A new concept of skeletal dysplasias

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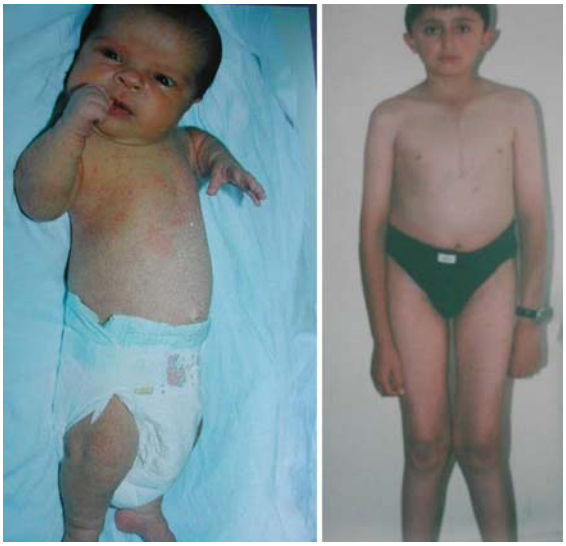
The skeletal dysplasias form a large group of hereditary disorders characterized by abnormal growth and malformations of bone and cartilage. The clinical severity ranges from mildly affected short stature to lethal forms. Spranger classified approximately 200 different skeletal dysplasias in 1992, based on the clinical and radiographic features and the mode of genetic transmission. Etiopathogenesis of skeletal dysplasias is better documented now, with rapid accumulation of knowledge concerning defective genes and proteins causing this group of disorders. Mutations responsible for skeletal dysplasias may cause defects in the synthesis of structural proteins and in metabolic pathways, degradation of macromolecules, growth factors and receptors and transcription factors. Classifications by the International Working Group on Constitutional Diseases of Bone were based on the mutations in the same group gene taking into consideration the clinical and radiological findings (achondroplasia group, dysplasia with decreased bone density group and type II collagenopathies...). Clinical manifestations and radiological investigations are crucial for the differential diagnosis in skeletal dysplasias. However, prenatal diagnosis and postnatal definitive diagnosis are most often achieved by molecular analysis of the patient. Therefore, these groups of disorders require management by a multidisciplinary team of specialists, including pediatricians, genetic specialists, orthopedists and psychiatrists.

Key words: classification, genetics, mutation, skeletal dysplasia, osteochondrodysplasia.

The skeletal dysplasias are a large group of heterogeneous disorders characterized by short stature (mainly disproportionate), deformations and malformations of bone and cartilage (Fig. 1). The clinical severity ranges from mildly affected short stature to lethal forms (Fig. 2). Although rare, many different forms of skeletal dysplasias are described and the incidence, including the lethal forms, is reported to be 1/3000-5000[1-3]. Many of them, with the exception of enzyme deficiency are inherited autosomal dominant inheritance. Since this group of disorders affects both bone and cartilage, they are also called osteochondrodysplasias. Osteodysplasias are disorders of decreased or increased bone density with proportionate short stature, whereas chondrodysplasias may cause deformations and malformations with short trunk or short limb short stature.

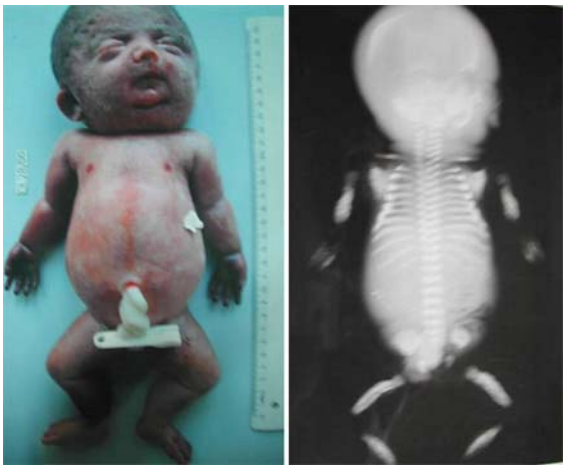


(a) (b)

Fig. 1. Disproportional short stature
a: Short limb short stature in achondroplasia,
b: Short trunk short stature in spondyloepiphyseal dysplasia tarda.

How is a skeletal dysplasia diagnosed?

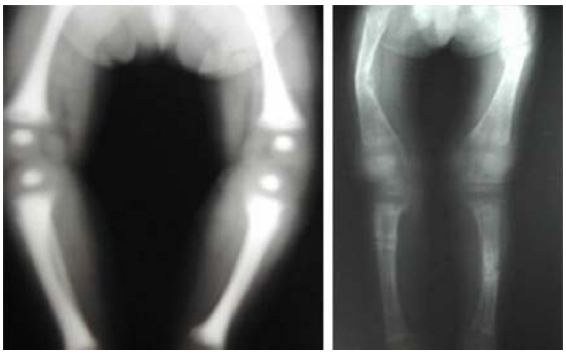
1. Clinical examination: In the differential diagnosis of osteochondrodysplasias, the presence



(a) (b)

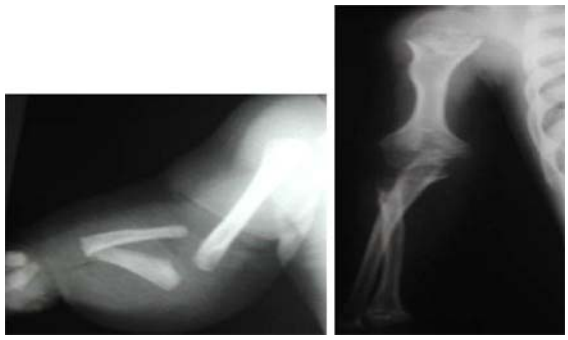
Fig. 2 a, b: Lethal skeletal dysplasia (Perinatal Caffey disease).

of short stature, whether proportionate or disproportionate, should be assessed. The body proportions are important clues to an exact diagnosis. Some skeletal dysplasias result in a reduced rate of growth of the limbs. Other skeletal dysplasias result in a reduced growth rate of the trunk. If there is short limb stature, rhizomelic, mesomelic or acromelic shortening of the limbs should be defined. Age at onset of the disease, dysmorphic features, specific extraskeletal anomalies, and associated malformations and deformations also have to be noted and inheritance of the disorder should be investigated. **2. Radiology:** Radiographic surveying is of major importance in defining the skeletal disease. Bone density should be assessed; decreased or increased changes should be noted (Fig. 3a, b). Primary location of the shortening of the limb (rhizomelic, mesomelic) should be evaluated (Fig. 3c, d).



(a) (b)

Fig. 3. a: Increased bone density in osteopetrosis,
b: Decreased bone density in osteogenesis imperfecta,



(c) (d)

Fig. 3. c: Mesomelic short limb in Robinow syndrome,
d: Rhizomelic short limb in achondroplasia.

Metaphyseal, epiphyseal and diaphyseal irregularity should be examined separately, as well as the vertebral body shape, especially in short trunk dwarfism (Fig. 4a, b, c, d). Dysostosis multiplex should be searched in lysosomal storage diseases (Fig. 5a, b, c, d). **3.** In addition, biochemical analysis of blood and examination of tissue samples such as cartilage or bone should be performed in some cases if necessary.

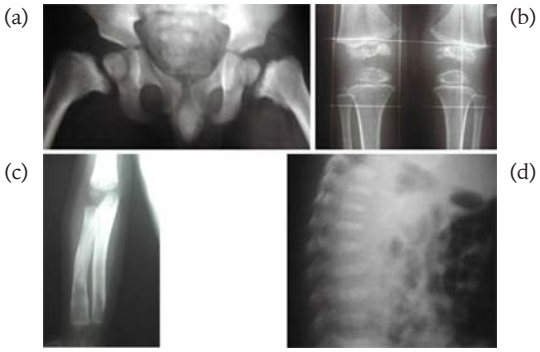
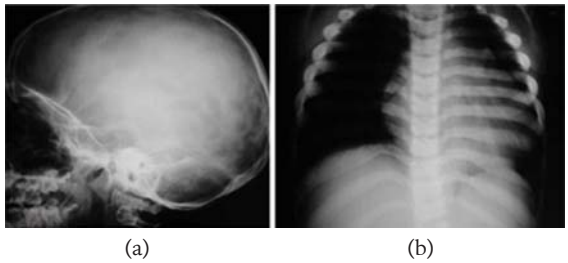
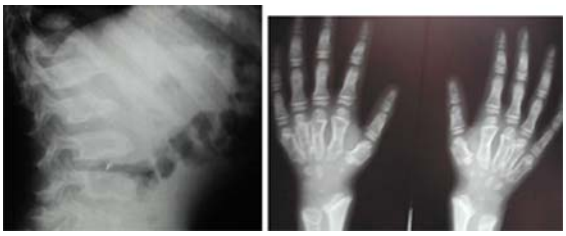


Fig. 4. a: Metaphyseal irregularity in Schmid type metaphyseal dysplasia,
b: Epiphyseal irregularity in MED,
c: Diaphyseal irregularity in diaphyseal dysplasia,
d: Platyspondyly in SED congenita.



(a) (b)

Fig. 5. Radiological finding of storage diseases (disostosis multiplex)
a: The calvarium is with C-shaped sella,
b: Widening of the ribs,



(c) (d)

Fig. 5. c: Marked platyspondyly and hypoplasia of the anterior portion of the vertebral bodies,
d: Short and wide metacarpal bones and V-shaped deformity of the distal ulna and radius.

How can skeletal dysplasias be classified?

Spranger[4] classified approximately 200 different skeletal dysplasias, based on the clinical and radiographic features and the mode of genetic transmission, in 1992. Etiopathogenesis of skeletal dysplasias is better documented currently, with rapid accumulation of knowledge concerning defective genes and proteins causing this group of disorders[5-7]. In 1997, classifications by the International Working Group on Constitutional Diseases of Bone, were first based on the mutations in the same group gene taking into consideration the clinical and radiological findings (achondroplasia group, dysplasia with decreased bone density group and type II collagenopathies...)[8]. Dysostoses (malformations of certain bones or groups of bones) were neglected in the 1997 revision. Later, in 2001, the same research groups enlarged the osteodysplasia classification to 33 main group and three different dysostosis groups (craniosynostosis, spondylocostal dysplasia and Fanconi syndrome groups A-G) with identified genes included[9]. Superti-Furga[10] from the International Working Group on Constitutional Diseases of Bone classified the gene and protein identified skeletal dysplasias based on only their molecular-pathogenetics (Table I). In the present study this classification is used.

Table I. Molecular-Pathogenetic Classification of Osteochondrodysplasias[10]

Gene and protein	Clinical phenotype
1. Defects in structural proteins	
Collagen:	
COL1	Osteogenesis imperfecta
COL2	Achondrogenesis type II Hypochondrogenesis Spondyloepiphyseal dysplasia (SED) congenita Spondyloepimetaphyseal dysplasia Kniest dysplasia Stickler syndrome I
COL9	Multiple epiphyseal dysplasia (MED) type 2
COL10	Metaphyseal dysplasia (Schmid type)
COL11	Stickler syndrome II Otospondylomegaepiphyseal dysplasia
COMP	Pseudoachondroplasia Multiple epiphyseal dysplasia type 1
Matrillin-3 (MATN-3)	Multiple epiphyseal dysplasia type 3
Perlecan	Schwartz-Jampel type-1,2
2. Defects in metabolic pathways:	
Diastrophic dysplasia sulfate transporter (DTDST)	Achondrogenesis 1B Athelosteogenesis II Diastrophic dysplasia Recessive MED
Arylsulfatase E	X-linked chondrodysplasia punctata
ANKH (Pyrophosphate transporter)	Craniometaphyseal dysplasia
CIC7	Severe osteopetrosis
Carboanhydrase II	Osteopetrosis with renal tubular acidosis
3. Defects in degradation of macromolecules:	
Lysosomal enzymes	Mucopolysaccharidoses Mucolipidosis
Cathepsin K	Pyknodysostosis
Sedlin	X-linked SED tarda

Table I. (Continuation)

Gene and protein	Clinical phenotype
4. Defects in growth factors and receptors	
Fibroblast growth factor receptor 1, 2	Craniosynostosis
Fibroblast growth factor receptor 3	Achondroplasia Hypochondroplasia Thanatophoric dysplasia I,II
PTH receptor	Jansen type metaphyseal dysplasia
Fibroblast growth factor receptor 23	Autosomal dominant hypophosphatemic rickets
PEX proteinase	X linked hypophosphatemic rickets
GNAS1	Pseudohypoparathyroidism
ROR-2	Robinow, brachydactyly type B
5. Defects in transcription factors	
SOX9	Campomelic dysplasia
GI13	Greig cephalopolysyndactyly
TRPS1	Trichorhinophalangeal dysplasia 1-3
TWIST	Saethre-Chotzen
CBFA-1	Cleidocranial dysplasia
SHOX	Leri-Weill syndrome

Mutations responsible for skeletal dysplasias that cause defects in the synthesis of structural proteins, and in metabolic pathways, degradation of macromolecules, growth factors and receptors, and transcription factors:

1. Defects in structural proteins

Organic matrix in bone consists of 90% collagen and 10% non-collagen proteins (Table II)[11]. Approximately 20 types of collagen proteins have been described in the human body. Type 1 collagen is primarily found in bone, skin and tendons, whereas types 2, 9, 10, and 11 are found mostly in cartilage[12].

Table II. The Structure of Bone Organic Matrix

Type I collagen	90%
Noncollagen protein	10%

- Proteoglycans (heparan sulfate, perlecan, dermatan sulfate, chondroitin sulfate, keratan sulfate)
- Glycoproteins and others: alkaline phosphate, Thrombospondin (COMP), matrillin, fibronectin, sialoprotein, osteopontin, osteocalcin, osteonectin

a) Mutations in type 1 collagen (dysplasia with decreased bone density): Type 1 collagen defects result in osteogenesis imperfecta (OI) which is characterized by short stature with classical bone fragility, blue sclerae, defective dentinogenesis and deafness. Sillence et al.[13] classified the major forms of OI into four types: type I, a common form with blue sclerae; type II, a perinatal lethal form; type III, a progressively deforming type with normal sclerae; and type IV with normal sclerae which is similar to type 1. Type 1 collagen protein has two chains, which are alpha-1 and alpha-2. The genes of these chains are located at different chromosomes. The common genetic features of type I OI are mutations in COL1A1 and COL1A2 leading to complete absence of the protein that they encode, and a quantitatively reduced amount of type 1 collagen in bone. Unlike type I OI, in types II, III, and IV OI structurally abnormal alpha-1 and 2 chains are synthesised[14].

b) Mutations in type 2 collagen: Type 2 collagen gene mutation may cause a variety of osteochondrodysplasias[15]. Congenital spondyloepiphyseal dysplasia (SED) is the most frequent type 2 collagen gene (COL2A) disorder. This clinical spectrum is associated with disproportionate short trunk short stature, epiphyseal dysplasia and platyspondylia. The other mutations of COL2A gene result in mild SED and Kniest syndrome, which resemble congenital SED. The other disorders in the same group are Stickler syndrome and two lethal types, namely achondrogenesis type II and hypochondrogenesis.

c) Mutations in type 9 collagen, COMP and matrillin (multiple epiphyseal dysplasia & pseudoachondroplasia group): Type 9 is a minor collagen, which regulates cartilage fibril formation. Mutation in the gene of type 9 collagen results in multiple epiphyseal dysplasia

(MED) 2, presented as severe knee and ankle pain. Cartilage oligomeric matrix protein (COMP) is a major component of the chondrocyte matrix. It is a member of the thrombospondin gene family and causes MED type 1 and pseudoachondroplasia[16]. In the Fairbank type of MED type 1, irregularities of the capital femoral epiphyses and acetabula are noticed and it is characterized by mild shortening of stature and knobby joints. Pseudoachondroplasia is characterized by shortlimb short stature, deformity of extremities, waddling gait and typical radiographic changes that include small, deformed epiphyses and expanded, irregular metaphyses. Matrillin-3 (MATN-3) is known to hold the extracellular matrix proteins together and the mutation in the protein results in MED type 3. Only two families with MED have been reported with a MATN-3 mutation.

d) Mutations in type 10 collagen and perlecan: Mutations of the type 10 collagen gene have been shown to be responsible for Schmid type metaphyseal dysplasia[17]. This disorder is the mildest and the most common metaphyseal dysplasia and is characterized by small stature and bowed legs; and rickets must sometimes be considered in the differential diagnosis. Perlecan is a large heparan sulfate present in various tissues and is a component of all basement membrane extracellular matrices. In Schwartz-Jampel syndrome and dissegmental dysplasia, mutations of the perlecan gene have been shown[18].

2. Defects in metabolic pathways (diastrophic dysplasia group)

The exact function of the diastrophic dysplasia sulfate transporter (DTDST) gene is unclear; however, it may affect endochondral bone formation in chondrocytes. The mutation of the gene has been shown to be the cause of several recessively inherited osteochondrodysplasias. Some of these are diastrophic dysplasia, recessive MED, achondrogenesis 1B and athelosteogenesis 2.

Arylsulfatase E, which is a steroid sulfatase, was shown in human osteoblast cell lines. Although the exact function is unknown, it may have an important role in bone and cartilage formation[19]. The mutation of this protein gene causes X-linked chondrodysplasia punctata. In addition it was reported that three proteins (TCIRG2, CIC7, and carboanhydrase 2) are involved in the acidification of the osteoclasts; all three are associated with osteopetrosis[10].

3. Defects in degradation of macromolecules (dysostosis multiplex group): The group mainly includes the lysosomal storage disorders, which are recessively inherited. The deficiencies of the enzyme necessary in the degradation of the glycosaminoglycans cause mucopolysaccharidoses. Cathepsin K (CTSK) is an endoprotease that is suspected to play a role in the degradation of extracellular matrix components. A number of mutations in the CTSK gene have been found in patients with pyknodysostosis, which is a form of dwarfism characterized by osteosclerosis and bone fragility[20]. Sedlin is a protein that has role in protein transport. The mutation of sedlin causes X linked spondylo-epiphyseal dysplasia (SED) tarda which is the common type of SED[21].

4. Mutations in fibroblast growth factor receptor (achondroplasia group)

The fibroblast growth factors (FGFs) are involved in cell proliferation and wound healing. They also play important roles in human limb and craniofacial development[22]. Mutations in fibroblast growth factor receptors (FGFR) 1 and 2 cause craniosynostoses[23]. Mutations of FGFR3 give rise to achondroplasia, and hypochondroplasia (a milder form of achondroplasia), and to thanatophoric dysplasia, a lethal form of dwarfism that resembles homozygous achondroplasia. The defect affects enchondral bone formation (Fig. 6). During enchondral ossification development, cartilage normally develops into bone. However,

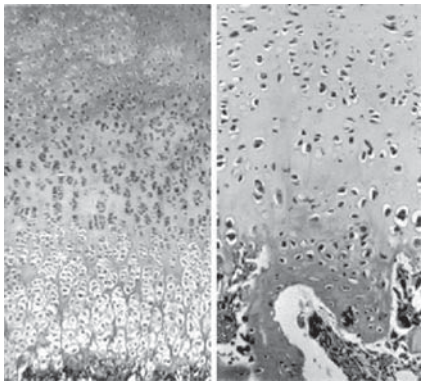


Fig. 6. Cartilage development at the growth plate of the long bones.
a: Normal growth plate,
b: Disorganized growth plate in thanatophoric dysplasia.

the cartilage cells in cases with achondroplasia develop into bone more slowly than normal, especially in the long bones of the arms and legs, leading to shorter bones and shorter final height. Therefore the trunk of a patient with achondroplasia is relatively normal in length but the arms and legs are short.

Parathyroid hormone (PTH) receptor function has a direct effect on terminal differentiation of pre-hypertrophied chondrocytes into hypertrophied chondrocytes in the growth plate. The mutation in PTH receptor causes Jansen metaphyseal chondrodysplasia[24]. A mutation of FGF23, which is a phosphaturic protein, causes autosomal dominant hypophosphatemic rickets, whereas the mutations in PEX proteinase, which is cleavage of FGF23, causes X-linked hypophoshatemic rickets[25,26].

5. Defects in transcription factors

Mutations in transcription factors cause some autosomal inherited skeletal dysplasias[27]. SOX9 is a transcription factor that is highly expressed in cartilaginous tissue. Mutations of SOX9, a sex-related protein, cause campomelic dysplasia, which is a form of neonatal dwarfism, characterized by anterolateral bowing and angulation of the legs and talipes equinovarus. Defects of CBFA1, a transcription factor of osteoblasts, result in delayed intramembranous and enchondral ossification. The mutation of the gene results in cleidocranial dysplasia where both flat and tubular bones are affected[28].

Conclusion

Clinical manifestations and radiological investigations are crucial for the differential diagnosis in skeletal dysplasias. However, prenatal diagnosis and postnatal definitive diagnosis are most often achieved by molecular analysis of the patient. Defining the etiopathogenesis by molecular analysis also helps to investigate the probability of therapeutic applications. Patients with osteogenesis imperfecta, idiopathic juvenile osteoporosis and hyperphosphatasia may benefit from drugs that increase mineralization. Orthopedic surgeons may perform correction, prosthesis and length heightening operations. Since most patients with skeletal dysplasias are not affected mentally, they also have to cope with psychological in addition to orthopedic problems. Thus, these groups of disorders require management by a multidisciplinary team of specialists, including pediatricians, genetic specialists, orthopedists and psychiatrists.

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