Human Skeletal Dysplasias

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October 27, 2022

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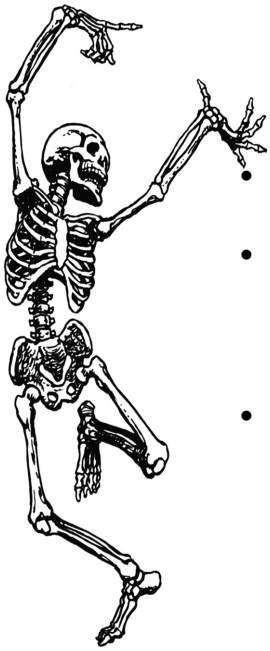

Human Skeleton

from the Greek, *skeletos,* "dried up"

- 206 bones
  - (126 appendicular, 74 axial, and 6 ossicles)
- Component of the musculoskeletal system
  - cartilage, tendons, ligaments & muscle
- Involved in
  - linear growth
  - mechanical support
  - movement
  - blood cell and mineral reservoir
  - protection of vital organs.

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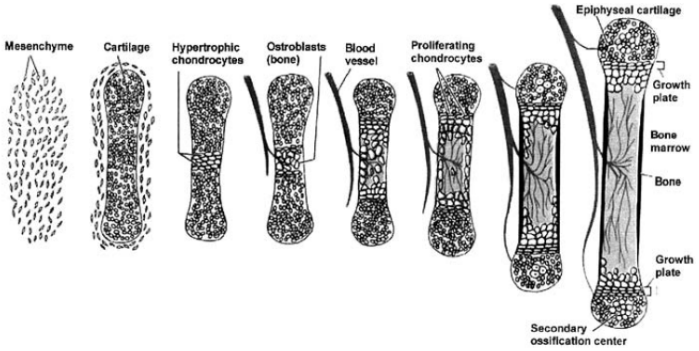
Skeletal Embryology



- All components derived from mesenchymal precursor cells
- Uncondensed mesenchyme undergoes cellular condensations at sites of future bones and joints
  - *Endochondral ossification*
  - *Membranous ossification*

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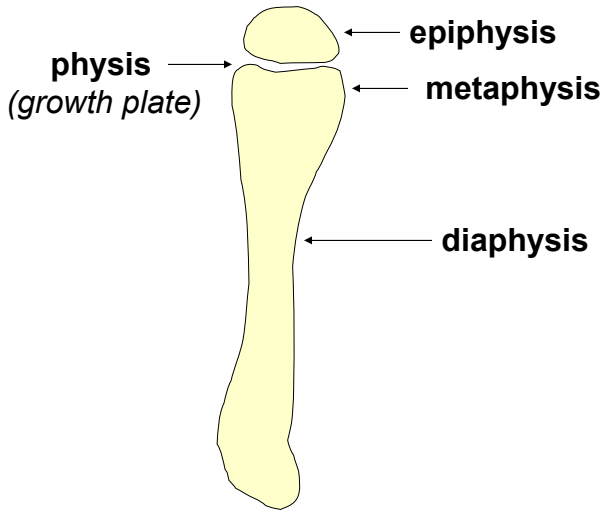
Long Bone Developmental Anatomy



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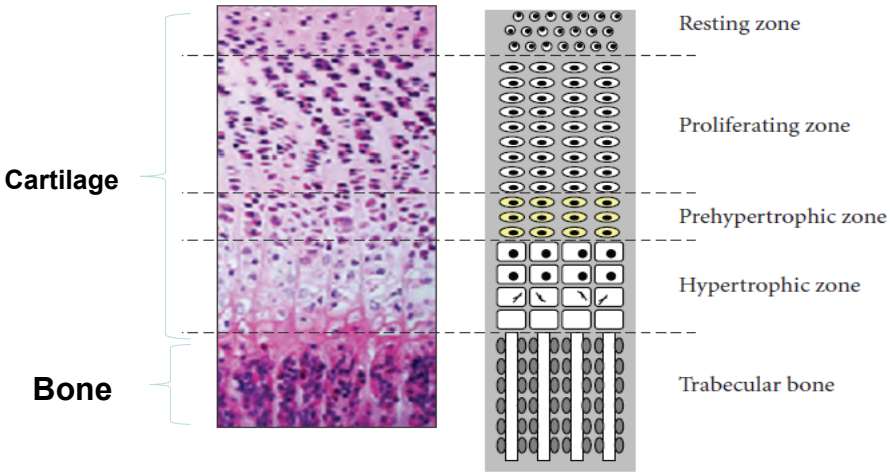
Endochondral Ossification



Tightly regulated program of proliferation, hypertrophy, degradation, and then replacement by bone (primary spongiosa)

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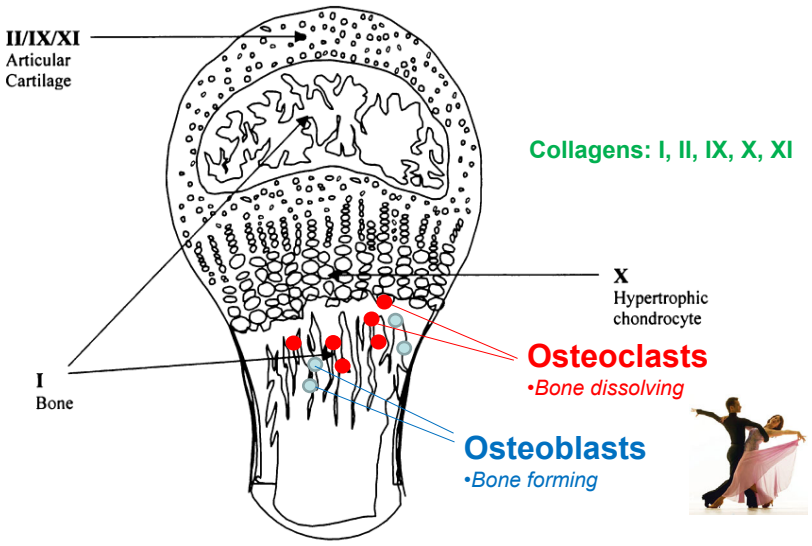
Bone Formation: *Constant Dynamic Remodeling Process*



"Calcium salts fixed on a protein matrix"

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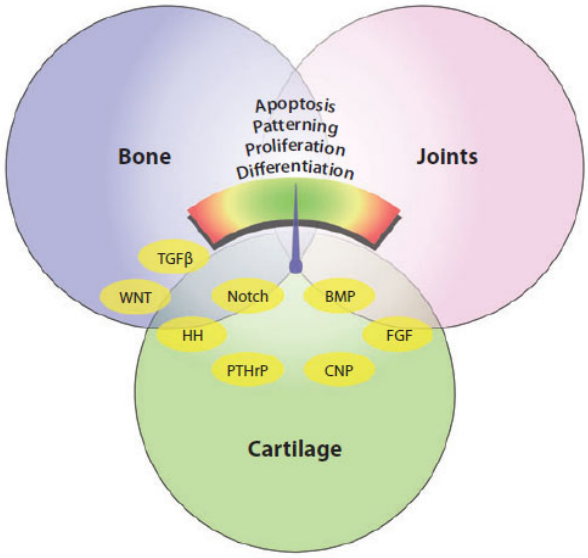

Signal Transduction

Baldridge et al. 2010 Annu. Rev. Genomics Hum. Genet. 11:189–217

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Skeletal Dysplasias

- Defined by a generalized abnormality in the skeleton
- Individually rare but collective incidence ~ 1 in 5000
- Range in phenotype from premature arthropathy in average stature individuals to severe skeletal dysplasia with perinatal mortality
- Associated with a variety of orthopedic, neurologic, auditory, visual, pulmonary, cardiac, renal, and psychological complications.
- Genetic etiology in most cases

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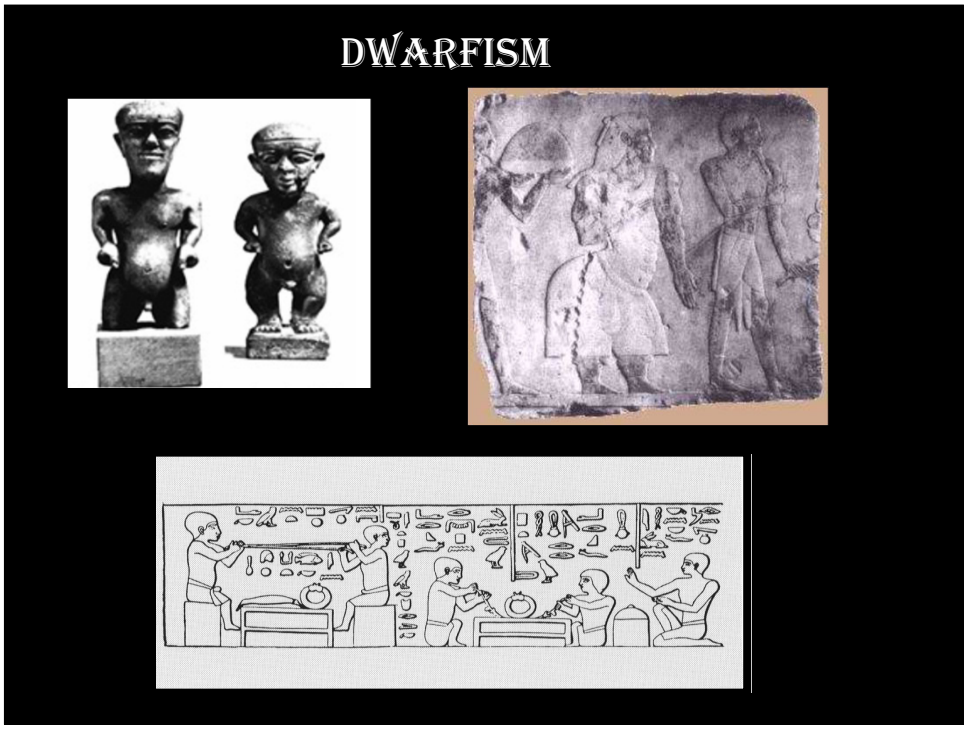

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Implications of Skeletal Dysplasia

- Some forms not compatible with survival
- Limited physical capacity
- Pain
- Syndrome specific other medical complications
- Social stigma
  - Short stature
  - Altered physical appearance
  - Subject of memes

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Short Stature

Definition: Below 5%ile height for age

Normal Growth Velocity

- Rule of 5s: 5 cm / year from age 4 years - puberty
  - ❖Familial short stature
  - ❖Constitutional growth delay

Growth Failure *(Decreased Growth Velocity)*

- Endocrine
- Systemic illness
- Genetic
- Idiopathic

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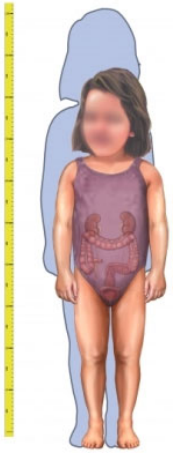
When to consider skeletal dysplasia in a child with growth failure?

- **Disproportionate body habitus**
  - ✓Trunk
  - ✓Extremities
  - ✓Head
- **Dysmorphic features**
  - ✓Face
  - ✓Spine
  - ✓Limbs



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Classification of Dwarfsim

- **Up until ~ 1960**
  - Pituitary dwarfism - **Proportionate**
  - Achondroplasia
  - Morquio syndrome

  } **Disproportionate**
- **1970s**
  - Increasing recognition of the genetic and clinical heterogeneity
  - Initial categories were purely descriptive and clinically based

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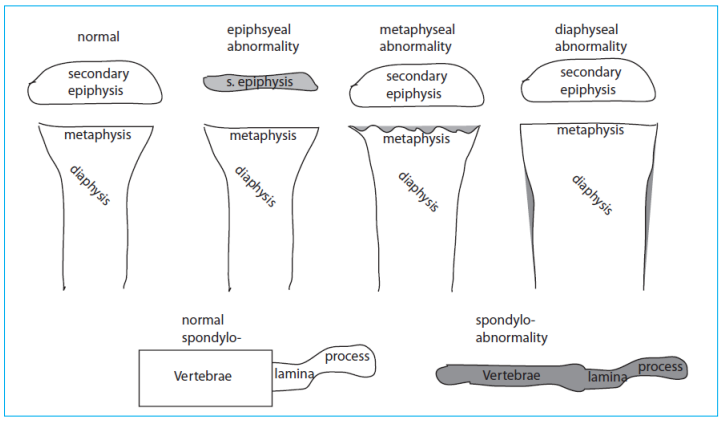
Classification of Skeletal Dysplasias

Initially based on clinical and radiographic findings



International Nomenclature of Constitutional Diseases of Bone
• 1970, 1977, 1983, 1992, 2001, 2005, 2009, 2011, 2015, 2019

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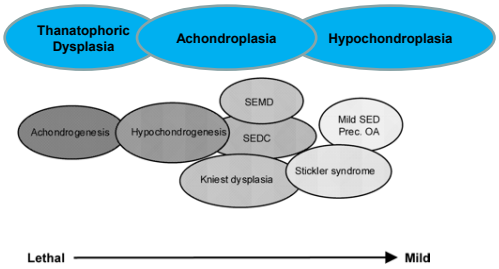
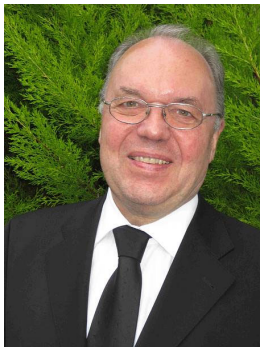
Classification of Skeletal Dysplasias

•Based on similarities in clinical, radiographic, and histomorphology, the skeletal dysplasias were classified into bone dysplasia families thought to share common pathophysiologic mechanisms

•Many of the predictions that were made based on plain film radiology were later confirmed by molecular and genetic analysis.





Jurgen Spranger, MD

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Current State of the Art:

AJMG AMERICAN JOURNAL OF medical genetics PART A

ORIGINAL ARTICLE

Nosology and classification of genetic skeletal disorders: 2019 revision

Geert R. Mortier, Daniel H. Cohn, Valerie Cormier-Daire, Christine Hall, Deborah Krakow, Stefan Mundlos, Gen Nishimura, Stephen Robertson, Luca Sangiorgi, Ravi Savarirayan, David Sillence, Andrea Superti-Furga, Sheila Unger, Matthew L. Warman . PMID: 31633310

461 conditions
42 groups

Pathogenic variants in 437 genes have been found in 425 (92%) of these disorders

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TABLE I.

Group/name of disorder	Inheritance	MIM No.	Locus	Gene	Protein	Notes
1. FGFR3 chondrodysplasia group						
Thanatophoric dysplasia type 1 (TD1)	AD	187600	4p16.3	*FGFR3*	FGFR3	Includes previous San Diego type
Thanatophoric dysplasia type 2 (TD2)	AD	187601	4p16.3	*FGFR3*	FGFR3	
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	AD	See 187600	4p16.3	*FGFR3*	FGFR3	
Achondroplasia	AD	100800	4p16.3	*FGFR3*	FGFR3	
Hypochondroplasia	AD	146000	4p16.3	*FGFR3*	FGFR3	
Camptodactyly, tall stature, and hearing loss syndrome (CATSHL)	AD	187600	4p16.3	*FGFR3*	FGFR3	Inactivating mutation
Hypochondroplasia-like dysplasia(s)	AD, SP					Similar to hypochondroplasia but unlinked to FGFR3, probably heterogeneous; uncertain diagnostic criteria
See also group 33 for craniosynostoses syndromes linked to FGFR3 mutations, as well as LADD syndrome in group 39 for another FGFR3-related phenotype						
2. Type 2 collagen group and similar disorders						
Achondrogenesis type 2 (ACG2; Langer–Saldino)	AD	200610	12q13.1	*COL2A1*	Type 2 collagen	
Platyspondylic dysplasia, Torrance type	AD	151210	12q13.1	*COL2A1*	Type 2 collagen	See also severe spondylodysplastic dysplasias (group 13)
Hypochondrogenesis	AD	200610	12q13.1	*COL2A1*	Type 2 collagen	
Spondyloepiphyseal dysplasia congenita (SEDC)	AD	183900	12q13.1	*COL2A1*	Type 2 collagen	
Spondyloepimetaphyseal dysplasia (SEMD) Strudwick type	AD	184250	12q13.1	*COL2A1*	Type 2 collagen	
Kniest dysplasia	AD	156550	12q13.1	*COL2A1*	Type 2 collagen	
Spondyloperipheral dysplasia	AD	271700	12q13.1	*COL2A1*	Type 2 collagen	
Mild SED with premature onset arthrosis	AD		12q13.1	*COL2A1*	Type 2 collagen	Often associated with p.R719C and p.G474S mutations
SED with metatarsal shortening (formerly Czech dysplasia)	AD	609162	12q13.1	*COL2A1*	Type 2 collagen	Often associated with the p.R275C mutation
Stickler syndrome type 1 Stickler-like syndrome(s)	AD	108300	12q13.1	*COL2A1*	Type 2 collagen	Unlinked to either COL2A1, COL11A1, or COL11A2. See also COL9A1 for recessive form

Mortier *et al.* Am J Med Genet. 2019:179A:2393-2419
PMID: 31633310

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Osteochondrodysplasias

- Abnormalities intrinsic to bone and cartilage
- Phenotypes evolve throughout life
- Multiple bones affected
- Divided into 2 general groups /37 subgroups
  - **Dysplasias**
    - Largest group
    - Abnormal bone and/or cartilage growth
  - **Osteodystrophies**
    - Abnormal bone and/or cartilage texture

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Dysostoses

- Abnormalities of blastogenesis
- Occur during first 6 weeks of fetal development
- Phenotype may evolve but does not affect other bones
- **3 Groups**
  - *A. Predominant craniofacial involvement*
  - *B. Predominant axial involvement*
  - *C. Predominant involvement of hands and feet*

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Diagnosis of Skeletal Dysplasias

- **Medical History**
  - Prenatal
  - Age of onset
  - Family History
  - Other medical issues
- **Physical Exam**
  - Height
  - Body proportions
  - Dysmorphic features
- **Radiographic Skeletal Survey**
  - Assessment of specific bone changes
- **Molecular Genetic Testing**
  - Selection of possible genes based on all of the above

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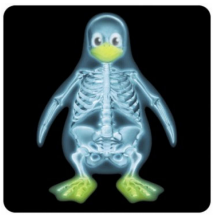
Diagnosis of Skeletal Dysplasias is Based Primarily on Radiographic Features



Essential Radiographs for a Genetic Skeletal Survey

- AP & Lateral skull
- AP & Lateral Spine *(cervical, thoracic, lumbar)*
- AP pelvis
- AP views of all four extremities
- Other films as needed *(e.g. lateral knee for MED)*

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Synopsis of Some of the More Common Forms of Skeletal Dysplasia

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FGFR3 Group

Autosomal Dominant
Map: 4p16.3
Gene: FGFR3

- Achondroplasia
- Hypochondroplasia
- Thanatophoric Dysplasia, Type I
- Thanatophoric Dysplasia, Type II
- SADDAN

Osteochondrodysplasia

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Achondroplasia

- Most common form of human short limbed dwarfism
- Autosomal dominant inheritance
- > 80% of cases are spontaneous
- Incidence ~1/20,000

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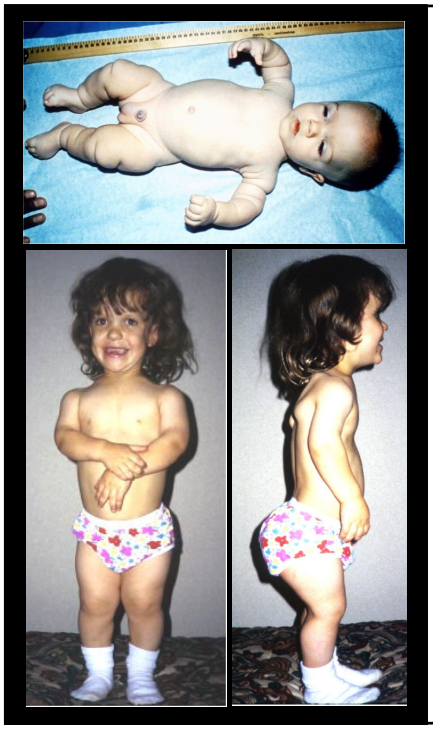

Clinical Features of Achondroplasia

- Rhizomelia
- Trident hand
- Megalencephaly
- Limitation of elbow extension
- Midface hypoplasia
- Exaggerated lumbar lordosis
- Frontal bossing
- Genu varum

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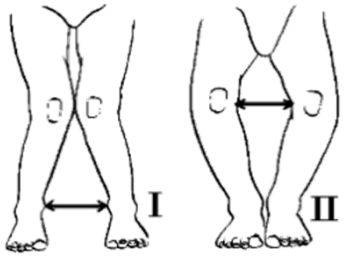
"Knock Knees" vs. "Bow Legs"

Genu valgum

Genu varum



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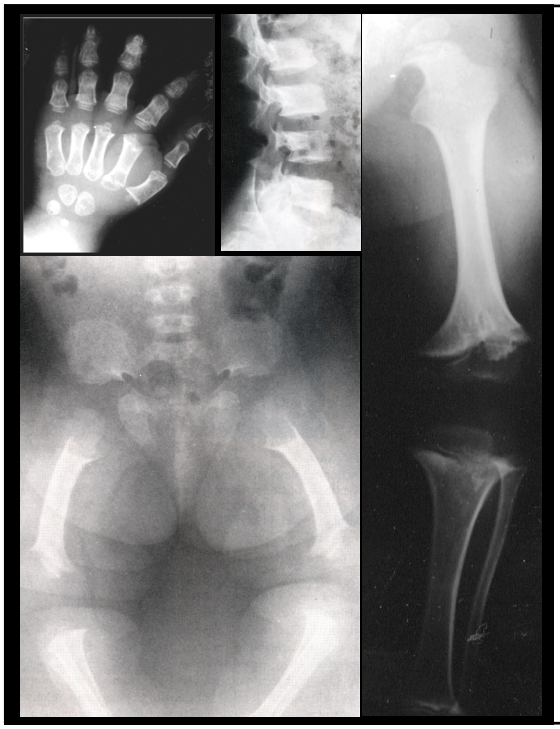

Radiologic Features of Achondroplasia

- Small cuboid vertebral bodies
- Progressive narrowing of caudal interpedicular distance
- Lumbar lordosis
- Thoracolumbar kyphosis
- Anterior beaking of L-1 & L-2
- Small iliac wings with narrow greater sciatic notch
- Short tubular bones with metaphyseal flare and cupping

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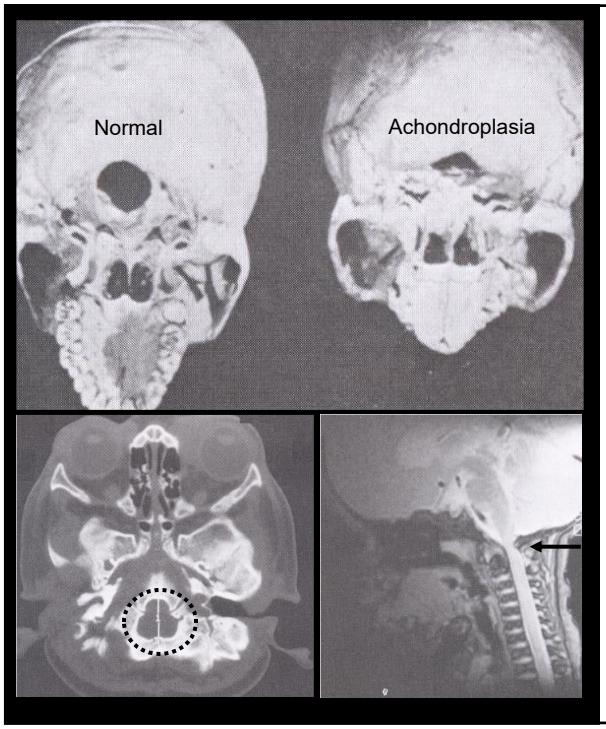

Clinical Issues in Achondroplasia

Small Foramen Magnum

- Hydrocephalus
- Spinal cord compression

Other Issues:

- Tibial bowing
- Kyphosis
- Otitis media
- Spinal stenosis

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Recently Published Guidelines for Clinical Care

CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

Pediatrics. 2020;145(6):e20201010
PMID: 32457214

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Health Supervision for People With Achondroplasia

Julie Hoover-Fong, MD, PhD, FACMG,[a] Charles I. Scott, MD, FAAP,[b] Marilyn C. Jones, MD, FAAP,[c] COMMITTEE ON GENETICS

Consensus Statement | Published: 26 November 2021

International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia

Ravi Savarirayan, Penny Ireland, Melita Irving, Dominic Thompson, Inês Alves, Wagner A. R. Baratela, James Betts, Michael B. Bober, Silvio Boero, Jenna Briddell, Jeffrey Campbell, Philippe M. Campeau, Patricia Carl-Innig, Moira S. Cheung, Martyn Cobourne, Valérie Cormier-Daire, Muriel Deladure-Molla, Mariana del Pino, Heather Elphick, Virginia Fano, Brigitte Fauroux, Jonathan Gibbins, Mari L. Groves, Lars Hagenäs, ... Svein Otto Fredwall + Show authors

Nature Reviews Endocrinology **18**, 173–189 (2022) | Cite this article

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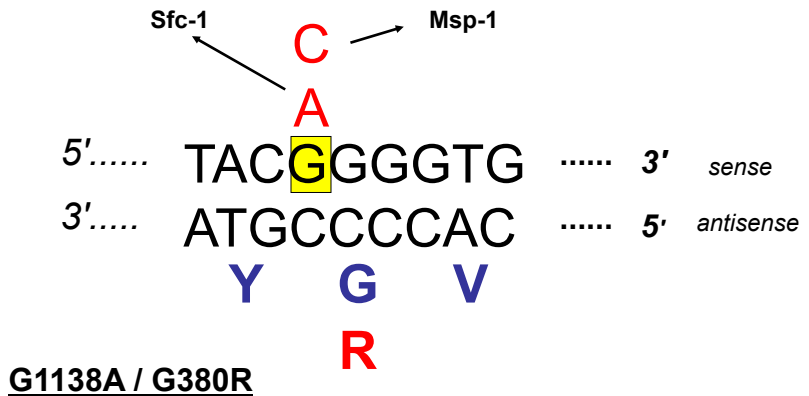
Achondroplasia Mutations

FGFR3 Exon 10



G1138A / G380R

"FGFR3 G1138 is the single most highly mutable nucleotide in the human genome"

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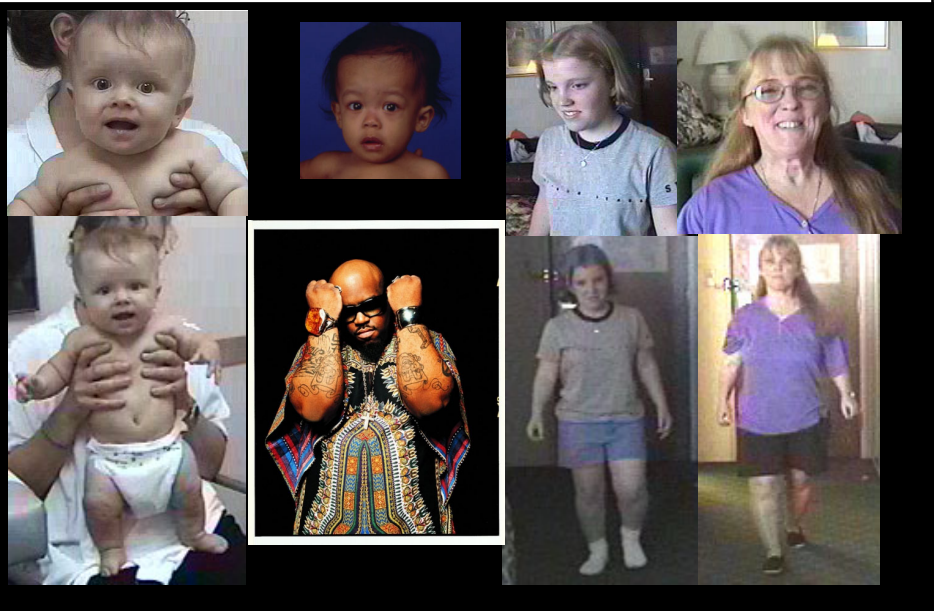
Hypochondroplasia



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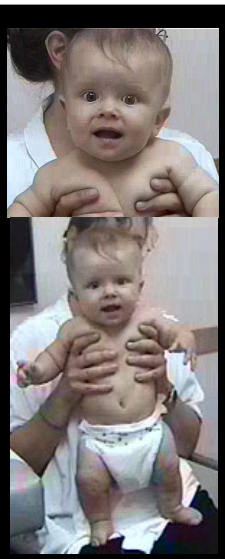
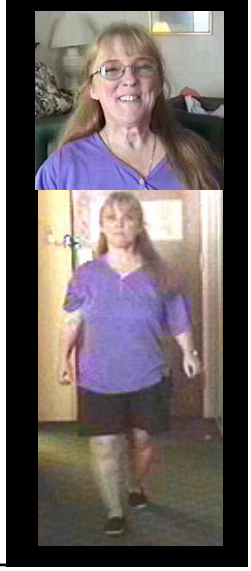
Hypochondroplasia



- Clinical and radiographic features are similar to but milder than achondroplasia
- Fewer medical complications
- May have higher incidence of developmental disabilities



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Thanatophoric Dysplasia

- Lethal skeletal dysplasia
- Sporadic occurrence
- Similar incidence to achondroplasia
- Two types recognized
  - **Type 1**
    - ✓Bent, short femurs
    - ✓Wafer thin vertebral bodies
    - ✓+/- cloverleaf skull
  - **Type 2**
    - ✓Straight, longer femurs
    - ✓Thicker vertebral bodies
    - ✓+ cloverleaf skull

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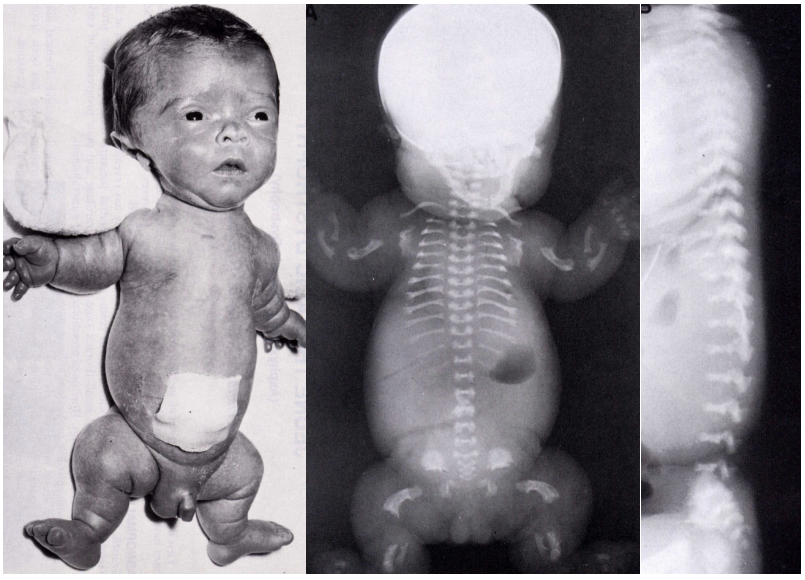
Thanatophoric Dysplasia, Type I



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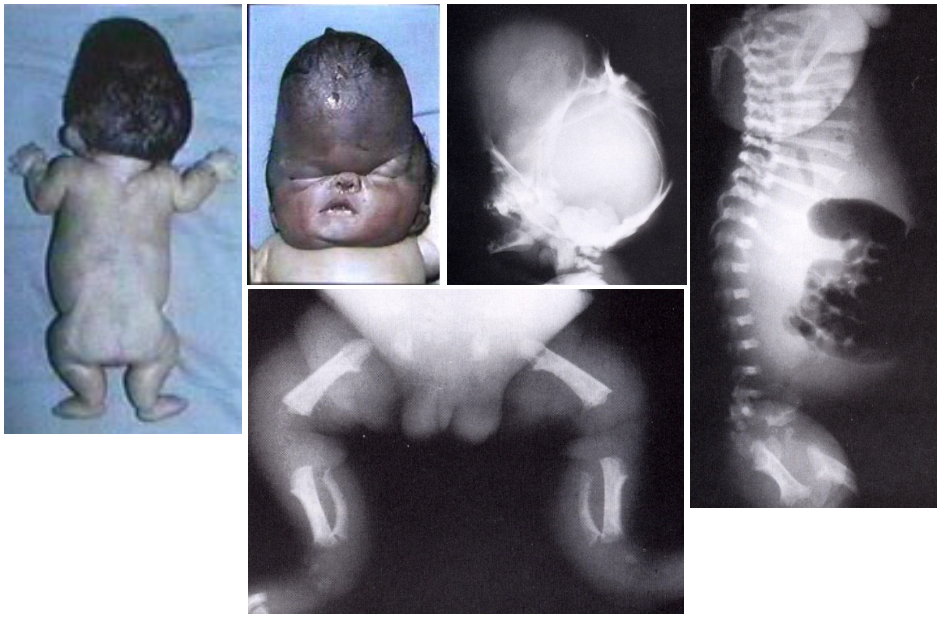
Thanatophoric Dysplasia, Type II



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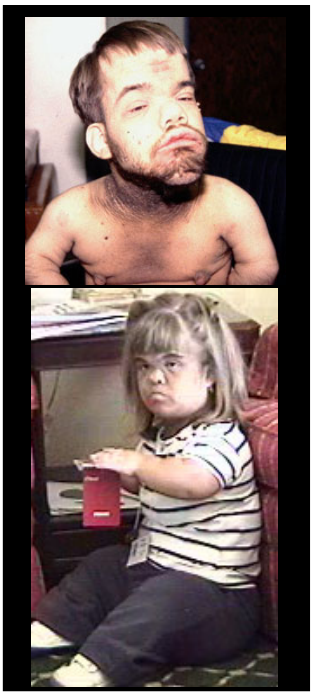
Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans (SADDAN)

- Severe skeletal dysplasia
- Profound developmental delay
- Seizures
- Acanthosis nigricans



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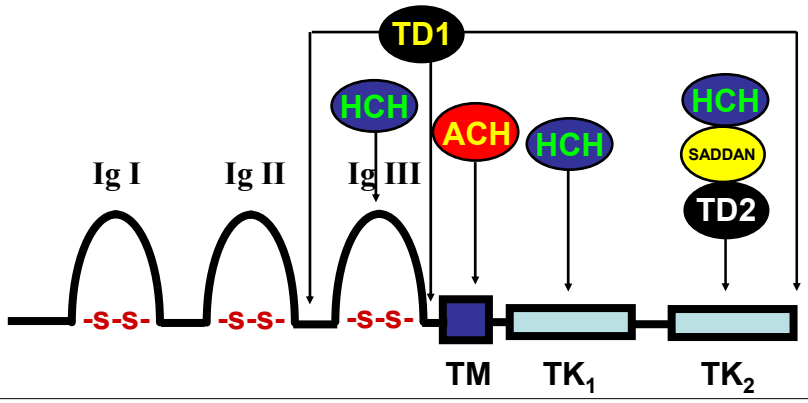
FGFR3 Mutations in Skeletal Dysplasias



TD1	TD2	ACH	HCH
R248C	K650E	G380R	N540K
S249C		G375C	N540T
G370C			I538V
S371C			K650N
Y373C			K650Q
X807G, C, L, R, W			

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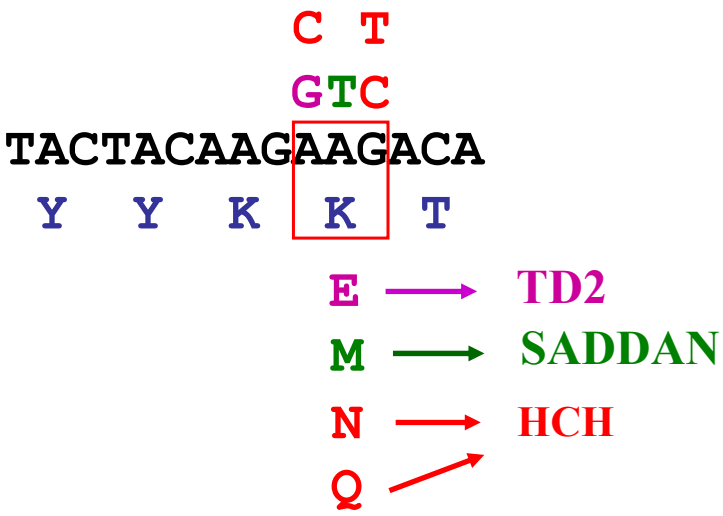
FGFR3: Exon 15



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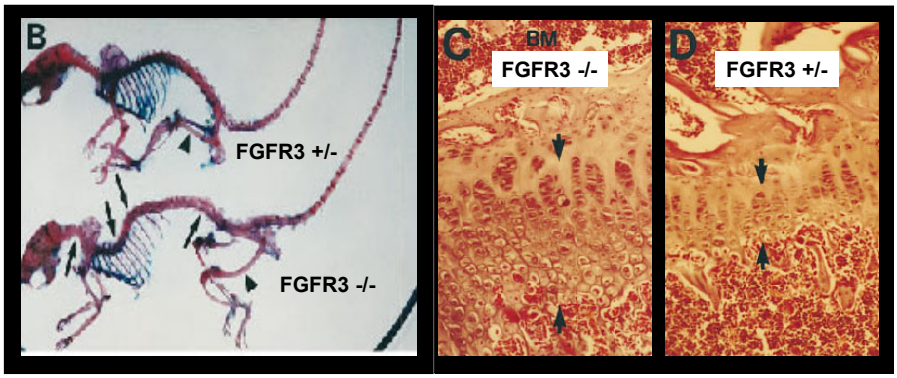
FGFR3 Is a Negative Regulator of Bone Growth



Deng, C.; Wynshaw-Boris, A.; Zhou, F.; Kuo, A.; Leder, P. Fibroblast growth factor receptor 3 is a negative regulator of bone growth. Cell 84: 911-921, 1996.

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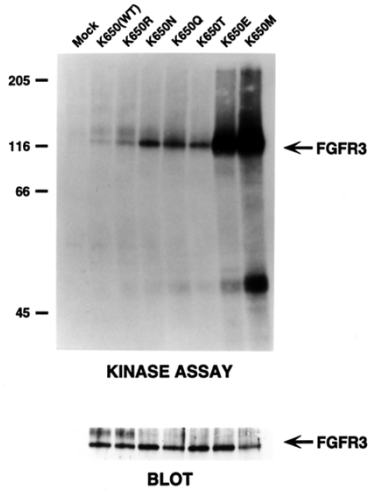
Intensity of FGFR3 Activation Correlates Well With Severity of Chondrodysplasia Phenotype

Exon 15:Lys 650 mutations



Bellus GA *et al.* Am J Hum Genet. 2000 Dec;67(6):1411-21.

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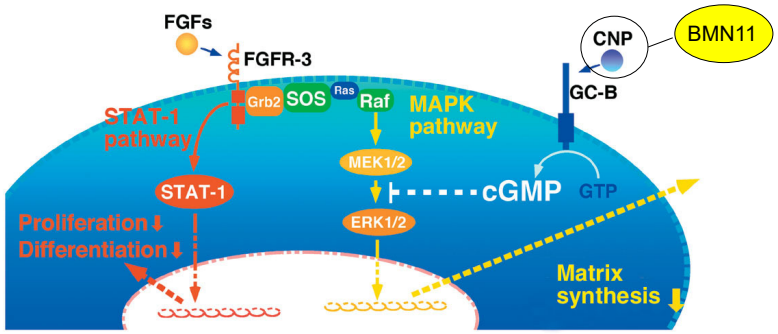
Proposed Treatment Strategy for Achondroplasia



•FGFR-3 inhibits endochondral bone growth by inhibiting proliferation and differentiation of growth-plate chondrocytes through the STAT-1 pathway and by decreasing extracellular matrix synthesis through the MAPK pathway.
•cGMP, the second messenger of CNP–GC-B, inhibits the MAPK pathway of FGFR-3 signaling, restores the decreased synthesis of the extracellular matrix and partially counteracts the dwarfism of achondroplastic bones

Yasoda *et al. Nature Medicine* 2004

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Type II Collagenopathies

Autosomal Dominant
Map: 12q13.1-q13.3
Gene: COL2A1

- **Achondrogenesis II (Langer-Saldino)**
- **Hypochondrogeneis**
- **Kneist dysplasia**
- **Spondyloepiphyseal dysplasia (SED) congenita**
- **Spondyloepimetaphseal dysplasia (SEMD) Strudwick**
- **SED with brachydactyly**
- **Mild SED with premature onset arthrosis**
- **Stickler dysplasia**

Osteochondrodysplasia

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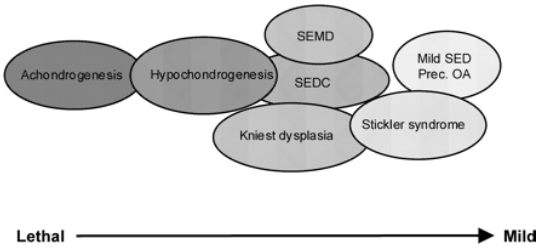
Type II Collagenopathies



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Kniest Dysplasia

- Marked short stature (39 -55")
- C-spine instability (hypoplastic dens)
- Enlarged joints, severe arthritis
- Kyphoscoliosis
- Flat facies, low nasal bridge
- Severe myopia
- Cleft palate is common
- Hearing loss
- Respiratory compromise
  - •Laryngotracheobronomalacia
  - •Micorgnathia /Robin sequence
  - •Narrow airways
  - •Chest constriction

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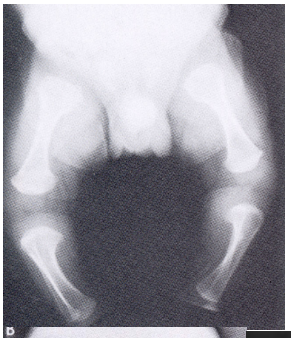
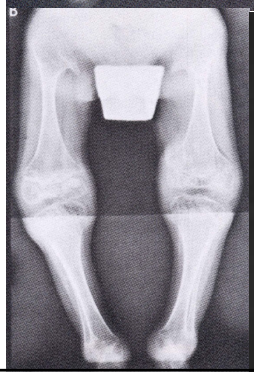
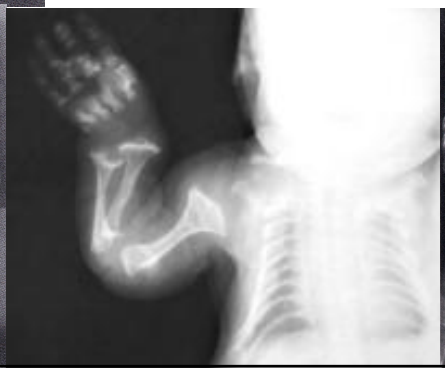
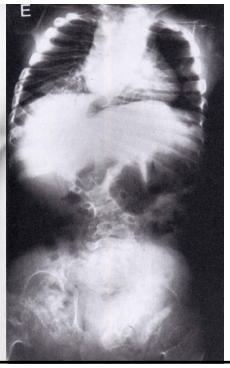


Kniest Dysplasia

- Platyspondyly
- Broad Ilia
- Broad short femoral necks
- Late ossification of capitol femoral epiphyses
- Short tubular bones with broad metaphyses
- Deformed epiphyses







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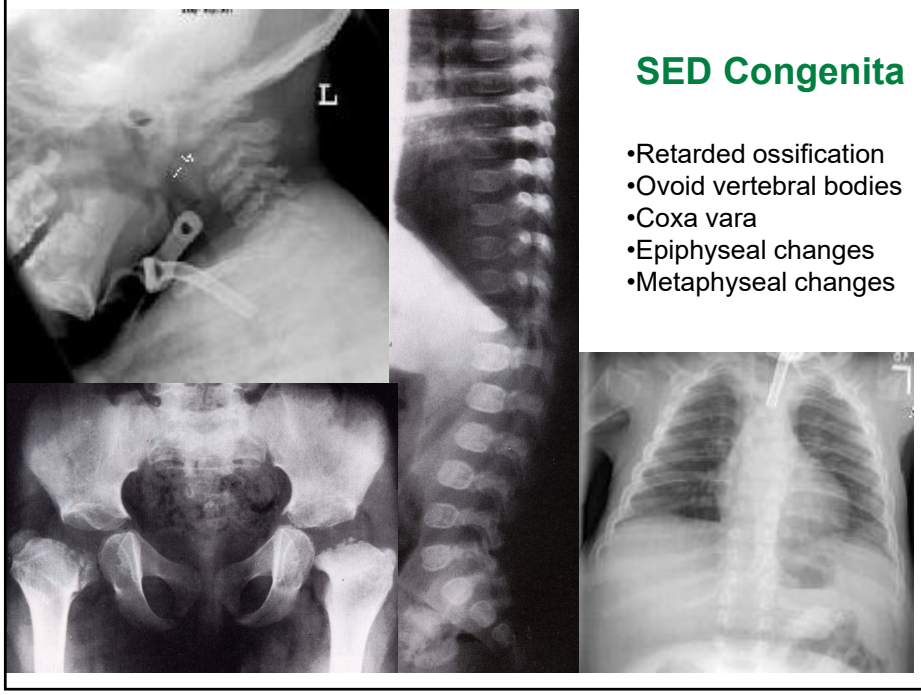
Greg & John Rice with LP friend

SED Congenita

- Marked short stature (36 - 48")
- Cervical instability (hypoplastic dens)
- Kyphoscoliosis
- Macrocephaly (hydrocephalus)
- Variable flat facies, malar hypoplasia
- Hearing loss
- Severe myopia
- Cleft palate relatively common
- Premature hip degeneration
- Respiratory compromise
  - Laryngotracheobronchomalacia
  - Chest constriction

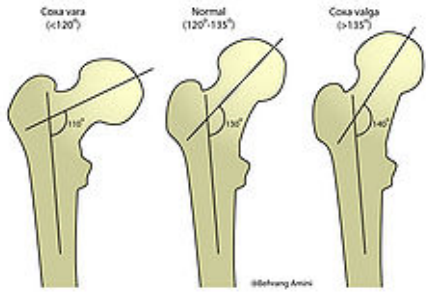
46



SED Congenita

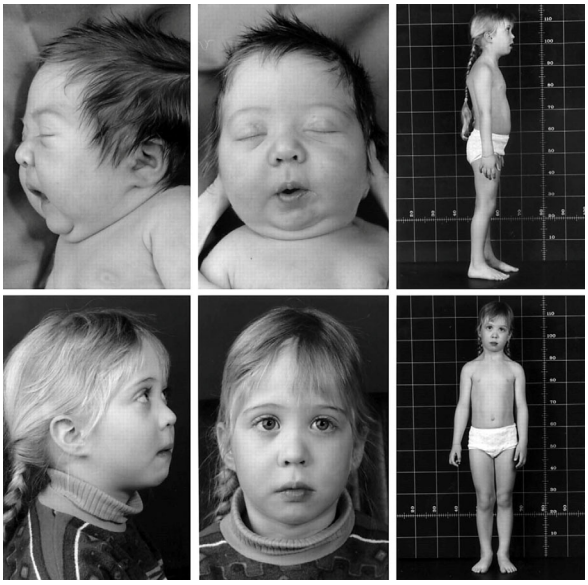
- Retarded ossification
- Ovoid vertebral bodies
- Coxa vara
- Epiphyseal changes
- Metaphyseal changes

47



Coxa vara is a deformity of the hip, whereby the angle between the ball and the shaft of the femur is reduced to less than 120 degrees. This results in the leg being shortened,

48

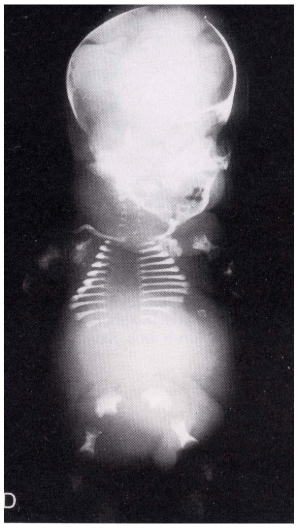


Stickler Syndrome

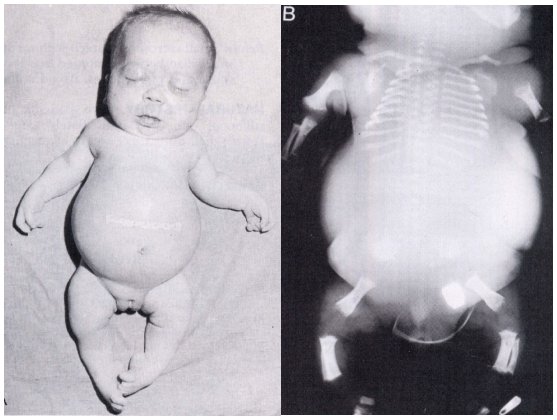
- Cleft palate
- Flat facies
- Depressed nasal bridge
- Severe myopia
- Average stature
- Arachnodactyly
- Hearing loss
- Arthritis
- Genetically heterogeneous
  - Col 2A1
  - Col 11A1
  - Col 11A2
  - Col 9A1 (recessive)

49

Achondrogenesis II
(Langer-Saldino)



Hypochondrogeneis



Neonatal lethal skeletal dysplasias

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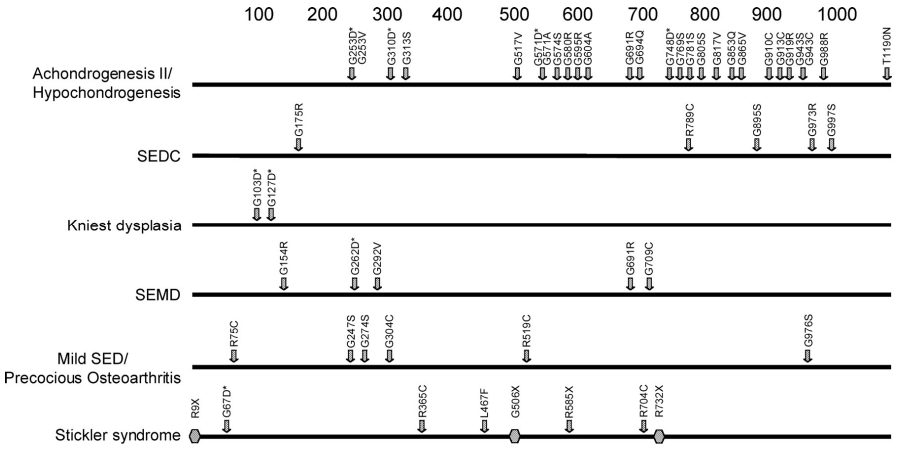
COL2A1 Mutations



Destabilize collagen protein matrix of bone

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Sulphation Disorders Group

Autosomal Recessive
Map: 5q32-q33
Gene: SOLUTE CARRIER FAMILY 26 (SULFATE TRANSPORTER), MEMBER 2; SLC26A2 / DTDST *(Diastrophic dysplasia sulfate transporter)*

- **Diastrophic dysplasia**
- **Achondrogenesis 1B**
- **Atelosteogenesis, type II**
- **Multiple Epiphyseal Dysplasia**

SEMD Omani Type –Chondroitin 6-sulfotransferase -CHST6 -10q22.1
SEMD Pakistani Type – PAPS-synthetase 2 -PAPSS2 -10q23-q24

Osteochondrodysplasia

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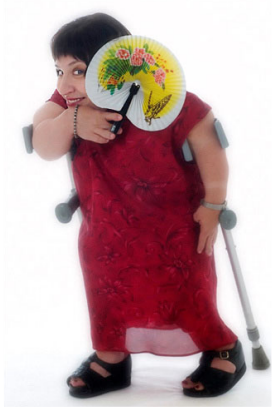

Diastrophic Dysplasia

- Delineated by Maroteaux & Lamy (1960)
- Name comes from geological term describing undulating rock formations
- Short limbed dysplasia
- Relatively rare but more common in Finland (~ 1:30,000)
- Normal lifespan past infancy

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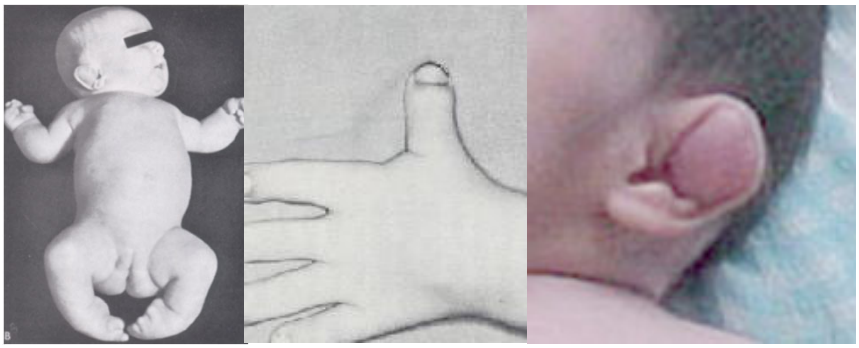
Diastrophic Dysplasia



- Short stature with prenatal onset
- Cystic mass in auricle that develops into hypertrophic cartilage is typical
- High incidence of laryngeal stenois (increased infant mortality)
- Severe talipes varus, “hitchhiker thumbs”, limited elbow extension, scoliosis
- Orthopedic surgical procedures are challenging
- Severity of clinical findings highly variable

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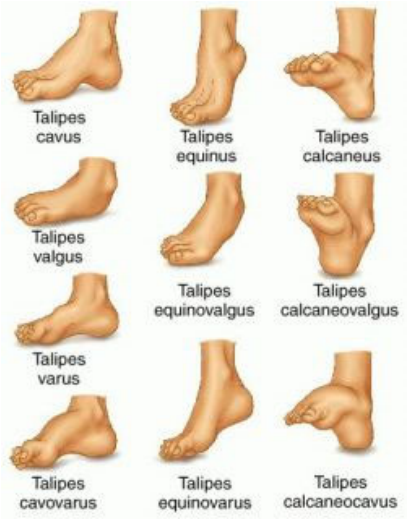
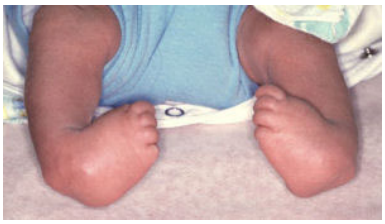
Classification of Foot Deformities





Bilateral club feet
Talipies equinovarus

Talipes *('ta-le-peas)*
Deformity of the foot. Condensation of Latin words for ankle (*talus*) and foot (*pedis*)

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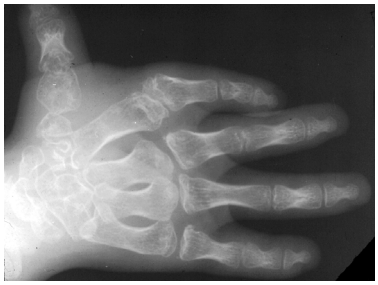
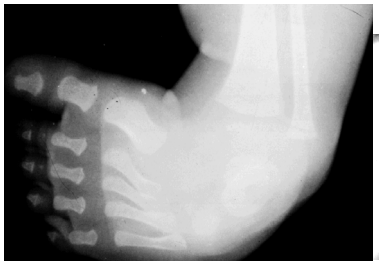
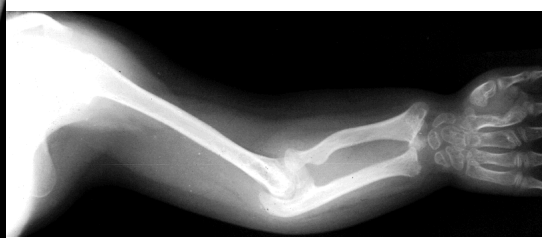
Radiologic Findings: Diastrophic Dysplasia



- Long bones are short and thick
- Mesomelic shortening
- Metaphyseal flaring
- Delayed epiphyseal development
- Early appearance of carpal centers
- Ankylosis of PIP joints





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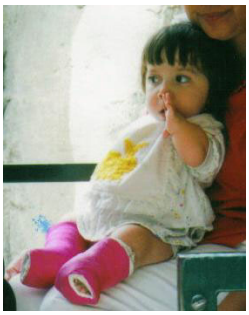
Clinical Issues: Diastrophic Dysplasia

A diastrophic baby may be born with, or develop, the following characteristics:



1. Severe shortening of limbs
2. Cleft palate
3. Ear deformities (85% of cases)
4. Progressive deformities and contractures of joints (100% of cases)
5. Progressive hip dysplasia (70% of cases; dislocation, 22% of cases)
6. Typical hand deformities, including "hitchhiker" thumbs (100% of cases)
7. Severe clubfoot (almost 100% of cases)
8. Progressive spinal curvature (lumbar lordosis ["swayback"], 100% of cases; scoliosis [s-shaped curves], 80% of cases; cervical kyphosis [abnormal neck flexion], percentage unknown)
9. Early degenerative changes of joints (100% of cases)

Online information booklet available
http://pixelscapes.com/ddhelp

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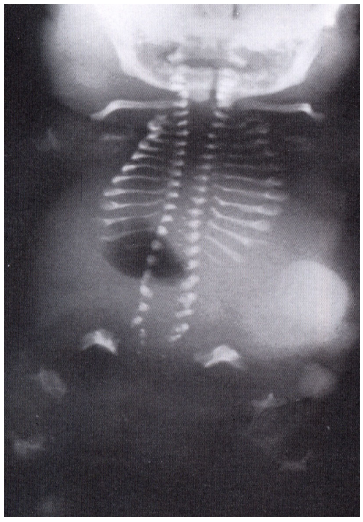
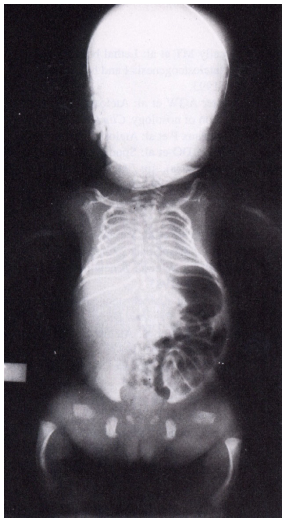
Achondrogenesis 1B



Atelosteogenesis, type II



Neonatal lethal skeletal dysplasias

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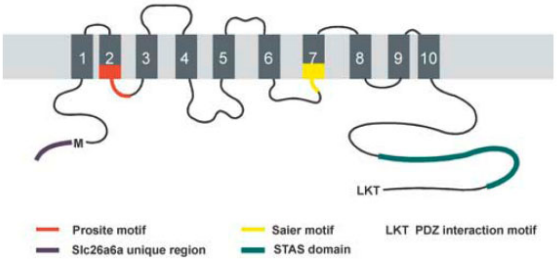
SLC26A2 (DTDST)

SOLUTE CARRIER FAMILY 26 (SULFATE TRANSPORTER), MEMBER 2

(Diastrophic dysplasia sulfate transporter)



- Sodium independent sulfate/chloride transporter
- Finnish mutation GT->GC transition in splice site
  - Reduced levels of DTDST mRNA
- **Pathogenesis:** Decreased levels of sulfated proteoglycans
  - Abnormal extracellular matrix impedes bone formation
  - Level of residual sulfate transport activity correlates with the severity of phenotype

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Metaphyseal Dysplasias

- Jansen type
- Schmid type
- McKusick type (cartilage-hair-hypoplasia)
- Schwachman-Diamond
- Adenosine deaminase deficiency

Osteochondrodysplasia

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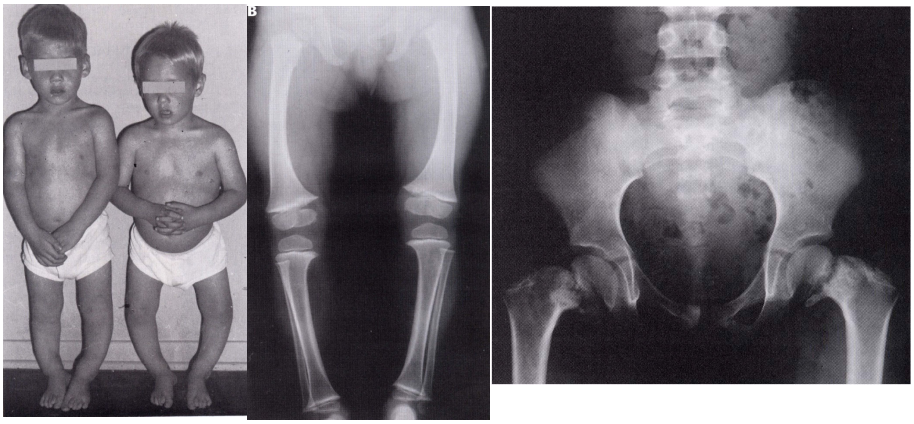
Schmid Metaphyseal Dysplasia



- Relatively mild skeletal dysplasia
- Splaying of metaphyses
- Coxa vara / genu varum
- Dominant / Col 10A1 mutations / 6q21-q22.3

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Cartilage-Hair Hypoplasia

- Severe short stature
- Fine, sparse, fragile hair
- Hypoplastic nails
- Cellular immunodeficiency
- Congenital hypoplastic anemia
- Increased malignancy risk *(lymphomas)*
- Recessive

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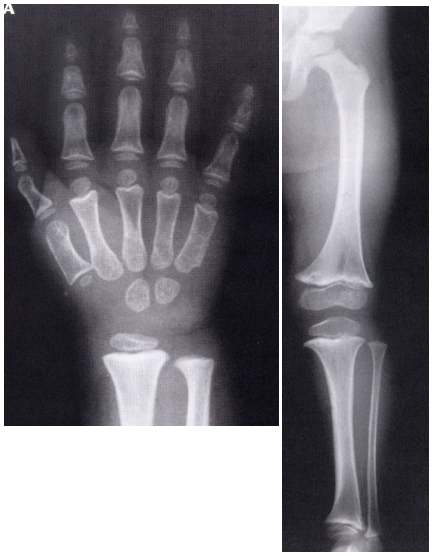
Cartilage-Hair Hypoplasia



- Scalloped metaphyses
- Shortened long tubular bones
- Shortened phalanges
- Long fibulas

Genetics

-Mutations in *RMPR*

- RNA component of Mitochondrial RNA-Processing Endoribonuclease
- Functions in ribosome assembly
- Allelic with
  - MD without hypotrichosis
  - Anauxetic dysplasia

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Multiple Epiphyseal Dysplasias

- Pseudoachondroplasia
- Multiple epiphyseal dysplasia (MED)
  (Fairbanks & Ribbing types)
- Other MEDs

Osteochondrodysplasia

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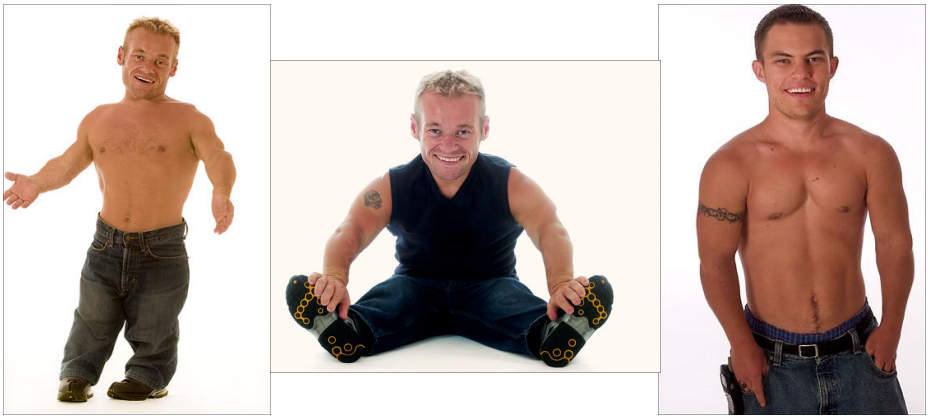
Pseudoachondroplasia



- Postnatal onset / severe short stature
- Short limbs
- Joint hypermobility (except elbows)
- Normal facies
- Genu varum or valgum (wind swept deformity)

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Ovitz Family

Musicians
Concentration camp survivors

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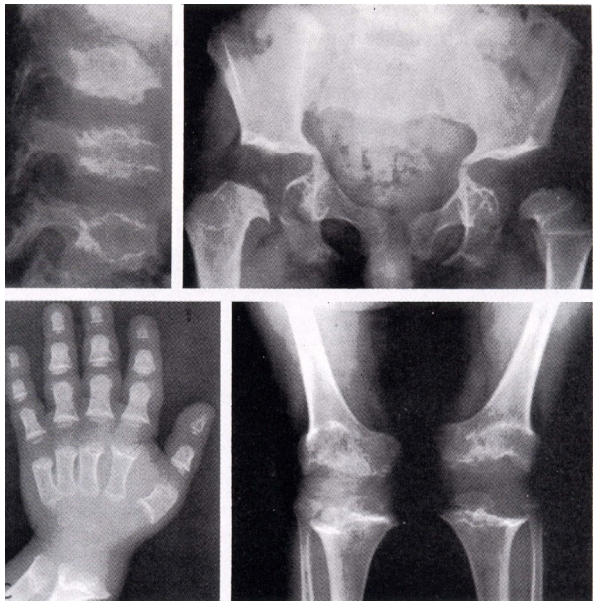
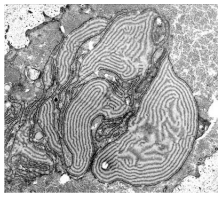
Pseudoachondroplasia



- Classified as MED but metaphyses often involved
- Severe spine changes
- Irregular epiphyses
- Flared dysplastic metaphyses

- **Genetics**
- Dominant / 19p13.1
- Collagen Oligomatrix Protein mutations (COMP)



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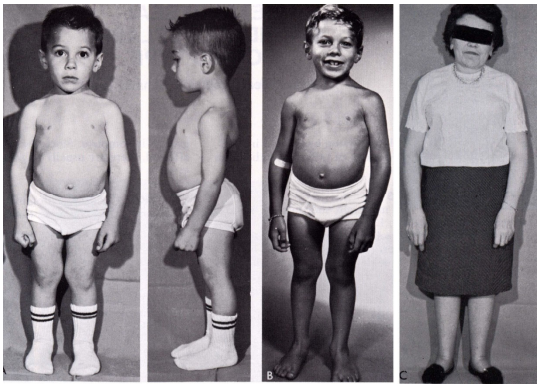

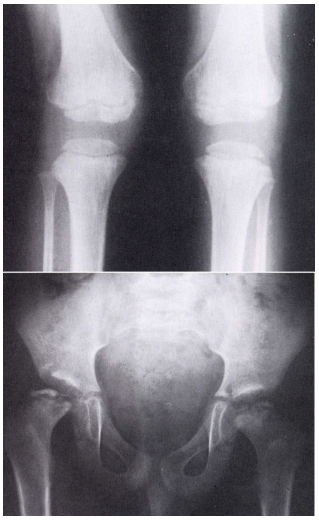

Multiple Epiphyseal Dysplasias

- Slight to moderate short stature
- Late ossifying epiphyses, mottled, irregular
- Osteoarthritis due to lack of articular cartilage in many joints
- Autosomal dominant / COMP/ Col9A1 /Col9A2 /Col9A3 /MATN3
- Autosomal recessive / DDST

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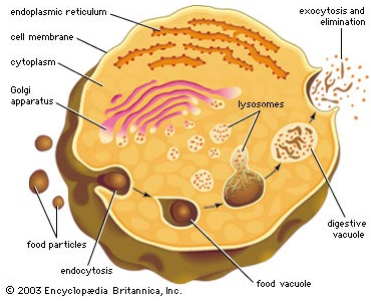
Lysosomal Storage Disorders with Skeletal Involvement "Dysostosis Multiplex"

- Mucopolysaccharidoses:
  1H/1S, 2, 3A, 3B, 3C, 4A, 4B, 6, 7
- Fucosidosis
- Alpha & beta mannosidoses
- Aspartylglucosaminuria
- GM1 Gangliosidosis
- Sialidosis
- Sialic acid storage diseases
- Galactosialidosis
- Mulitple sulfatase defciency
- Mucolipidosis II (I-cell disease)
- Mucolipidosis III (Pseudo-Hurler polydystrophy)



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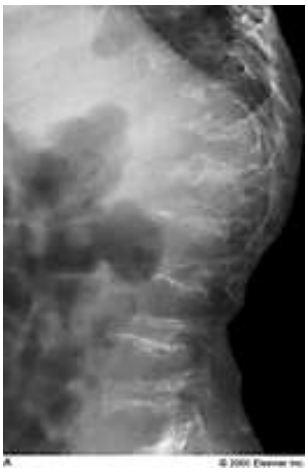

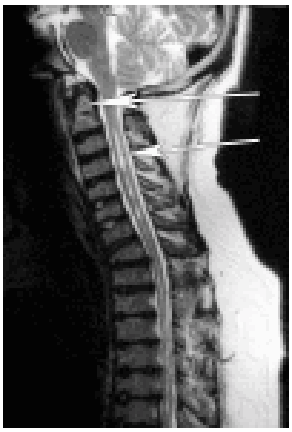

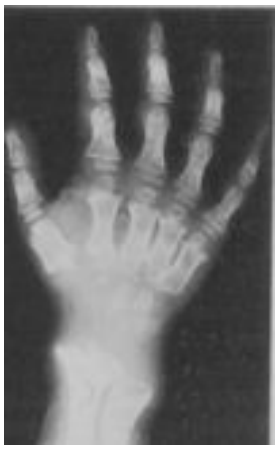

Dysostosis Multiplex

- Platyspondyly with central beaking of anterior VBs
- Odontoid hypoplasia with subluxation
- Marked dysplasia of radial and ulna metaphyses
- Short metacarpals
- Pointed distal ends of middle and distal phalanges

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Morquio Syndrome
(MPS 4A and 4B)

Autosomal Recessive
4A: galactosamine 6 sulfatase defciency (GALNS)
4B: beta galactosidase deficiency (GLB1)

Increased urinary excretion of keratan sulfate

Normal at birth
Onset at 1-3 years
- Coarse facial features
- Corneal opacities
- Mild hepatomegaly
- Short trunk
- Dysotosis multiplex
- Normal intelligence

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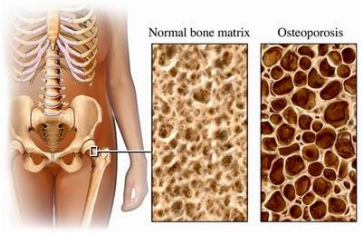
Decreased Bone Density Group



- **Osteogenesis Imperfecta**
- Bruck syndrome Type 1 & 2
- Singleton Merten dysplasia
- Geoderma osteodysplasticum
- Calvarial donut lesions with bone fragility
- Idiopathic junvenile osteoporosis
- Cole-Carpenter dysplasia
- Spondylo-ocular dysplasia
- Osteopenia with radiolucent lesion of the mandible

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Classification of Osteogenesis Imperfecta

Type of OI	Inheritance	Phenotype	Genetic defect
Classical Sillence Types			
I	AD	Mild	*COL1A1*
	X-linked	Mild	*PLS3*
II	AD	Letal	*COL1A1* or *COL1A2*
III	AD	Progressive deformity	*COL1A1* or *COL1A2*
IV	AD	Moderate	*COL1A1* or *COL1A2*
V	AD	Moderate, hypertrophic callus and ossification of the interosseous membrane	*IFITM5*
VI	AR	Moderate to severe	*SERPINF1*
VII	AR	Severe to letal	*CRTAP*
VIII	AR	Severe to letal	*LEPRE1*
IX	AR	Severe to letal	*PPIB*
X	AR	Severe	*SERPINH1*
XI	AR	Progressive deformity, contractures	*FKBP10*
XII	AR	Moderate	*SP7*
XIII	AR	Severe	*BMP1*
XIV	AR	Variable severity	*TMEM38B*
XV	AR	Variable severity	*WNT1*
	AD	Early-onset osteoporosis	

Valadares ER, Carneiro TB, Santos PM, Oliveira AC, Zabel B. What is new in genetics and osteogenesis imperfecta classification? J Pediatr (Rio J). 2014;90:536---41.

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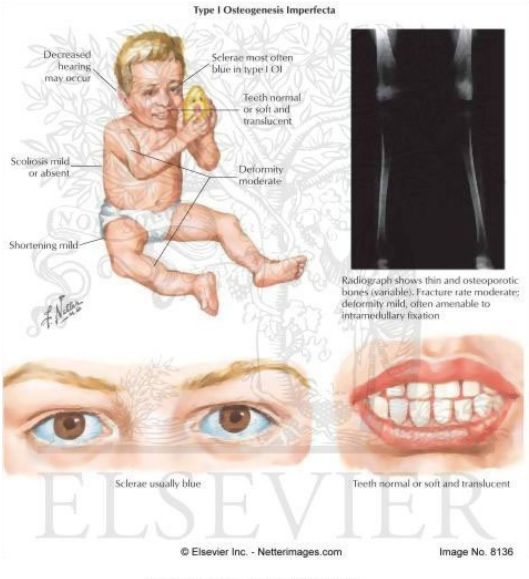
Osteogenesis Imperfecta

Type 1
- Decreased bone density
- Multiple fractures
- Blue sclera
- Hearing loss (variable)
- Soft, translucent teeth (variable)

Autosomal Dominant
COL1A1 & COL1A2



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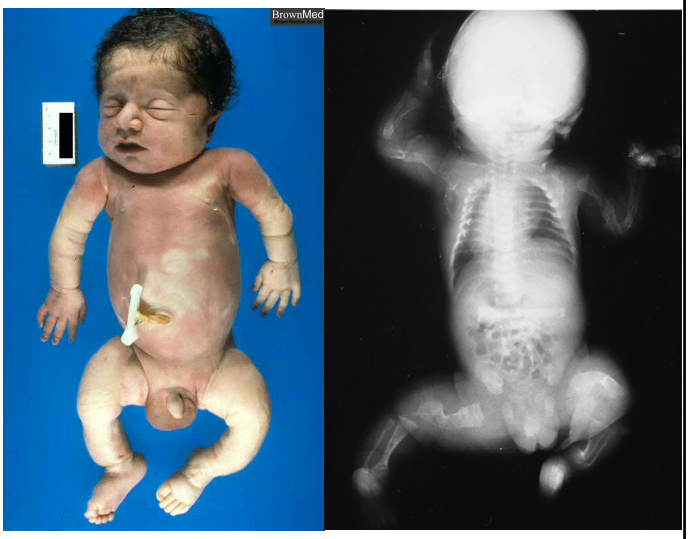
Osteogenesis Imperfecta

Type 2
- Usually lethal
- Prenatal growth delay
- Prenatal fractures

Sporadic
COL1A1 & COL1A2



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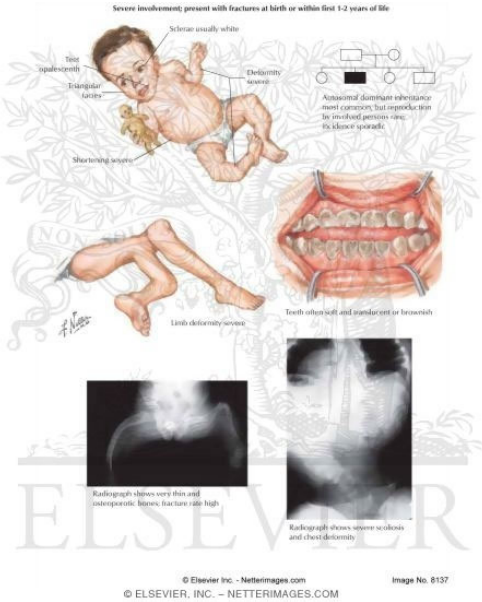
Osteogenesis Imperfecta

Type 3
- Decreased bone density
- Multiple fractures
- Progressive deformities
- Basilar impression
- Blue sclera
- Hearing loss
- Soft, translucent teeth (variable)

Autosomal Dominant
COL1A1 & COL1A2



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http://www.lpaonline.org/

LPA's new annual report now online

LPA Online

Welcome to the official website of Little People of America

"The Foos Family." Photograph copyright © 2006 by Gary Parker.
To view more of Parker's work, visit his website, GaryParker.com.

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Perception of Dwarfsim: 1900's

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2000's

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