CDPX1 (Brachytelephlangic)

- X-linked recessive - affects males
- No limb asymmetry
- Hypoplastic distal phalanges
- Short proximal phalanges, metacarpals and metatarsals
- Stippling:
  - Tarsal bones
  - Long bones, vertebrae, hips, chostochondral junctions, hyoid bone, tracheal cartilage
- Spine: mild platyspondyly, coronal and sagittal vertebral body clefts

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CDPX2 Conradi-Hünermann

- X-linked dominant
  - Mainly affects females / lethal in males
- Asymmetric rhizomelia, sometimes bowing
- Scoliosis
- Flexion contractures (hips, knees), clubfoot
- Stippling: generalized
- Other: polyhydramnios, Dandy-Walker spectrum, cataracts, skin abnormalities

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Prognosis

- Most severe forms lethal
  - Neonatal period or by the age of 2 years
  - Respiratory complications leading cause of death
- Milder phenotypes may have better prognosis

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Differential Diagnosis

- Warfarin embryopathy – phenocopy of CDPX1
  - Look for cerebral/internal organ hemorrhages
- Multiple other conditions:
  - Trisomies 18 and 21
  - Hydantoin and alcohol exposure
  - Maternal SLE, hyperemesis, Sjögren
  - Neonatal hypothyroidism
  - Multiple sulphatase deficiency
  - Zellweger syndrome
  - SLO
  - Mucolipidosis type 2
  - GM1 gangliosidosis
  - Cornelia de Lange syndrome

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Less Frequent but Still Among the 10 Most Common

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- Asphyxiating thoracic dysplasia
- Chondrodysplasia punctata
- Diastrophic dysplasia

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Diastrophic Dysplasia

- Autosomal recessive
- Caused by mutations in the diastrophic dysplasia sulfate transporter gene (DTDTS)
- Highly prevalent in Finland, carrier frequency 1-2%
- Not uniformly lethal
- Classified under the sulphation disorders group, which also includes achondrogenesis type 1B and atelosteogenesis type 2:
- Hitchhiker thumb

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Diastrophic Dysplasia Phenotype

- Rhizomelic micromelia
- Scoliosis
- Multiple joint contractures and subluxations
- Ulnar deviation of fingers
- Abducted thumb (“Hitchhiker thumb”)
- Multiple joint contractures and subluxations
- Occasional cleft palate, micrognathia and cardiac anomalies

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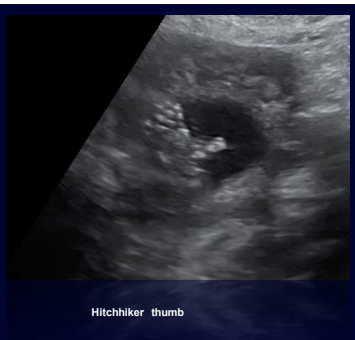

Diastrophic Dysplasia

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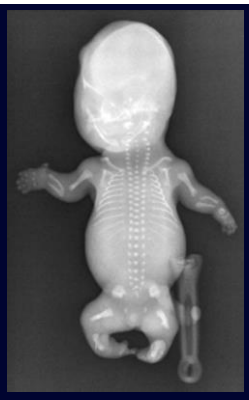

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Wax et al. J Ultrasound Med 2003;22:805

Conclusions

- Prenatal diagnosis of skeletal dysplasias is extremely challenging
  - Demands diligence and meticulous imaging
  - Multidisciplinary approach and postnatal confirmation are key

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Conclusions

- Most common lethal skeletal dysplasias:
  - Thanatophoric dysplasias
  - Osteogenesis imperfecta type 2
  - Achondrogenesis (types 1A, 1B, and 1C)

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Conclusions

- Differential diagnosis for demineralized skull:
  - Osteogenesis imperfecta type 2
  - Achondrogenesis type 1A
    - Types 1B and 1C have no demineralized skull
    - All have demineralized vertebral bodies
    - Type 1B is caused by DTST mutation and has a hitchhiking thumb
  - Hypophosphatasia
  - Cleidocranial dysplasia
    - Sutures are wide
    - Clavicles: absent, hypoplastic or pseudoarthrosis

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Conclusions

- Campomelic dysplasia:
  - Bowing anterior third of femur
  - Bowing of tibia
  - Upper extremities relatively unaffected
  - Hypoplastic scapulae
  - Sex reversal in 75%
    - Male karyotype / female or ambigous genitalia

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Conclusions

- Midface hypoplasia + stippling
  - Think chondrodysplasia punctata
    - Various forms
  - Think warfarin embryopathy

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Conclusions

- Skeletal dysplasias with hitchhiker thumb:
  - Diastrophic dysplasia
  - Achondrogenesis type 1B
  - Atelosteogenesis type 2

Lethality

- No single parameter is 100% sensitive or specific
- Best predictor = accurate diagnosis
- Commonly used parameters:
  - FL / AC < 0.16
  - CC / AC < 0.60
  - Lung volumes by 3DUS
  - Lung diameter measurement (right lung)

Key References

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Thank you