
International Foundation for Pediatric Imaging Aid

The diagnostic dilemmas of skeletal dysplasia:

classification, frequency and mode of inheritance of different type (a clinical and radiological overview)

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Definition

- Dysplasia (osteochondroplasia)

  Conditions with an abnormal skeletal development, primarily resulted from mutated genes that are expressed in chondro-osteous tissue.

- Dysostosis

  Skeletal malformation occuring singely or in combination, and occuring during blastogenesis in the first eight weeks of embryonic life.

Definition

- In contrast to dysostosis, the skeletal dysplasias have a more general involvement and continue throughout life as a result of active gene.

- Skeletal disruption

  An additional entity following to substances or infection agents to which an embryo may be exposed.

Diagnostic of skeletal dysplasia

- The consulting pediatrician is mostly the first one who is involved in the diagnostic of skeletal dysplasia.
- Skeletal dysplasia should be suspected in patients with disproportionated skeletal development, unusual habitus or mental retardation.
- The next step in diagnosis of skeletal dysplasia is a radiological evaluation including skeletal survey.

Diagnostic of skeletal dysplasia

- A genetic councelling is indicated to determine the hereditary and molecular pathology in differentiation of dysplasia.

- Second opinion of national or international experts is needed in cases of rare skeletal dysplasia.

Important clinical and radiological terms

- Micromelia: severe shortening of all four limbs
- Rhizomelia: shortening of upper segment of extremities
- Mesomelia: shortening of middle segment of extremities
- Acromelia: shortening of lower segment of extremities
- Trunk shortening: following spinal deformaties

Radiological assessments in diagnostic of skeletal dysplasia

1. Disproportionated skeletal development
2. Abnormalities of epiphyseal, metaphyseal and spinal ossification
3. Craniofacial deformities, structural changes and cranial sutures
4. Assessment of bone densities
5. Primary or secondary changes of joints and soft tissues

Classification

- The classification of skeletal dysplasia was updated in 2001 by an international nomenclature group.
- The skeletal dysplasia were divided in 33 groups including 296 different types and subtypes of dysplasia.
- 3 groups (including 39 disorders) of genetically determined dysostosis were added to the classification.

Classification of Constitutional Disorders of Bone

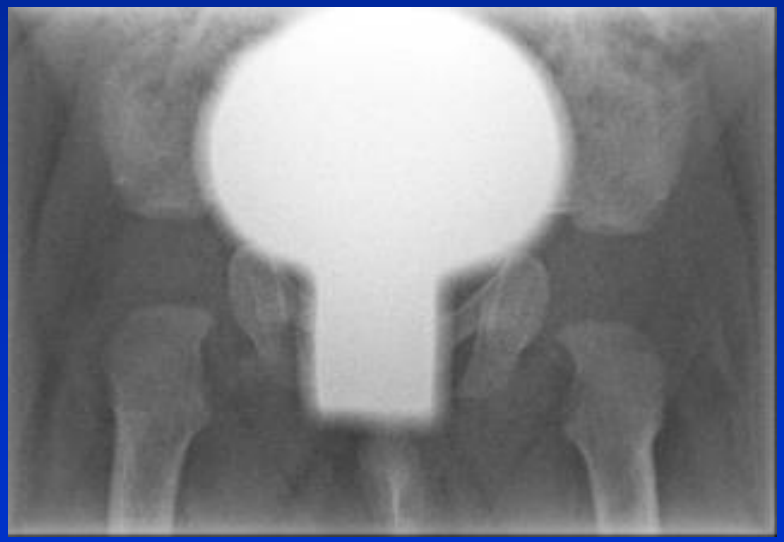
1. Achondroplasia group (6)
2. Severe spondylodysplastic dysplasias (4)
3. Metatropic dysplasia group (3)
4. Short-rib dysplasia (SRP) (with or without polydactyly) group (6)
5. Atelosteogenesis-omodysplasia group (5)
6. Diastrophic dysplasia group (3)
7. Dyssegmental dysplasia group (2)
8. Type II collagenopathies (9)
9. Type XI collagenopathies (5)
10. Other spondyloepi-(meta)-physeal (SE(M)D) dysplasias (12)
11. Multiple epiphyseal dysplasias & pseudoachondroplasia (6)
12. Chondrodysplasia punctata (CDP) (stippled epiphyses group) (10)
13. Metaphyseal dysplasias (8)
14. Spondylometaphyseal dysplasias (SMD) (3)
15. Brachyolmia spondylodysplasias (3)
16. Mesomelic dysplasias (11)
17. Acromelic dysplasias (19)

Classification of Constitutional Disorders of Bone

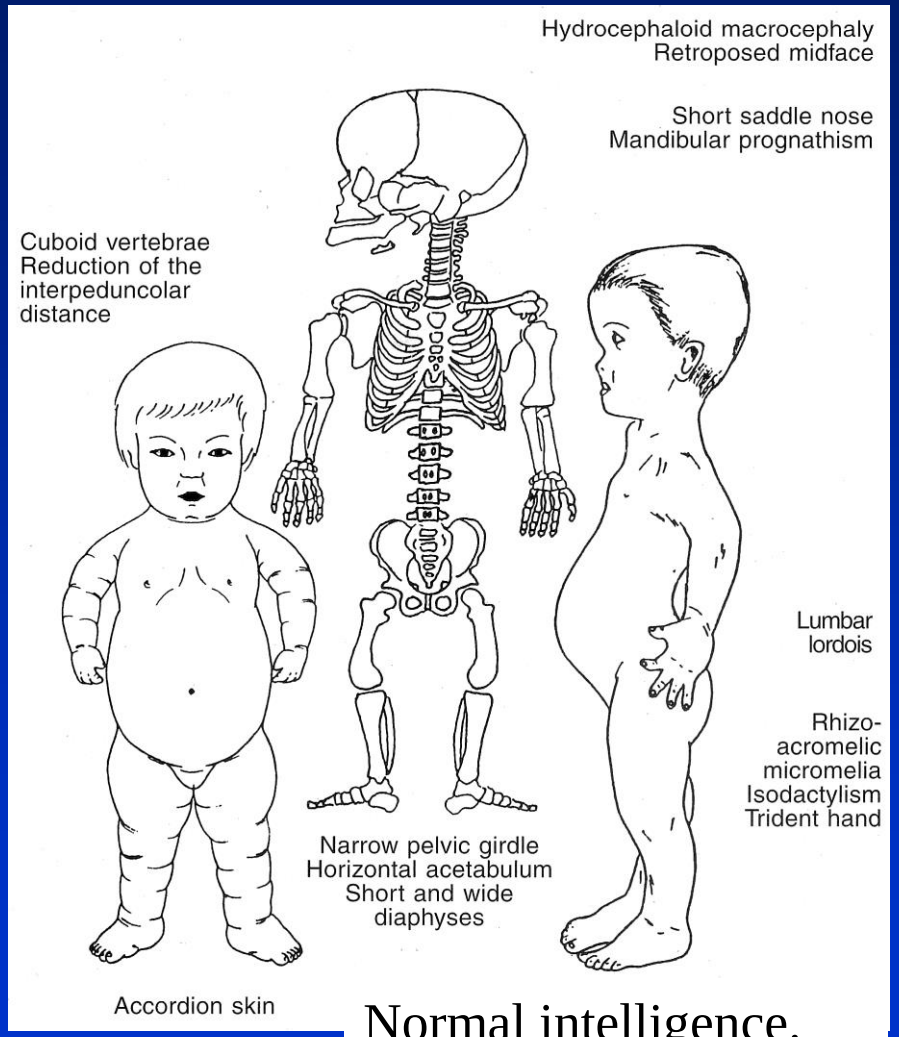
18. Acromesomelic dysplasias (6)
19. Dysplasia with predominant membranous bone involvement (4)
20. Bent-bone dysplasia group (3)
21. Multiple dislocations with dysplasias (4)
22. Dysostosis multiplex group (22)
23. Low birthweight slender bone group (4)
24. Dysplasias with decreased bone density (21)
25. Dysplasias with defective mineralization (5)
26. Increased bone density without modification of bone shape (17)
27. Increased bone density with diaphyseal involvement (14)
28. Increased bone density with metaphyseal involvement (3)
29. Craniotubular digital dysplasias (5)
30. Neonatal severe osteosclerotic dysplasias (5)
31. Disorganized development of cartilaginous and fibrous components of the skeleton (17)
32. Osteolyses (7)
33. Patella dysplasias (5)

Achondroplasia

MI: AD
MP: Ch.L.: 4p16.3
Gene: FGFR3
Fr.:1:26.000

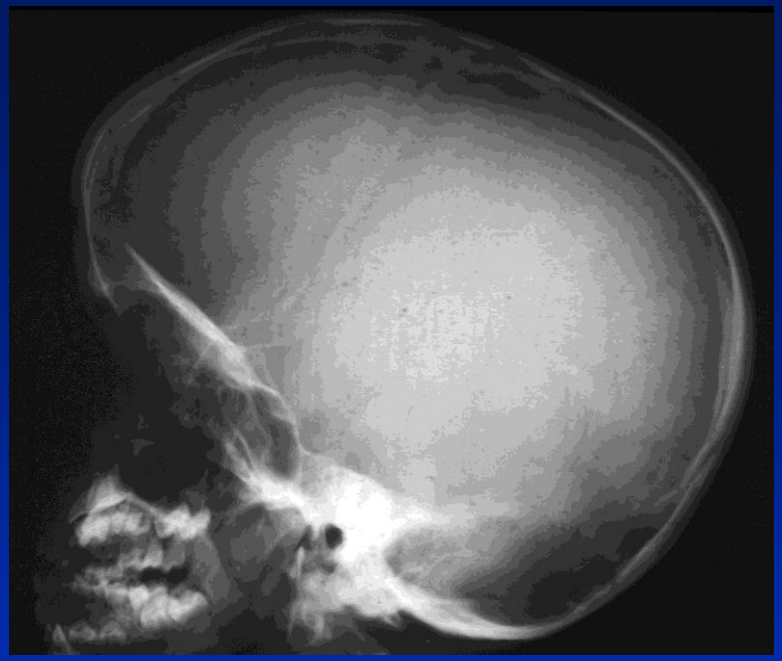


Flat, rounded iliac bones

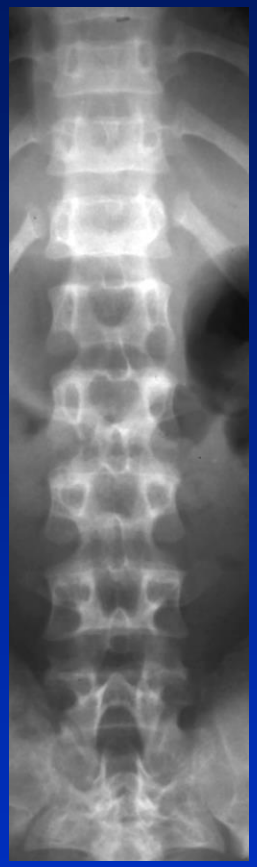


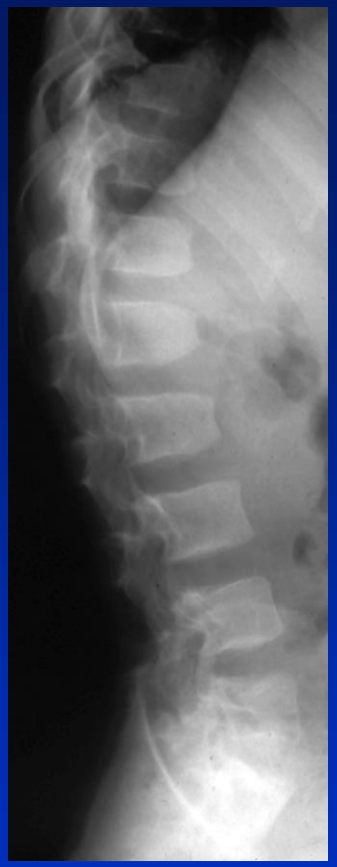
Normal intelligence.

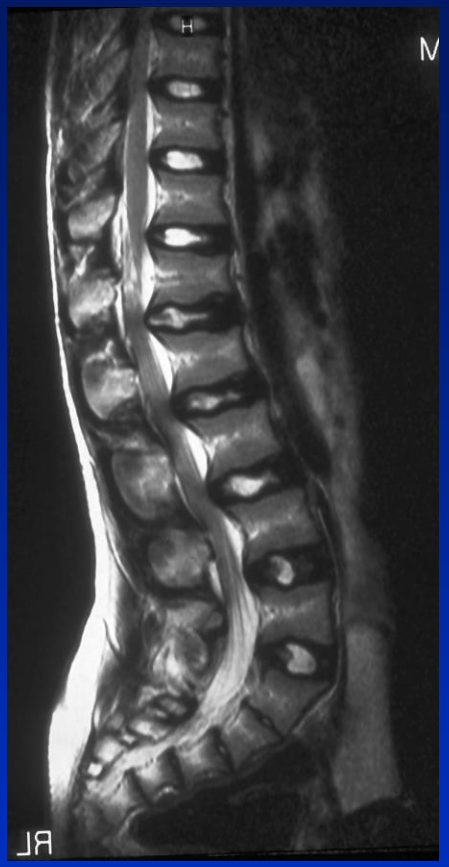
Micromelic dwarfism



Large calvaria





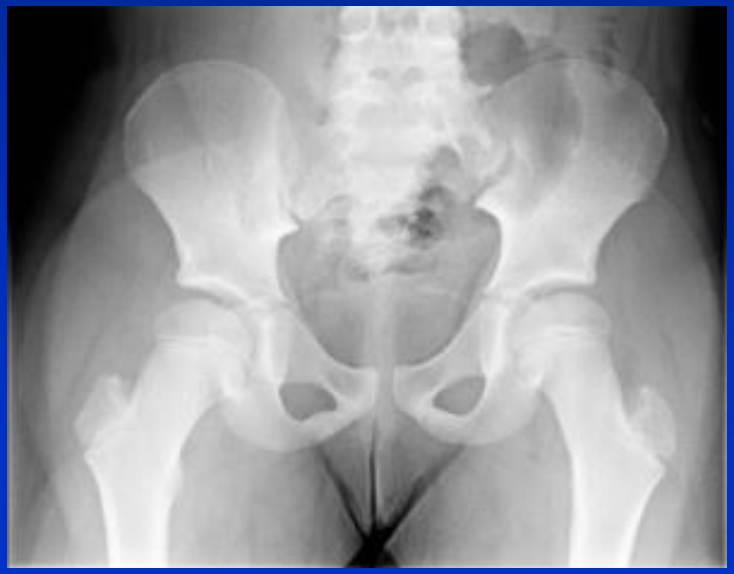


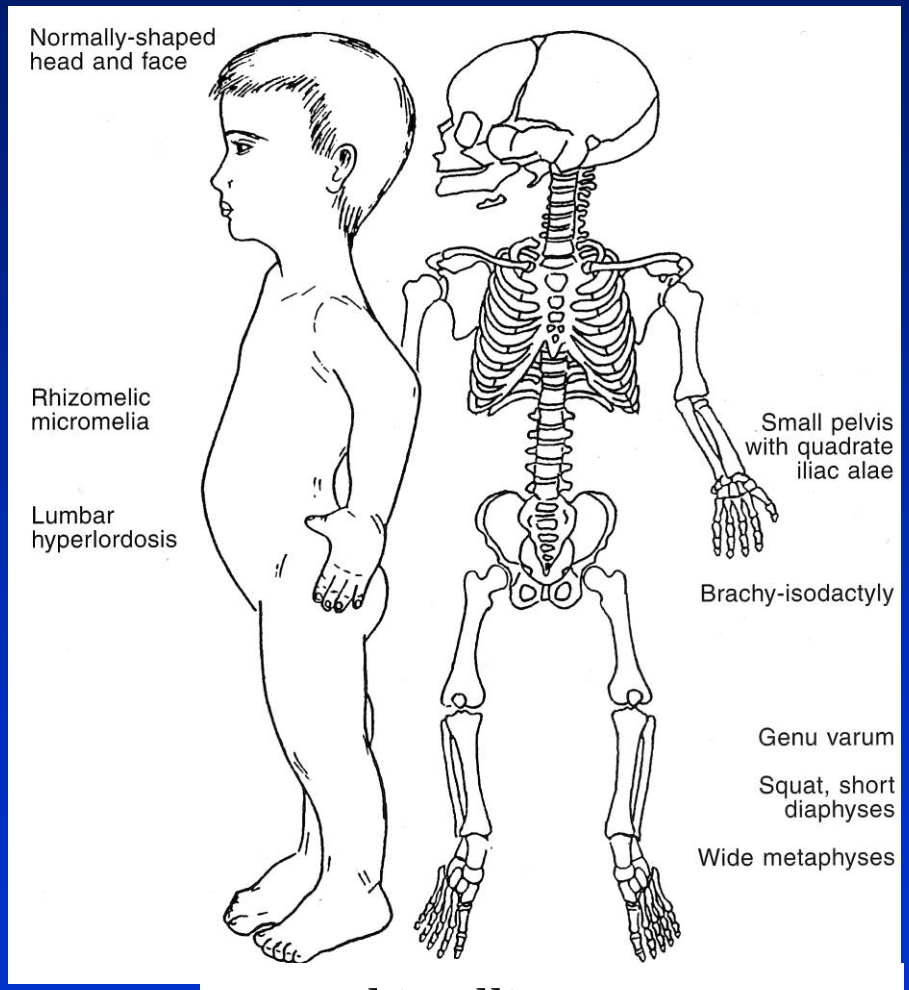
Decreased interpediculate distance

Narrowing of spinal canal

Hypochondroplasia

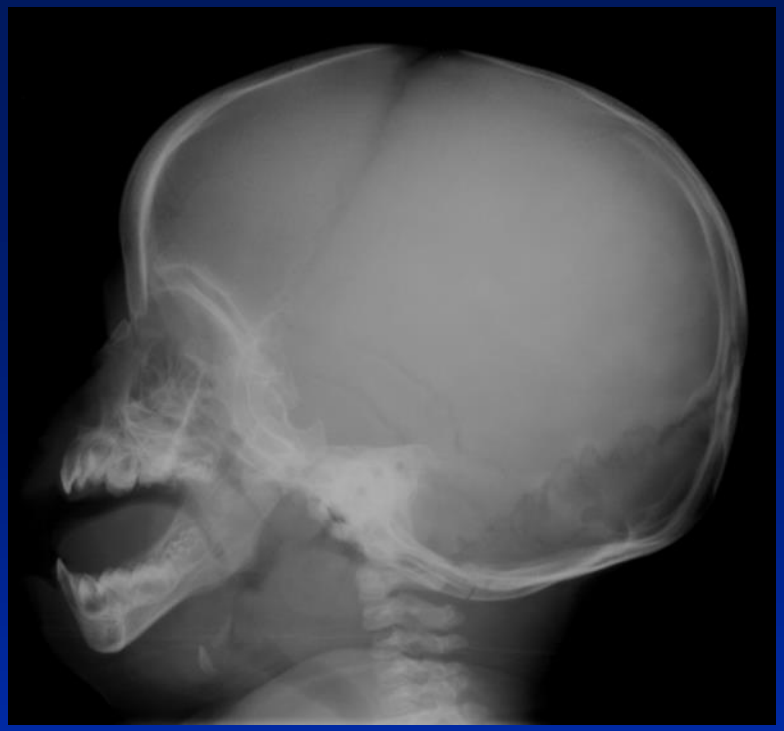
MI: AD
MP: Ch.L.: 4p16.3
Gene: FGFR.3
Fr.: one of the 5 most frequent AD disorders

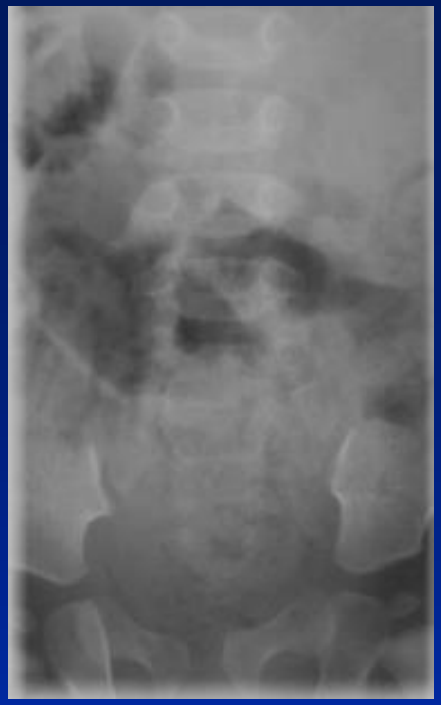


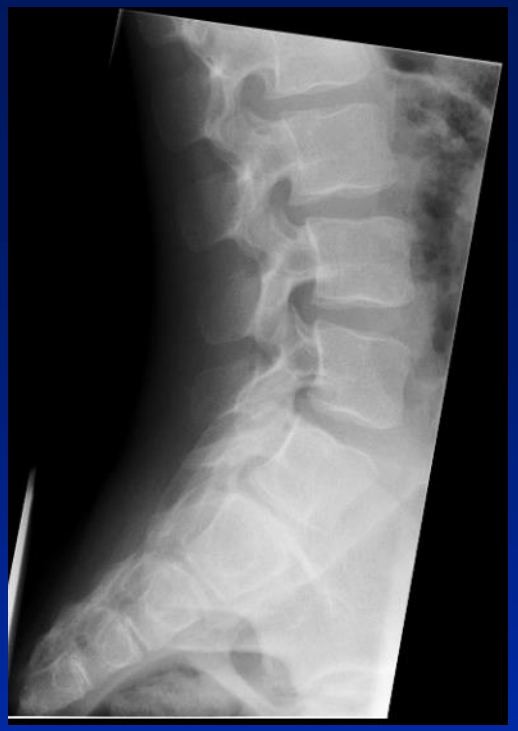


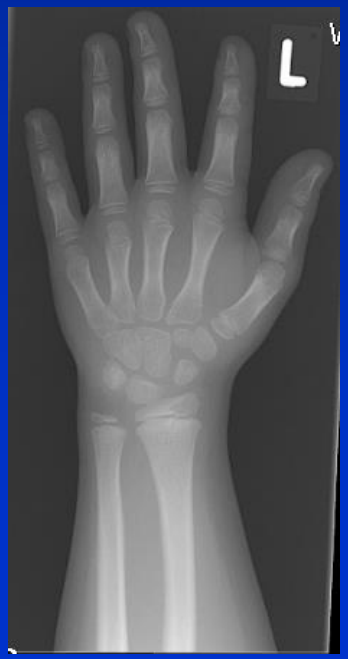
Normal intelligence.

Short stature or dwarfism.





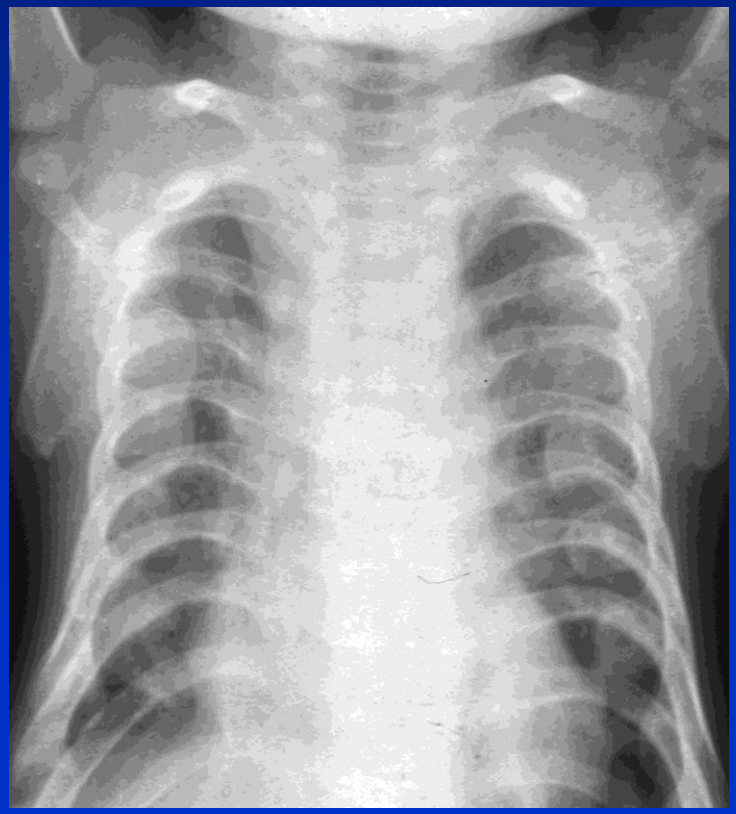


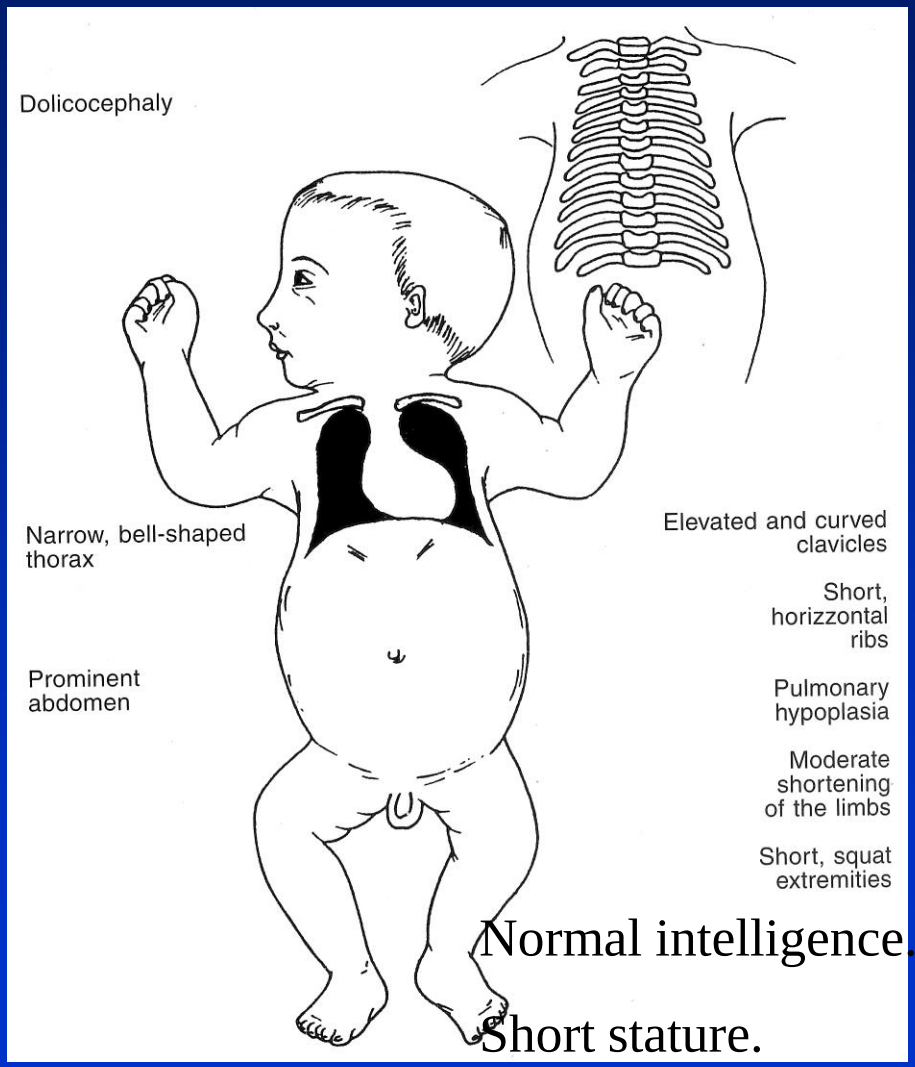


Skeletal changes are qualitatively similar but quantitatively milder than those of achondroplasia

Asphyxiating thoracic dysplasia

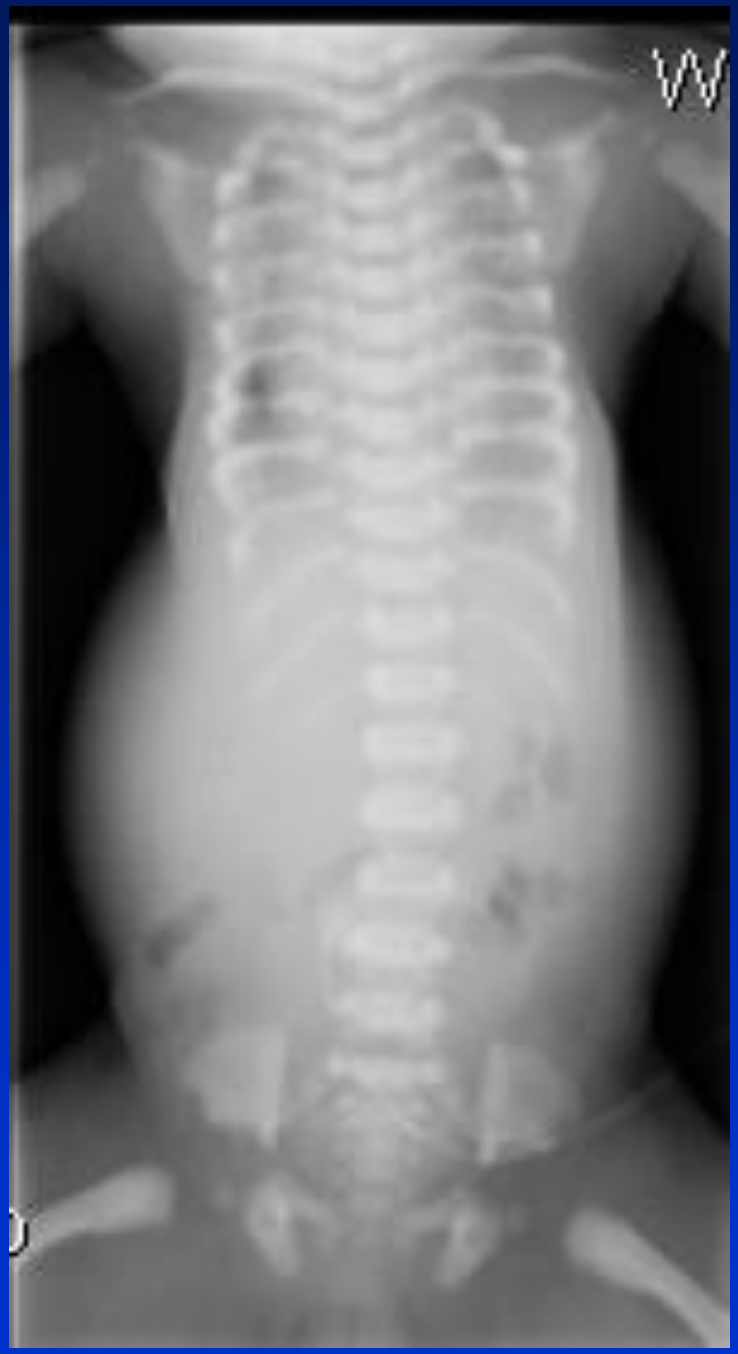
MI: AR
MP: Ch.L.: unknown
Gene: unknown
Fr.: 1:100.000-130.000

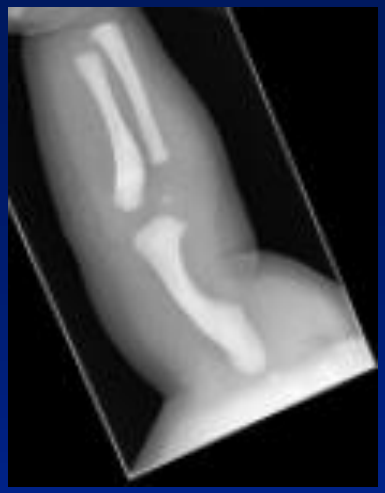


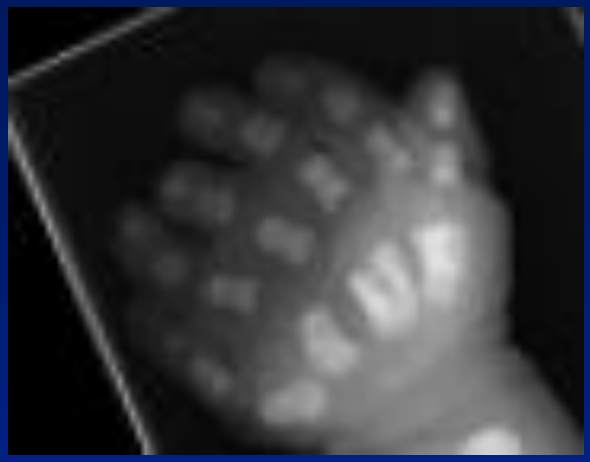


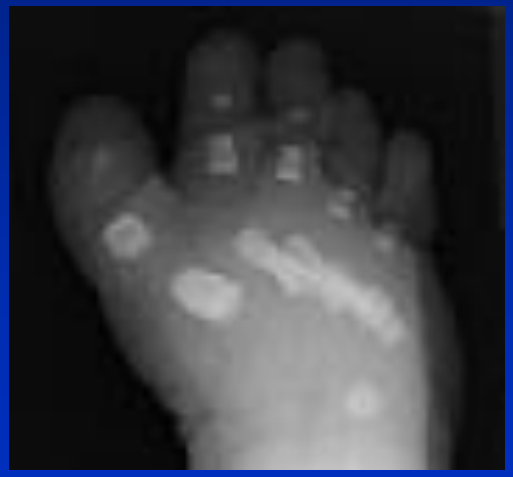
Normal intelligence.

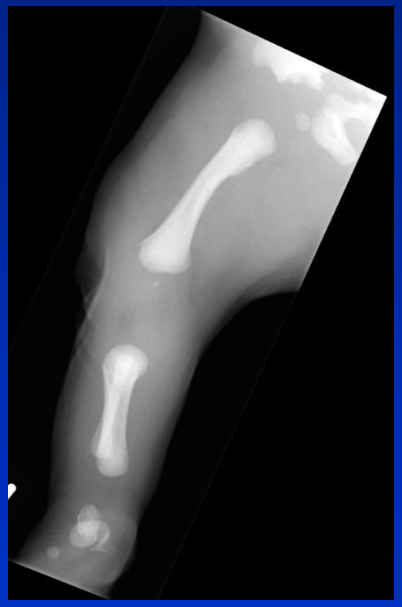
Short stature.







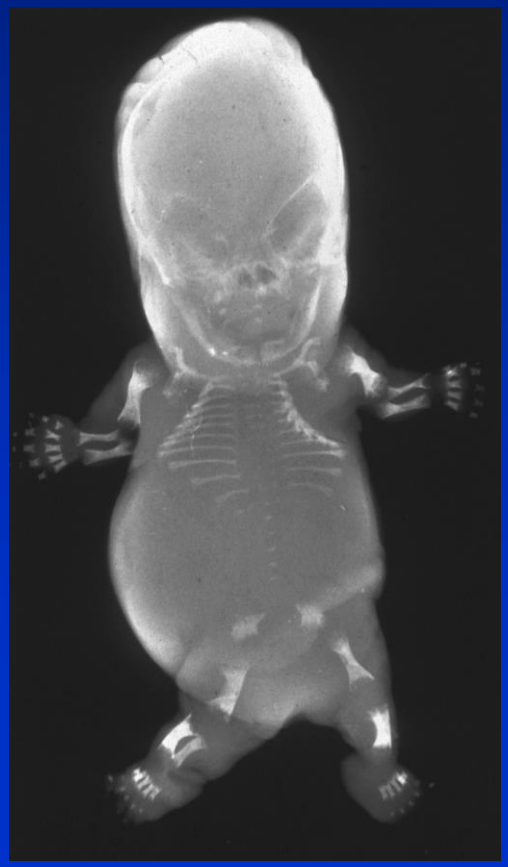


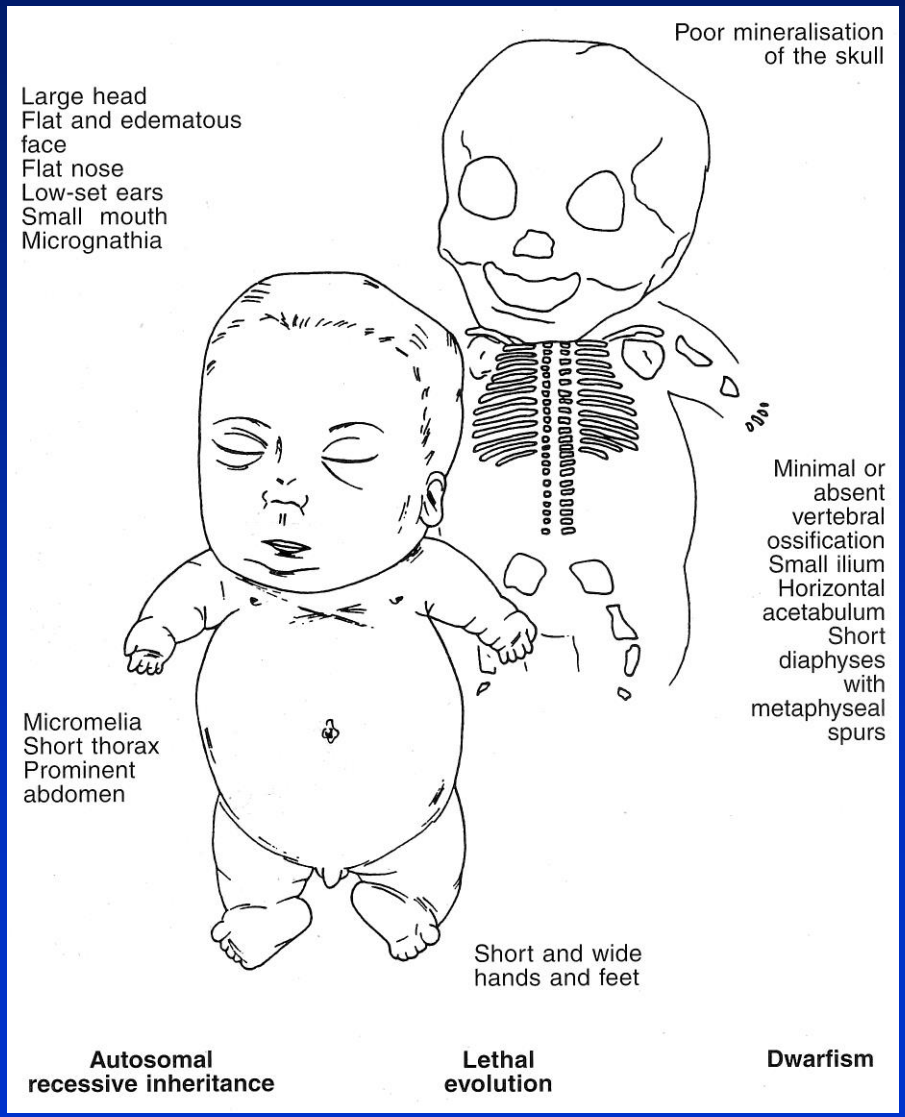


- Small thorax
- Cephalocaudal shortness of the iliac bones
- Disproportionately short extremities
- Hexadactyli

Achondrogenesis

MI: AD
MP: Ch.L: 12q13.1-q13.3
Gene: COL2A1
Fr.: 0,2 : 100.000





Stickler dysplasia type I

MI: AD

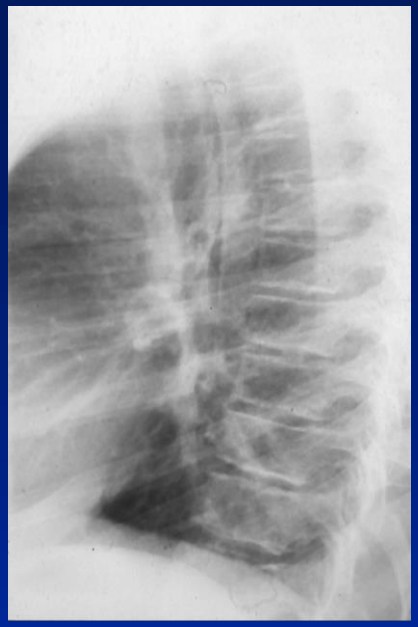
MP; Ch.L: 12q13.1-q13.3

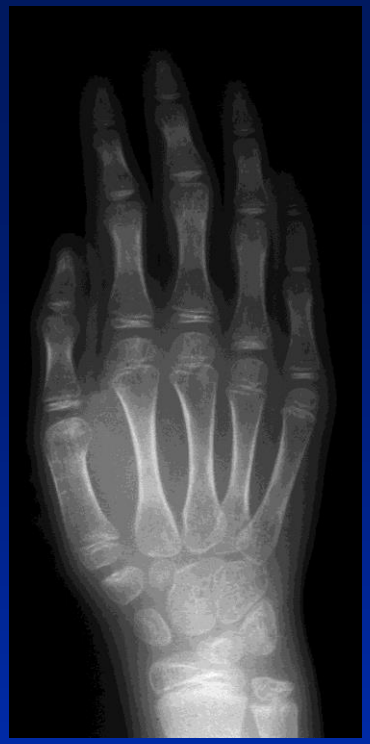
Gene: COL2A1

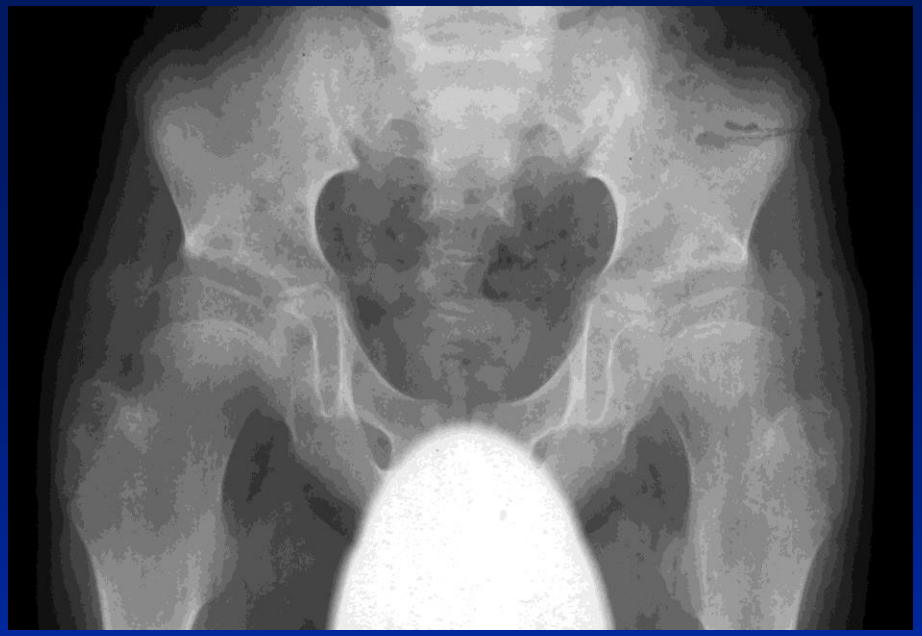
Fr.: unknown

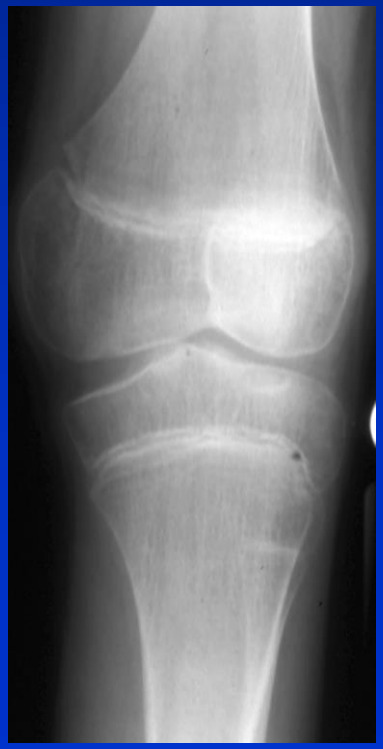
Major clinical findings:

- Midface hypoplasia
- Congenital nonprogressive myopia
- Sensorineural hearing loss
- Joint hypermobility
- Mild shortness of stature





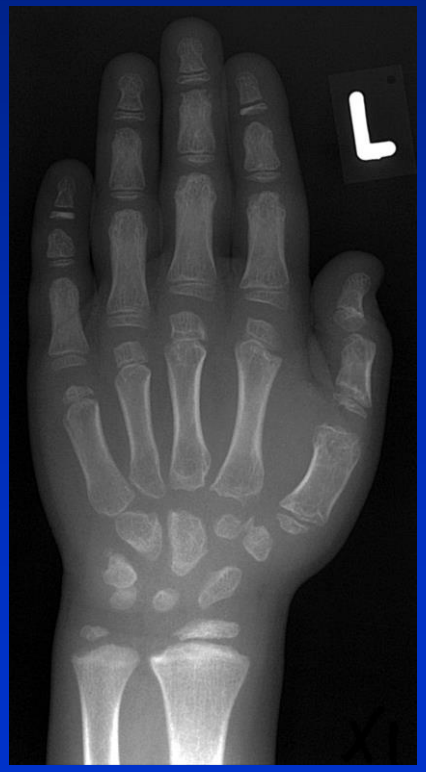


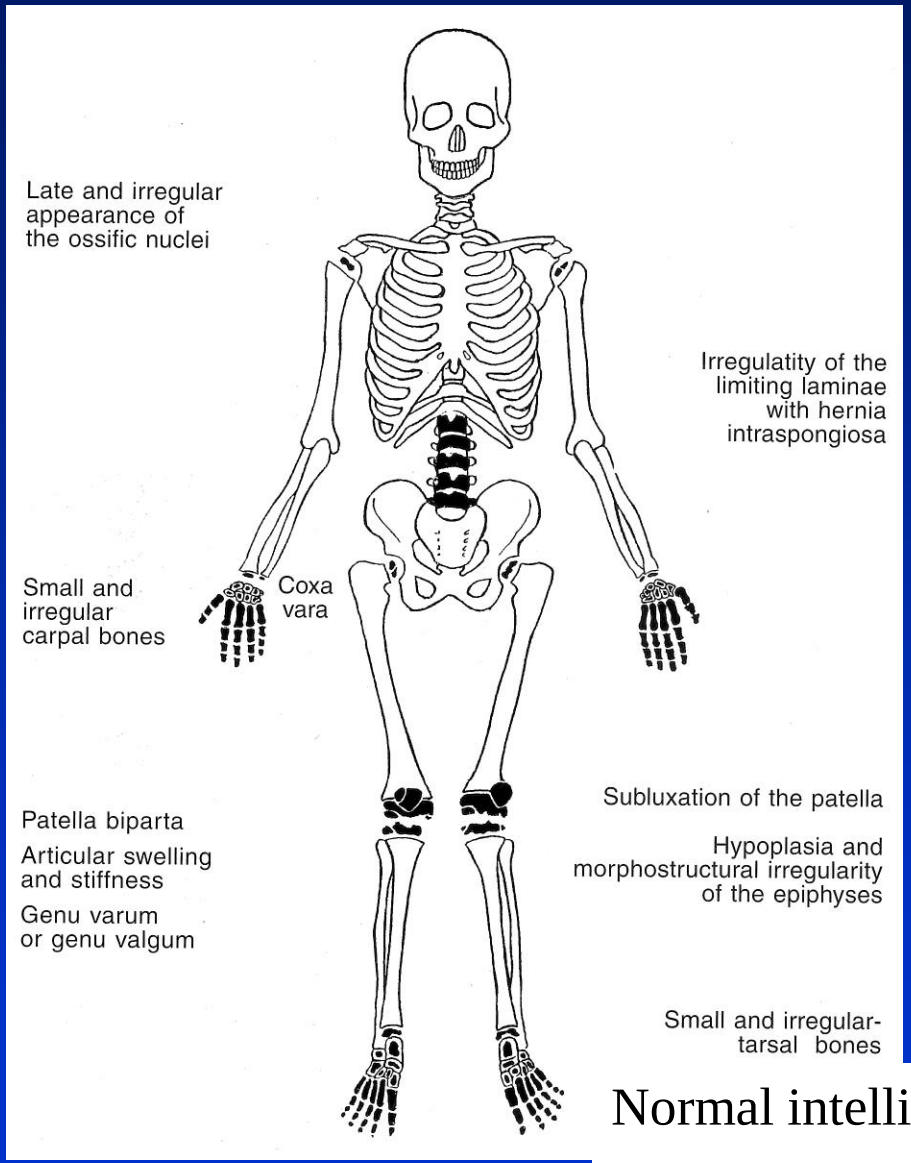


- Platyspondyly of thoracal spine
- Wide ends of femora and tibiae
- Flattend epiphyses of phalanx and carpalia

Multiple epihyseal dysplasia

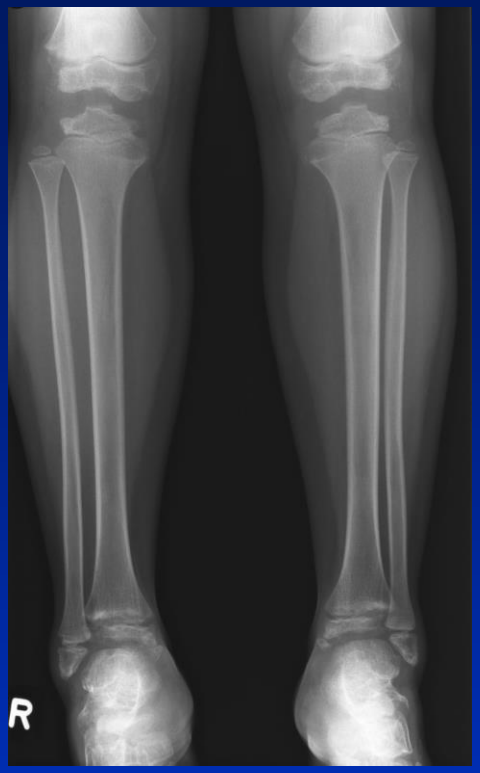
MI: AD
MP: Ch.L: 1p32.2-33
Gene: COL9A1
Fr.: 9 : 100.000

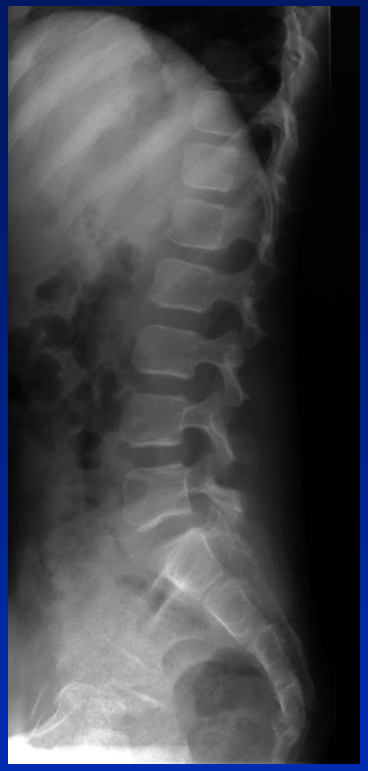


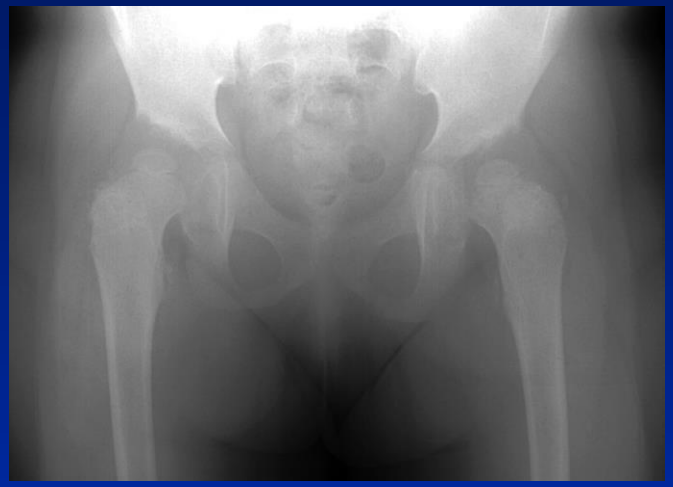


Normal intelligence.

Short stature.







Irregularity of the epiphyses, predominantly in the hip, knee, ankles and wrist

Sometimes flattening of the vertebral bodies

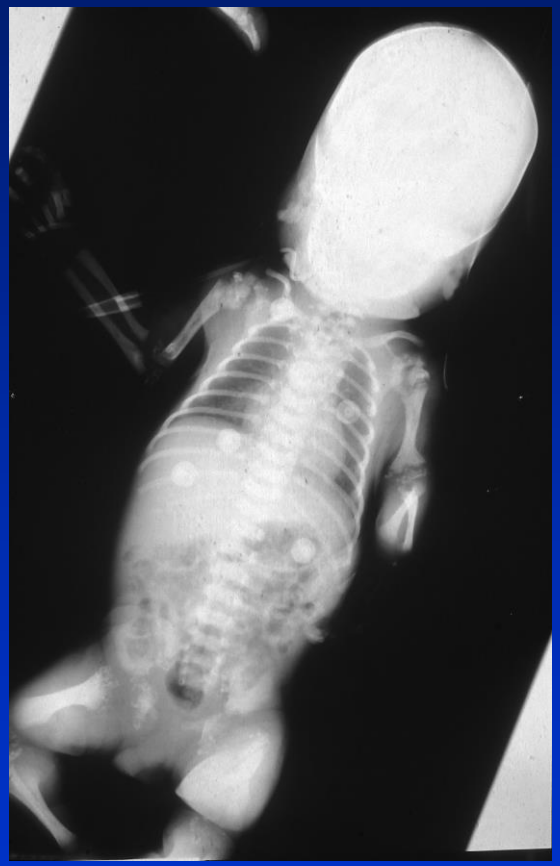
Normal metaphyses

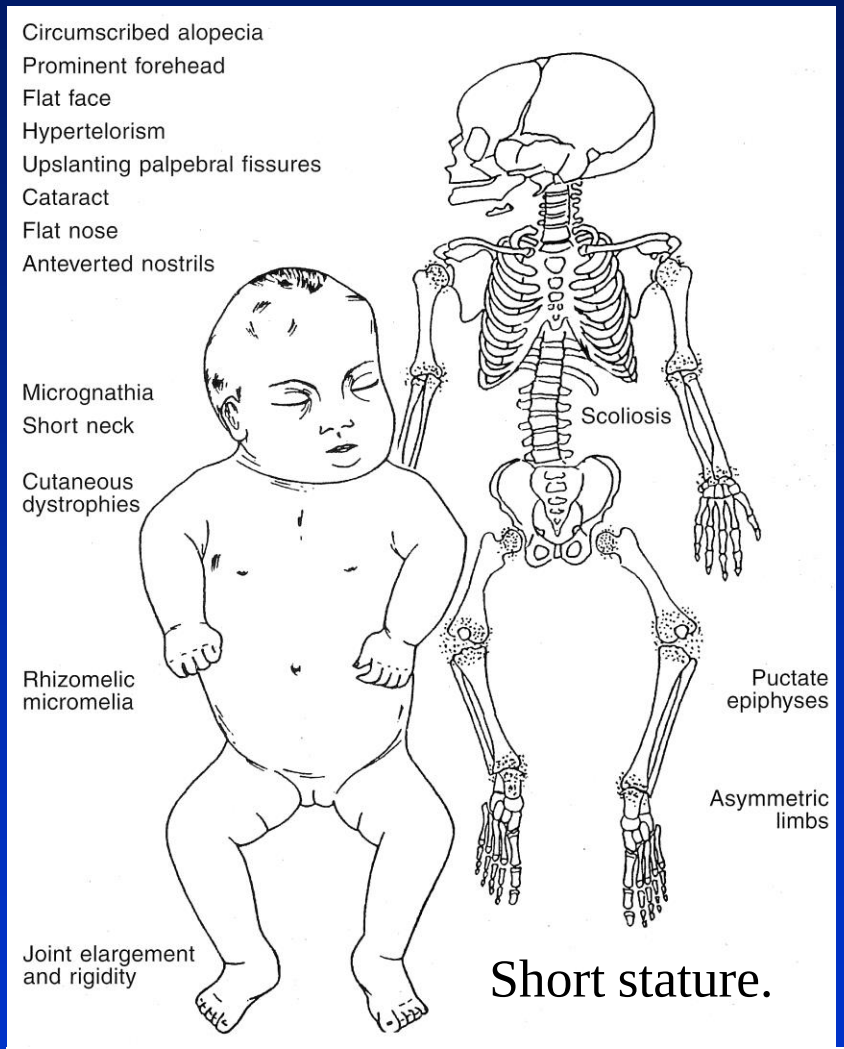
Chondrodysplasia punctata (CDP) Different types

1. Type 1 rhizomelic
   MI: AR; MP: Ch.L: 6q22-24; Gene PEX7
2. Type 2 rhizomelic
   MI: AR; MP: Ch.L: 1q42; Gene: DHPAT
3. Type 3 rhizomelic
   MI: AR; MP: Ch.L: 2q31; Gene: AGPS
4. Conradi Hünermann type
   MI: XLD; MP: Ch.L: Xp11.23-11.22; Gene: EBP (Emopamilbinding protein)
5. X-linked recessive type
   MI: XLR; MP: Ch.L: Xp22.3; Gene: ARSE

Total frequency of all types: 1:100.000

Chondroplasia punctata

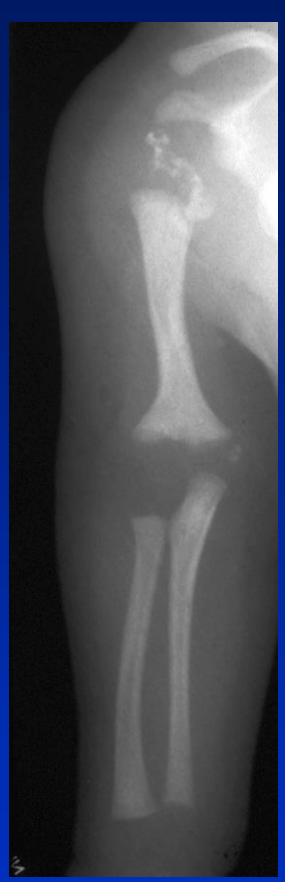


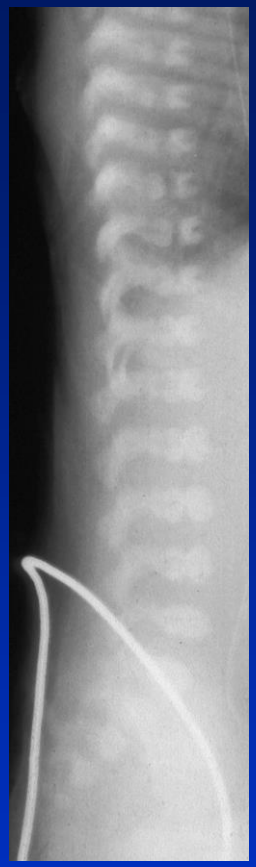


Normal intelligence in dominant type.

Mental retardation in recessive type.

Rhizomelic type



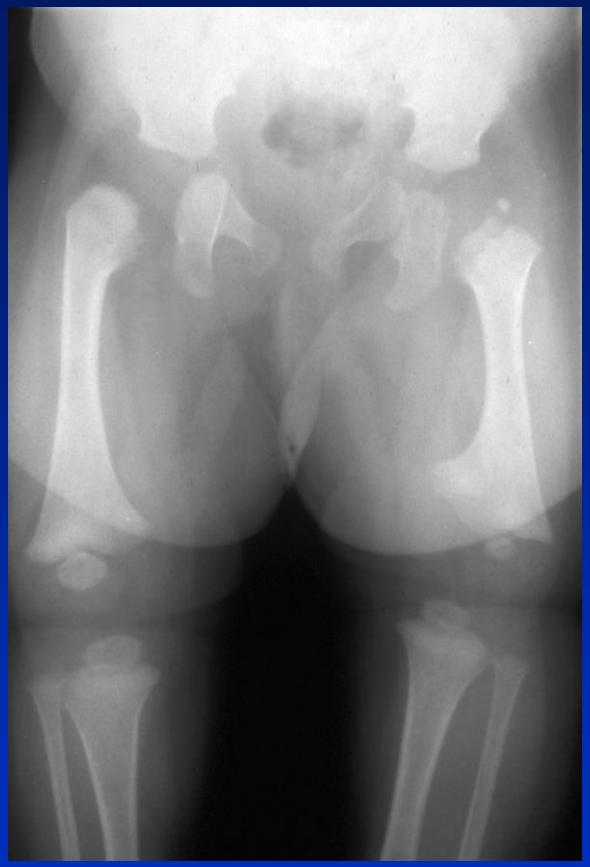


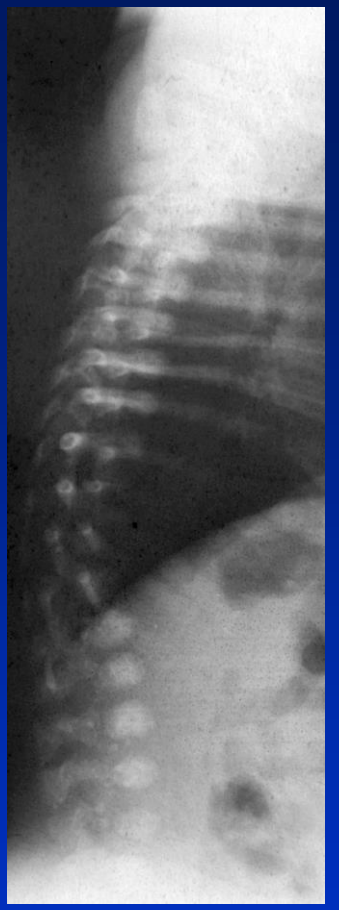
Coronal clefts

Short humeri

Punctate epiphyses

Conradi Hünermann type





Punctate calcification end of the long bones

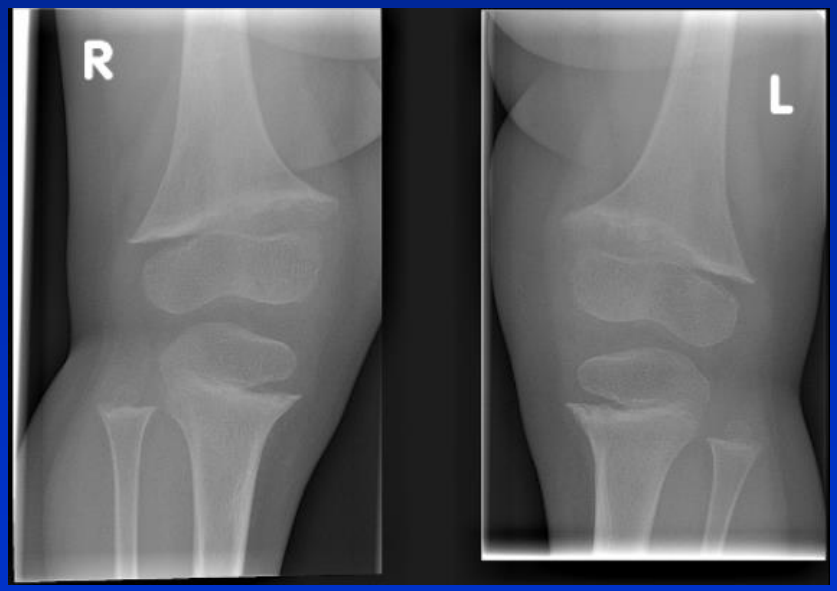
Asymmetric shortening of the long bones

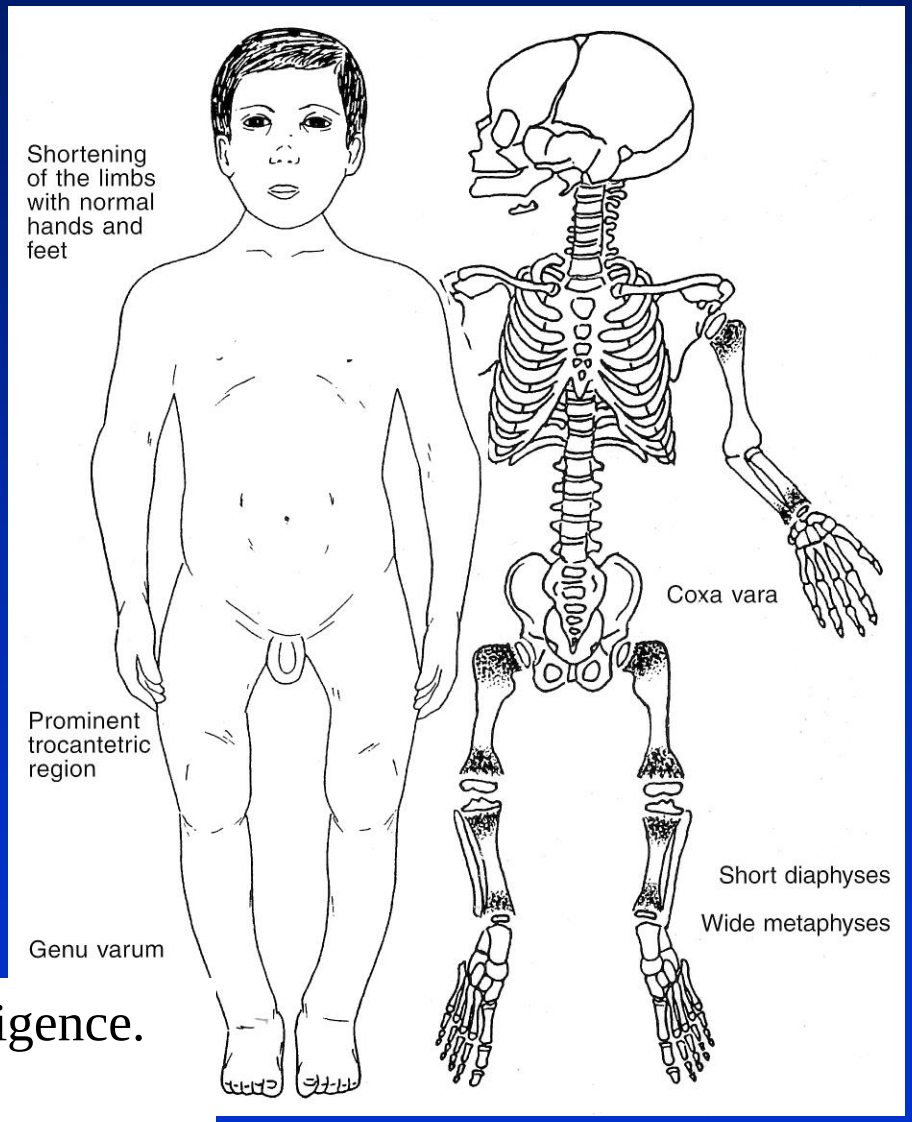
Irregular deformities of the vertebrae

Metaphyseal chondroplasia

Type Schmid

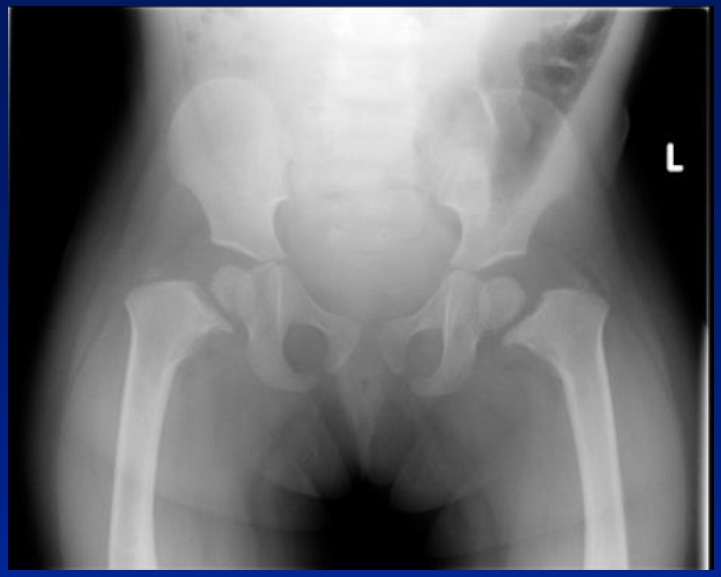
MI: AD
MP: Ch.L.: 6q21-q22.3
Gene: COL10A1
Fr.: about 100 cases are reported

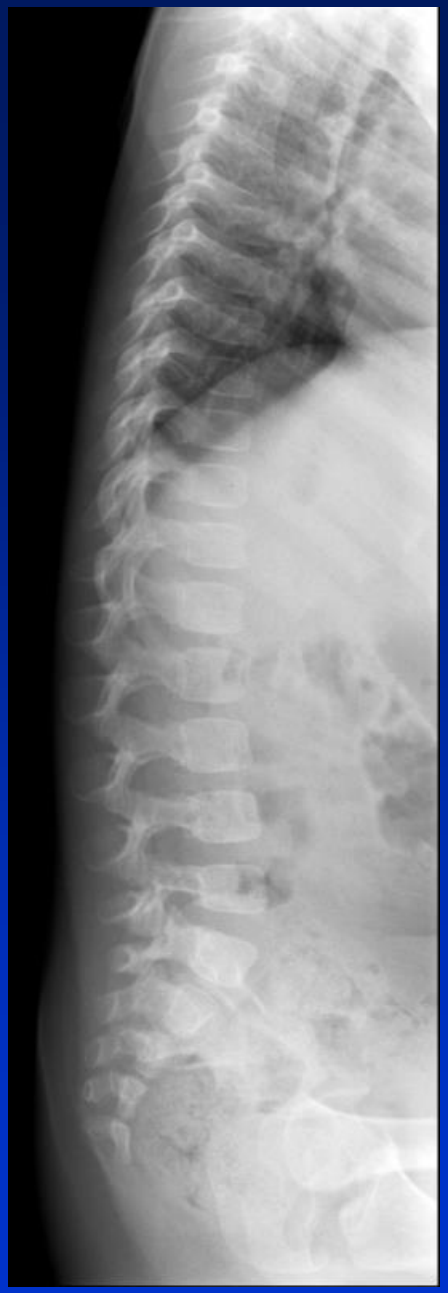


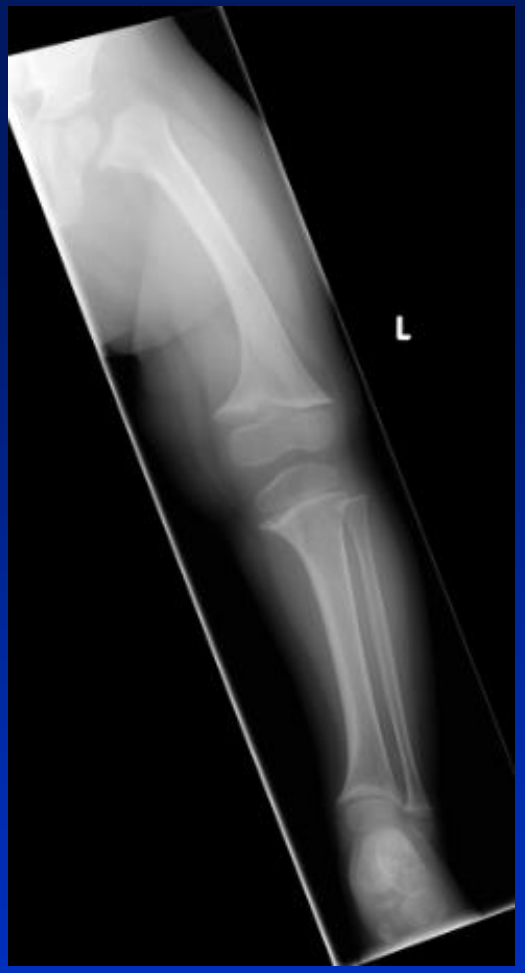


Normal intelligence.

Short stature.







- Shortening of tubular bones
- Cupping, fraying and splaying of the metaphyses
- Coxa vara
- Short femoral neck
- Large capital femoral epiphyses
- Occasionally mild platyspondyly

Spondylometafysaire dysplasie
Corner fracture type

MI: AD

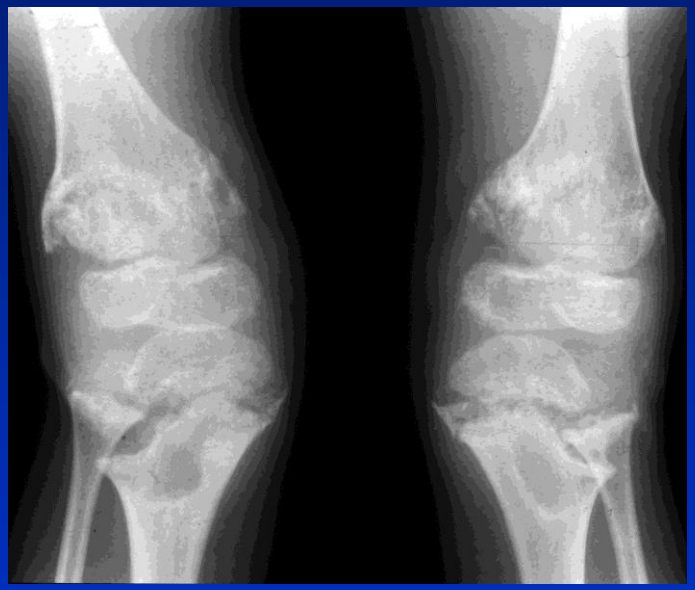
MP: unknown

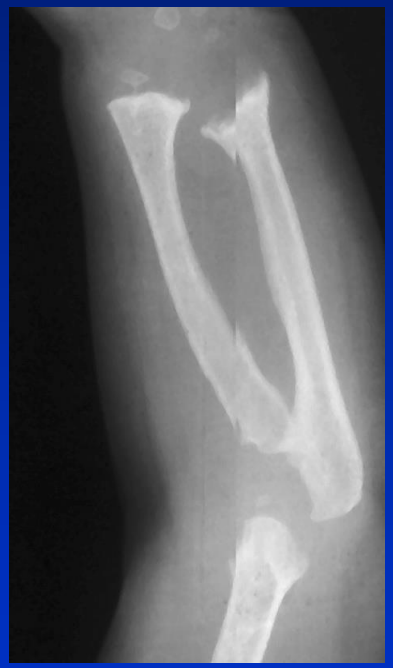
Fr.: 21 cases reported

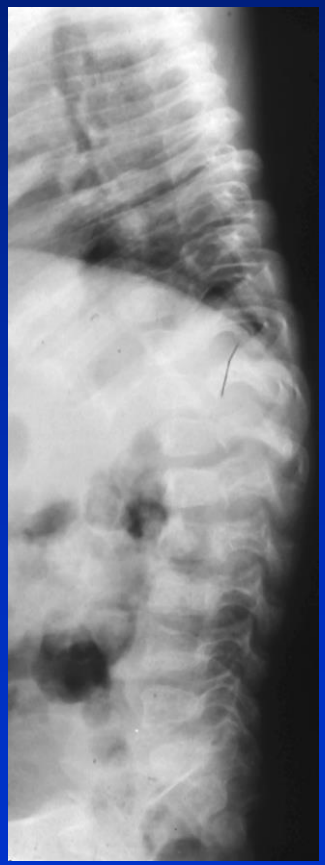
Major clinical findings:

- Moderately short stature
- Waddling gait
- Occasionally leg pain

Spondylometafysaire dysplasie
Corner fracture type





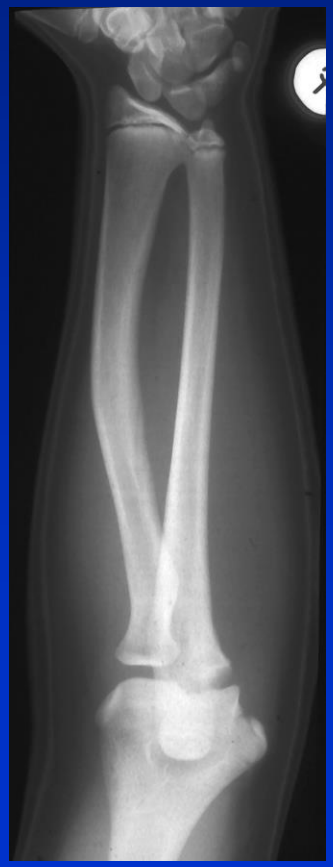


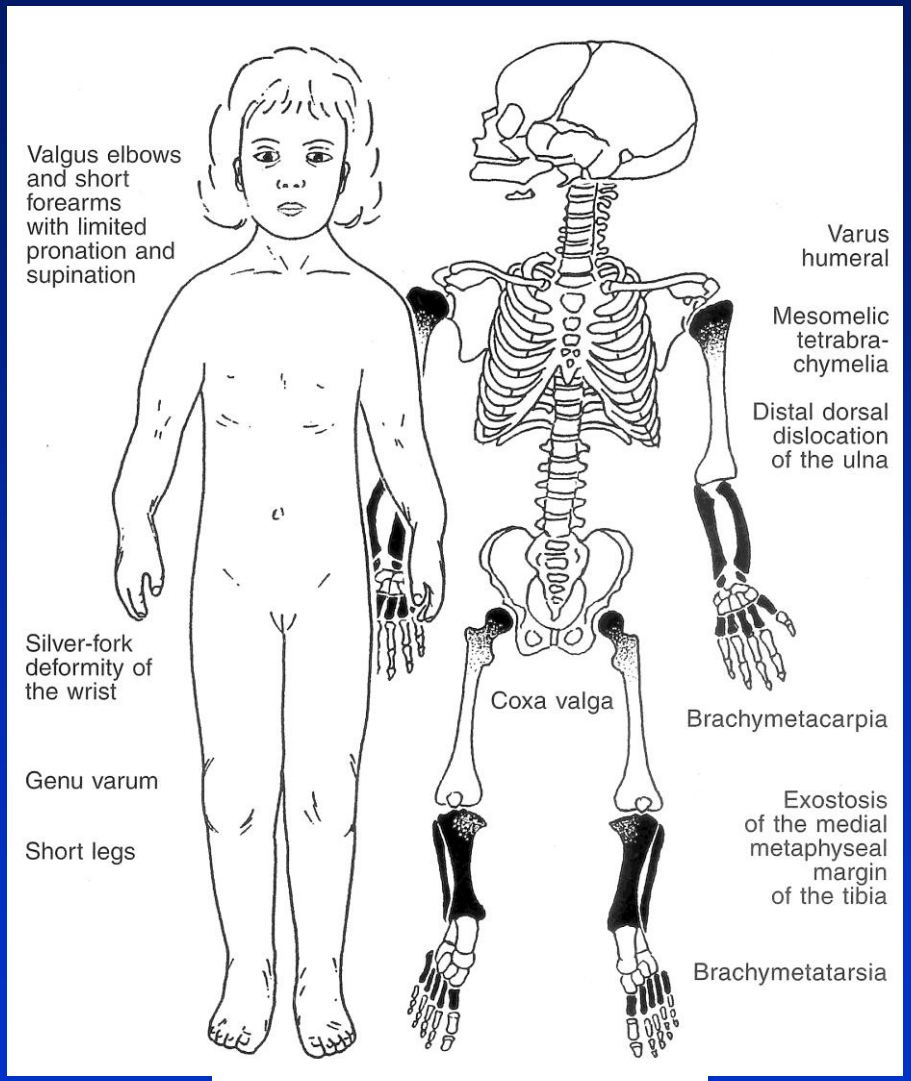
Biconcave plates vertebral bodies

Corner fracture of metyphyses

Dyschondro-osteosis

MI: AD
MP: Ch.L: Xpter-p22.32
Gene: SHOX located on the distal end of the X
Fr.: most common form of mesomelic dysplasia



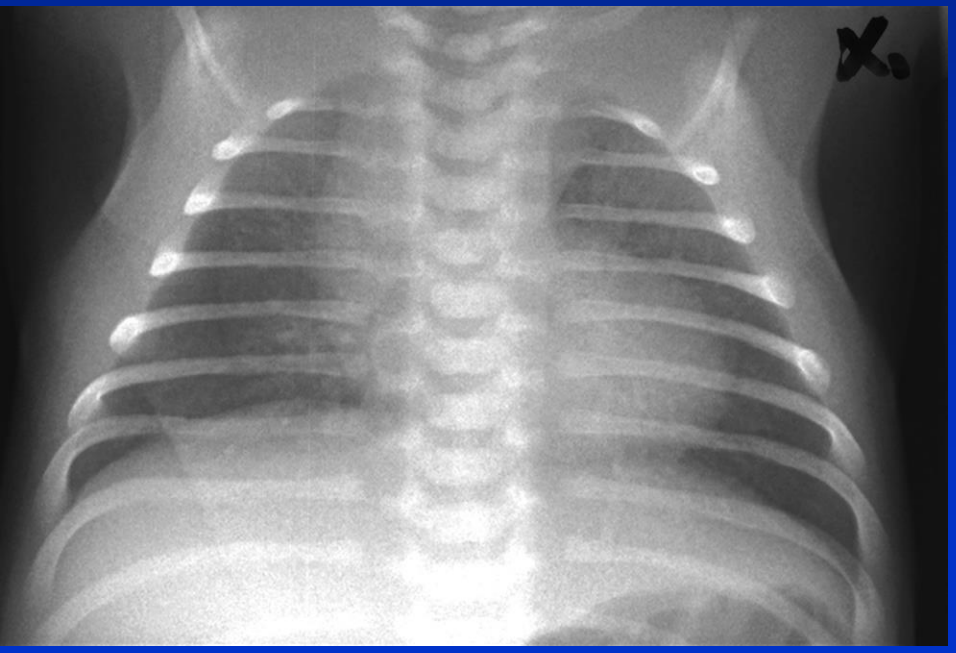


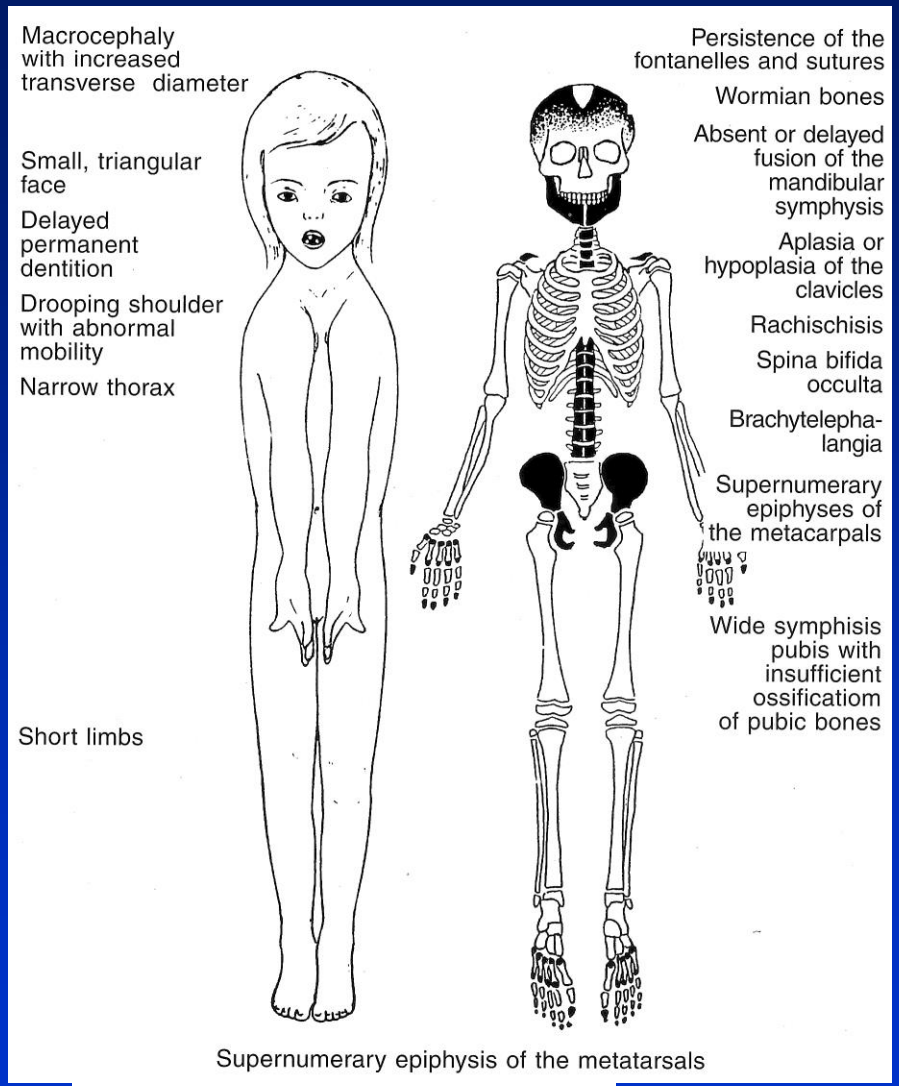
Normal intelligence.

Short stature.

Cleidocranial dysplasia

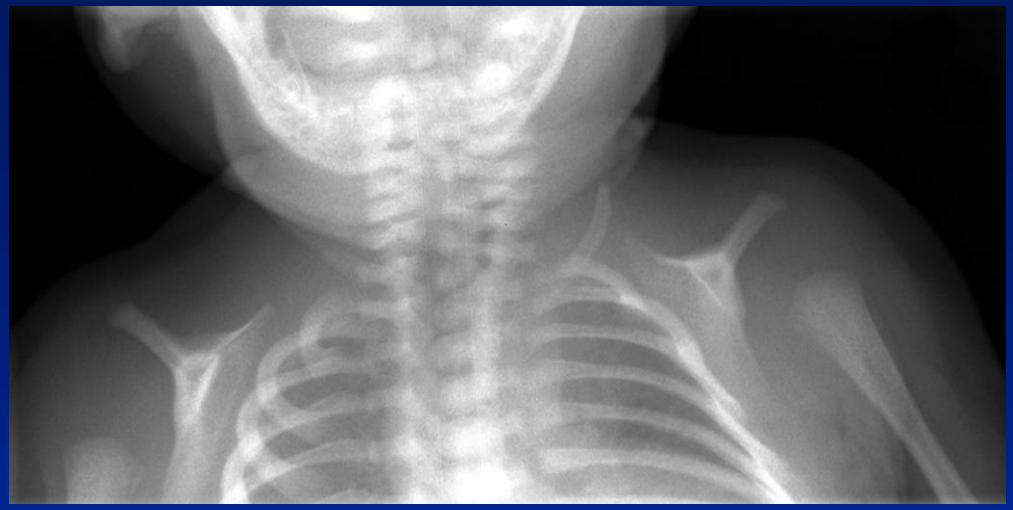
MI: AD
MP.: Ch.L: 6p21
Gene: CBFA1 (Core Binding Factor α 1-subunit)
Fr. 1 : 200.000

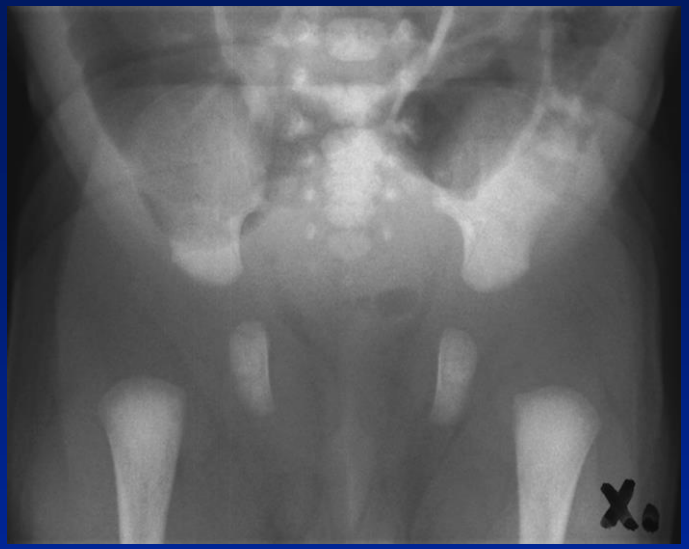


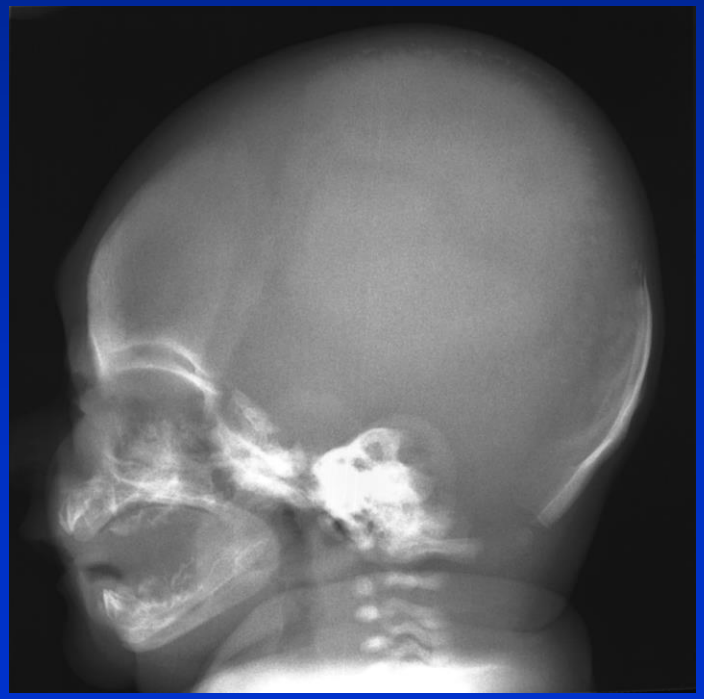


Normal intelligence.

Normal stature.







Retarded ossification of skull with parietal lack of ossification of the calvaria

Partial of total absence of clavicles

Absent ossification of pubic bones

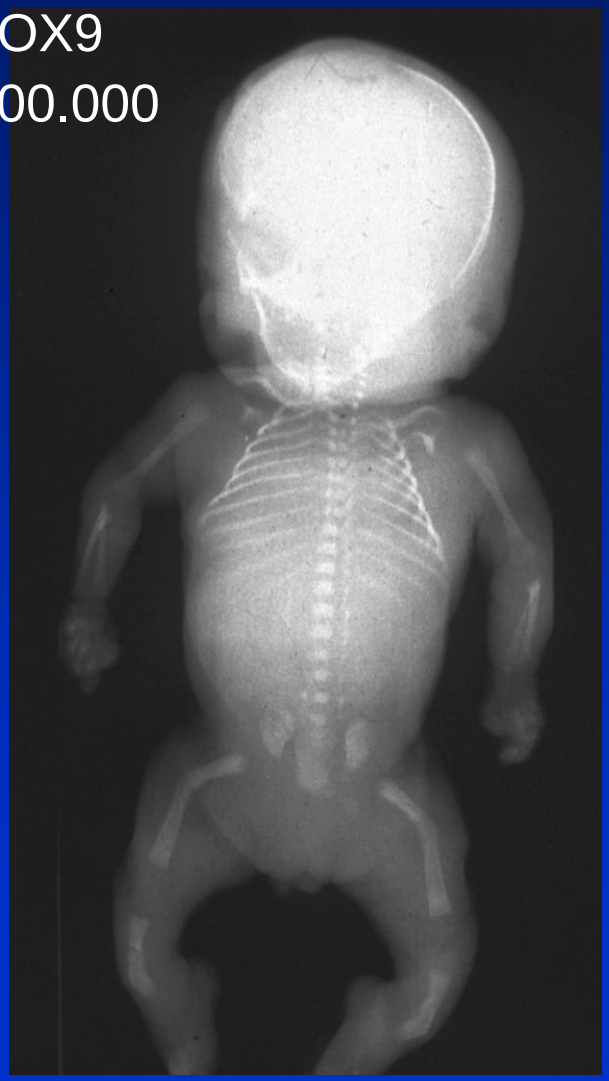
Campomelic dysplasia

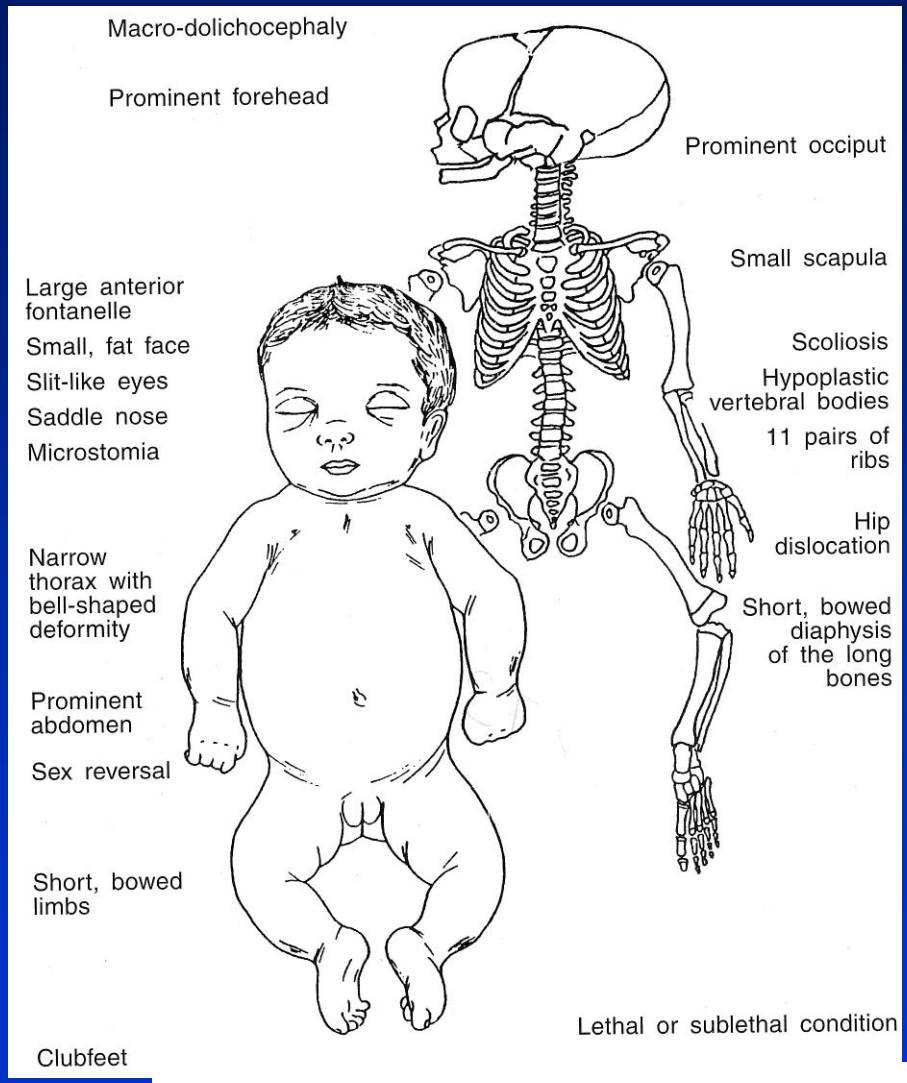
MI: AD

MP: Ch.L: 17q24.3-q25.1

Gene: SOX9

Fr.: 1 : 200.000





Occasionally mental retardation.

Neonatal dwarfism.

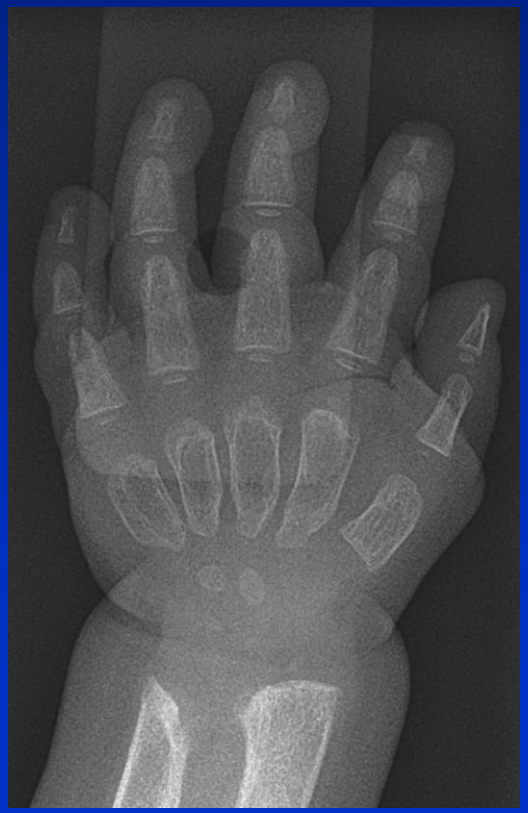
Mucopolysaccharidosis type I-H

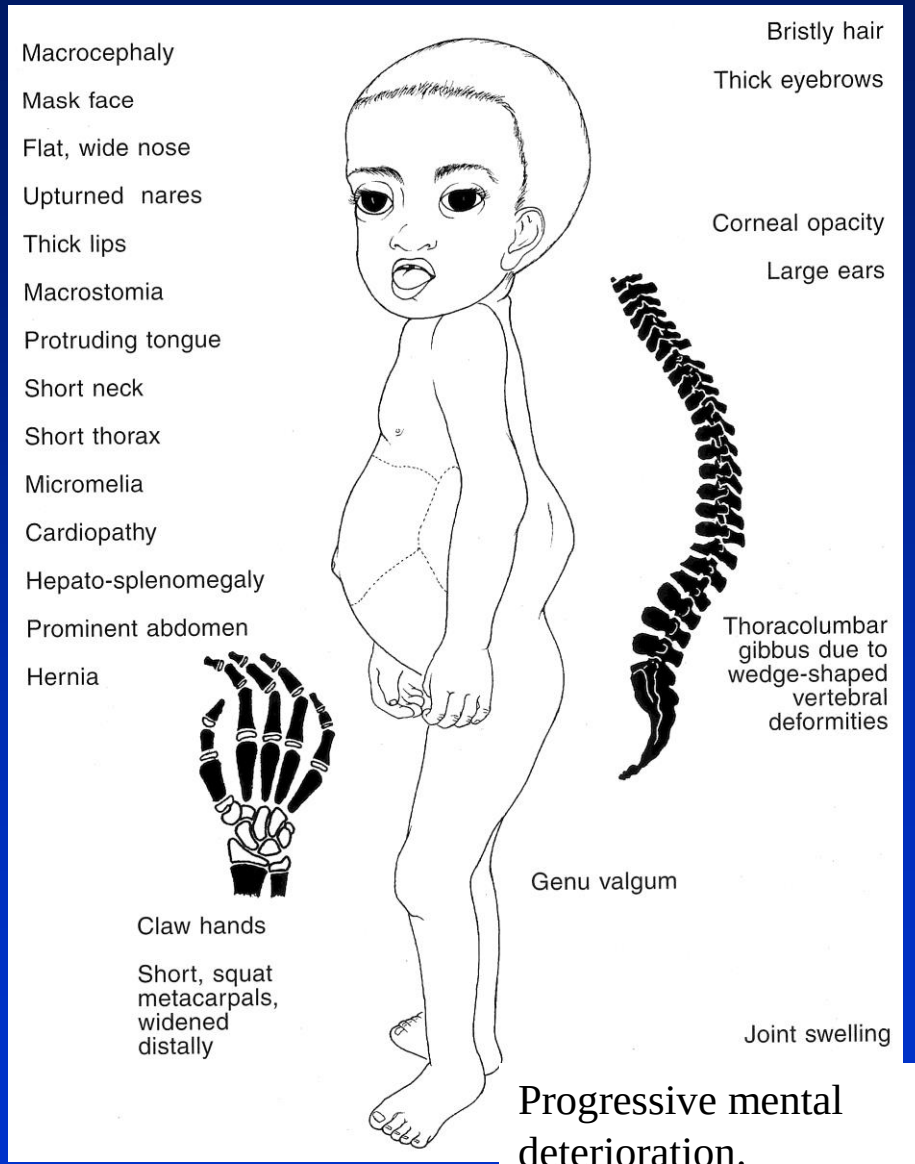
MI: AR

MP: Ch.L: 4p16.3

Gene: IDA (α-1-Iduronidase)

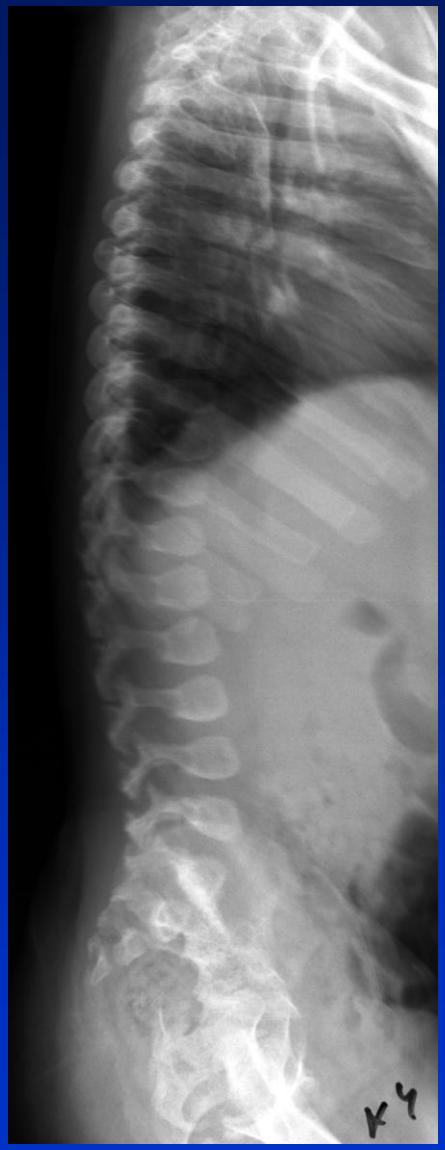
Fr.: 1 : 100.000

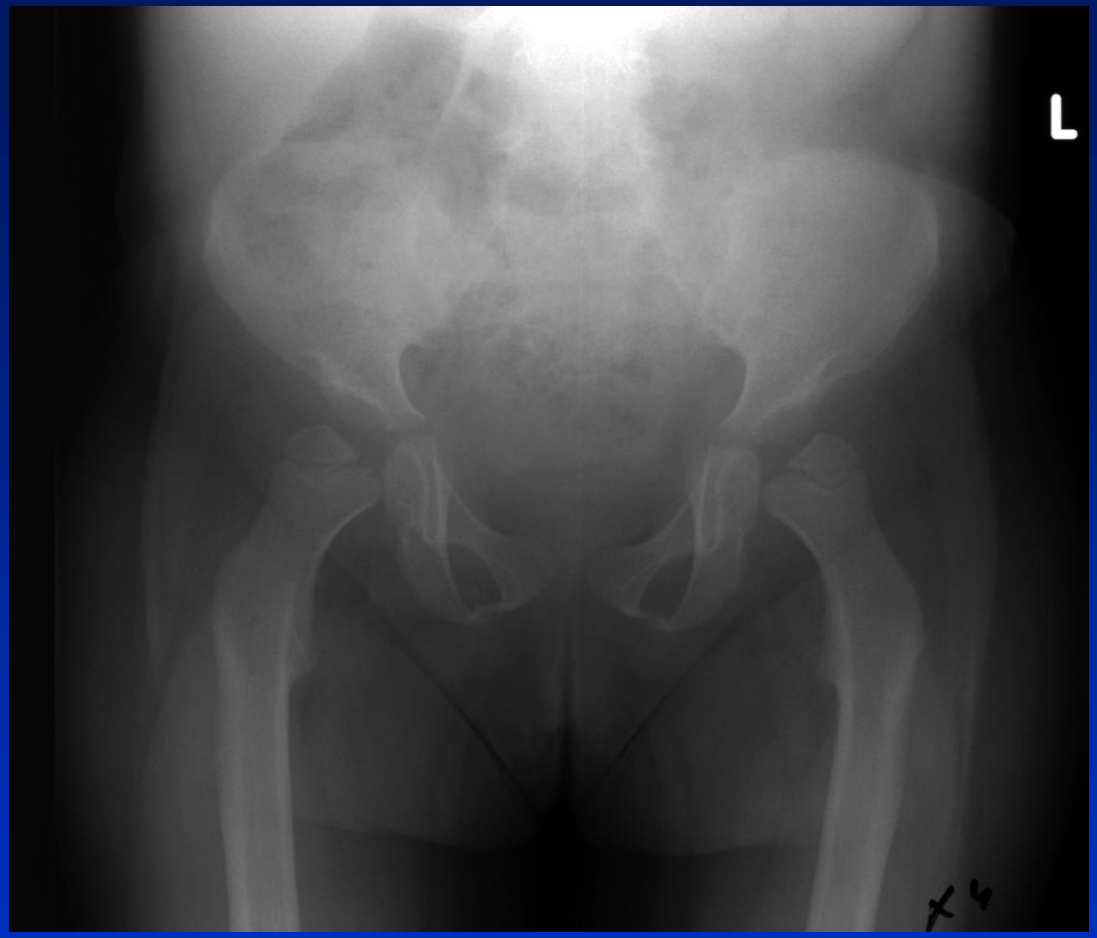




Progressive mental deterioration.

Dwarfism.

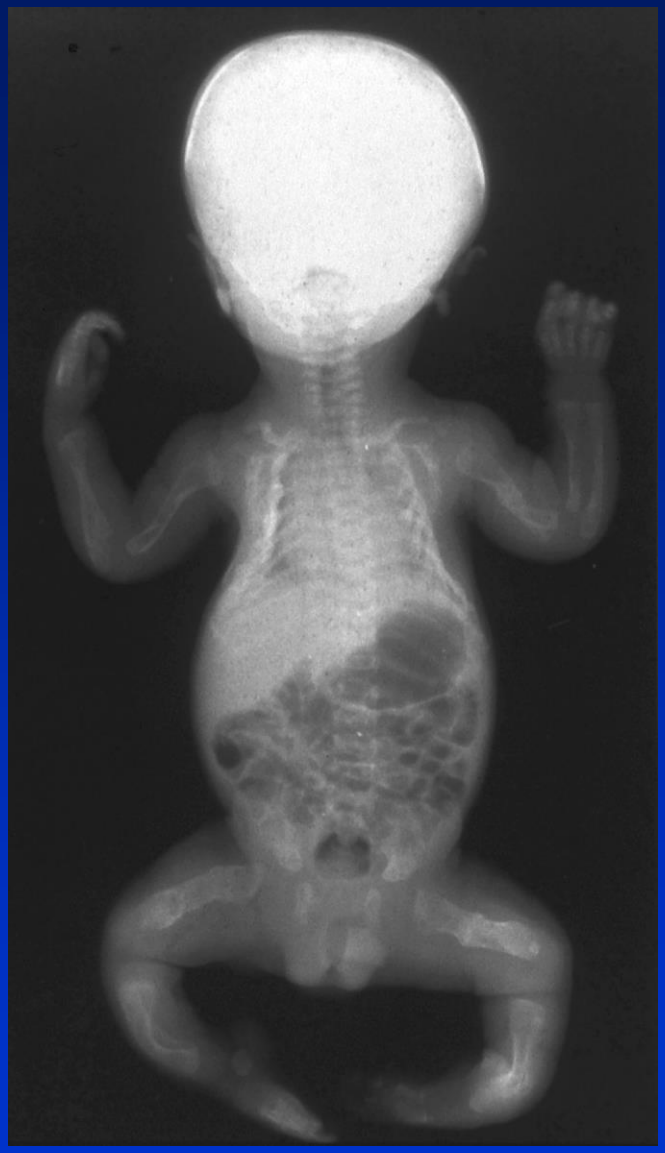


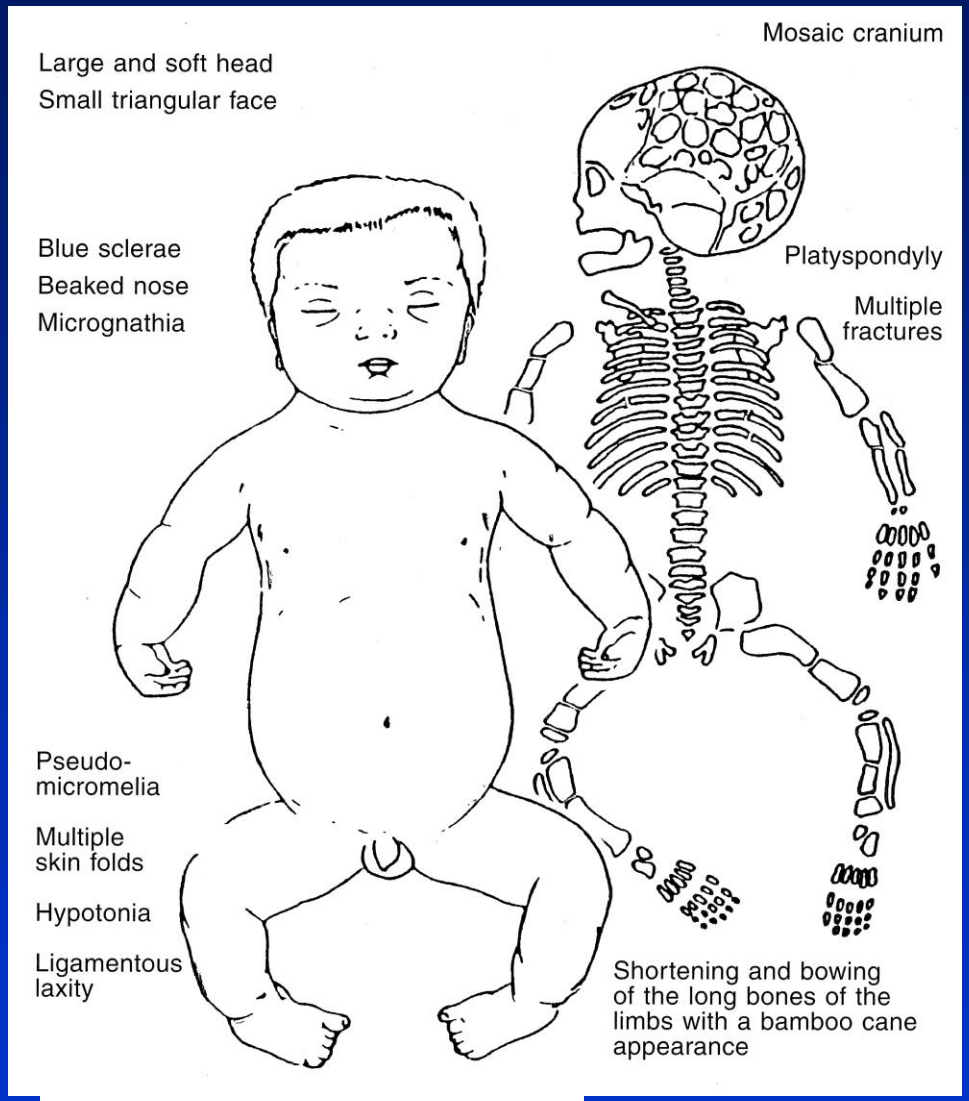

L

Osteogenesis imperfecta
Classification

Type	Sclerae	Prognosis	Tubular bone	Inheritance
I	Blue	Good	Mild bowing	AD
IIA	Blue	Early death	Short, thick	AD
IIB/III	White	Severe handicap	Deformity	AD
IIC	Blue	Early death	Slender, twisted	AR
IV	White	Good	Straight	AD
V	White	Good	Hyperplastic callus	AD
Note: type II B is the neonatal form of type III				

Osteogenesis imperfecta type IIA

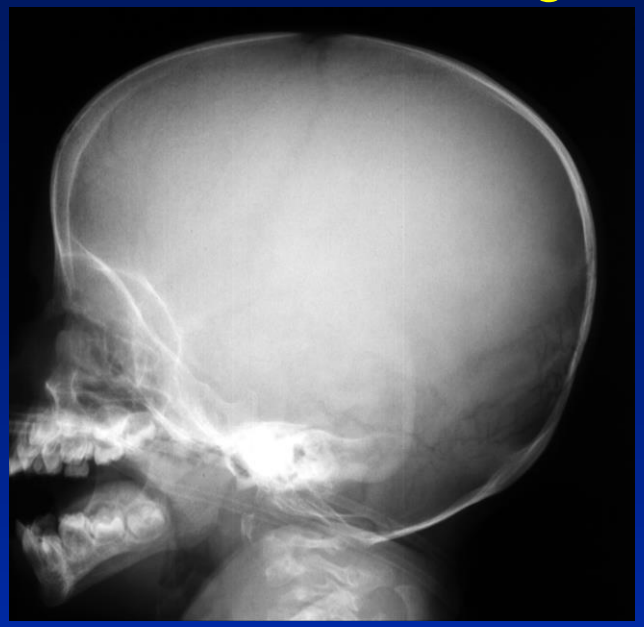


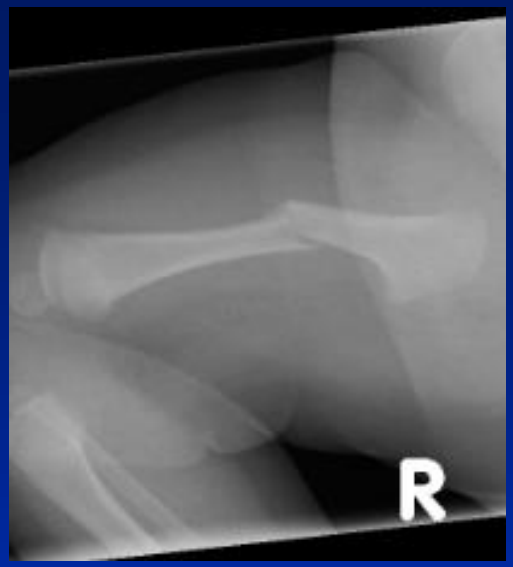


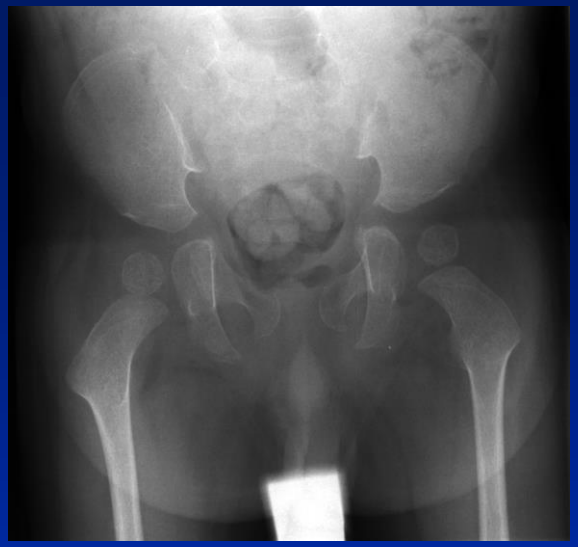
Normal intelligence.

Dwarfism.

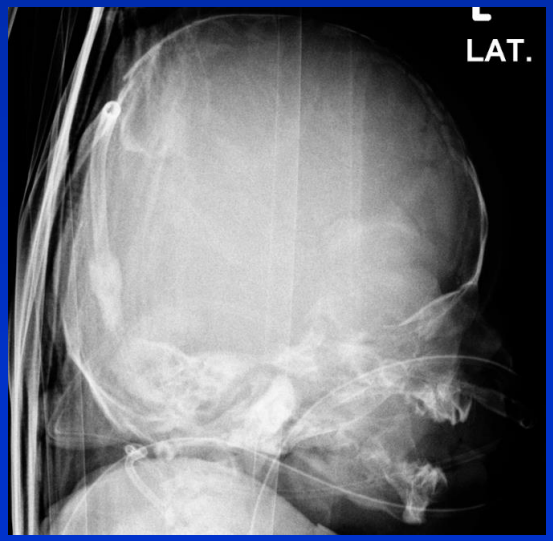
Osteogenesis imperfecta type I

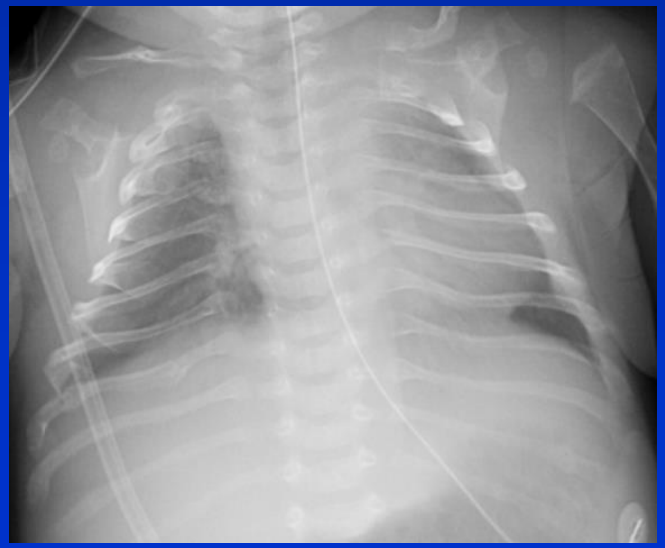


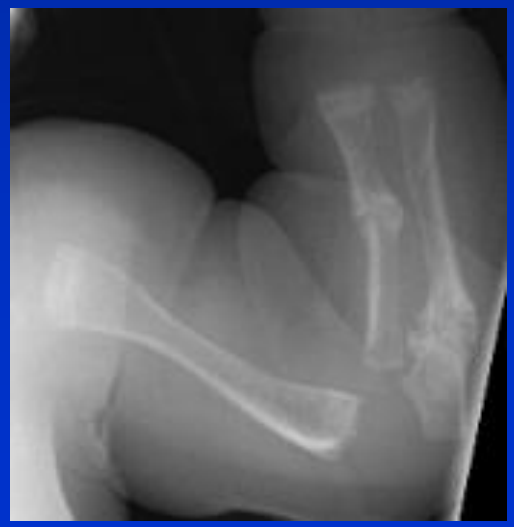




Osteogenesis imperfecta type IIB







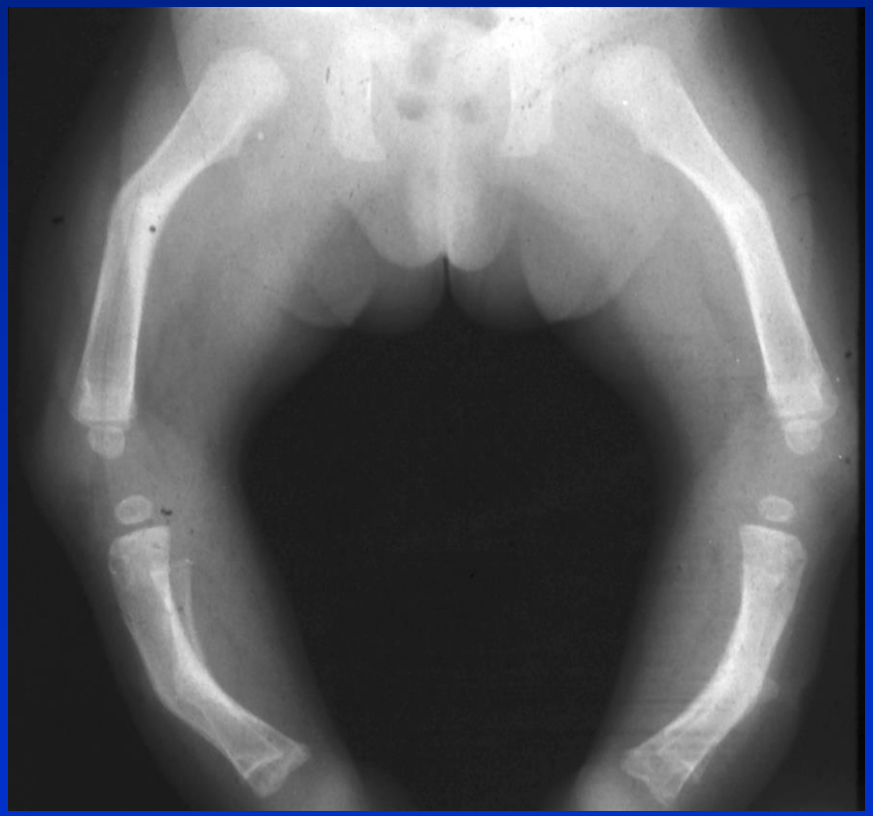
Hypophosphatasia

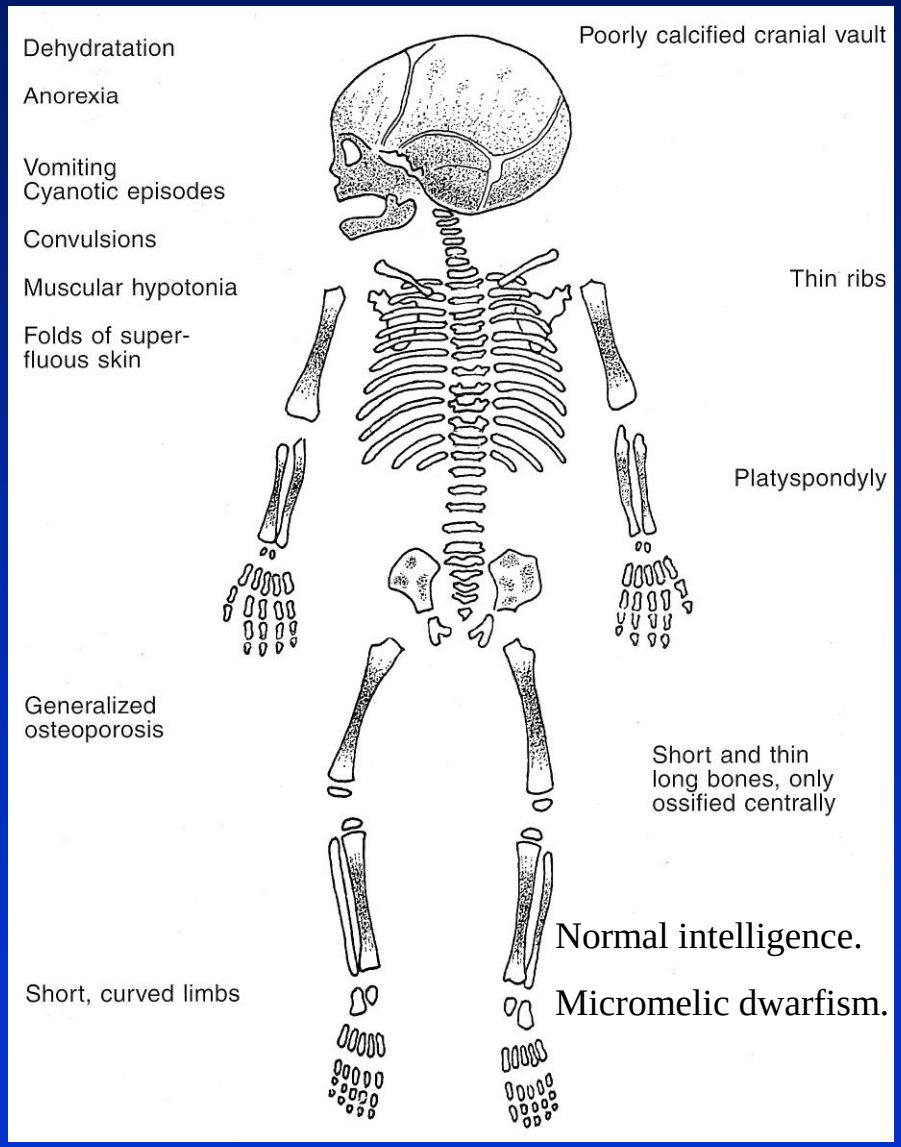
MI: AR

MP: Ch.L: 1p36.1-p34

Gene: ALPL (Alkaline phosphatase)

Fr.: 1:100.000





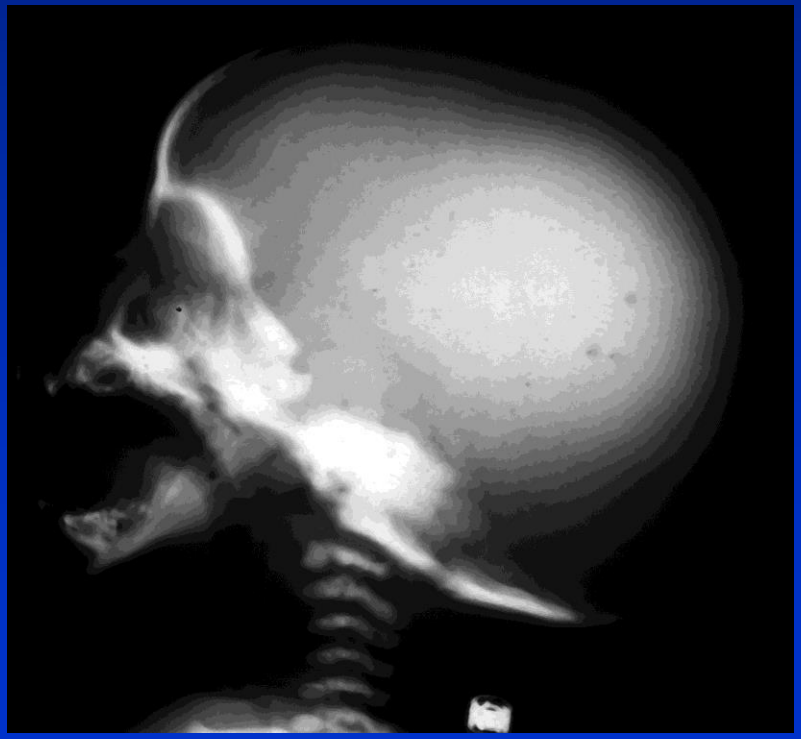
Osteopetrosis infantile type

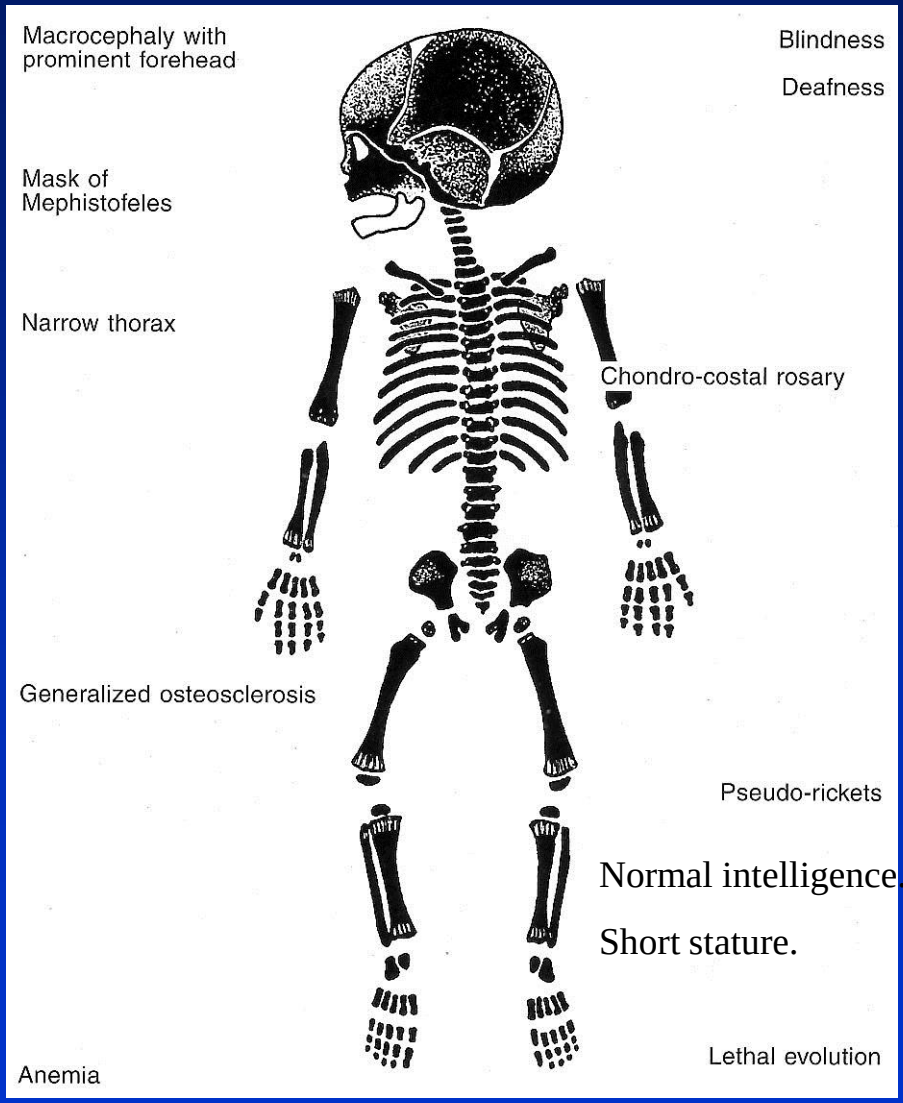
MI: AR

MP: Ch.L: 11q13.4-q13.5

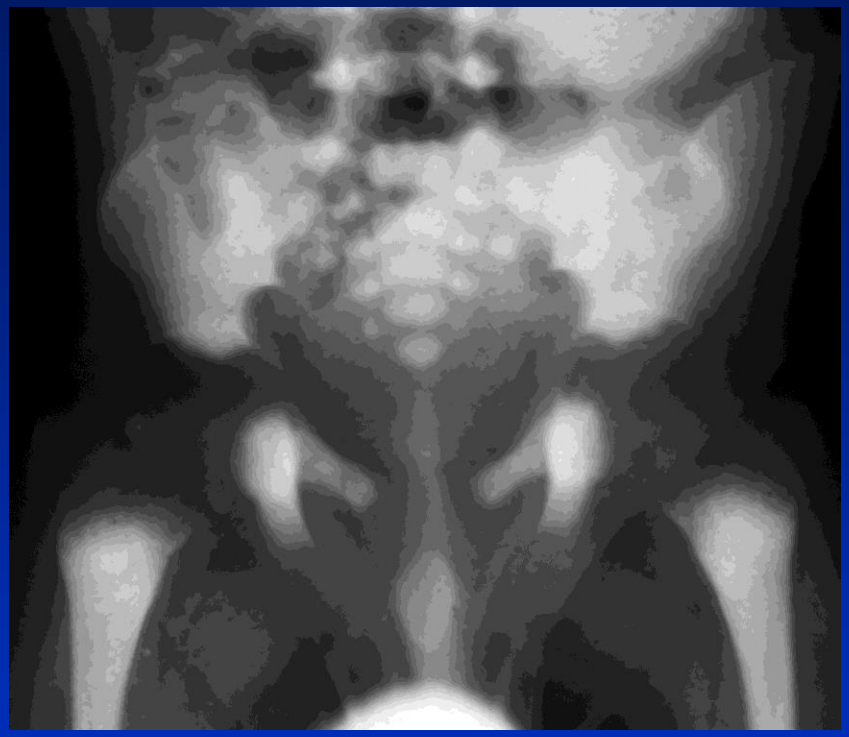
Gene: CLCN7

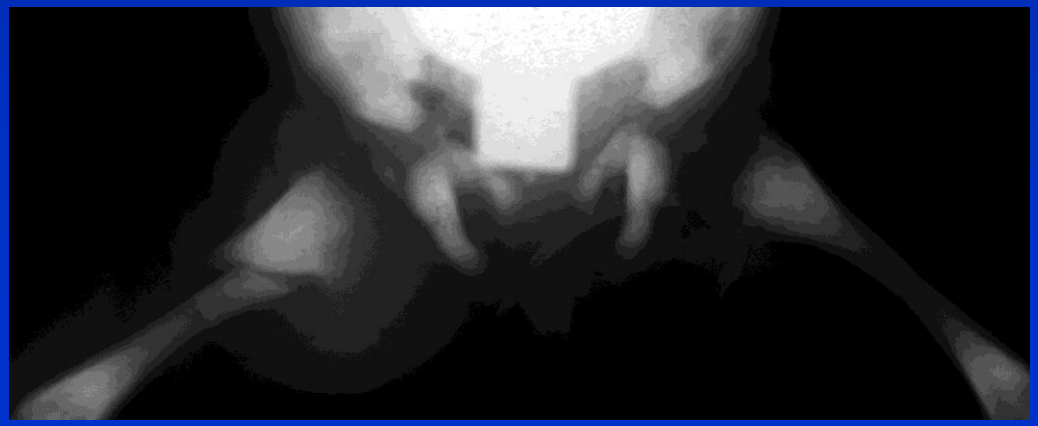
Fr.: 11 : 200.000





Osteopetrosis infantile type





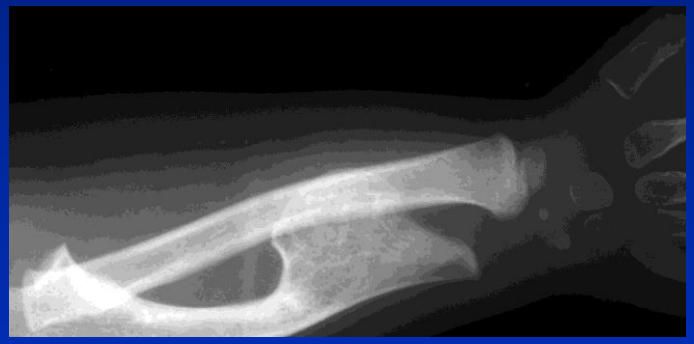
Multiple cartilaginous exostoses

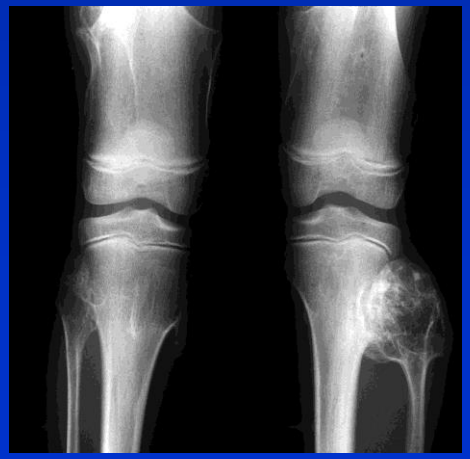
MI: AD

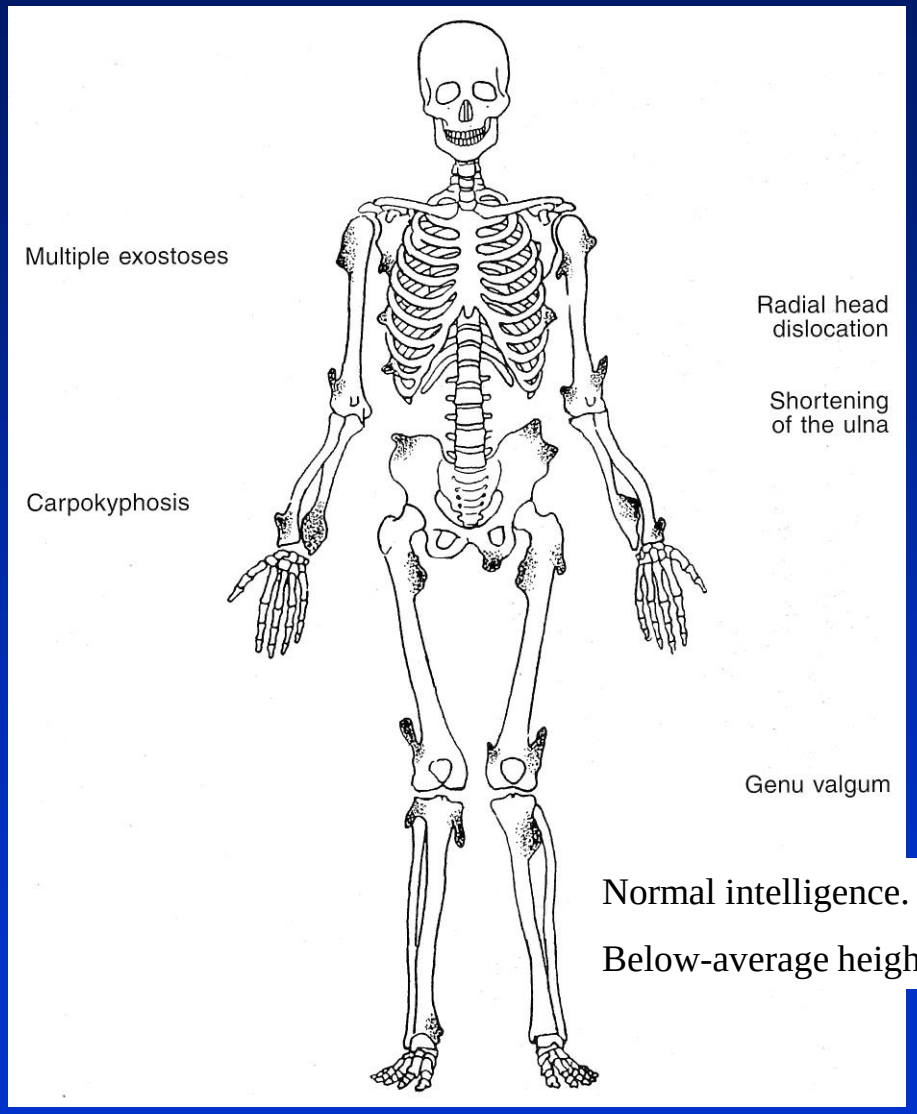
MP: Ch.L.: 8q23-q24.1/ 11p12-p11

Gene: EXT1/ EXT2

Fr.: variable in different rates up to 13% in some communities.







Normal intelligence.

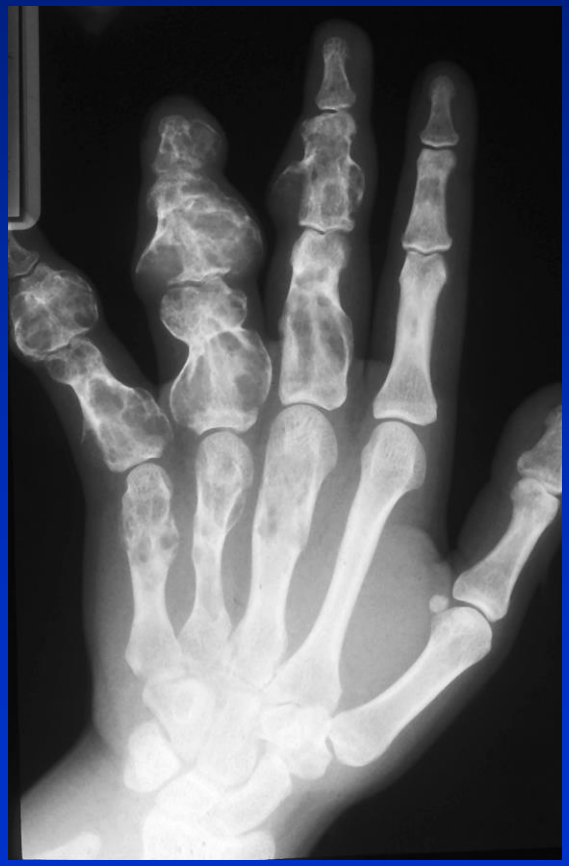
Below-average height

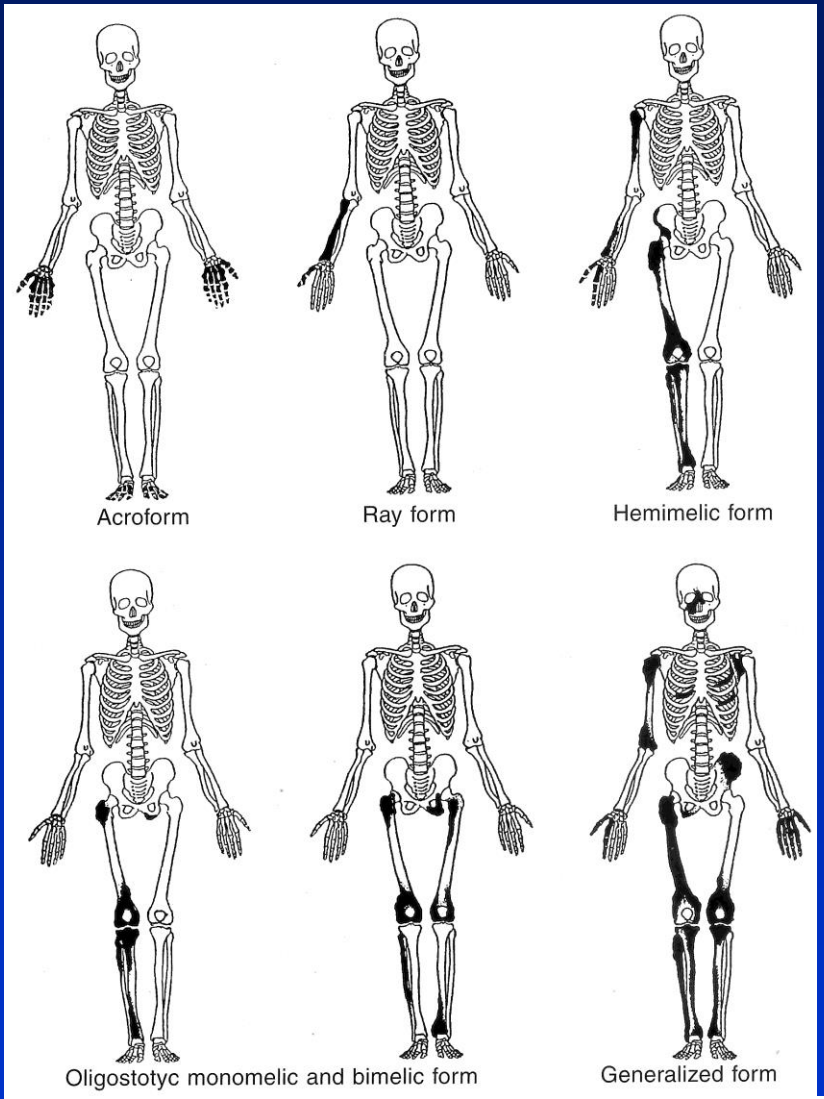
Enchondromatosis (M. Ollier)

MI: SP

MP: unknown

Fr.: unknown





Normal intelligence.

Shorter than normal stature. Asymétrie corporelle.

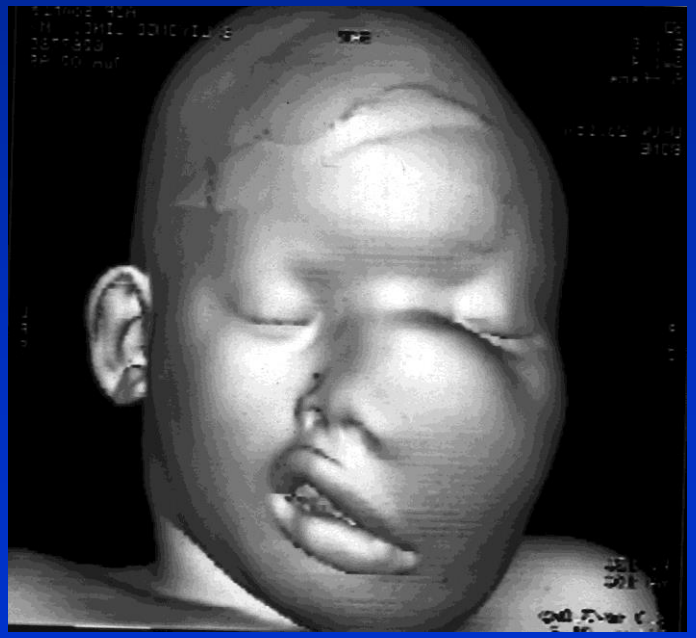
Fibrous dysplasia (McCune Albright syndrome)

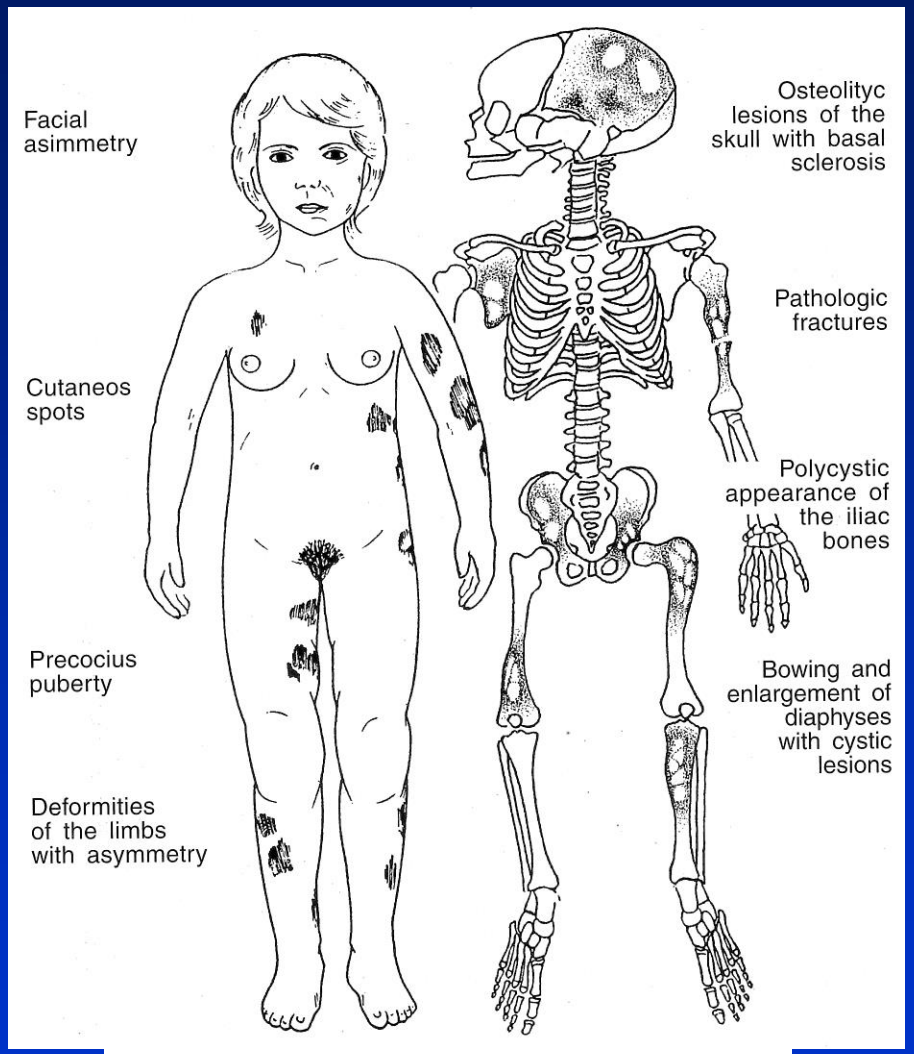
MI: SP

MP: Ch.L.: 20q13

Gene: GNAS1 (guanine nucleotide protein, α-subunit)

Fr.: unknown

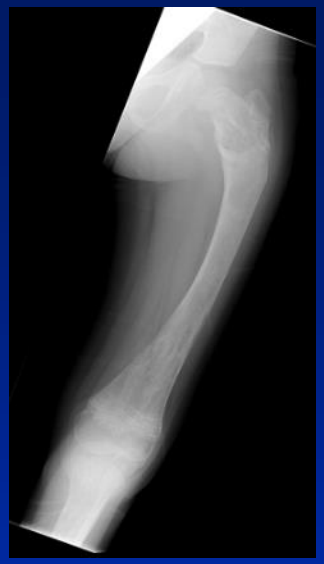


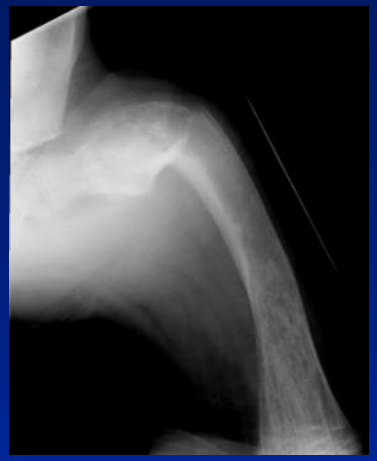


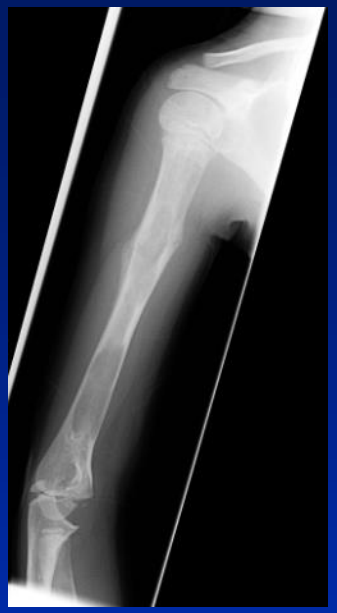
Normal intelligence.

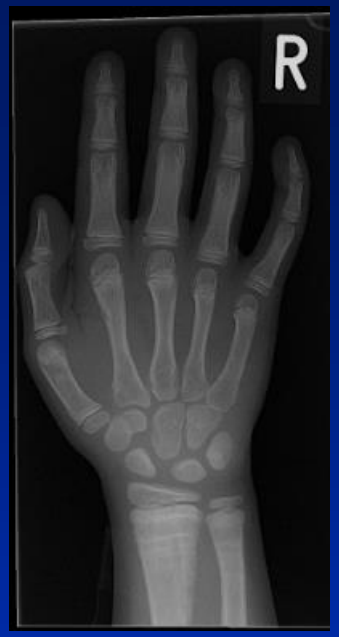
Short stature.

McCune Albright syndrome

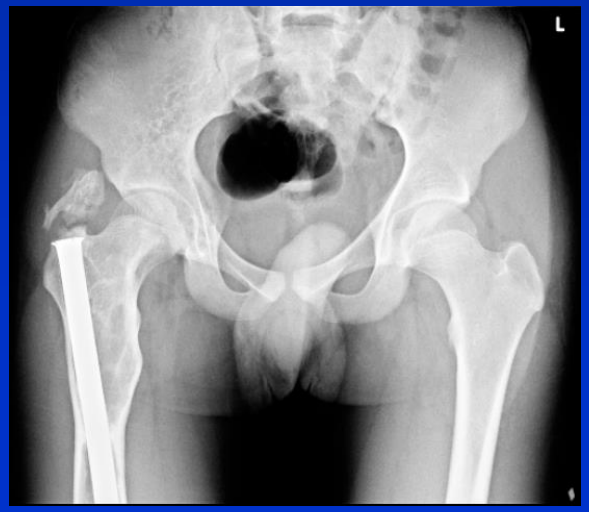


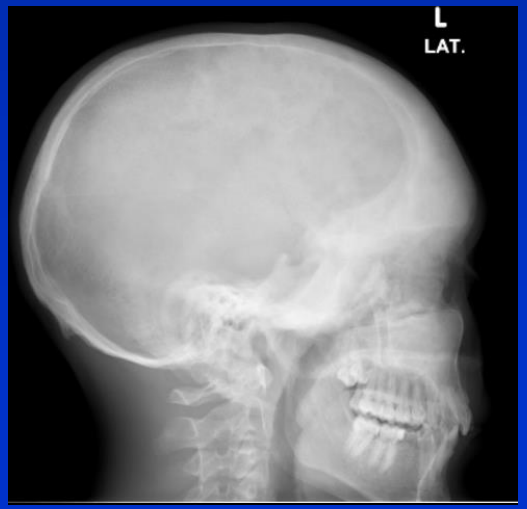


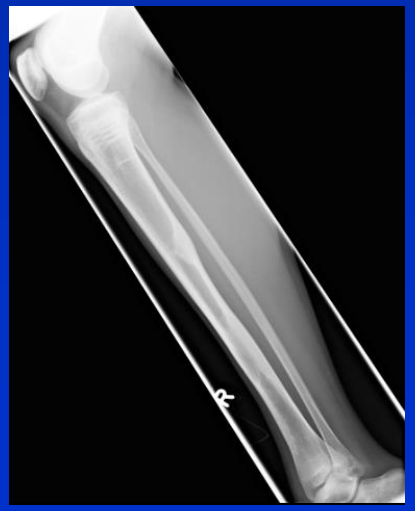




Poly-ostotic fibrous dysplasia







Conclusion I

- Disproportionated skeletal development, unusual habitus, mental retardation with unknown etiology are the most frequent clinical signs of skeletal dysplasia.
- Radiologic evaluation is the first step in morphological study of skeletal dysplasia.
- Antenatal sonography with special attention on skeletal development is a useful procedure in diagnostic search for skeletal dysplasia.

Conclusion II

- Molecular genetic studies should be performed ante- and postnatally in affected patients and their families with skeletal dysplasia.
- Genetic counselling in an essential part of the clinical evaluation in skeletal dysplasia.
- Finally the low incidence and diversity in manifestion of skeletal dysplasia is a reason to ask for second opinion by national or international experts, with the possibility to find a new type or subtype of skeletal dysplasia in some cases.