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 occurring singly or in combination, and occurring 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.
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 counselling 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 deformities
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
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. Mesomorphic dysplasias (11)
17. Acromelic dysplasias (19)
## Classification of Constitutional Disorders of Bone

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
<th>Count</th>
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<tbody>
<tr>
<td>18</td>
<td>Acromesomelic dysplasias</td>
<td>6</td>
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<tr>
<td>19</td>
<td>Dysplasia with predominant membranous bone involvement</td>
<td>4</td>
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<tr>
<td>20</td>
<td>Bent-bone dysplasia group</td>
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<tr>
<td>21</td>
<td>Multiple dislocations with dysplasias</td>
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<td>22</td>
<td>Dysostosis multiplex group</td>
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<tr>
<td>23</td>
<td>Low birthweight slender bone group</td>
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<tr>
<td>24</td>
<td>Dysplasias with decreased bone density</td>
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<tr>
<td>25</td>
<td>Dysplasias with defective mineralization</td>
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<tr>
<td>26</td>
<td>Increased bone density without modification of bone shape</td>
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<td>27</td>
<td>Increased bone density with diaphyseal involvement</td>
<td>14</td>
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<tr>
<td>28</td>
<td>Increased bone density with metaphyseal involvement</td>
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<td>29</td>
<td>Craniotubular digital dysplasias</td>
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<td>30</td>
<td>Neonatal severe osteosclerotic dysplasias</td>
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<td>31</td>
<td>Disorganized development of cartilaginous and fibrous components of the skeleton</td>
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<td>32</td>
<td>Osteolyses</td>
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<tr>
<td>33</td>
<td>Patella dysplasias</td>
<td>5</td>
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</tbody>
</table>
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

Dolicocephaly
Narrow, bell-shaped thorax
Prominent abdomen
Elevated and curved clavicles
Short, horizontal ribs
Pulmonary hypoplasia
Moderate shortening of the limbs
Short, squat extremities
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
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
• Flattened epiphyses of phalanx and carpalia
Multiple epiphyseal 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 (Emopamamilbinding 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.

Short stature.

Circumscribed alopecia
Prominent forehead
Flat face
Hypertelorism
Upsslanting palpebral fissures
Cataract
Flat nose
Anteverted nostrils

Micrognathia
Short neck
Cutaneous dystrophies
Rhizomelic micromelia
Joint enlargement and rigidity
Scoliosis
Puctate epiphyses
Asymmetric limbs
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
Spondylometaphysaire dysplasie
Corner fracture type

Major clinical findings:
• Moderately short stature
• Waddling gait
• Occasionally leg pain

MI: AD
MP: unknown
Fr.: 21 cases reported
Spondylometaphysaire 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.
# Osteogenesis imperfecta

## Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Sclerae</th>
<th>Prognosis</th>
<th>Tubular bone</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Blue</td>
<td>Good</td>
<td>Mild bowing</td>
<td>AD</td>
</tr>
<tr>
<td>IIA</td>
<td>Blue</td>
<td>Early death</td>
<td>Short, thick</td>
<td>AD</td>
</tr>
<tr>
<td>IIB/III</td>
<td>White</td>
<td>Severe handicap</td>
<td>Deformity</td>
<td>AD</td>
</tr>
<tr>
<td>IIC</td>
<td>Blue</td>
<td>Early death</td>
<td>Slender, twisted</td>
<td>AR</td>
</tr>
<tr>
<td>IV</td>
<td>White</td>
<td>Good</td>
<td>Straight</td>
<td>AD</td>
</tr>
<tr>
<td>V</td>
<td>White</td>
<td>Good</td>
<td>Hyperplastic callus</td>
<td>AD</td>
</tr>
</tbody>
</table>

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
Hypophosphatemia

MI: AR
MP: Ch.L: 1p36.1-p34
Gene: ALPL (Alkaline phosphatase)
Fr.: 1:100,000

Normal intelligence.
Micromelic dwarfism.
Osteopetrosis infantile type

MI: AR
MP: Ch.L: 11q13.4-q13.5
Gene: CLCN7
Fr.: 11 : 200.000

Normal intelligence.
Short stature.
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.
• Molecular genetic studies should be performed ante- and postnatally in affected patients and their families with skeletal dysplasia.

• Genetic counselling is an essential part of the clinical evaluation in skeletal dysplasia.

• Finally, the low incidence and diversity in manifestation 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.